Clinical Trial Protocol

# 1. Title

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

Subtitle: An Observational, Retrospective Analysis Using Secondary Data Sources

Structured Synopsis:

1. Study Concept: This study investigates the comparative effectiveness of apalutamide versus enzalutamide in treating mHSPC by utilizing secondary real-world evidence (RWE).

2. Background & Rationale: Apalutamide and enzalutamide, as androgen receptor inhibitors, have shown to improve outcomes for patients with mHSPC. However, there is a need to understand their comparative effectiveness in real-world settings, which may differ from controlled clinical trial environments. This study will provide insights into the real-world performance of these treatments.

3. Study Objectives:  
• To compare the overall survival and progression-free survival of mHSPC patients treated with apalutamide versus enzalutamide.  
• To evaluate the quality-of-life outcomes and adverse event profiles for each treatment in a real-world context.

4. Study Design: This is an observational, retrospective study that will analyze secondary RWE sources to compare the effectiveness of apalutamide and enzalutamide.

5. Data Sources: The study will utilize databases such as Flatiron Health, SEER-Medicare, and other EHR and claims databases to gather patient data.

6. Key Inclusion Criteria:  
• Adult males diagnosed with mHSPC.  
• Patients who have received treatment with either apalutamide or enzalutamide.  
• Outcomes measured will include overall survival, progression-free survival, quality of life, and adverse events.

7. Data Extraction & Analysis: Data on patient characteristics, treatment regimens, and outcomes will be extracted from the selected databases. Comparative analyses will be conducted using methods such as propensity score matching or IPTW to adjust for potential confounders.

8. Expected Outcomes:  
• A better understanding of the relative effectiveness of apalutamide versus enzalutamide in a real-world setting.  
• Information on the safety profiles of the treatments to support clinical decision-making.

9. Timeline: The study is expected to be completed within 8 months, starting from data extraction to the final analysis.

This title and structured synopsis are designed to meet the RECORD (Reporting of studies Conducted using Observational Routinely-collected health Data) guidelines for reporting observational studies using health data routinely collected for administrative and clinical purposes.

# 2. Background

Background

Prostate cancer remains a leading cause of cancer-related mortality among men worldwide. Metastatic hormone-sensitive prostate cancer (mHSPC) represents a clinical stage where the disease has spread beyond the prostate gland and still responds to androgen deprivation therapy (ADT). The management of mHSPC has evolved with the introduction of novel androgen receptor inhibitors, such as apalutamide and enzalutamide, which have demonstrated efficacy in improving patient outcomes in clinical trials.

However, the performance of these agents in real-world settings may differ from controlled clinical trial environments due to variations in patient populations, treatment adherence, and other factors. Therefore, understanding the comparative effectiveness of apalutamide and enzalutamide in routine clinical practice is essential for informed decision-making by healthcare providers and patients.

This study seeks to address this knowledge gap by leveraging secondary real-world evidence (RWE) sources. The analysis of real-world data (RWD) can provide insights into the effectiveness, safety, and quality of life associated with these treatments in a broader patient population. By comparing overall survival, progression-free survival, and adverse event profiles between apalutamide and enzalutamide, this study aims to generate evidence that may guide clinical strategies and optimize patient care in mHSPC.

The use of secondary RWE sources, such as electronic health records (EHRs), claims databases, and cancer registries, offers a unique opportunity to assess outcomes in a large and diverse patient cohort. This approach also allows for the evaluation of long-term effects and the identification of patterns that may not be apparent in the more controlled setting of a clinical trial.

The findings from this study are expected to contribute to the growing body of knowledge on the management of mHSPC and support healthcare professionals in making evidence-based treatment decisions that reflect the realities of clinical practice. The study's design, which includes the use of advanced statistical methods to adjust for confounding factors, is intended to ensure that the results are robust and applicable to real-world settings.

In summary, this observational, retrospective comparative effectiveness study will provide valuable RWE on the use of apalutamide and enzalutamide in the treatment of mHSPC, with the potential to impact clinical guidelines and patient care strategies. The study aligns with the RECORD guidelines, ensuring that the reporting of the study will be transparent, comprehensive, and of high quality.

# 3. Objectives

Study Objectives

The objectives of this observational, retrospective comparative effectiveness study are as follows:

1. To compare the overall survival (OS) of patients with metastatic hormone-sensitive prostate cancer (mHSPC) treated with apalutamide versus those treated with enzalutamide in real-world clinical settings.

2. To compare the progression-free survival (PFS) of mHSPC patients treated with apalutamide versus those treated with enzalutamide, using secondary real-world evidence (RWE) sources.

3. To assess and compare the quality-of-life (QoL) outcomes for mHSPC patients treated with either apalutamide or enzalutamide, as reflected in real-world data (RWD).

4. To evaluate and compare the adverse event (AE) profiles associated with apalutamide and enzalutamide treatments in the real-world setting, to understand the differential safety profiles of these therapies.

5. To conduct a robust analysis that accounts for potential confounding factors, ensuring that the comparative effectiveness results are reflective of true clinical outcomes.

These objectives are designed to address the knowledge gap regarding the performance of apalutamide and enzalutamide in routine clinical practice and to provide evidence that may guide treatment decisions for patients with mHSPC. The study will adhere to the RECORD guidelines, ensuring that the reporting of the study is transparent, comprehensive, and of high quality, thereby contributing valuable insights into the management of mHSPC in real-world clinical settings.

# 4. Study Design

Study Design

Design Overview  
This observational, retrospective comparative effectiveness study is designed to assess the real-world effectiveness of apalutamide versus enzalutamide in the treatment of metastatic hormone-sensitive prostate cancer (mHSPC). The study will utilize secondary real-world evidence (RWE) sources, including electronic health records (EHRs), claims databases, and cancer registries, to compare outcomes for patients treated with these androgen receptor inhibitors.

Study Setting  
The study will be conducted using data from multiple sources, which may include academic medical centers, community hospitals, and outpatient clinics, as represented within the databases such as Flatiron Health and SEER-Medicare.

Participants  
The study population will consist of adult males diagnosed with mHSPC who have been treated with either apalutamide or enzalutamide. Patients will be identified based on diagnostic codes, treatment records, and other relevant data available within the selected databases.

Variables  
The primary variables of interest are overall survival (OS) and progression-free survival (PFS). Secondary variables include quality-of-life (QoL) outcomes and adverse event (AE) profiles associated with the treatments. Patient characteristics, such as age, race, comorbidities, and prior treatments, will also be collected to adjust for potential confounding factors.

Data Sources/Measurement  
Data will be sourced from comprehensive databases that include patient demographics, clinical characteristics, treatment details, outcomes, and follow-up information. The integrity and validity of these data sources are critical for the reliability of the study findings.

Bias  
Efforts to minimize bias will include careful selection of appropriate databases with high-quality data, the use of validated outcome measures, and the application of advanced statistical methods such as propensity score matching or inverse probability of treatment weighting (IPTW) to adjust for known confounders.

Study Size  
The study size will be determined by the number of eligible patients identified within the selected databases who meet the inclusion criteria during the specified study period.

Quantitative Variables  
Statistical analyses will be conducted to compare OS and PFS between the treatment groups using Kaplan-Meier survival curves and Cox proportional hazards models. QoL and AE data will be analyzed using appropriate statistical tests based on the nature of the data (e.g., t-tests, chi-squared tests).

Data Analysis  
The analysis will include a descriptive summary of patient characteristics, treatment patterns, and outcomes. Comparative effectiveness analyses will be performed using multivariable regression models, adjusting for potential confounders. Sensitivity analyses will be conducted to test the robustness of the findings.

This study design adheres to the RECORD guidelines, ensuring that the reporting of the study will be transparent, comprehensive, and of high quality. The findings are expected to provide valuable insights into the comparative effectiveness of apalutamide versus enzalutamide in the treatment of mHSPC in real-world clinical settings.

# 5. Data Sources

Data Sources

The data sources for this observational, retrospective comparative effectiveness study are critical to the reliability and validity of the findings. The following elements outline the data sources and measures that will be used in compliance with the RECORD guidelines:

1. Database Selection:  
• The study will utilize secondary real-world evidence (RWE) sources, including electronic health records (EHRs), claims databases, and cancer registries.  
• Specific databases such as Flatiron Health and SEER-Medicare have been identified as primary sources due to their comprehensive coverage of oncology patient data and linkage capabilities between clinical and administrative data.

2. Data Coverage:  
• The selected databases are expected to provide a wide range of patient demographics, clinical characteristics, treatment details, outcomes, and follow-up information.  
• These databases are known for their high-quality data, which include information from various healthcare settings such as academic medical centers, community hospitals, and outpatient clinics.

3. Data Extraction Period:  
• The study will include data from a predefined period, which will be determined based on the availability and completeness of the data within the selected databases.  
• The extraction period will be chosen to ensure a sufficient number of patients are included to achieve adequate statistical power for the analysis.

4. Data Integrity and Validation:  
• The databases have been chosen for their use of validated data collection methods and quality control processes.  
• Data integrity checks will be performed to ensure the accuracy and consistency of the data extracted for the study.

5. Data Variables:  
• The primary variables of interest include overall survival (OS) and progression-free survival (PFS).  
• Secondary variables include quality-of-life (QoL) outcomes and adverse event (AE) profiles.  
• Patient characteristics such as age, race, comorbidities, prior treatments, and other relevant clinical data will be extracted to adjust for potential confounding factors.

6. Data Linkage:  
• If applicable, data linkage across different sources will be performed to enrich the dataset with additional variables or to validate the outcomes.  
• Data linkage procedures will adhere to privacy regulations and ethical standards to protect patient confidentiality.

7. Data Access and Governance:  
• Access to the databases will be obtained following the respective data governance policies and procedures.  
• The study team will ensure that all necessary ethical approvals and data use agreements are in place prior to data access and extraction.

8. Data Handling and Storage:  
• Extracted data will be handled and stored securely in compliance with data protection laws and regulations.  
• Only authorized personnel will have access to the data, and all analyses will be conducted in a secure environment to maintain data confidentiality.

By adhering to these data source guidelines, the study aims to ensure the transparency, comprehensiveness, and high quality of the reporting, in line with the RECORD guidelines. The robustness of the data sources will contribute to the reliability of the study's findings and the generation of valuable insights into the comparative effectiveness of apalutamide versus enzalutamide in the treatment of mHSPC in real-world clinical settings.

# 6. Population

Population

The population for this observational, retrospective comparative effectiveness study will consist of adult male patients diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). The study will include patients who have received treatment with either apalutamide or enzalutamide, as documented in the selected secondary real-world evidence (RWE) sources.

Eligibility Criteria

The key inclusion criteria for the study population are as follows:

1. Adult males (age ≥ 18 years) with a confirmed diagnosis of mHSPC.  
2. Patients who have been prescribed and have received treatment with apalutamide or enzalutamide during the study period.  
3. Availability of outcome data on overall survival (OS), progression-free survival (PFS), quality of life (QoL), and adverse events (AEs) within the selected databases.

Exclusion Criteria

Patients will be excluded from the study based on the following criteria:

1. Patients with incomplete data on treatment exposure (apalutamide or enzalutamide) or key outcome measures (OS, PFS, QoL, AEs).  
2. Patients who have participated in clinical trials for mHSPC during the study period, as their outcomes may not reflect real-world clinical practice.  
3. Patients with other malignancies that could confound the assessment of treatment effectiveness and safety profiles.

Identification of the Study Population

Patients will be identified through the selected databases using a combination of diagnostic codes (e.g., ICD-10 codes for prostate cancer), treatment records (e.g., pharmacy claims, medication administration records), and other relevant clinical data. The study period and data extraction timeframe will be defined based on the availability and completeness of data within the databases.

Demographic and Clinical Characteristics

The following demographic and clinical characteristics of the study population will be extracted and reported:

1. Age at diagnosis of mHSPC.  
2. Race/ethnicity.  
3. Comorbidities and co-medications.  
4. Prior treatments for prostate cancer (e.g., androgen deprivation therapy).  
5. Tumor characteristics (e.g., Gleason score, PSA levels).  
6. Treatment details (e.g., dosages, duration of treatment with apalutamide or enzalutamide).

These characteristics will be used to describe the study population and to adjust for potential confounding factors in the comparative effectiveness analysis.

Data Collection and Management

Data will be collected in accordance with the data governance policies of the respective databases. Patient confidentiality and data privacy will be maintained throughout the study. Data will be de-identified and stored securely, with access restricted to authorized study personnel.

In compliance with the RECORD guidelines, this section provides a transparent and comprehensive description of the study population, including the inclusion and exclusion criteria, the process of patient identification, and the demographic and clinical characteristics to be collected. This ensures the quality and reliability of the study findings in assessing the comparative effectiveness of apalutamide versus enzalutamide in the treatment of mHSPC in real-world clinical settings.

# 7. Variables

Variables

The Variables section of this observational, retrospective comparative effectiveness study will detail the specific data elements to be collected and analyzed in accordance with the RECORD guidelines. The following variables will be extracted from the secondary real-world evidence (RWE) sources:

1. Primary Outcomes:  
• Overall Survival (OS): Time from initiation of treatment (apalutamide or enzalutamide) to death from any cause.  
• Progression-Free Survival (PFS): Time from initiation of treatment to disease progression or death from any cause, whichever occurs first.

2. Secondary Outcomes:  
• Quality of Life (QoL): Measured by patient-reported outcome measures available within the databases.  
• Adverse Events (AEs): Documented side effects associated with apalutamide or enzalutamide treatment.

3. Patient Characteristics (Covariates):  
• Age at diagnosis of mHSPC.  
• Race/ethnicity.  
• Comorbidities and co-medications.  
• Prior treatments for prostate cancer (e.g., androgen deprivation therapy).  
• Tumor characteristics (e.g., Gleason score, PSA levels).  
• Treatment details (e.g., dosages, duration of treatment with apalutamide or enzalutamide).

4. Statistical Variables:  
• Propensity scores for use in matching or weighting to adjust for confounding factors.  
• Variables for sensitivity analyses to test the robustness of the findings.

5. Data Integrity and Validation Variables:  
• Indicators for data completeness and accuracy.  
• Variables used for cross-referencing and validating data across multiple sources.

6. Data Management Variables:  
• Patient identifiers for de-identification purposes.  
• Audit trail variables for tracking data extraction, transformation, and analysis processes.

The data extraction process will ensure that all variables are collected in a manner that allows for accurate and reliable comparative effectiveness analysis. The study will use appropriate statistical methods to handle missing data and to adjust for confounding factors, ensuring the validity of the study findings.

The variables will be defined prior to data extraction, and a data dictionary will be created to ensure consistency in data handling and analysis. The study team will adhere to data governance policies and ethical standards throughout the data collection and analysis process.

By detailing the variables in this manner, the study complies with the RECORD guidelines, ensuring transparent and comprehensive reporting of the variables used in the analysis of the comparative effectiveness of apalutamide versus enzalutamide in the treatment of mHSPC in real-world clinical settings.

# 8. Statistical Analysis

Statistical Analysis

The statistical analysis plan for this observational, retrospective comparative effectiveness study is designed to meet the RECORD guidelines for reporting studies conducted using observational routinely-collected health data. The following elements outline the statistical methods and analytical approaches that will be employed:

1. Descriptive Statistics:  
• Patient demographics, clinical characteristics, and treatment patterns will be summarized using means and standard deviations for continuous variables, and frequencies and percentages for categorical variables.  
• Baseline characteristics will be compared between the apalutamide and enzalutamide cohorts using chi-squared tests for categorical variables and t-tests or Wilcoxon rank-sum tests for continuous variables, as appropriate.

2. Outcome Analysis:  
• Overall Survival (OS) and Progression-Free Survival (PFS) will be the primary endpoints. OS is defined as the time from treatment initiation to death from any cause, and PFS is defined as the time from treatment initiation to disease progression or death, whichever occurs first.  
• Kaplan-Meier survival curves will be used to estimate survival probabilities, and differences between treatment groups will be assessed using the log-rank test.  
• Cox proportional hazards models will be used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and PFS, adjusting for potential confounders identified during the study design phase.

3. Propensity Score Analysis:  
• To address confounding by indication, propensity score matching or inverse probability of treatment weighting (IPTW) will be employed.  
• Propensity scores will be estimated using logistic regression based on covariates that may influence treatment selection and outcomes, such as age, race, comorbidities, prior treatments, and tumor characteristics.  
• Balance diagnostics will be performed to assess the success of the matching or weighting procedure.

4. Secondary Outcomes Analysis:  
• Quality of life (QoL) outcomes and adverse event (AE) profiles will be analyzed using appropriate statistical tests, such as chi-squared tests for categorical outcomes and t-tests or non-parametric equivalents for continuous outcomes.  
• Multivariable regression models may be used to adjust for confounding factors when comparing QoL and AE outcomes between treatment groups.

5. Sensitivity Analyses:  
• Sensitivity analyses will be conducted to test the robustness of the findings, including analyses using different propensity score models, varying the inclusion criteria, and performing analyses with and without imputation for missing data.  
• Subgroup analyses may be performed to explore the consistency of treatment effects across different patient subpopulations.

6. Handling of Missing Data:  
• The extent of missing data will be reported, and the impact on the study results will be assessed.  
• Multiple imputation or other appropriate methods will be used to handle missing data, if necessary.

7. Statistical Software:  
• All analyses will be performed using statistical software such as R, SAS, or Stata, with the choice of software documented in the final report.

8. Reporting of Results:  
• Results will be reported in accordance with the RECORD guidelines, including the presentation of both unadjusted and adjusted estimates of treatment effects.  
• A detailed description of all statistical methods, including model specifications, variable selection, and rationale for the chosen methods, will be provided.

9. Transparency and Reproducibility:  
• The statistical analysis plan will be pre-specified and, if possible, registered or published before the commencement of the analysis.  
• The study will provide sufficient detail to allow replication of the analysis by independent researchers, subject to data availability and confidentiality constraints.

By adhering to these statistical analysis guidelines, the study aims to ensure the transparency, comprehensiveness, and high quality of the reporting, in line with the RECORD guidelines. The robustness of the statistical methods will contribute to the reliability of the study's findings and the generation of valuable insights into the comparative effectiveness of apalutamide versus enzalutamide in the treatment of mHSPC in real-world clinical settings.

# 9. Limitations

Limitations

This observational, retrospective comparative effectiveness study, while designed to provide valuable insights into the real-world effectiveness of apalutamide versus enzalutamide in treating metastatic hormone-sensitive prostate cancer (mHSPC), has several limitations that must be acknowledged.

1. Retrospective Design: The study's retrospective nature may introduce selection bias, as the treatment groups may differ in ways that are not fully accounted for, even after propensity score matching or inverse probability of treatment weighting (IPTW).

2. Confounding Variables: Despite the use of advanced statistical methods to adjust for known confounders, residual confounding by unmeasured or unknown factors may still affect the results.

3. Data Source Limitations: The study relies on secondary real-world evidence (RWE) sources, which may have missing or incomplete data, coding errors, or variability in data collection practices across different databases.

4. Generalizability: The findings may not be generalizable to all mHSPC patients, as the study population is derived from specific databases that may not fully represent the diversity of the broader patient population.

5. Treatment Adherence: The study may not accurately capture treatment adherence, as real-world data typically lack detailed information on medication-taking behavior.

6. Outcome Measures: The quality-of-life outcomes and adverse event profiles are dependent on the availability and accuracy of these data within the databases, which may be subject to underreporting or misclassification.

7. Changes in Practice Patterns: The study's results may be influenced by temporal changes in clinical practice patterns and guidelines that are not captured within the study period.

8. Data Linkage: If data linkage is required, mismatches or errors in linkage could affect the accuracy of the outcome data.

9. Statistical Power: The study size is determined by the number of eligible patients within the databases, which may limit the statistical power to detect differences between treatment groups, especially for subgroup analyses.

10. Multiple Testing: The study involves multiple comparisons, which increases the risk of type I error (false positives). Appropriate statistical adjustments for multiple testing will be necessary.

11. Loss to Follow-Up: The study may be affected by loss to follow-up, which can introduce bias if it is related to the treatment or outcomes of interest.

12. Ethical and Privacy Considerations: The use of secondary RWE must adhere to ethical standards and privacy regulations, which may limit access to certain types of data or require de-identification that could impact data quality.

In conclusion, while this study aims to provide a robust analysis of the comparative effectiveness of apalutamide versus enzalutamide in mHSPC patients using secondary RWE, these limitations must be considered when interpreting the results. Future research may involve prospective designs, more comprehensive data sources, and additional methods to minimize the impact of these limitations.