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 globally. It is a heterogeneous disease characterized by several histological subtypes, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The prognosis for NSCLC varies widely depending on factors such as stage at diagnosis, molecular characteristics, and comorbidities. Despite advances in early detection and treatment, NSCLC remains a leading cause of cancer-related mortality worldwide, necessitating continuous efforts to improve patient outcomes.

Current Treatment Landscape  
The treatment landscape for NSCLC has evolved markedly over the past decade with the advent of molecularly targeted therapies and immunotherapies. Traditional chemotherapy regimens, which were once the cornerstone of NSCLC treatment, are now often supplemented or replaced by these newer modalities in specific patient populations. Targeted therapies that inhibit specific oncogenic drivers, such as EGFR mutations and ALK rearrangements, have shown significant improvements in response rates and progression-free survival. Additionally, immune checkpoint inhibitors targeting PD-1/PD-L1 pathways have revolutionized the treatment paradigm for NSCLC, offering new hope for patients with advanced disease. Nevertheless, the effectiveness and broader applicability of these therapies in real-world settings need thorough evaluation.

Product Background  
In this context, "product" refers to the broad category of advanced therapies encompassing targeted treatments and immunotherapies used in the management of NSCLC. These therapies have been approved based on robust clinical trial data demonstrating their efficacy in controlled environments. However, real-world evidence (RWE) is crucial to understanding how these therapies perform outside the confines of clinical trials, where patient populations are more diverse, and various treatment regimens may be applied. Real-world studies can offer invaluable insights into long-term survival, quality of life, and safety across heterogeneous NSCLC populations, providing a comprehensive picture of therapeutic impact across broader demographics.

Study Rationale  
The integration of real-world evidence is key to optimizing NSCLC treatment and ensuring that therapeutic strategies align effectively with clinical practice. While clinical trials remain the gold standard for establishing efficacy and safety, real-world data capture the complexity of everyday clinical practice and patient diversity. This systematic literature review aims to synthesize existing real-world data, evaluating the effectiveness, safety, and patient-specific outcomes associated with contemporary NSCLC therapies. By examining real-world outcomes, this study endeavors to bridge the gap between clinical trials and day-to-day clinical practice, ultimately contributing to more personalized, evidence-based care strategies for NSCLC patients.

# 6.1 Objectives

Objectives

Primary Objective(s)

1. • To evaluate the effectiveness of novel non-small cell lung cancer (NSCLC) therapies in real-world settings.

Primary Endpoint(s)

1. • Measurement of treatment effectiveness through survival rates and progression-free survival in real-world NSCLC populations.

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. • Comparison of survival and progression-free survival outcomes among different NSCLC sub-populations.
2. • Documentation and analysis of adverse events and safety profiles associated with targeted therapies, immunotherapies, and standard chemotherapy treatments in real-world settings.

# 11.1 Study Design

Study Design

Overall Design

This study will be conducted as a systematic literature review (SLR) following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review aims to consolidate real-world evidence (RWE) on the effectiveness and safety of novel therapies for non-small cell lung cancer (NSCLC). By synthesizing existing literature, the study will evaluate treatment outcomes, including survival rates and progression-free survival, and assess the safety profiles across various patient populations within real-world clinical settings.

Study Schema

The study will involve a comprehensive literature search, data extraction, and analysis process:

1. • Conduct an extensive literature search using databases such as PubMed, EMBASE, and the Cochrane Library, employing search terms related to NSCLC, real-world evidence, treatment outcomes, and safety.
2. • Screen identified studies based on predefined inclusion criteria focusing on adult NSCLC populations treated with targeted therapies, immunotherapies, or standard chemotherapy.
3. • Extract relevant data on patient characteristics, treatments, and outcomes from the selected studies.
4. • Analyze the data to create a meta-summary of effectiveness, safety, and patient-specific outcomes for NSCLC therapies.

Study Duration

The estimated duration for completing this systematic literature review is six months. This timeline includes the phases of literature search, screening, data extraction, synthesis, and manuscript preparation. Efforts will be made to adhere to this schedule to provide timely insights into the real-world treatment landscape for NSCLC.

Treatment Groups

Although this study does not involve active interventions, it will categorize collected data based on the types of treatments reported in the literature. The focus will be on the following therapeutic groups and associated outcomes:

|  |  |  |
| --- | --- | --- |
| Treatment Group | Description | Outcomes Assessed |
| ----------------------- | ---------------------------------------------- | ---------------------------------------------- |
| Targeted Therapies | Therapies directed at specific molecular targets, such as EGFR mutations or ALK rearrangements | Survival rates, progression-free survival, safety profiles |
| Immunotherapies | Treatments aimed at enhancing the immune system's ability to fight cancer, including PD-1/PD-L1 inhibitors | Survival, progression-free survival, adverse events |
| Standard Chemotherapy | Conventional cytotoxic drugs used in NSCLC management | Effectiveness compared to novel therapies, quality of life outcomes, safety |

# 16.1 Population

Study Population

Overview of Study Population

The study population for this systematic literature review consists of adult patients diagnosed with non-small cell lung cancer (NSCLC). This review aims to include diverse real-world populations treated with novel NSCLC therapies, including targeted therapies and immunotherapies, as well as standard chemotherapy regimens, to evaluate treatment outcomes and safety profiles.

Inclusion Criteria

1. • Diagnosis Related:\*\*
2. • Adults (≥18 years) diagnosed with non-small cell lung cancer (NSCLC).

2. \*\*Treatment Related:\*\*  
 - Patients receiving treatment with targeted therapies, such as EGFR inhibitors or ALK inhibitors.  
 - Patients treated with immunotherapies, including PD-1/PD-L1 inhibitors.  
 - Patients undergoing standard chemotherapy regimens.

3. \*\*Outcome Related:\*\*  
 - Studies reporting outcomes related to survival, including overall survival or progression-free survival.  
 - Studies including data on quality of life post-treatment.  
 - Reports detailing adverse events associated with the therapies.

Exclusion Criteria

1. • Diagnosis Related:\*\*
2. • Patients not diagnosed with NSCLC or with a diagnosis of small cell lung cancer.

2. \*\*Treatment Related:\*\*  
 - Studies focusing exclusively on experimental treatments not widely available in clinical practice.  
 - Literature solely discussing palliative care without therapeutic intent.

3. \*\*Study Design Related:\*\*  
 - Non-systematic reviews, editorials, or opinion pieces lacking original data.  
 - Studies with insufficient data to assess primary outcomes, such as missing information on patient survival or treatment specifics.

Withdrawal Criteria

While this systematic review does not involve direct participation of study subjects, any included study may be withdrawn from the analysis if:  
- There are significant methodological flaws discovered post-inclusion.  
- The data presented is found to be duplicative or not conforming to initial inclusion criteria upon further verification.

Replacement Policy

In the event that a study is withdrawn from the review, alternative studies matching the inclusion criteria may be considered for inclusion if they add substantial new evidence to the analysis. This process will ensure the comprehensiveness of the literature review and uphold the quality and relevance of the synthesized findings.

# 22.1 Procedures

Study Procedures

Study Procedures Overview  
This study is a systematic literature review (SLR) designed to consolidate and synthesize real-world evidence (RWE) on the effectiveness and safety of novel non-small cell lung cancer (NSCLC) therapies. The procedures outlined will follow the PRISMA guidelines, encompassing all aspects from literature search to data analysis.

Screening/Baseline Procedures  
- \*\*Timing\*\*: Conducted within the first month of the study.  
- \*\*Specific Requirements\*\*:   
 - Perform a comprehensive literature search using databases such as PubMed, EMBASE, and the Cochrane Library.  
 - Utilize search terms relevant to NSCLC, real-world evidence, treatment outcomes, and safety.  
 - Screen studies based on predefined inclusion criteria focusing on adult NSCLC populations treated with targeted therapies, immunotherapies, or standard chemotherapy.  
- \*\*Responsible Personnel\*\*: Literature reviewers and research assistants.

Treatment Phase Procedures  
This phase refers to the collection and categorization of data regarding interventions described in the literature.  
- \*\*Timing\*\*: Initiated upon completion of screening.  
- \*\*Specific Requirements\*\*:   
 - Extract detailed data on interventions including targeted therapies, immunotherapies, and standard chemotherapy.  
 - Classify collected data according to therapy type and subgroup analysis for different patient populations.  
- \*\*Responsible Personnel\*\*: Research analysts and data extraction specialists.

Follow-up Procedures  
This phase involves continued monitoring and updating of the literature as needed to incorporate the latest evidence.  
- \*\*Timing\*\*: Throughout the study duration until data synthesis.  
- \*\*Specific Requirements\*\*:   
 - Regularly check for new publications or updates on existing studies until data synthesis is completed.  
 - Ensure all relevant data is captured adequately for the synthesis phase.  
- \*\*Responsible Personnel\*\*: Literature reviewers.

Safety Assessments  
- \*\*Timing\*\*: Conducted during data extraction and synthesis phases.  
- \*\*Specific Requirements\*\*:   
 - Document safety data and adverse events associated with NSCLC therapies from selected studies.  
 - Evaluate the completeness and consistency of safety reporting across different studies.  
- \*\*Responsible Personnel\*\*: Safety specialists and research analysts.

Efficacy Assessments  
- \*\*Timing\*\*: Conducted concurrently with safety assessments.  
- \*\*Specific Requirements\*\*:   
 - Analyze data on treatment outcomes such as survival rates and progression-free survival.  
 - Compare efficacy outcomes across different sub-populations.  
- \*\*Responsible Personnel\*\*: Efficacy analysts and statisticians.

Laboratory Assessments  
While the review focuses on literature data, any specifics of laboratory findings relevant to treatment outcomes will be documented.  
- \*\*Timing\*\*: During data extraction phase.  
- \*\*Specific Requirements\*\*:   
 - Extract relevant laboratory data described in study outcomes where applicable.  
 - Document methodology and validity of laboratory findings as stated.  
- \*\*Responsible Personnel\*\*: Data extraction specialists.

Other Assessments  
- \*\*Timing\*\*: Integrated throughout the data extraction and synthesis phases.  
- \*\*Specific Requirements\*\*:   
 - Evaluate data on quality of life metrics and other patient-reported outcomes as available in the literature.  
 - Analyze studies' methodological quality and relevance.  
- \*\*Responsible Personnel\*\*: Quality assessors and research analysts.

This systematic literature review does not involve direct clinical procedures or patient contact but relies on meticulous data extraction and analysis to achieve comprehensive insights into the real-world application of NSCLC therapies. Consistent adherence to designed procedures ensures accuracy and relevance in synthesizing the evidence.

# 31.1 Statistical

Statistical Analysis

Statistical Hypotheses  
This systematic literature review (SLR) is descriptive in nature and is not designed to test specific statistical hypotheses. The focus is on summarizing the effectiveness, safety, and patient-specific outcomes of novel non-small cell lung cancer (NSCLC) therapies from real-world evidence.

Sample Size Determination  
As this is an SLR, the concept of sample size determination is not directly applicable. However, the aim is to include as many relevant studies as possible to provide a comprehensive synthesis. The inclusion will focus on studies meeting predefined criteria rather than a fixed sample size.

Analysis Populations  
The analysis will include:  
- All identified studies that meet inclusion criteria detailing adult patients diagnosed with NSCLC treated with targeted therapies, immunotherapies, or standard chemotherapy.

Statistical Methods  
Data extracted from the eligible studies will be synthesized using descriptive statistics to summarize key findings such as survival rates, progression-free survival, and safety profiles. Meta-analytic techniques may be employed when applicable to provide pooled estimates of treatment outcomes. Forest plots will be used to visualize the effect sizes across studies when meta-analysis is feasible.

Interim Analyses  
Given the nature of the systematic review, there will be no formal interim analyses. Data synthesis will be conducted once all suitable studies have been identified and data extraction is complete.

Missing Data Handling  
In studies included in the review, any missing data will be addressed by contacting the original study authors where feasible or noting the limitations in the data synthesis. Sensitivity analyses may be conducted by excluding studies with significant missing or unclear data to ensure robustness of the findings.

Significance Levels  
This SLR aims for descriptive synthesis; hence, specific significance levels are not applicable. Should meta-analysis be conducted, a p-value threshold of 0.05 will be used to denote statistical significance for effect estimates.

Multiplicity Adjustments  
Multiplicity adjustments are not anticipated in this review as it primarily summarizes existing literature rather than multiple hypotheses testing. However, in pooled analyses, Bonferroni correction or similar methods may be applied if necessary to account for multiple comparisons.

# 31.2 Safety

Safety

Safety Parameters

The safety parameters for this systematic literature review (SLR) focus on the evaluation of adverse events and safety profiles associated with NSCLC therapies. These parameters include adverse event incidence, severity, and outcome, which will be systematically extracted and analyzed to provide a comprehensive understanding of therapy tolerability in real-world settings.

Adverse Event Definitions

Adverse events (AEs) are defined according to standard medical lexicon, referring to any unfavorable or unintended sign, symptom, or disease temporally associated with the use of a treatment. When possible, AEs will be categorized based on severity—graded from 1 (mild) to 5 (death), following the Common Terminology Criteria for Adverse Events (CTCAE). Severity grading will help in comparing the impact of different therapies within NSCLC populations.

Adverse Event Reporting

For the purposes of this SLR, adverse event reporting will involve extracting data from selected studies that describe AE frequency, types, and severity. The timeframe for reporting is aligned with the life of the study, extending from initial literature search to the completion of data synthesis. All reported AEs that meet defined severity thresholds will be documented.

Safety Monitoring

Safety monitoring in this context is performed through a rigorous analysis of adverse events reported in the literature. While there is no direct monitoring of patients, the SLR aims to identify patterns in safety data that might suggest new or undocumented risks in NSCLC therapies.

Risk Management

Risk management involves the identification of common safety issues associated with NSCLC therapies and strategic dissemination of these findings to inform clinical practice. This includes a summary of significant risks based on data extracted, which will be highlighted in the study's findings and conclusions to support dynamic risk management strategies in NSCLC treatment.

Data Monitoring Committee

Although a Data Monitoring Committee (DMC) is typically not established for a systematic literature review, the review team acts in a similar capacity by ensuring the integrity and accuracy of data extracted. This team, consisting of experienced research and safety professionals, oversees data collection and evaluates inconsistencies or anomalies in safety data across studies.

Stopping Rules

Stopping rules apply primarily to interventional studies; however, for the SLR context, literature review processes such as search and data extraction may be halted if a threshold number of studies are achieved, ensuring sufficient evidence has been gathered or if continued research adds no significant value. Such decisions will be accompanied by justifications documented in the review's progress records.

By synthesizing real-world evidence of safety, this systematic literature review delivers critical insights into adverse event profiles and provides guidance for improving patient safety in the clinical management of NSCLC.