Clinical Trial Protocol

# 1.1 Table of Contents

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# 1.2 Title

Title Section

Full Study Title:  
Systematic Literature Review of Real-World Evidence in Non-Small Cell Lung Cancer: Evaluating Treatment Outcomes and Safety Profiles

Short Title or Acronym:  
SLR-RWE-NSCLC

Protocol Version and Date:  
Version 1.0, [Insert Date]

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# 1.3 Background

Background Section

1. • Introduction to Non-Small Cell Lung Cancer (NSCLC)
2. • Non-small cell lung cancer (NSCLC) is the most prevalent form of lung cancer, accounting for approximately 85% of all lung cancer cases worldwide. NSCLC encompasses a range of histological types, with adenocarcinoma, squamous cell carcinoma, and large cell carcinoma being the most common subtypes. The prognosis for NSCLC is often poor, with a five-year survival rate that remains low despite advances in detection and treatment. The disease is frequently diagnosed at an advanced stage, which complicates treatment efforts and underscores the importance of ongoing research into more effective therapeutic strategies.

2. Current Treatment Landscape  
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 exploit specific genetic mutations or to enhance the immune system's ability to fight cancer cells. While these advancements have shown promise in clinical trials, there is a gap in knowledge regarding their effectiveness and safety in real-world clinical practice, where patient populations are more heterogeneous and may not strictly adhere to clinical trial protocols.

3. Rationale for a Systematic Literature Review (SLR) of Real-World Evidence (RWE)  
Real-world evidence (RWE) is derived from the analysis of data collected outside the context of randomized controlled trials (RCTs). It includes observational studies, registries, electronic health records, and other data sources that reflect the practical realities of healthcare delivery. RWE is increasingly recognized as a valuable complement to RCT data, providing insights into the effectiveness and safety of treatments in a broader patient population. Given the complexity of NSCLC and the diversity of treatment options available, an SLR of RWE is essential to capture a comprehensive picture of current treatment outcomes and safety profiles.

4. Importance of Evaluating Real-World Treatment Outcomes and Safety Profiles  
Evaluating treatment outcomes such as survival rates and progression-free survival in real-world settings is crucial for understanding the actual impact of therapies on patients with NSCLC. Additionally, analyzing safety and tolerability profiles can inform clinicians and patients about the potential risks associated with new treatments. This SLR aims to address these critical aspects by systematically collecting and synthesizing existing RWE, which will help in guiding clinical decision-making and improving patient care.

5. Objectives of the Study  
The primary objectives of this SLR are to evaluate the effectiveness of novel NSCLC therapies in real-world settings, assess treatment outcomes among various sub-populations within NSCLC, and analyze the safety and tolerability profiles of new therapies in real-world NSCLC populations. By achieving these objectives, the study seeks to provide a robust synthesis of RWE that can inform future research, policy-making, and clinical practice in the management of NSCLC.

In conclusion, this SLR will fill a critical gap in the literature by providing a detailed analysis of real-world treatment outcomes and safety profiles for patients with NSCLC. The findings are expected to offer valuable insights that will contribute to the optimization of therapeutic strategies and ultimately improve patient outcomes in this challenging disease area.

# 1.4 Objectives

Section: Objectives

1. • Primary Objective
2. • The primary objective of this systematic literature review (SLR) is to evaluate the effectiveness of novel therapies in the treatment of non-small cell lung cancer (NSCLC) in real-world clinical settings. This encompasses a comprehensive analysis of patient outcomes, including overall survival and progression-free survival, in response to targeted therapies, immunotherapies, and standard chemotherapy.

2. Secondary Objectives  
a. To assess treatment outcomes such as survival rates and progression-free survival among various sub-populations within NSCLC, including but not limited to different histological subtypes, stages of disease, and genetic mutations. This will provide insights into the heterogeneity of treatment responses and identify potential disparities in treatment efficacy.

b. To analyze the safety and tolerability profiles of new NSCLC therapies in real-world populations. This includes the identification and quantification of adverse events associated with these treatments, which is crucial for understanding the risk-benefit balance in routine clinical practice.

c. To synthesize the collected real-world evidence to generate a meta-summary that reflects the current landscape of NSCLC treatment outcomes and safety profiles. This synthesis will aim to identify gaps in knowledge and areas where further research is needed.

3. Exploratory Objectives  
a. To explore the impact of novel NSCLC therapies on quality of life outcomes in real-world settings. This will involve examining patient-reported outcomes and other quality of life measures to understand the broader implications of treatment beyond traditional clinical endpoints.

b. To investigate the utilization patterns of NSCLC treatments in real-world practice, including adherence to treatment protocols and the influence of socio-economic factors on treatment accessibility and outcomes.

c. To provide a contextual analysis of the real-world evidence within the framework of existing randomized controlled trial (RCT) data, thereby offering a comparative perspective on the applicability and generalizability of RCT findings to everyday clinical practice.

By fulfilling these objectives, the SLR aims to deliver a nuanced and actionable understanding of the real-world impact of NSCLC treatments, thereby informing clinical decision-making, patient care strategies, and future research directions in the management of NSCLC.

# 1.5 Methods

Methods Section

Systematic Literature Review Protocol

1. • Framework and Methodology
2. • This systematic literature review (SLR) will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA framework will guide the identification, screening, eligibility assessment, and inclusion of relevant studies to ensure a rigorous and transparent review process. The methodology will involve a structured approach to literature search, data extraction, quality assessment, and synthesis of findings.

2. Literature Search Strategy  
A comprehensive literature search will be performed across multiple electronic databases, including PubMed, EMBASE, and the Cochrane Library, to identify studies that provide real-world evidence in non-small cell lung cancer (NSCLC). The search strategy will utilize a combination of keywords and MeSH terms related to NSCLC, real-world evidence, treatment outcomes, and safety. The search will be limited to studies published in English and conducted on adult populations diagnosed with NSCLC. The literature search will be supplemented by manual searches of reference lists from included studies and relevant review articles to ensure completeness.

3. Study Selection  
Following the literature search, all identified records will be collated and uploaded into a reference management software where duplicates will be removed. Two independent reviewers will screen the titles and abstracts against the inclusion criteria. Full texts of potentially eligible studies will be retrieved and assessed for eligibility. Any discrepancies between reviewers will be resolved through discussion or by consulting a third reviewer if necessary.

4. Inclusion and Exclusion Criteria  
Studies will be included if they meet the following 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.  
Studies will be excluded if they are case reports, editorials, commentaries, or studies not providing empirical data on the outcomes of interest.

5. Data Extraction and Management  
Data extraction will be performed by two independent reviewers using a standardized data extraction form. Extracted information will include study characteristics (e.g., author, year of publication, study design), participant demographics, interventions, and outcomes of interest. Any disagreements will be resolved through discussion or by involving a third reviewer.

6. Quality Assessment  
The quality of included studies will be assessed using appropriate tools based on study design, such as the Newcastle-Ottawa Scale for observational studies. The quality assessment will evaluate the risk of bias and the validity of study findings. Studies will not be excluded based on quality assessment, but the results will be considered in the interpretation of the review findings.

7. Data Synthesis and Analysis  
The extracted data will be synthesized to provide a narrative summary and, where possible, a quantitative meta-analysis. Meta-analytic techniques will be employed to combine data from studies that are sufficiently homogenous in terms of interventions and outcomes. Heterogeneity among studies will be assessed using the I² statistic. Subgroup analyses will be conducted to explore differences in treatment outcomes among various NSCLC sub-populations.

8. Presentation of Results  
The results of the SLR will be presented in accordance with the PRISMA guidelines. A flow diagram will illustrate the study selection process. Tables and figures will summarize the characteristics and findings of the included studies. A narrative synthesis will discuss the evidence in the context of the review objectives, and the implications for clinical practice and future research.

9. Timeline  
The SLR process, from the initial literature search to the final manuscript preparation, is expected to be completed within 6 months. This timeline includes the stages of study selection, data extraction, quality assessment, data synthesis, and drafting of the report.

10. Ethical Considerations  
As this study will be a review of published literature, ethical approval is not required. However, the review will be conducted with full respect for the integrity of the original research and the confidentiality of patient data.

By adhering to this systematic and transparent methodology, the SLR aims to provide a comprehensive synthesis of real-world evidence on the effectiveness and safety of treatments for NSCLC, thereby contributing valuable insights to the field of oncology.

# 1.6 Search Strategy

Search Strategy Section

1. • Database Selection
2. • To ensure a comprehensive and systematic search of the literature, the following electronic databases will be utilized: PubMed, EMBASE, and the Cochrane Library. These databases were chosen due to their extensive coverage of biomedical literature, including a wide range of journals relevant to oncology, clinical medicine, and healthcare outcomes. Additional sources such as conference proceedings, clinical trial registries, and grey literature databases may also be searched to capture unpublished studies and ongoing research.

2. Search Terms and Concepts  
The search strategy will be developed using a combination of controlled vocabulary terms (e.g., MeSH terms in PubMed) and free-text words. The main concepts to be included in the search are "Non-Small Cell Lung Cancer," "Real-World Evidence," "Treatment Outcomes," and "Safety." These concepts will be expanded to include various synonyms, related terms, and specific interventions such as "Targeted Therapies," "Immunotherapies," and "Chemotherapy."

3. Search String Construction  
The search strings will be constructed using Boolean operators (AND, OR) to combine the different concepts and terms. An example of a search string for PubMed might be:

("Non-Small Cell Lung Carcinoma" [MeSH] OR "NSCLC" OR "Non-Small Cell Lung Cancer") AND ("Real World Evidence" OR "Observational Study" OR "Registry Study" OR "Electronic Health Records") AND ("Treatment Outcome" OR "Survival Rate" OR "Progression-Free Survival" OR "Quality of Life" OR "Adverse Events") AND ("Targeted Therapy" OR "Immunotherapy" OR "Chemotherapy")

The search strings will be adapted as necessary for each database to accommodate different syntax and controlled vocabulary.

4. Search Limits and Filters  
Searches will be limited to studies published in the English language and conducted on adult populations diagnosed with NSCLC. The time frame for publication will not be restricted initially to capture the broadest range of evidence; however, depending on the volume of literature retrieved, date restrictions may be applied.

5. Search Execution and Management  
The search will be executed by the principal investigators or a trained medical librarian to ensure accuracy and completeness. All search results will be exported to a reference management software, where duplicates will be removed. The search history, including the date of the search, databases searched, and the number of results obtained, will be recorded to ensure reproducibility and transparency.

6. Supplementary Search Strategies  
To complement the electronic database searches, manual searches of the reference lists of included studies and relevant review articles will be conducted to identify additional studies. Experts in the field may also be consulted for potential sources of unpublished data or ongoing studies.

7. Search Updates  
The search will be updated during the review process to include the most recent studies before the final analysis. This will ensure that the review incorporates the latest available evidence.

The search strategy outlined above is designed to be comprehensive and systematic, adhering to the PRISMA guidelines and ensuring that the review captures a wide range of real-world evidence on the effectiveness and safety of treatments for NSCLC.

# 1.7 Selection Criteria

Selection Criteria Section

1. • Inclusion Criteria
2. • To be included in this systematic literature review, studies must meet the following criteria:
3. • Population: Studies must focus on adults diagnosed with non-small cell lung cancer (NSCLC).
4. • Interventions: The review will include studies that evaluate the effectiveness and safety of targeted therapies, immunotherapies, and standard chemotherapy treatments.
5. • Outcomes: Studies must report on at least one of the following outcomes: overall survival, progression-free survival, quality of life, and adverse events.
6. • Study Design: The review will consider observational studies, registry analyses, retrospective and prospective cohort studies, and other non-randomized studies that provide real-world evidence.
7. • Language: Studies must be published in English.
8. • Publication Status: Peer-reviewed articles, conference abstracts, and grey literature that meet the inclusion criteria will be considered.

2. Exclusion Criteria  
Studies will be excluded based on the following criteria:

1. • Population: Studies focusing on pediatric populations or non-NSCLC lung cancers.
2. • Interventions: Studies that do not specifically address the interventions of interest (targeted therapies, immunotherapies, and chemotherapy).
3. • Outcomes: Studies that do not report on the predefined outcomes of interest.
4. • Study Design: Case reports, editorials, commentaries, opinion pieces, and reviews without original data.
5. • Language: Non-English language studies.
6. • Publication Status: Unpublished data that are not accessible or verifiable.

3. Screening Process  
The study selection process will involve several steps to ensure a comprehensive and unbiased review:

1. • Initial Screening: Two independent reviewers will screen titles and abstracts of studies identified through the literature search strategy to assess their relevance based on the inclusion and exclusion criteria.
2. • Full-Text Review: Studies that appear to meet the inclusion criteria or require further assessment will undergo full-text review by the same reviewers.
3. • Discrepancy Resolution: Any disagreements between reviewers at each stage of the screening process will be resolved through discussion. If consensus cannot be reached, a third reviewer will be consulted to make the final decision.
4. • Record Keeping: A PRISMA flow diagram will be used to document the study selection process, including the number of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage.

4. Data Management  
All records identified during the search will be managed using reference management software. Duplicate records will be removed. The selection process will be documented in detail to ensure transparency and reproducibility.

By adhering to these selection criteria and screening processes, the systematic literature review will provide a robust synthesis of real-world evidence on the effectiveness and safety of treatments for NSCLC, contributing to the optimization of therapeutic strategies and improving patient outcomes.

# 1.8 Data Extraction

Data Extraction Section

1. • Data Extraction Form

To systematically collect and analyze data from the included studies, a standardized data extraction form will be developed. This form will be designed to capture all relevant information required to address the study objectives and will include the following fields:

1. • Study identification: Author(s), year of publication, title, journal/source.
2. • Study characteristics: Study design, country, setting, sample size, duration of follow-up.
3. • Participant demographics: Age, sex, NSCLC stage, histological subtype, genetic mutations, comorbidities.
4. • Interventions: Type of therapy (targeted therapies, immunotherapies, chemotherapy), dosage, treatment duration.
5. • Outcomes: Overall survival, progression-free survival, quality of life measures, adverse events, and any other relevant outcomes reported.
6. • Methodological quality indicators: Risk of bias, confounders controlled for, statistical methods used.

The data extraction form will be pilot-tested on a small number of included studies and refined as necessary to ensure that it adequately captures all pertinent information.

2. Data Extraction Process

The data extraction process will be conducted by two independent reviewers to minimize the risk of bias and errors. The reviewers will extract data from each eligible study using the standardized data extraction form. The following steps will be taken:

1. • Calibration exercise: Prior to the commencement of data extraction, reviewers will perform a calibration exercise using the data extraction form on a sample of studies to ensure consistency in data recording.
2. • Independent extraction: Each reviewer will independently extract data from the included studies. Any use of software tools for data extraction will be documented.
3. • Cross-checking: Upon completion of the independent data extraction, reviewers will compare their forms to identify any discrepancies. Disagreements will be resolved through discussion or, if necessary, by consulting a third reviewer.
4. • Data entry: The final agreed-upon data will be entered into a database designed for analysis. The database will be backed up regularly to prevent data loss.

3. Handling Missing or Incomplete Data

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

1. • Contact authors: Attempts will be made to contact the original authors of the studies to request missing information or clarification.
2. • Document assumptions: If data cannot be obtained, any assumptions made to deal with missing data will be clearly documented.
3. • Sensitivity analysis: Sensitivity analyses will be conducted to assess the impact of missing data on the overall findings of the review.

4. Data Management

All data extracted from the studies will be managed confidentially and stored securely. Access to the data will be restricted to the review team members. Electronic data will be password-protected, and any hard copies of data will be kept in a locked file cabinet in a secure location.

By adhering to this systematic and transparent data extraction process, the systematic literature review will provide a comprehensive synthesis of real-world evidence on the effectiveness and safety of treatments for NSCLC, contributing to the optimization of therapeutic strategies and improving patient outcomes.

# 1.9 Quality Assessment

Quality Assessment Section

1. • Overview of Quality Assessment

The quality assessment of studies included in this systematic literature review (SLR) is a critical step to ensure the reliability and validity of the findings. Given the focus on real-world evidence (RWE) in non-small cell lung cancer (NSCLC), the quality assessment will involve evaluating the methodological rigor and potential for bias in observational studies, registries, and other non-randomized studies that contribute to the body of RWE.

2. Quality Assessment Tools

The quality of the included studies will be appraised using standardized tools that are appropriate for the study designs encountered. The primary tool for assessing the quality of observational studies will be the Newcastle-Ottawa Scale (NOS). This scale evaluates studies based on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest. The NOS provides a star system, in which studies can be awarded up to nine stars, with more stars indicating higher quality.

For studies that do not fit the criteria for the NOS, other validated assessment tools will be used as appropriate, such as the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for observational studies or the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) statement for studies utilizing routinely collected health data.

3. Quality Assessment Process

The quality assessment will be conducted independently by two reviewers to minimize bias and ensure consistency. The following steps will outline the process:

a. Training and Calibration: Prior to the assessment, reviewers will undergo training on the use of the quality assessment tools. A calibration exercise will be conducted to ensure consistent application of the assessment criteria.

b. Independent Assessment: Each reviewer will independently assess the quality of each included study using the designated tools. Discrepancies between reviewers will be documented and discussed.

c. Consensus Meeting: In cases of disagreement, reviewers will meet to discuss and reach a consensus. If a consensus cannot be reached, a third reviewer will be consulted.

d. Documentation: The quality assessment findings will be documented in detail, with explanations provided for the ratings assigned to each study. This documentation will be included in the final report to provide transparency regarding the assessment process.

4. Use of Quality Assessment in Data Synthesis

The results of the quality assessment will not be used to exclude studies from the review. Instead, they will inform the synthesis and interpretation of the findings. Studies with lower quality ratings will be critically appraised to understand how their methodological limitations might affect the overall conclusions of the SLR. The quality assessment will also guide sensitivity analyses, where the impact of including or excluding lower-quality studies on the overall findings will be examined.

5. Reporting Quality Assessment Results

The quality assessment results will be reported in a tabular format, summarizing the quality scores and key methodological strengths and weaknesses of each study. A narrative summary will accompany the table, discussing the overall quality of the evidence base and the implications for the review's conclusions.

By incorporating a rigorous and transparent quality assessment process, this SLR will provide a comprehensive and trustworthy synthesis of RWE on the effectiveness and safety of treatments for NSCLC, thereby informing clinical decision-making and future research directions in the management of this disease.

# 1.10 Synthesis Methods

Data Synthesis and Analysis Methods Section

1. • Approach to Data Synthesis
2. • The synthesis of data in this systematic literature review (SLR) will involve a narrative summary and, where appropriate, a quantitative meta-analysis. The narrative synthesis will provide a descriptive overview of the findings from the included studies, focusing on the effectiveness and safety of novel therapies for non-small cell lung cancer (NSCLC) in real-world settings. The synthesis will consider the diversity of interventions, patient populations, and outcomes reported across studies.

For the quantitative synthesis, meta-analytic techniques will be employed to combine results from studies that are sufficiently homogenous with respect to interventions and outcomes. Pooled estimates of treatment effects on survival rates, progression-free survival, and adverse events will be calculated using random-effects models to account for between-study variability.

2. Methods for Combining Results  
When combining results for meta-analysis, we will use the inverse variance method for continuous outcomes and the Mantel-Haenszel method for dichotomous outcomes. Heterogeneity will be assessed using the I² statistic and the Chi-square test. An I² value greater than 50% or a p-value less than 0.10 on the Chi-square test will be indicative of substantial heterogeneity.

3. Assessment of Reporting Biases  
To assess reporting biases, such as publication bias, we will create funnel plots for each meta-analysis containing ten or more studies. Asymmetry in funnel plots will be evaluated using Egger's test. We will also conduct a comprehensive search strategy, including grey literature, to minimize the potential for publication bias.

4. Investigation of Heterogeneity  
Heterogeneity among studies will be explored through subgroup analyses and meta-regression, where appropriate. Potential sources of heterogeneity, such as differences in study design, patient demographics, NSCLC subtypes, and types of interventions, will be investigated. Sensitivity analyses will be conducted to determine the robustness of the findings by excluding studies with high risk of bias or those that are outliers.

5. Sensitivity Analysis Plans  
Sensitivity analyses will be performed to assess the impact of various factors on the robustness of the meta-analytic results. This will include analyses excluding studies with lower methodological quality or high risk of bias, as well as studies that have a significant impact on heterogeneity. Additionally, we will conduct sensitivity analyses based on the study design (e.g., prospective vs. retrospective studies).

6. Subgroup Analyses if Planned  
Subgroup analyses will be conducted to explore differences in treatment outcomes among various NSCLC sub-populations, such as those defined by histological subtype, stage of disease, presence of specific genetic mutations, and prior treatment history. These analyses will help to identify whether certain patient groups derive more or less benefit from the interventions under study.

By employing these rigorous data synthesis and analysis methods, the SLR will provide a comprehensive and reliable synthesis of real-world evidence on the effectiveness and safety of treatments for NSCLC, thereby contributing to the optimization of therapeutic strategies and improving patient outcomes.