Clinical Trial Protocol

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# 1.2 Background

Background

Disease Background  
Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer, accounting for approximately 85% of all lung cancer cases worldwide. It encompasses several histological subtypes, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Despite advancements in detection and management, NSCLC remains a leading cause of cancer-related mortality globally. The prognosis for NSCLC can vary significantly based on factors such as disease stage at diagnosis, genetic mutations, and patient comorbidities. Traditionally, the management of NSCLC involved surgery, radiation, and chemotherapy; however, these treatments often have limitations related to efficacy and tolerability.

Current Treatment Landscape  
In recent years, the treatment landscape for NSCLC has evolved dramatically with the introduction of targeted therapies and immunotherapies. Targeted therapies have been developed to specifically inhibit the pathways involved in cancer growth and proliferation, particularly in tumors with specific genetic mutations such as EGFR, ALK, and ROS1. These therapies have significantly improved outcomes in patients with corresponding molecular alterations. Additionally, immunotherapy, especially immune checkpoint inhibitors targeting PD-1/PD-L1, has transformed the treatment paradigm by harnessing the patient’s immune system to recognize and destroy cancer cells. Despite these advancements, the challenge remains to determine the most effective treatment combinations and sequences, as well as to manage adverse events associated with these therapies.

Product Background  
Effective therapies for NSCLC continue to be a focus of oncological research and development. Targeted therapies and immunotherapies represent a pivotal shift in treating advanced NSCLC, offering hope for improved survival and quality of life for patients. However, the introduction of these novel agents has also brought new challenges, such as identifying patients who would benefit most and understanding the effects in broader, more diverse patient populations outside of clinical trials. The diversity in tumor biology and patient characteristics necessitates ongoing evaluation and optimization of treatment strategies to extend the benefits observed in controlled environments to the real-world setting.

Study Rationale  
Real-world evidence (RWE) provides insights that can bridge the gap between clinical trials and routine clinical practice. As the use of novel NSCLC treatments becomes widespread, understanding their effectiveness, safety, and tolerability in real-world settings becomes crucial. This systematic literature review aims to compile and analyze existing RWE to evaluate the outcomes of these therapies across various NSCLC populations. The study seeks to integrate data on survival rates, progression-free survival, and adverse events, thereby contributing valuable information on the application of emerging therapies in diverse clinical settings. This synthesis will aid in optimizing treatment strategies and improving patient care in NSCLC.

# 6.1 Objectives

Objectives

Primary Objective(s)  
1. To evaluate the effectiveness of novel NSCLC therapies in real-world settings.

Primary Endpoint(s)  
1. Measurement of real-world survival rates and progression-free survival among patients receiving novel therapies for NSCLC.

Secondary Objectives  
1. To assess treatment outcomes among various sub-populations within NSCLC.  
2. To analyze the safety and tolerability profiles of new therapies in real-world NSCLC populations.

Secondary Endpoints  
1. Evaluation of subgroup-specific outcomes such as survival rates and progression-free survival in different NSCLC patient populations.  
2. Assessment of adverse events and safety profiles associated with the use of new therapies in real-world settings.

# 11.1 Study Design

Study Design

Overall Design  
This study is a systematic literature review (SLR) designed to collect and synthesize real-world evidence (RWE) on the effectiveness, safety, and tolerability of novel therapies for non-small cell lung cancer (NSCLC). The review will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The primary focus is on evaluating outcomes such as survival rates and progression-free survival across different sub-populations of NSCLC patients and characterizing the safety profiles of targeted therapies, immunotherapies, and standard chemotherapy treatments.

Study Schema  
The study will systematically identify and appraise relevant literature, followed by data extraction and analysis. The schematic process will include the following steps:  
1. Literature search across multiple databases including PubMed, EMBASE, and the Cochrane Library to retrieve studies meeting pre-defined inclusion criteria.  
2. Screening of titles and abstracts to determine eligibility.  
3. Full-text review of selected studies.  
4. Extraction of relevant data on patient demographics, interventions, and treatment outcomes.  
5. Synthesis and meta-summary of findings to elucidate treatment effectiveness and safety across various NSCLC treatments.

Study Duration  
The estimated duration for the completion of this systematic literature review is six months. This timeframe includes activities such as conducting the literature search, screening and selecting studies, data extraction, synthesis of findings, and preparation of the final manuscript for dissemination.

Treatment Groups  
The systematic review will focus on evaluating the impact of different treatment modalities for NSCLC as reported in the existing literature. These treatment groups include:  
- Targeted therapies aimed at specific genetic mutations in NSCLC tumors.  
- Immunotherapies, specifically immune checkpoint inhibitors.  
- Standard chemotherapy regimens used in the management of NSCLC.

|  |  |  |
| --- | --- | --- |
| Treatment Type | Key Characteristics | Outcomes Assessed |
| --------------------- | -------------------------------------- | ------------------------------------------ |
| Targeted Therapies | EGFR, ALK, ROS1 inhibitors | Survival, progression-free survival |
| Immunotherapies | PD-1/PD-L1 inhibitors | Survival, quality of life, adverse events |
| Chemotherapy | Conventional chemotherapeutic agents | Safety profile, progression-free survival |

# 16.1 Population

Study Population

Overview of Study Population

The study population for this systematic literature review comprises adults diagnosed with non-small cell lung cancer (NSCLC). This includes individuals who have received various treatment modalities, such as targeted therapies, immunotherapies, and standard chemotherapy. The focus is on understanding treatment outcomes and safety profiles in real-world settings, involving diverse patient demographics and clinical characteristics.

Inclusion Criteria

1. • Disease Diagnosis\*\*
2. • Adults (≥18 years of age) diagnosed with non-small cell lung cancer (NSCLC). NSCLC encompasses subtypes such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

2. \*\*Treatment Modalities\*\*  
 - Studies reporting on targeted therapies, including but not limited to EGFR, ALK, and ROS1 inhibitors.  
 - Studies involving immunotherapies, particularly immune checkpoint inhibitors such as PD-1/PD-L1 inhibitors.  
 - Reports on standard chemotherapy regimens used in NSCLC management.

3. \*\*Outcome Measures\*\*  
 - Studies evaluating outcomes such as overall survival, progression-free survival, quality of life, and adverse events related to the aforementioned treatments.

Exclusion Criteria

1. • Non-NSCLC Diagnoses\*\*
2. • Studies involving small cell lung cancer or other non-lung cancer diagnoses.

2. \*\*Non-Real-World Settings\*\*  
 - Clinical trial data not representative of real-world evidence.

3. \*\*Lack of Clear Outcomes\*\*  
 - Studies that do not provide quantifiable outcomes related to survival, treatment efficacy, or adverse events.

Withdrawal Criteria

As this is a systematic literature review and not an interventional study, traditional withdrawal criteria applicable to clinical trial participants are not relevant. However, articles may be retracted or omitted post-inclusion if they are subsequently deemed to have significant methodological flaws or inaccuracies.

Replacement Policy

In the event that an eligible study is excluded or withdrawn due to updated information or identified errors, additional studies identified during the initial search phase may be considered for inclusion. These replacement studies will adhere strictly to the predefined inclusion criteria to maintain the integrity of the review process.

# 22.1 Procedures

Study Procedures

Study Procedures Overview

This systematic literature review will involve several key procedures, outlined below, to comprehensively assess real-world evidence in the treatment of non-small cell lung cancer (NSCLC). The study will adhere strictly to PRISMA guidelines throughout the process.

Screening/Baseline Procedures

1. • Timing\*\*: Early phase of the study, following database search.
2. • Specific Requirements\*\*:
3. • Conduct a comprehensive search across databases such as PubMed, EMBASE, and the Cochrane Library using predefined search terms related to NSCLC, real-world evidence, treatment outcomes, and safety.
4. • Screen articles at the title and abstract levels for relevance to the inclusion criteria.
5. • Conduct a full-text review to confirm eligibility.
6. • Responsible Personnel\*\*: The screening process will be conducted by a team of experienced research analysts, supervised by the principal investigator (PI).

Treatment Phase Procedures

1. • Timing\*\*: Systematic throughout the study.
2. • Specific Requirements\*\*:
3. • Extract relevant data from eligible studies, including patient demographics, treatment types, and outcomes.
4. • Classify treatments into specific categories: targeted therapies, immunotherapies, and chemotherapy.
5. • Responsible Personnel\*\*: Data extraction will be performed by designated research assistants under the PI’s oversight.

Follow-up Procedures

1. • Timing\*\*: Concluding phases of the study.
2. • Specific Requirements\*\*:
3. • Conduct a follow-up review of the literature to identify any newly published studies during the study timeline.
4. • Incorporate findings from any relevant additions into the meta-summary.
5. • Responsible Personnel\*\*: Research analysts will carry out the follow-up review, coordinated by the PI.

Safety Assessments

1. • Timing\*\*: Concurrent with data extraction.
2. • Specific Requirements\*\*:
3. • Evaluate and categorize reported adverse events across different treatment modalities.
4. • Assess the safety profile of therapies in diverse NSCLC patient populations.
5. • Responsible Personnel\*\*: Safety assessments will be managed by a clinical safety expert on the study team.

Efficacy Assessments

1. • Timing\*\*: Concurrent with data extraction.
2. • Specific Requirements\*\*:
3. • Analyze treatment outcomes such as overall survival, progression-free survival, and quality of life.
4. • Compare and contrast effectiveness across sub-populations and treatment types.
5. • Responsible Personnel\*\*: Efficacy data will be analyzed by biostatisticians and included in the meta-summary.

Laboratory Assessments

Not applicable as this is a literature review and not an interventional or observational study involving samples.

Other Assessments

1. • Quality Assessment\*\*
2. • Timing\*\*: Ongoing throughout the review process.
3. • Specific Requirements\*\*:
4. • Perform quality assessments of included studies to ensure methodological rigor.
5. • Use standardized tools such as risk of bias (RoB) assessments to evaluate study quality.
6. • Responsible Personnel\*\*: The quality assessment will be conducted by trained methodologists.

Please note that any sensitive data will be handled in accordance with ethical guidelines, with strict confidentiality maintained throughout the study process.

# 31.1 Statistical

Statistical Analysis

Statistical Hypotheses  
As this study is a systematic literature review, there are no specific statistical hypotheses to be tested.

Sample Size Determination  
This analysis does not involve primary data collection or a fixed sample size. Instead, the sample size is determined by the volume of relevant literature available meeting the inclusion criteria. The aim is to include a comprehensive set of studies that provide robust evidence on the treatment of non-small cell lung cancer in real-world settings.

Analysis Populations  
The analysis will focus on studies reporting on adult patients diagnosed with non-small cell lung cancer (NSCLC) who have received targeted therapies, immunotherapies, or standard chemotherapy. The populations analyzed will reflect the variety of treatment settings and patient demographics found within the literature.

Statistical Methods  
Descriptive statistics will be applied to summarize the characteristics, interventions, and outcomes reported across the included studies. Meta-analyses will be conducted where appropriate, utilizing statistical software such as RevMan or STATA, with specific methods including:

1. • Calculation of pooled survival rates and progression-free survival using the inverse-variance method for meta-analysis.
2. • Assessment of heterogeneity across studies using the I^2 statistic and Cochran's Q test. A random-effects model will be applied in cases of significant heterogeneity (I^2 > 50%).
3. • Subgroup analyses to evaluate outcomes among different NSCLC sub-populations, such as those defined by genetic mutations or treatment type.

The significance level for the meta-analyses will be set at α = 0.05.

Interim Analyses  
Interim analyses are not applicable to this study, as this is a systematic literature review without ongoing data collection.

Missing Data Handling  
For this review, the issue of missing data pertains to incomplete reporting within the identified studies. When data are missing, attempts will be made to contact study authors for clarification. In cases where data cannot be retrieved, sensitivity analyses will be conducted to assess the potential impact of missing data on the overall findings.

Multiplicity Adjustments  
Multiplicity adjustments are not directly applicable as there are no multiple testing scenarios associated with specific interventions or outcomes. However, interpretation of subgroup analyses will be cautious, recognizing the potential for multiplicity-related errors.

# 31.2 Safety

Safety

Safety Parameters

The safety assessment within this systematic literature review will focus on the identification and analysis of adverse events (AEs) associated with novel NSCLC therapies in real-world settings. Specific safety parameters include:

1. • Incidence and severity of adverse events.
2. • Types of adverse events related to targeted therapies, immunotherapies, and chemotherapy.
3. • Comparisons of adverse event profiles across different NSCLC treatment sub-populations.

Adverse Event Definitions

Adverse events are defined as any unfavorable and unintended sign, symptom, or disorder temporally associated with the use of a treatment or intervention. Key definitions include:

1. • Adverse Event (AE)\*\*: Any occurrence of an undesirable sign or symptom following treatment.
2. • Serious Adverse Event (SAE)\*\*: An AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Adverse Event Reporting

AE reporting in this context involves documenting the incidence and characteristics of events as reported in the literature. Timeframes for AE reporting in included studies will be cataloged, with efforts made to align and interpret reporting periods consistently.

Safety Monitoring

The safety monitoring process will include:

1. • Continuous evaluation of safety data extracted from the literature.
2. • Categorization and synthesis of AEs to identify patterns or emerging safety concerns.
3. • Periodic review by the study team to ensure that safety data accurately reflect real-world clinical experiences.

Risk Management

Risk management involves assessing the benefit-risk profile of treatments, informed by the synthesis of reported AEs. Particular attention will be given to:

1. • Identifying specific patient populations that may be at increased risk of AEs.
2. • Contextualizing the risk of AEs in relation to treatment efficacy and patient quality of life.

Data Monitoring Committee

As this is a systematic literature review, a formal Data Monitoring Committee (DMC) is not applicable. However, oversight of safety data integrity will be maintained by the study's principal investigator and senior research team members.

Stopping Rules

Stopping rules for the review are not applicable as no interventions are being applied or tested. The review’s progress and continuation are contingent upon the ongoing evaluation of the robustness and completeness of data extracted from the literature.

Severity Grades

Adverse events will be graded based on severity using a standardized grading scale, where applicable, as outlined in the referenced studies. Typical grading includes:

1. • Grade 1 (Mild)\*\*: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. • Grade 2 (Moderate)\*\*: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
3. • Grade 3 (Severe)\*\*: Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4. • Grade 4 (Life-threatening)\*\*: Life-threatening consequences; urgent intervention indicated.
5. • Grade 5 (Death)\*\*: Death related to an adverse event.

Reporting Requirements

Results of safety assessments, including AE types, frequencies, and severity, will be reported in the final manuscript. Safety data will be presented using descriptive statistics, with detailed tables summarizing adverse events across studies and treatment modalities.

Safety Oversight Procedures

1. • A clinical safety expert will oversee the integrity and accuracy of safety data interpretation.
2. • Routine meetings will be held among study team members to discuss safety findings and potential impacts on clinical practice.
3. • Any discrepancies or significant findings related to AEs will be escalated to higher-level investigators for review and guidance.