Clinical Trial Protocol

# 1.1 Table of Contents

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# 1.2 Background

Background

Disease Background  
Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, making it the most common type of lung cancer worldwide. It is characterized by its slow growth and tendency to spread to other parts of the body, including the bones, brain, and liver. NSCLC is a heterogeneous group of cancers, typically including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Despite advancements in treatment, NSCLC remains a leading cause of cancer-related mortality, and its prognosis is generally poor, with survival outcomes highly dependent on the stage at diagnosis and molecular characteristics of the tumor.

Current Treatment Landscape  
The treatment landscape for NSCLC has evolved significantly in recent years, particularly with the introduction of targeted therapies and immunotherapies. Traditional treatment options include surgery, radiation therapy, and chemotherapy. However, advancements in molecular biology have led to the development of therapies targeting specific genetic mutations and pathways involved in NSCLC, such as EGFR, ALK, and ROS1 inhibitors. Additionally, immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 have gained prominence due to their ability to harness the host immune system to combat cancer cells. These novel treatments have improved outcomes for many patients, yet substantial challenges remain, including treatment resistance and variability in patient response.

Product Background  
While there is no specific product focus in this systematic literature review, the analysis encompasses a range of novel NSCLC therapies, including targeted therapies, immunotherapies, and standard chemotherapy treatments. The emphasis is on synthesizing real-world evidence regarding these therapies to provide a comprehensive overview of their effectiveness and safety in everyday clinical practice. Understanding how these therapies perform outside the controlled conditions of clinical trials is crucial for further optimizing treatment strategies for NSCLC patients.

Study Rationale  
The increasing introduction of novel treatment options in NSCLC underscores the necessity to assess their real-world effectiveness and safety. While randomized clinical trials remain the gold standard for evaluating therapeutic interventions, they often involve highly selected patient populations and controlled environments that may not accurately reflect typical clinical practice. This systematic literature review aims to bridge this gap by summarizing and synthesizing existing real-world evidence. The findings will provide valuable insights into treatment outcomes, such as survival rates and progression-free survival, as well as adverse event profiles among various NSCLC sub-populations. By doing so, this study aims to inform clinical decision-making and ultimately improve patient care.

# 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 treatment effectiveness through survival rates and progression-free survival among NSCLC patients in real-world settings.

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. Documentation of survival rates and progression-free survival across different NSCLC sub-populations.  
2. Analysis of safety profiles, including the incidence and type of adverse events, for new therapies within real-world NSCLC populations.

# 11.1 Study Design

Study Design

Overall Design  
This study is designed as a systematic literature review (SLR) conducted following the PRISMA guidelines. The primary objective is to gather and synthesize real-world evidence (RWE) on the effectiveness, safety, and patient outcomes associated with novel therapies for non-small cell lung cancer (NSCLC). The review focuses on interventions including targeted therapies, immunotherapies, and standard chemotherapy treatments applied to adult NSCLC patients. Relevant data will be extracted from eligible studies to generate a comprehensive meta-summary of treatment efficacy, progression-free survival, adverse events, and quality of life outcomes.

Study Schema  
The study follows a non-interventional, observational schema typical of a systematic literature review. The initial step involves defining the research question and inclusion criteria, followed by a structured and comprehensive literature search across multiple databases like PubMed, EMBASE, and the Cochrane Library. Eligible studies will then be screened and selected based on predefined criteria. Data extraction will focus on key parameters such as patient demographics, treatment regimens, and clinical outcomes. The final step includes data synthesis and the development of a narrative report summarizing the key findings.

Study Duration  
The estimated duration of this systematic literature review is 6 months. This timeline includes all stages of the review process, from the initial literature search through to data extraction, synthesis, and manuscript preparation. Each phase will be systematically managed to ensure comprehensive coverage and timely completion.

Treatment Groups  
This study does not involve the direct participation of patients or administration of treatments. Instead, it categorizes existing studies based on the treatment interventions reported. Studies will be grouped into categories such as targeted therapies, immunotherapies, and standard chemotherapy, enabling a comparative and holistic synthesis of existing real-world evidence on each intervention type.

|  |  |  |
| --- | --- | --- |
| Intervention Type | Key Studies | Outcomes Analyzed |
| -------------------- | ------------------------------------------------- | ------------------------------------- |
| Targeted Therapies | Studies involving EGFR, ALK, ROS1 inhibitors | Survival, progression-free survival |
| Immunotherapies | Studies involving PD-1, PD-L1, CTLA-4 inhibitors | Adverse events, quality of life |
| Chemotherapy | Studies on standard chemotherapy regimens | Safety profiles, efficacy |

Study Schema

```mermaid  
graph TD  
 A[Screening] --> B[Randomization]  
 B --> C[Treatment Group 1]  
 C --> F[Follow-up]  
 B --> D[Treatment Group 2]  
 D --> F[Follow-up]  
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# 17.1 Population

Study Population

Overview of Study Population  
The study population for this systematic literature review consists of adults diagnosed with non-small cell lung cancer (NSCLC). The focus is on summarizing real-world evidence related to treatment effectiveness, patient outcomes, and safety profiles of novel therapies, including targeted therapies and immunotherapies. The review targets diverse NSCLC sub-populations to provide comprehensive insights applicable to various clinical settings.

Inclusion Criteria  
1. \*\*Population Characteristics\*\*  
 - Adults aged 18 years and older.  
 - Diagnosed with non-small cell lung cancer, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma subtypes.

2. \*\*Interventions\*\*  
 - Studies must involve one or more of the following treatments: targeted therapies (e.g., EGFR, ALK, ROS1 inhibitors), immunotherapies (e.g., PD-1, PD-L1, CTLA-4 inhibitors), or standard chemotherapy regimens.

3. \*\*Outcomes\*\*  
 - Reported outcomes must include survival rates, progression-free survival, quality of life measures, or adverse events related to treatment.

4. \*\*Study Design\*\*  
 - Studies must provide real-world evidence through observational designs, including cohort studies, case-control studies, or registry-based studies.

Exclusion Criteria  
1. \*\*Population Characteristics\*\*  
 - Studies focusing exclusively on small cell lung cancer (SCLC).  
 - Pediatric populations (under 18 years of age).

2. \*\*Interventions\*\*  
 - Interventions outside the scope of targeted therapies, immunotherapies, and standard chemotherapy.  
 - Studies evaluating treatments in investigational or experimental phase without real-world applicability.

3. \*\*Outcomes\*\*  
 - Absence of specific outcomes related to survival, progression-free survival, quality of life, or adverse events.

4. \*\*Study Design\*\*  
 - Exclusion of randomized controlled trials (RCTs) and other controlled studies not primarily focused on real-world settings.

Withdrawal Criteria  
As this review is a systematic literature analysis and does not involve patient enrollment, withdrawal criteria are not applicable. However, studies may be withdrawn from analysis if they are found to significantly deviate from predefined inclusion and exclusion criteria upon detailed review.

Replacement Policy  
In the event a study is excluded post-initial screening due to inaccuracies in representing real-world settings or meeting eligibility criteria, additional studies that meet the inclusion criteria and were not initially selected will be considered and included in the analysis. This ensures the integrity and comprehensiveness of the data synthesis.

# 23.1 Procedures

Study Procedures Overview

This section outlines the systematic processes to be undertaken during the study, including procedures during the screening, treatment, and follow-up phases, as well as safety, efficacy, laboratory, and other assessments. The activities in each phase are designed to ensure a comprehensive evaluation of the available literature on real-world evidence for NSCLC therapies.

Screening/Baseline Procedures

1. • Literature Screening\*\*
2. • Timing: Initial 2 weeks
3. • Requirements: Identify relevant studies from databases including PubMed, EMBASE, and the Cochrane Library using predefined search terms.
4. • Personnel: Research team members
5. • Special Handling: Ensure that studies meet the inclusion criteria and are peer-reviewed.

2. \*\*Eligibility Assessment\*\*  
 - Timing: Concurrent with literature screening  
 - Requirements: Confirm studies meet population, intervention, and outcome inclusion criteria.  
 - Personnel: Senior researcher  
 - Special Handling: Record decisions with a rationale for study exclusion.

Treatment Phase Procedures

1. • Data Extraction\*\*
2. • Timing: Weeks 3-8
3. • Requirements: Extract data on patient demographics, interventions, outcomes, and adverse events.
4. • Personnel: Data extraction team
5. • Special Handling: Use standardized forms; ensure data accuracy through double-checking by a second researcher.

2. \*\*Data Synthesis\*\*  
 - Timing: Weeks 9-12  
 - Requirements: Compile extracted data into a meta-summary, distinguishing results by therapy and patient populations.  
 - Personnel: Data analysts  
 - Special Handling: Aggregate data uniformly; resolve discrepancies through team discussion.

Follow-up Procedures

1. • Data Validation\*\*
2. • Timing: Week 13
3. • Requirements: Review synthesized data for accuracy and completeness.
4. • Personnel: Lead investigator with cross-verification by another team member
5. • Special Handling: Utilize data validation software tools; make corrections as necessary.

Safety Assessments

1. • Analysis of Safety Profiles\*\*
2. • Timing: Integrated during data extraction and synthesis phases
3. • Requirements: Categorize and evaluate reported adverse events across studies.
4. • Personnel: Safety analysis team
5. • Special Handling: Highlight significant safety concerns and variations across therapies.

Efficacy Assessments

1. • Evaluation of Treatment Outcomes\*\*
2. • Timing: During data synthesis phase
3. • Requirements: Analyze survival rates, progression-free survival, and quality of life outcomes.
4. • Personnel: Clinical outcomes assessment team
5. • Special Handling: Cross-reference outcomes with statistical software for additional validation.

Laboratory Assessments

1. • Biomarker Data Collection\*\*
2. • Timing: Ongoing as data is extracted
3. • Requirements: Catalogue available biomarker information from studies.
4. • Personnel: Laboratory data team
5. • Special Handling: Evaluate quality and relevance of biomarkers reported.

Other Assessments

1. • Quality Assurance Review\*\*
2. • Timing: Final 2 weeks of study timeline
3. • Requirements: Ensure all components of the systematic review are completed accurately.
4. • Personnel: Quality assurance officer
5. • Special Handling: Perform external review if necessary; document any methodological deviations.

This systematic literature review will follow these structured processes to ensure comprehensive and reliable aggregation and analysis of real-world evidence for NSCLC therapies.

# 31.1 Statistical

Statistical Analysis

Statistical Hypotheses  
The primary hypothesis of this systematic literature review (SLR) is that treatment effectiveness, as measured by survival rates and progression-free survival, varies among different novel therapies for non-small cell lung cancer (NSCLC) in real-world settings. The secondary hypotheses involve evaluations of treatment outcomes across various NSCLC sub-populations and the analysis of safety and tolerability profiles of these therapies.

Sample Size Determination  
Sample size determination does not apply to this systematic literature review as it involves the synthesis of previously published studies rather than the enrolment of new participants. The scope will include all relevant studies meeting the inclusion criteria, thus maximizing the comprehensiveness of the data synthesis.

Analysis Populations  
Analysis populations pertain to the sub-groups analyzed within the included studies. This review will categorize studies into therapy-specific groups such as targeted therapies, immunotherapies, and standard chemotherapy. These groups will be further stratified by patient demographics and NSCLC subtypes to ensure diverse representation of real-world populations.

Statistical Methods  
Descriptive statistics will be used to summarize the data extracted from eligible studies. The main effect sizes, such as hazard ratios (HR) for survival outcomes and incident rate ratios for adverse events, will be calculated when appropriate. Meta-analyses will be performed using random-effects models to account for heterogeneity between studies. Significance levels for statistical tests will be set at 0.05. Additionally, heterogeneity will be assessed using the I² statistic. In cases where meta-analysis is feasible, forest plots will be utilized for graphical presentations.

Interim Analyses  
Interim analyses are not applicable to this study, as it involves a retrospective synthesis of published literature rather than a prospective clinical trial.

Missing Data Handling  
Handling of missing data will involve sensitivity analyses to assess the potential impact on outcomes. Any study with critical missing data relevant to primary outcomes will be noted but may be excluded from quantitative syntheses depending on the degree and nature of the missing information. The review will document instances of missing data and the methods used for addressing them.

Multiplicity Adjustments  
Given the exploratory nature of synthesizing real-world evidence across multiple therapies and endpoints, multiplicity adjustments will not be applied. However, where multiple comparisons are made between therapy groups, the implications of potential type I error inflation will be considered in the interpretation of results.

This Statistical Analysis section outlines the methodologies that will be utilized to synthesize and interpret real-world evidence on NSCLC treatments, ensuring a robust and transparent approach to data analysis.

# 31.2 Safety

Safety

Safety Parameters  
Safety parameters for this systematic literature review (SLR) of non-small cell lung cancer (NSCLC) treatments will focus on adverse events (AEs) associated with targeted therapies, immunotherapies, and standard chemotherapy. Specific parameters include the incidence, severity, and type of adverse events reported in the real-world clinical settings.

Adverse Event Definitions  
Adverse events are defined as any undesirable experiences associated with the use of medical treatments. For this review, AEs will be categorized based on the Common Terminology Criteria for Adverse Events (CTCAE). Severity grades will range from mild (Grade 1) to death (Grade 5), providing a standardized assessment of the clinical impact reported in each study.

Adverse Event Reporting  
Studies included in the review must clearly report adverse event data, including the frequency and severity of each event. The timeframe for AE reporting within individual studies should align with the typical follow-up periods in real-world settings, commonly ranging from several months to multiple years depending on the patient and treatment pathway.

Safety Monitoring  
Safety monitoring involves the evaluation of adverse event reports across all included studies. Each study’s monitoring approach as detailed within its methodology will be scrutinized to ensure comprehensive data collection and accurate AE reporting. The review will focus on identifying trends and patterns in safety data that emerge from diverse real-world patient populations.

Risk Management  
Risks identified through the analysis of adverse event data will be managed by contextualizing findings within clinical practice. Consideration will be given to the balance between treatment efficacy and the occurrence of adverse events. Recommendations based on potential risks will be formulated to guide clinicians in optimizing patient management strategies.

Data Monitoring Committee  
As this study is a literature review and does not involve direct patient interaction, a data monitoring committee is not applicable. However, rigorous internal review processes will be instituted to ensure the integrity and quality of data synthesis and interpretation.

Stopping Rules  
Stopping rules do not apply to this SLR, as it synthesizes existing literature rather than collecting new clinical data. However, should significant discrepancies or methodological flaws be identified in a substantial portion of the included studies during the review, appropriate modifications to data interpretation and subsequent recommendations will be considered.

In summary, this Safety section details the comprehensive evaluation of adverse events related to NSCLC treatments in real-world settings, ensuring that safety profiles are thoroughly analyzed and accurately reported to inform clinical practice.