Clinical Trial Protocol

# 1. Title

Title

Systematic Literature Review of Real-World Evidence in Non-Small Cell Lung Cancer

Background & Rationale

Non-small cell lung cancer (NSCLC) represents a significant proportion of global lung cancer cases. With advancements in targeted therapies and immunotherapies, there is an increasing need to evaluate the effectiveness of these treatments in real-world clinical settings. This systematic literature review (SLR) aims to summarize and synthesize existing real-world evidence (RWE) to better understand treatment outcomes, patient populations, and safety profiles.

Study Objectives  
• To evaluate the effectiveness of novel NSCLC therapies in real-world settings.  
• To assess treatment outcomes (e.g., survival rates, progression-free survival) among various sub-populations within NSCLC.  
• To analyze the safety and tolerability profiles of new therapies in real-world NSCLC populations.

Study Design

Systematic literature review based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Key Inclusion Criteria  
• Population: Adults diagnosed with NSCLC.  
• Interventions: Targeted therapies, immunotherapies, and standard chemotherapy treatments.  
• Outcomes: Survival, progression-free survival, quality of life, and adverse events.

Literature Search Strategy

A comprehensive search will be conducted in databases such as PubMed, EMBASE, and the Cochrane Library. Terms will include NSCLC, real-world evidence, treatment outcomes, and safety.

Data Extraction & Analysis

Relevant data on patient characteristics, interventions, and outcomes will be extracted from eligible studies and analyzed to produce a meta-summary of findings across different treatment categories.

Expected Outcomes  
• Summarized evidence on real-world treatment efficacy.  
• Insights into patient-specific outcomes by therapy type.  
• Comprehensive understanding of safety profiles for new therapies.

Timeline

Estimated completion within 6 months, including data extraction, synthesis, and manuscript preparation.

# 2. Background

Background

Epidemiology of Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 85% of all lung cancer cases. It encompasses several histological subtypes, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The incidence of NSCLC varies globally, with a high prevalence in regions with increased tobacco consumption and exposure to carcinogens. Despite advances in early detection and treatment, NSCLC remains a leading cause of cancer-related mortality worldwide.

Advances in NSCLC Treatment

The treatment landscape for NSCLC has evolved significantly over the past decade with the introduction of targeted therapies and immunotherapies. These novel treatment options have been designed to improve patient outcomes by exploiting specific genetic alterations or by enhancing the immune system's ability to fight cancer cells. Targeted therapies, such as tyrosine kinase inhibitors (TKIs), have shown efficacy in patients with specific genetic mutations like EGFR and ALK. Immunotherapies, including checkpoint inhibitors, have broadened the scope of treatable patient populations by targeting the PD-1/PD-L1 pathway.

Real-World Evidence in NSCLC

Clinical trials are the gold standard for evaluating the efficacy and safety of new treatments. However, they often have strict inclusion criteria, which may limit the generalizability of their findings to the broader NSCLC patient population encountered in routine clinical practice. Real-world evidence (RWE) complements data from randomized controlled trials by providing insights into how these novel therapies perform outside of the controlled trial setting. RWE encompasses data from a variety of sources, including electronic health records, patient registries, and observational studies, and can inform on treatment outcomes, safety profiles, and health economics.

Rationale for Systematic Literature Review

Given the dynamic nature of NSCLC treatment and the growing body of RWE, there is a need for a systematic approach to synthesize this information. A systematic literature review (SLR) can aggregate and critically appraise existing RWE to provide a comprehensive overview of the real-world effectiveness, safety, and patient-reported outcomes associated with NSCLC treatments. This SLR will specifically focus on the impact of targeted therapies and immunotherapies in routine clinical practice and will aim to identify any gaps in knowledge that could guide future research and clinical decision-making.

# 3. Objectives

Objectives

Primary Objective  
• To systematically evaluate the effectiveness of novel therapies for non-small cell lung cancer (NSCLC) in real-world clinical settings.

Secondary Objectives  
• To assess and compare treatment outcomes, including survival rates and progression-free survival, among different sub-populations of patients with NSCLC.  
• To analyze and synthesize the safety and tolerability profiles of novel NSCLC therapies, as reported in real-world evidence studies.

Exploratory Objectives  
• To explore patient-specific outcomes based on the type of therapy received (targeted therapies, immunotherapies, and standard chemotherapy).  
• To identify any gaps in the current literature regarding the real-world effectiveness and safety of NSCLC treatments, which may inform future research directions and clinical practice guidelines.

# 4. Methods

METHODS

Literature Search Strategy

A systematic search of the literature will be conducted following the PRISMA guidelines to identify relevant studies. The databases to be searched include PubMed, EMBASE, and the Cochrane Library. The search strategy will employ a combination of Medical Subject Headings (MeSH) and free-text terms related to NSCLC, real-world evidence, treatment outcomes, and safety. The search will be limited to studies published in English. Additional records will be identified through cross-referencing and hand-searching the bibliographies of key articles.

Study Selection

Two independent reviewers will screen titles and abstracts for eligibility based on predefined inclusion criteria. Full-text articles will be retrieved for further assessment if the information in the abstract suggests that the study meets the inclusion criteria or if there is insufficient information to make a clear decision. Discrepancies between reviewers will be resolved through discussion or consultation with a third reviewer if necessary.

Inclusion and Exclusion Criteria

Studies will be included if they meet the following criteria:  
• Population: Adults diagnosed with NSCLC.  
• Interventions: Studies evaluating targeted therapies, immunotherapies, and standard chemotherapy treatments.  
• Outcomes: Reports on survival, progression-free survival, quality of life, and adverse events.

Studies will be excluded if they:  
• Are not observational studies or do not provide real-world evidence.  
• Do not report on the predefined outcomes of interest.  
• Are case reports, editorials, commentaries, or reviews without original data.

Data Extraction

Data extraction will be performed by two independent reviewers using a standardized data extraction form. Extracted information will include study characteristics (author, year of publication, study design), patient demographics and clinical characteristics, details of the intervention (type of therapy, dosage, duration), and outcomes (survival rates, progression-free survival, quality of life, adverse events). Any discrepancies in data extraction will be resolved through discussion or by involving a third reviewer.

Quality Assessment

The quality of included studies will be assessed using an appropriate tool, such as the Newcastle-Ottawa Scale for observational studies. Each study will be evaluated for its methodological quality, and the risk of bias will be determined. The results of the quality assessment will be reported and considered in the synthesis of evidence.

Data Synthesis and Analysis

Data will be synthesized to provide a narrative summary and, where possible, a meta-summary of findings across different treatment categories. Meta-analytic techniques will be employed if the data are sufficiently homogenous. Statistical heterogeneity will be assessed using the I² statistic, and a random-effects model will be used in the presence of significant heterogeneity. Subgroup analyses will be conducted to explore differences in treatment outcomes among various NSCLC sub-populations.

Timeline

The systematic literature review is expected to be completed within 6 months from the commencement date. This timeline includes the literature search, study selection, data extraction, quality assessment, data synthesis, and manuscript preparation.

Ethical Considerations

As this study is a systematic literature review of published data, ethical approval is not required. All analyses will be based on previously published data, and no primary data collection will be involved.

# 5. Search Strategy

Literature Search Strategy

Databases and Search Platforms  
A comprehensive and systematic search will be conducted across multiple electronic databases to ensure a broad capture of relevant literature. The databases to be searched include:  
• PubMed/MEDLINE: A primary source for health-related articles including clinical studies and reviews.  
• EMBASE: A biomedical and pharmacological database of published literature, especially strong in its coverage of drug and pharmaceutical research.  
• The Cochrane Library: A collection of high-quality databases in healthcare and evidence-based medicine.

Search Terms and Strategy  
The search strategy will be developed using a combination of Medical Subject Headings (MeSH) and free-text terms. The search terms will be related to the following concepts:  
• Non-Small Cell Lung Cancer: "NSCLC", "non-small cell lung carcinoma", "lung adenocarcinoma", "squamous cell lung carcinoma", "large cell lung carcinoma".  
• Real-World Evidence: "real-world data", "observational study", "registry study", "retrospective study", "prospective study", "electronic health records".  
• Treatment Outcomes: "survival", "progression-free survival", "quality of life", "treatment response", "disease progression".  
• Safety and Tolerability: "adverse events", "side effects", "drug safety", "tolerability".  
• Therapies: "targeted therapy", "immunotherapy", "chemotherapy", "tyrosine kinase inhibitors", "checkpoint inhibitors", "PD-1 inhibitors", "PD-L1 inhibitors".

The search strategy will be tailored to each database to account for differences in indexing terms and search functionalities. Boolean operators (AND, OR) will be used to combine search terms within and across the different concepts.

Search Limits  
The search will be limited to studies published in the English language. No date restrictions will be applied initially to capture the full extent of available literature; however, date limits may be applied during the review process if deemed necessary.

Additional Search Methods  
To supplement the electronic database search, the following methods will be used:  
• Cross-referencing: Checking the reference lists of included studies and relevant reviews for additional sources.  
• Hand-searching: Manually searching key journals and conference proceedings in the field of lung cancer.  
• Expert Consultation: Engaging with subject matter experts who may recommend additional studies or databases.

Study Records Management  
All identified citations will be imported into a reference management software, such as EndNote or Mendeley, and duplicates will be removed. The software will be used to manage records throughout the screening and selection process.

Selection of Studies  
Following the search, all identified records will be screened by two independent reviewers based on the title and abstract. Studies that potentially meet the inclusion criteria will undergo full-text review for final inclusion. Any disagreements between reviewers will be resolved through discussion or with the involvement of a third reviewer.

Documentation of Search Strategy  
The search strategy, including the date of the last search, will be documented in detail to ensure reproducibility. This documentation will include the search terms used, databases searched, number of records identified, and the process of study selection. The PRISMA flow diagram will be used to illustrate the search and selection process.

# 6. Data Extraction

Data Extraction

Data Extraction Process

Data extraction will be conducted systematically to minimize bias and ensure the accuracy of the data collected from the included studies. The process will involve the following steps:

1. Development of a Data Extraction Form: A standardized data extraction form will be created to capture all relevant information consistently across studies. The form will be pilot-tested on a small number of included studies and refined as necessary.

2. Extraction by Independent Reviewers: Two reviewers will independently extract data from each included study using the data extraction form. The data extracted will include:  
• Study characteristics: author(s), year of publication, study design, sample size, and study duration.  
• Patient demographics and clinical characteristics: age, gender, smoking status, histology, stage of disease, and performance status.  
• Intervention details: type of therapy (targeted therapies, immunotherapies, chemotherapy), dosage, treatment duration, and treatment regimen.  
• Outcomes: overall survival, progression-free survival, quality of life measures, and adverse events.

3. Cross-Verification: The two reviewers will compare their extracted data for each study to identify and resolve any discrepancies. If consensus cannot be reached, a third reviewer will be consulted.

4. Data Management: Extracted data will be entered into a database or spreadsheet software for organization and analysis. This will facilitate the identification of trends and synthesis of data across studies.

Handling of Missing or Incomplete Data

In cases where data are missing or incomplete, the following steps will be taken:

1. Contact Study Authors: Attempts will be made to contact the authors of the original studies to request missing information.

2. Use of Available Data: If the missing data cannot be obtained, the available data will be used, and the potential impact of the missing data on the findings will be discussed in the analysis.

3. Reporting: The extent of missing data and the strategies used to address it will be transparently reported in the final manuscript.

Data Items to be Extracted

The specific data items to be extracted from each study will include:  
• Publication Details: Title, authors, journal, year of publication.  
• Study Design: Observational study type (prospective, retrospective), duration of follow-up.  
• Population: Number of participants, inclusion/exclusion criteria, baseline characteristics.  
• Interventions: Description of the NSCLC therapies, including drug names, dosages, and treatment durations.  
• Outcomes: Definitions and measurements of outcomes, including survival rates, progression-free survival, adverse events, and quality of life indicators.  
• Statistical Analysis: Summary measures (e.g., hazard ratios, odds ratios), confidence intervals, p-values, and methods used to control for confounding factors.

Data Extraction Training and Calibration

Prior to beginning the data extraction process, reviewers will undergo training to ensure familiarity with the data extraction form and to calibrate their approach to data extraction. This training will include a review of the study protocol, discussion of the data extraction form, and practice on example studies.

Data Extraction Quality Assurance

To ensure the quality of the data extraction process, the following measures will be implemented:  
• Reviewer Meetings: Regular meetings will be held to discuss progress, challenges, and to ensure consistency in data extraction.  
• Audit of Extracted Data: A sample of the extracted data will be audited by a third reviewer to check for accuracy and consistency.  
• Documentation of Decisions: All decisions made during the data extraction process, including the resolution of discrepancies, will be documented for transparency and to inform the discussion of potential biases in the systematic review.

Data Extraction Timeline

The data extraction phase is expected to be completed within 2 months from the start of the study selection process. This timeline may be adjusted based on the volume of studies included and the complexity of the data to be extracted.

# 7. Quality Assessment

Quality Assessment

Overview

The quality assessment of the included studies in this systematic literature review (SLR) will be a critical step to ensure the reliability and validity of the findings. The assessment will focus on evaluating the methodological quality of each study and determining the risk of bias.

Assessment Tool

For the quality assessment of observational studies, the Newcastle-Ottawa Scale (NOS) will be utilized. This scale is designed to appraise non-randomized studies included in a systematic review and meta-analysis. The NOS assesses three broad perspectives:

1. Selection of the Study Groups: Includes the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study.

2. Comparability of the Groups: Evaluates the comparability of cohorts based on the design or analysis controlled for confounding factors.

3. Ascertainment of the Outcome of Interest: Involves the assessment of the method of outcome assessment and the follow-up period for outcomes to occur.

Each study will be judged in these three domains and awarded a star system, which will be used to quantify the quality of each study.

Process of Quality Assessment

1. Independent Review: Two independent reviewers will conduct the quality assessment for each eligible study. Any disagreements will be resolved through discussion or by involving a third reviewer.

2. Scoring: Each study will be scored according to the NOS criteria. Studies will be awarded stars for each quality item within the selection and outcome categories. A maximum of two stars can be given for comparability.

3. Documentation: The results of the quality assessment will be documented in a tabular format, summarizing the scores for each study. This table will be included in the final report to provide transparency.

4. Interpretation: The scores will be interpreted to provide an overall assessment of each study's quality. Studies with higher scores are considered to have a lower risk of bias.

5. Influence on Synthesis: The quality scores will be considered during the data synthesis phase. Studies with low-quality scores may be given less weight in the analysis, or sensitivity analyses may be conducted to determine the impact of including such studies on the overall findings.

Quality Assessment Timeline

The quality assessment will be conducted concurrently with the data extraction process. It is anticipated that the quality assessment will be completed within the 2-month data extraction period.

Reporting of Quality Assessment

The findings from the quality assessment will be reported in the results section of the final manuscript. A narrative summary, supplemented by the quality assessment table, will describe the overall quality of the evidence and the risk of bias within the included studies. This will provide context for interpreting the results of the SLR and may highlight potential areas for improvement in future research.

# 8. Data Synthesis

Data Synthesis

Overview of Synthesis Process

The data synthesis process will integrate findings from the included studies to create a comprehensive summary of real-world evidence in the treatment of non-small cell lung cancer (NSCLC). This process will involve a narrative synthesis and, where possible, a quantitative synthesis or meta-analysis of the data.

Narrative Synthesis

The narrative synthesis will provide a descriptive summary of the findings from the included studies. It will focus on the effectiveness of novel NSCLC therapies in real-world settings, treatment outcomes among various sub-populations, and the safety and tolerability profiles of these therapies. The synthesis will be structured around the key themes and variables of interest, such as:  
• Patient demographics and disease characteristics  
• Types of interventions (targeted therapies, immunotherapies, and chemotherapy)  
• Outcome measures (overall survival, progression-free survival, quality of life, adverse events)

The narrative synthesis will highlight patterns, similarities, and differences across studies and will discuss the implications of these findings for clinical practice.

Quantitative Synthesis (Meta-Analysis)

If the data across studies are sufficiently homogenous, a meta-analysis will be conducted to quantitatively synthesize the results. The following steps will be taken:

1. Data Pooling: Outcome data from individual studies will be pooled using appropriate statistical methods.  
2. Assessment of Heterogeneity: The I² statistic will be used to assess the degree of heterogeneity among the studies. A random-effects model will be applied in the presence of significant heterogeneity.  
3. Subgroup Analyses: To explore variations in treatment outcomes among different patient sub-populations, subgroup analyses will be performed based on factors such as age, gender, histology, and specific genetic mutations.  
4. Sensitivity Analyses: To assess the robustness of the findings, sensitivity analyses will be conducted by excluding studies with a high risk of bias or low methodological quality.

Presentation of Synthesis Results

The results of the data synthesis will be presented in both tabular and graphical formats. Tables will summarize the study characteristics, patient populations, interventions, and outcomes. Graphs, such as forest plots, will be used to visually represent the results of the meta-analysis.

Interpretation of Findings

The synthesis will interpret the findings in the context of the current NSCLC treatment landscape. It will discuss the real-world effectiveness of novel therapies, the variability in treatment outcomes among different patient sub-populations, and the safety profiles of the interventions. The synthesis will also identify any gaps in the literature and suggest areas for future research.

Consideration of Quality of Evidence

The quality of evidence from the included studies will be a key consideration in the synthesis process. Studies with higher quality and lower risk of bias will be given more weight in the narrative and quantitative synthesis. The potential impact of study quality on the findings will be discussed.

Timeline for Data Synthesis

The data synthesis phase is expected to commence following the completion of the data extraction and quality assessment phases. It is anticipated that the synthesis will be completed within 2 months, allowing for the preparation of the final manuscript.

Reporting of Synthesis Findings

The findings from the data synthesis will be reported in the results section of the final manuscript. A detailed account of the synthesis process, including the narrative summary, meta-analysis results, subgroup analyses, and sensitivity analyses, will be provided. The discussion section will interpret the findings in relation to the study objectives and the broader NSCLC treatment context.