Clinical Trial Protocol

Background

Background

Metastatic hormone-sensitive prostate cancer (mHSPC) represents a significant clinical challenge, as it is a stage of prostate cancer where the disease has spread beyond the prostate gland but remains responsive to hormone therapy. The management of mHSPC has evolved considerably over the past decade, primarily due to the introduction of novel androgen receptor inhibitors such as apalutamide and enzalutamide. These agents have demonstrated efficacy in prolonging survival and delaying disease progression in clinical trials, thereby becoming integral components of treatment regimens for mHSPC.

Despite the promising results from randomized controlled trials (RCTs), there remains a critical need to evaluate the comparative effectiveness of these treatments in real-world settings. RCTs, while rigorous, often involve highly selected patient populations under controlled conditions, which may not fully represent the diversity and complexity of patients encountered in everyday clinical practice. This discrepancy underscores the importance of real-world evidence (RWE) to complement clinical trial data, providing insights into how these therapies perform across broader, more heterogeneous populations.

Current evidence gaps in the management of mHSPC include a lack of direct head-to-head comparisons between apalutamide and enzalutamide in real-world settings. Additionally, there is limited information on the quality-of-life outcomes and the real-world safety profiles of these treatments. Addressing these gaps is crucial for optimizing treatment strategies and improving patient care.

The rationale for utilizing real-world data in this study is multifaceted. Real-world data sources, such as electronic health records (EHRs), claims databases, and cancer registries, offer a wealth of information that can be leveraged to assess treatment outcomes in diverse patient populations. By analyzing data from sources like Flatiron Health and SEER-Medicare, this study aims to provide a comprehensive evaluation of the comparative effectiveness of apalutamide versus enzalutamide. This approach allows for the examination of outcomes such as overall survival, progression-free survival, quality of life, and adverse events, thereby offering valuable insights into the real-world impact of these therapies.

In summary, this study seeks to fill existing evidence gaps by utilizing secondary RWE to compare the effectiveness and safety of apalutamide and enzalutamide in mHSPC. The findings are expected to inform clinical decision-making and contribute

to the optimization of treatment strategies for patients with this challenging disease.

Objectives

Study Objectives

The primary and secondary objectives of this study are designed to address the critical evidence gaps in the management of metastatic hormone-sensitive prostate cancer (mHSPC) by comparing the real-world effectiveness and safety of apalutamide versus enzalutamide. These objectives will guide the analysis of secondary real-world evidence (RWE) to provide actionable insights for clinical practice.

Primary Objective:

1. To compare overall survival (OS) and progression-free survival (PFS) in mHSPC patients treated with apalutamide versus enzalutamide.
   - Primary Research Question: What are the differences in overall survival and progression-free survival between mHSPC patients treated with apalutamide compared to those treated with enzalutamide in real-world clinical settings?

Secondary Objectives:

1. To assess quality-of-life outcomes in mHSPC patients receiving apalutamide versus enzalutamide.
   - Secondary Research Question: How do quality-of-life outcomes differ between patients treated with apalutamide and those treated with enzalutamide in real-world settings?

2. To evaluate the adverse event profiles associated with apalutamide and enzalutamide in mHSPC patients.
   - Secondary Research Question: What are the differences in the incidence and severity of adverse events between mHSPC patients treated with apalutamide versus enzalutamide in real-world practice?

3. To explore the impact of patient characteristics and treatment regimens on the effectiveness and safety outcomes of apalutamide and enzalutamide.
   - Secondary Research Question: How do baseline patient characteristics and variations in treatment regimens influence the effectiveness and safety of apalutamide and enzalutamide in mHSPC?

By addressing these objectives, the study aims to provide comprehensive insights into the real-world performance of apalutamide and enzalutamide, thereby

informing clinical decision-making and optimizing treatment strategies for mHSPC patients.

Study Design

Study Design

Overall Approach:
This study is designed as an observational, retrospective comparative effectiveness analysis utilizing secondary real-world evidence (RWE) sources. The primary aim is to evaluate the comparative effectiveness of apalutamide versus enzalutamide in patients with metastatic hormone-sensitive prostate cancer (mHSPC). By leveraging existing data from electronic health records (EHRs), claims databases, and cancer registries, the study seeks to provide insights into overall survival, progression-free survival, quality of life, and adverse event profiles associated with these treatments in real-world clinical settings.

Study Period:
The study will encompass a retrospective analysis of data spanning several years, with the specific timeframe determined by the availability and comprehensiveness of the data sources. The data extraction and analysis phase is anticipated to be completed within an 8-month period, allowing for a thorough examination of patient outcomes and treatment patterns.

Key Design Considerations:

1. Data Sources:
   - The study will utilize comprehensive data from sources such as Flatiron Health, SEER-Medicare, and other relevant EHRs and claims databases. These sources provide rich datasets that capture diverse patient populations and treatment experiences in real-world settings.

2. Population and Cohorts:
   - The study will include adult male patients diagnosed with mHSPC who have been treated with either apalutamide or enzalutamide. Patients will be identified based on specific inclusion criteria to ensure the cohorts are comparable and representative of the broader mHSPC population.

3. Outcome Measures:
   - Primary outcomes include overall survival (OS) and progression-free survival (PFS). Secondary outcomes focus on quality-of-life assessments and the incidence and severity of adverse events, providing a comprehensive view of treatment impact.

4. Analytical Methods:
   - To address potential confounding factors and ensure robust comparisons between treatment groups, the study will employ statistical techniques such as propensity score matching or inverse probability of treatment weighting (IPTW). These methods will help balance baseline characteristics and enhance the validity of the findings.

5. Ethical Considerations:
   - As a retrospective study using de-identified data from secondary sources, ethical considerations will focus on data privacy and compliance with relevant regulations. Institutional review board (IRB) approval will be sought as necessary to ensure adherence to ethical standards.

6. Limitations:
   - The study acknowledges potential limitations inherent in observational research, such as residual confounding and data completeness. Efforts will be made to mitigate these limitations through rigorous data validation and sensitivity analyses.

By addressing these design considerations, the study aims to generate meaningful real-world evidence that can inform clinical decision-making and optimize treatment strategies for patients with mHSPC.

Population

Population Section

Target Population:
The target population for this study comprises adult male patients diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). This population is selected due to the clinical relevance of evaluating the effectiveness of androgen receptor inhibitors, specifically apalutamide and enzalutamide, in this disease context. The focus on mHSPC patients is driven by the need to understand treatment outcomes in a real-world setting, where patients often present with diverse clinical profiles and comorbidities not fully represented in clinical trials.

Inclusion Criteria:
To ensure the study population is appropriately defined and relevant to the research objectives, the following inclusion criteria will be applied:
- Adult male patients aged 18 years and older.
- Confirmed diagnosis of metastatic hormone-sensitive prostate cancer (mHSPC).
- Initiation of treatment with either apalutamide or enzalutamide during the study period.
- Availability of comprehensive electronic health records (EHRs) or claims data documenting treatment regimens and outcomes.

Exclusion Criteria:
Exclusion criteria are established to minimize confounding factors and enhance the validity of the study findings:
- Patients with incomplete or missing data on key variables, including treatment start date, survival outcomes, or adverse events.
- Prior treatment with both apalutamide and enzalutamide, to avoid confounding effects from cross-over treatments.
- Diagnosis of other concurrent malignancies that could significantly impact survival outcomes.
- Participation in clinical trials for mHSPC treatments during the study period, to ensure real-world treatment scenarios are captured.

Sample Selection Process:
The sample selection process will involve a systematic approach to identify eligible patients from secondary real-world evidence sources, such as Flatiron Health, SEER-Medicare, and other relevant EHRs and claims databases. The process will include:
1. Data Extraction: Utilizing database queries to extract records of patients diagnosed with mHSPC who have been treated with either apalutamide or enzalutamide.
2. Eligibility Screening: Applying the inclusion and exclusion criteria to the extracted dataset to ensure the study population is representative and comparable.
4. Propensity Score Matching/Weighting: Implementing statistical techniques such as propensity score matching or inverse probability of treatment weighting (IPTW) to adjust for baseline differences and potential confounders between the treatment groups, thereby enhancing the comparability of the cohorts.

By adhering to this structured sample selection process, the study aims to generate robust and reliable real-world evidence on the comparative effectiveness of apalutamide versus enzalutamide in mHSPC, ultimately contributing to informed clinical decision-making and optimized patient care.

Procedures

Variables Section

Exposures
- Treatment with Apalutamide: Defined as the initiation and continuation of apalutamide therapy in patients diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC).
- Treatment with Enzalutamide: Defined as the initiation and continuation of enzalutamide therapy in patients diagnosed with mHSPC.

Outcomes

- Overall Survival (OS): Time from the initiation of treatment (either apalutamide or enzalutamide) to death from any cause.
- Progression-Free Survival (PFS): Time from the initiation of treatment to the first documented disease progression or death from any cause, whichever occurs first.
- Quality of Life (QoL): Assessed using validated patient-reported outcome measures available in the data sources, capturing aspects such as physical functioning, pain, and overall well-being.
- Adverse Events (AEs): Incidence and severity of treatment-related adverse events, as documented in electronic health records or claims data.

Covariates
- Age: Age of the patient at the time of treatment initiation.
- Race/Ethnicity: Self-reported or documented race/ethnicity of the patient.
- Comorbidities: Presence of other medical conditions, assessed using comorbidity indices such as the Charlson Comorbidity Index.
- Baseline PSA Levels: Prostate-specific antigen levels at the time of treatment initiation.
- Performance Status: Baseline performance status, often recorded using scales such as ECOG or Karnofsky.
- Prior Treatments: Any prior treatments for prostate cancer, including hormone therapy or chemotherapy, before the initiation of apalutamide or enzalutamide.

Potential Confounders
- Socioeconomic Status: Indicators such as income level, education, or insurance status, which may influence treatment access and outcomes.
- Geographic Location: Region or location of treatment, which may affect healthcare access and practice patterns.
- Healthcare Utilization: Frequency of healthcare visits and interventions, which may reflect underlying health status and access to care.
- Treatment Adherence: Measures of how consistently patients adhere to their prescribed treatment regimens, potentially impacting effectiveness and outcomes.

By defining these variables, the study aims to comprehensively assess the comparative effectiveness of apalutamide versus enzalutamide in real-world settings, accounting for various factors that may influence treatment outcomes.

Statistical

Analytical Methods

Statistical Approaches

The primary analysis will focus on comparing overall survival (OS) and progression-free survival (PFS) between patients treated with apalutamide and those treated

with enzalutamide. Kaplan-Meier survival curves will be generated for both OS and PFS, and differences between treatment groups will be assessed using the log-rank test. Cox proportional hazards models will be employed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for potential confounders.

For secondary outcomes, such as quality of life (QoL) and adverse events (AEs), descriptive statistics will be used to summarize baseline characteristics and outcome measures. Differences in QoL scores will be analyzed using mixed-effects models to account for repeated measures over time. The incidence of AEs will be compared using chi-square tests or Fisher's exact tests, as appropriate.

Confounding Control

To address potential confounding, propensity score methods will be utilized. Propensity score matching (PSM) will be performed to create balanced cohorts of patients receiving apalutamide and enzalutamide, based on baseline characteristics such as age, race/ethnicity, comorbidities, baseline PSA levels, performance status, prior treatments, and socioeconomic status. Alternatively, inverse probability of treatment weighting (IPTW) will be applied to weight patients by the inverse probability of receiving their actual treatment, thus balancing covariates across treatment groups.

Covariate balance will be assessed using standardized mean differences, with a threshold of less than 0.1 indicating adequate balance. Sensitivity analyses will be conducted to evaluate the robustness of the results to different methods of confounding control.

Sensitivity Analyses

Several sensitivity analyses will be conducted to test the robustness of the findings:

1. Unmeasured Confounding: An E-value analysis will be performed to estimate the potential impact of unmeasured confounders on the observed associations. This will help assess how strong an unmeasured confounder would need to be to negate the observed treatment effect.

2. Subgroup Analyses: Subgroup analyses will be conducted based on key demographic and clinical characteristics, such as age, race/ethnicity, baseline PSA levels, and performance status, to explore potential effect modification.

3. Alternative Model Specifications: Different model specifications, including stratified Cox models and competing risks models, will be explored to ensure the robustness of survival estimates.

4. Missing Data: Multiple imputation techniques will be employed to handle missing data, and analyses will be repeated to assess the impact of missing data on study findings.

5. Time-Varying Covariates: Time-varying covariates, such as changes in performance status or comorbidities during follow-up, will be incorporated into the models to account for their potential influence on treatment outcomes.

By employing these analytical methods, the study aims to provide a comprehensive and robust evaluation of the comparative effectiveness of apalutamide versus enzalutamide in mHSPC, contributing valuable insights to inform clinical practice.

Safety

Limitations

This study, while providing valuable insights into the comparative effectiveness of apalutamide versus enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC) using real-world evidence (RWE), is subject to several limitations that should be considered when interpreting the findings.

Potential Biases

1. Selection Bias: As an observational retrospective study, there is an inherent risk of selection bias. Patients included in the study may not be representative of the broader mHSPC population due to the specific inclusion and exclusion criteria applied. Additionally, treatment decisions in real-world settings are often influenced by factors not captured in the data, such as physician preference or patient choice, which could introduce bias.

2. Confounding Bias: Despite the use of propensity score matching and inverse probability of treatment weighting to adjust for confounding factors, residual confounding may still exist. Unmeasured variables, such as genetic factors or detailed clinical characteristics, could influence treatment outcomes and are not accounted for in the analysis.

Data Quality Issues

1. Incompleteness of Data: The reliance on secondary data sources such as electronic health records (EHRs) and claims databases may lead to incomplete data capture. Important variables, such as detailed quality-of-life measures or specific adverse events, may be underreported or missing, potentially affecting the robustness of the findings.

2. Data Heterogeneity: The study utilizes data from multiple sources, which may vary in terms of data collection methods, coding practices, and completeness. This heterogeneity can introduce variability in the data quality and may impact the comparability of results across different datasets.

3. Misclassification: There is a possibility of misclassification of exposure or outcomes due to inaccuracies in coding or documentation within the data sources. Such misclassification could lead to biased estimates of treatment effectiveness or safety.

Generalizability

1. Population Representativeness: The study population is derived from specific databases, which may not fully represent the diversity of the global mHSPC patient population. Factors such as geographic location, healthcare system differences, and demographic diversity may limit the generalizability of the findings to broader populations.

2. Real-World Setting Variability: The real-world setting encompasses a wide range of clinical practices and healthcare environments, which may differ significantly from the controlled conditions of clinical trials. As a result, the study findings may not be directly applicable to settings with different healthcare infrastructures or patient management protocols.

3. Temporal Changes: The retrospective nature of the study means that the data may span several years, during which there could have been changes in treatment guidelines, diagnostic criteria, or healthcare practices. These temporal changes could affect the relevance of the findings to current clinical practice.

In conclusion, while this study provides important real-world evidence on the comparative effectiveness of apalutamide versus enzalutamide in mHSPC, the limitations related to potential biases, data quality issues, and generalizability must be acknowledged. These factors should be carefully considered when applying the study results to clinical decision-making and treatment strategy optimization. Future research could benefit from prospective designs and more comprehensive data collection to address these limitations.