Clinical Trial Protocol

# 1. Title

Title: Comparative Effectiveness of Apalutamide versus Enzalutamide in Metastatic Hormone-Sensitive Prostate Cancer (mHSPC): A Real-World Evidence Analysis

Background and Rationale: Recent advancements in androgen receptor inhibitors, such as apalutamide and enzalutamide, have significantly improved outcomes for patients with metastatic hormone-sensitive prostate cancer (mHSPC). Understanding the comparative effectiveness of these treatments in real-world settings is essential to assess their impact on diverse patient populations beyond the confines of controlled clinical trials. This study aims to utilize secondary real-world evidence (RWE) sources to evaluate the effectiveness of apalutamide and enzalutamide.

Objectives:   
1. To compare overall survival and progression-free survival in mHSPC patients treated with apalutamide versus enzalutamide.  
2. To evaluate quality-of-life outcomes and adverse event profiles associated with each treatment in real-world settings.

Study Design: This is an observational, retrospective comparative effectiveness study utilizing secondary RWE sources.

Data Sources: Data will be collected from databases such as Flatiron Health, SEER-Medicare, and other electronic health records (EHRs) and claims databases.

Key Inclusion Criteria:   
• Population: Adult males diagnosed with mHSPC.  
• Interventions: Treatment with apalutamide or enzalutamide.  
• Outcomes: Overall survival, progression-free survival, quality of life, and adverse events.

Data Extraction and Analysis: Patient characteristics, treatment regimens, and outcomes will be extracted and compared between cohorts. Propensity score matching or inverse probability of treatment weighting (IPTW) will be employed to adjust for confounding factors.

Expected Outcomes:   
• Provide insights into the relative effectiveness of apalutamide versus enzalutamide in real-world populations.  
• Offer evidence on differential safety profiles to inform clinical decision-making.

Timeline: The study is estimated to be completed within 8 months, from data extraction to final analysis.

# 2. Background

Background

Prostate cancer remains a significant health concern worldwide, being one of the most commonly diagnosed cancers among men. Metastatic hormone-sensitive prostate cancer (mHSPC) represents a stage where the cancer has spread beyond the prostate gland but still responds to hormone therapy. Recent advancements in the treatment of mHSPC have focused on androgen receptor inhibitors, particularly apalutamide and enzalutamide. These agents have shown promise in improving patient outcomes by delaying disease progression and extending survival in clinical trial settings.

However, the controlled environment of clinical trials often does not fully represent the diverse patient populations encountered in everyday clinical practice. Therefore, understanding the comparative effectiveness of apalutamide and enzalutamide in real-world settings is crucial. Real-world evidence (RWE) provides insights into how these treatments perform across broader and more varied patient groups, including those with comorbidities and different demographic backgrounds.

This study aims to leverage secondary RWE sources to assess the effectiveness of apalutamide and enzalutamide in mHSPC. By analyzing data from electronic health records (EHRs), claims databases, and other RWE sources, this research seeks to compare overall survival and progression-free survival outcomes between the two treatments. Additionally, it will evaluate quality-of-life measures and adverse event profiles, providing a comprehensive understanding of the benefits and risks associated with each therapy in a real-world context.

The findings from this study are expected to offer valuable insights into the relative effectiveness and safety profiles of apalutamide versus enzalutamide, thereby informing clinical decision-making and potentially guiding treatment strategies for mHSPC patients in routine practice.

# 3. Objectives

Objectives:

1. Primary Objective:  
• To compare overall survival (OS) and progression-free survival (PFS) in patients with metastatic hormone-sensitive prostate cancer (mHSPC) treated with apalutamide versus enzalutamide in real-world settings. This will provide insights into the relative effectiveness of these treatments outside the controlled environment of clinical trials.

2. Secondary Objectives:  
• To evaluate the quality-of-life (QoL) outcomes associated with apalutamide and enzalutamide treatments in mHSPC patients. This assessment will consider patient-reported outcomes and other relevant QoL measures to understand the impact of each treatment on daily living and well-being.  
• To assess the adverse event profiles of apalutamide and enzalutamide in a real-world context. This will involve analyzing the incidence and severity of treatment-related adverse events, contributing to a comprehensive understanding of the safety profiles of these therapies.

3. Exploratory Objectives:  
• To explore potential differences in treatment effectiveness and safety across various patient subgroups, including those defined by demographic factors, comorbidities, and prior treatment history. This analysis aims to identify any differential impacts of apalutamide and enzalutamide that may inform personalized treatment strategies.

These objectives are designed to leverage secondary real-world evidence (RWE) sources to provide a robust comparison of apalutamide and enzalutamide, thereby supporting informed clinical decision-making and optimizing treatment approaches for mHSPC patients in routine practice.

# 4. Study Design

Study Design:

This study is designed as an observational, retrospective comparative effectiveness analysis utilizing secondary real-world evidence (RWE) sources. The primary aim is to compare the effectiveness of apalutamide versus enzalutamide in patients with metastatic hormone-sensitive prostate cancer (mHSPC) in real-world settings. The study will focus on evaluating overall survival (OS), progression-free survival (PFS), quality of life (QoL), and adverse event profiles associated with these treatments.

Data for this study will be sourced from comprehensive databases such as Flatiron Health, SEER-Medicare, and other electronic health records (EHRs) and claims databases. These sources provide a rich repository of patient data, enabling the study to capture a broad spectrum of real-world clinical outcomes across diverse patient populations.

Key inclusion criteria for the study population include adult males diagnosed with mHSPC who have been treated with either apalutamide or enzalutamide. The study will focus on assessing outcomes such as overall survival, progression-free survival, quality of life, and adverse events.

Data extraction and analysis will involve the collection of patient characteristics, treatment regimens, and clinical outcomes. To address potential confounding factors and ensure robust comparative analysis, statistical techniques such as propensity score matching or inverse probability of treatment weighting (IPTW) will be employed. These methods will help balance the treatment cohorts and allow for a more accurate estimation of the treatment effects.

The expected outcomes of this study include gaining insights into the relative effectiveness of apalutamide versus enzalutamide in real-world clinical practice. Additionally, the study aims to provide evidence on the differential safety profiles of these treatments, which can inform clinical decision-making and optimize treatment strategies for mHSPC patients.

The study is anticipated to be completed within an 8-month timeline, from the initial data extraction phase through to the final analysis and reporting of results. This timeline ensures a comprehensive evaluation of the comparative effectiveness of these androgen receptor inhibitors in a real-world context, ultimately contributing to improved patient care and treatment outcomes in mHSPC.

# 5. Data Sources

Data Sources:

In accordance with the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) guidelines, this study will utilize a comprehensive array of secondary real-world evidence (RWE) sources to ensure robust data collection and analysis. The primary data sources include:

1. Flatiron Health Database: This oncology-specific electronic health record (EHR) database provides detailed clinical data on cancer patients, including demographic information, treatment regimens, clinical outcomes, and adverse events. It offers a rich dataset for evaluating the real-world effectiveness of apalutamide and enzalutamide in mHSPC patients.

2. SEER-Medicare Database: A linkage of the Surveillance, Epidemiology, and End Results (SEER) cancer registry data with Medicare claims, this database provides comprehensive information on cancer incidence, treatment, and survival among the elderly U.S. population. It is instrumental in assessing long-term outcomes such as overall survival and progression-free survival.

3. Other Electronic Health Records (EHRs) and Claims Databases: Additional data will be sourced from various EHR systems and claims databases to capture a broader patient population and enhance the generalizability of the study findings. These sources will provide supplementary data on patient demographics, treatment patterns, and clinical outcomes.

Data from these sources will be integrated and harmonized to ensure consistency and accuracy in the analysis. The study will adhere to all relevant data protection and privacy regulations, ensuring that patient confidentiality is maintained throughout the research process.

The selection of these data sources aligns with the study's objectives to evaluate the comparative effectiveness of apalutamide versus enzalutamide in a real-world setting, providing a comprehensive understanding of treatment outcomes across diverse patient populations.

# 6. Population

Population:

In alignment with the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) guidelines, the study population for this observational, retrospective comparative effectiveness analysis is defined as follows:

1. Target Population: The study will focus on adult male patients diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). This specific population is chosen due to the clinical relevance of androgen receptor inhibitors, such as apalutamide and enzalutamide, in managing mHSPC.

2. Inclusion Criteria:  
• Adult males aged 18 years and older.  
• Confirmed diagnosis of mHSPC, as identified through medical records and diagnostic codes within the selected databases.  
• Initiation of treatment with either apalutamide or enzalutamide during the study period, as documented in electronic health records (EHRs) or claims databases.  
• Availability of comprehensive baseline data, including demographic information, clinical characteristics, and prior treatment history, to facilitate robust comparative analysis.

3. Exclusion Criteria:  
• Patients with incomplete or missing data on key variables necessary for the analysis, such as treatment start date or outcome measures.  
• Patients who received both apalutamide and enzalutamide concurrently, as this would confound the comparative effectiveness analysis.  
• Individuals with a history of other malignancies that might interfere with the assessment of outcomes specific to mHSPC.

4. Data Sources: The study will utilize data from established databases such as Flatiron Health, SEER-Medicare, and other EHRs and claims databases. These sources provide a comprehensive and diverse dataset, ensuring representation of a wide range of patient demographics and clinical settings.

5. Sample Size Considerations: The sample size will be determined based on the availability of eligible patients within the data sources, ensuring sufficient power to detect clinically meaningful differences in outcomes between the treatment groups.

By adhering to these criteria, the study aims to capture a representative sample of the mHSPC population, enabling a robust evaluation of the real-world effectiveness and safety profiles of apalutamide versus enzalutamide. This approach ensures that the findings are generalizable to routine clinical practice, thereby informing treatment decisions and optimizing patient care.

# 7. Variables

Variables:

1. Demographic Variables:  
• Age: Continuous variable representing the age of the patient at the time of treatment initiation.  
• Race/Ethnicity: Categorical variable indicating the patient's self-reported race/ethnicity (e.g., Caucasian, African American, Hispanic, Asian, Other).  
• Socioeconomic Status: Categorical variable based on insurance type or other available indicators (e.g., private insurance, Medicare, Medicaid, uninsured).

2. Clinical Characteristics:  
• Baseline PSA Level: Continuous variable representing prostate-specific antigen levels at baseline.  
• Gleason Score: Categorical variable indicating the Gleason score at diagnosis (e.g., ≤6, 7, 8-10).  
• Comorbidities: Categorical variable indicating the presence of comorbid conditions, measured using the Charlson Comorbidity Index.

3. Treatment Variables:  
• Treatment Type: Categorical variable indicating the type of androgen receptor inhibitor received (apalutamide or enzalutamide).  
• Treatment Duration: Continuous variable representing the duration of treatment in months.  
• Prior Treatments: Categorical variable indicating any prior treatments received for prostate cancer (e.g., surgery, radiation, chemotherapy).

4. Outcome Variables:  
• Overall Survival (OS): Time-to-event variable measuring the time from treatment initiation to death from any cause.  
• Progression-Free Survival (PFS): Time-to-event variable measuring the time from treatment initiation to disease progression or death.  
• Quality of Life (QoL): Continuous variable derived from patient-reported outcome measures (e.g., EQ-5D, FACT-P).  
• Adverse Events: Categorical variable indicating the occurrence and severity of treatment-related adverse events, classified according to CTCAE criteria.

5. Analytical Variables:  
• Propensity Score: Continuous variable used for matching or weighting to adjust for confounding factors.  
• Inverse Probability of Treatment Weighting (IPTW): Continuous variable applied to balance treatment groups in the analysis.

6. Data Source Variables:  
• Data Source Identifier: Categorical variable indicating the source of the data (e.g., Flatiron Health, SEER-Medicare, other EHRs).  
• Data Collection Period: Continuous variable representing the time frame during which the data was collected.

These variables are structured to ensure comprehensive data collection and analysis, adhering to the RECORD guidelines for observational studies using routinely collected health data. They facilitate a robust comparison of the effectiveness and safety profiles of apalutamide versus enzalutamide in real-world settings.

# 8. Statistical Analysis

Statistical Analysis:

In compliance with the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) guidelines, the statistical analysis for this study will be conducted as follows:

1. Descriptive Statistics: We will begin by summarizing the baseline characteristics of the study population. Continuous variables such as age and baseline PSA levels will be reported as means with standard deviations or medians with interquartile ranges, depending on the distribution. Categorical variables such as race/ethnicity, Gleason score, and comorbidities will be presented as frequencies and percentages. This will provide an overview of the demographic and clinical profile of patients receiving apalutamide versus enzalutamide.

2. Propensity Score Matching (PSM) and Inverse Probability of Treatment Weighting (IPTW): To address potential confounding and ensure comparability between treatment groups, we will employ propensity score methods. Propensity scores will be estimated using logistic regression models that include relevant covariates such as age, race/ethnicity, baseline PSA levels, Gleason score, comorbidities, and prior treatments. We will perform 1:1 nearest neighbor matching without replacement and apply IPTW to balance the treatment groups. The balance of covariates post-matching and weighting will be assessed using standardized mean differences.

3. Survival Analysis: The primary outcomes, overall survival (OS) and progression-free survival (PFS), will be analyzed using Kaplan-Meier survival curves and log-rank tests to compare survival distributions between the two treatment groups. Cox proportional hazards regression models will be used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for any remaining imbalances in baseline characteristics. The proportional hazards assumption will be tested using Schoenfeld residuals.

4. Quality of Life (QoL) and Adverse Events Analysis: QoL outcomes, derived from patient-reported measures such as EQ-5D or FACT-P, will be analyzed using mixed-effects models to account for repeated measures over time. Adverse events will be compared between groups using chi-square tests or Fisher’s exact tests for categorical outcomes, and logistic regression models will be employed to adjust for confounders.

5. Subgroup Analyses: Exploratory analyses will be conducted to evaluate treatment effects across predefined subgroups, including age, race/ethnicity, comorbidity burden, and prior treatment history. Interaction terms will be included in the Cox models to assess differential treatment effects.

6. Sensitivity Analyses: Sensitivity analyses will be performed to assess the robustness of the findings. These may include alternative matching algorithms, different covariate sets for propensity score estimation, and analyses excluding patients with missing data.

7. Missing Data: Multiple imputation techniques will be used to handle missing data, assuming data are missing at random. Imputation models will include all variables used in the analysis to ensure unbiased estimates.

8. Software: All statistical analyses will be conducted using R or SAS software, ensuring reproducibility and adherence to best practices in statistical analysis.

This comprehensive statistical approach will provide robust estimates of the comparative effectiveness and safety profiles of apalutamide versus enzalutamide in a real-world setting, thereby informing clinical decision-making and optimizing treatment strategies for mHSPC patients.

# 9. Limitations

Limitations:

1. Data Source Limitations: The study relies on secondary real-world evidence (RWE) sources such as Flatiron Health, SEER-Medicare, and other electronic health records (EHRs) and claims databases. These sources may have inherent limitations, including incomplete data capture, variations in data quality, and potential misclassification of variables such as diagnosis, treatment, and outcomes. Additionally, the lack of randomization in observational data can introduce selection bias, which may affect the generalizability of the findings.

2. Confounding and Bias: Despite the use of statistical techniques such as propensity score matching and inverse probability of treatment weighting (IPTW) to adjust for confounding factors, residual confounding may still exist. Unmeasured confounders, such as patient lifestyle factors or physician treatment preferences, could influence the comparative effectiveness results.

3. Missing Data: The study may encounter missing data for key variables, which could impact the robustness of the findings. Although multiple imputation techniques will be employed to handle missing data, the assumption that data are missing at random may not hold true for all variables, potentially introducing bias.

4. Generalizability: The study population is limited to adult males diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC) who are treated with either apalutamide or enzalutamide. The findings may not be generalizable to other populations, such as those with different stages of prostate cancer or those receiving other treatments. Additionally, the study's reliance on U.S.-based databases may limit the applicability of the results to international populations.

5. Outcome Measurement: The assessment of quality-of-life outcomes and adverse events relies on data captured in routine clinical practice, which may not be as comprehensive or standardized as data collected in clinical trials. This could lead to underreporting or variability in the measurement of these outcomes.

6. Temporal Changes: The study's retrospective design may not fully account for temporal changes in clinical practice, treatment guidelines, or the availability of new therapies that could influence treatment patterns and outcomes over time.

7. Software and Analytical Limitations: The use of specific statistical software (R or SAS) and analytical methods may introduce limitations related to the assumptions and capabilities of these tools. While efforts will be made to ensure reproducibility and adherence to best practices, the choice of software and methods could impact the study's conclusions.

These limitations highlight the challenges inherent in conducting observational studies using routinely collected health data. Despite these challenges, the study aims to provide valuable insights into the real-world effectiveness and safety profiles of apalutamide versus enzalutamide, contributing to informed clinical decision-making in the management of mHSPC.