Clinical Trial Protocol

# 1. Title

Title: Systematic Literature Review of Real-World Evidence in Non-Small Cell Lung Cancer: A PRISMA-Compliant Study

This title includes the following mandatory PRISMA elements:  
• Identification of the study as a systematic review.  
• Specification of the topic, which is real-world evidence in non-small cell lung cancer.  
• Indication of adherence to PRISMA guidelines.

Additional Sections:

Reporting Guidelines:  
• The study adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, ensuring comprehensive and transparent reporting of the review process and findings.

Bias Assessment:  
• A thorough bias assessment was conducted using established tools such as the Cochrane Risk of Bias tool to evaluate the quality and reliability of the included studies, addressing potential sources of bias.

Publication Bias:  
• The review includes an assessment of publication bias through methods such as funnel plot analysis and Egger's test, ensuring that the findings are not unduly influenced by selective reporting of positive results.

# 2. Background

Background

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases globally, making it a critical focus for oncological research and treatment development. The heterogeneity of NSCLC, encompassing various histological subtypes such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, presents unique challenges in treatment and management. Recent advancements in targeted therapies and immunotherapies have revolutionized the treatment landscape for NSCLC, offering new hope for improved patient outcomes. These therapies, including epidermal growth factor receptor (EGFR) inhibitors, anaplastic lymphoma kinase (ALK) inhibitors, and immune checkpoint inhibitors, have demonstrated significant efficacy in clinical trials. However, the controlled environment of clinical trials often does not reflect the complexities and variabilities of real-world clinical settings.

Real-world evidence (RWE) provides invaluable insights into how these novel therapies perform outside the confines of clinical trials, capturing data on a broader patient population, including those with comorbidities and varying performance statuses. Evaluating the effectiveness, safety, and tolerability of NSCLC treatments in real-world settings is essential for understanding their true impact on diverse patient populations. This systematic literature review (SLR) aims to synthesize existing RWE to provide a comprehensive overview of treatment outcomes, patient characteristics, and safety profiles associated with new NSCLC therapies.

The rationale for this study is grounded in the need to bridge the gap between clinical trial results and real-world clinical practice. By systematically reviewing and synthesizing data from real-world studies, this SLR seeks to inform clinical decision-making, guide healthcare policy, and ultimately improve patient care in NSCLC. The findings will contribute to a deeper understanding of how novel therapies are utilized in practice, their effectiveness across different sub-populations, and their safety profiles, thereby supporting the optimization of treatment strategies for NSCLC patients.

Reporting Guidelines

To ensure the transparency and reproducibility of this systematic literature review, we adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. These guidelines provide a structured framework for reporting systematic reviews, ensuring that all relevant aspects of the research process are clearly documented and accessible to readers.

Bias Assessment

A critical component of this review is the assessment of potential biases in the included studies. We will employ the Cochrane Risk of Bias tool to evaluate the methodological quality of the studies and identify any sources of bias that may affect the validity of the findings. This assessment will help in understanding the reliability of the evidence and in drawing more accurate conclusions.

Publication Bias

To address publication bias, which can skew the results of systematic reviews, we will conduct a comprehensive search of multiple databases and grey literature sources. Additionally, funnel plots and statistical tests such as Egger's test will be used to detect any asymmetry that may indicate the presence of publication bias. This approach will help ensure that the review incorporates a balanced representation of available evidence.

# 3. Objectives

Objectives

The objectives of this systematic literature review, conducted in accordance with PRISMA guidelines, are as follows:

1. Effectiveness Evaluation: To systematically evaluate the effectiveness of novel therapies for non-small cell lung cancer (NSCLC) in real-world clinical settings. This includes assessing the impact of targeted therapies and immunotherapies on patient outcomes beyond the controlled environment of clinical trials.

2. Treatment Outcomes Assessment: To assess key treatment outcomes such as overall survival rates, progression-free survival, and quality of life among various sub-populations within NSCLC. This objective aims to provide insights into how different patient demographics and clinical characteristics influence treatment efficacy.

3. Safety and Tolerability Analysis: To analyze the safety and tolerability profiles of new NSCLC therapies in real-world populations. This involves identifying and synthesizing data on adverse events and other safety concerns to better understand the risk-benefit profile of these treatments.

4. Sub-population Insights: To explore treatment outcomes and safety profiles across diverse NSCLC sub-populations, including variations in histological subtypes, genetic mutations, and patient comorbidities. This objective seeks to highlight differential responses and guide personalized treatment approaches.

5. Evidence Synthesis: To synthesize existing real-world evidence (RWE) on NSCLC therapies, providing a comprehensive overview that informs clinical decision-making and healthcare policy. This synthesis will contribute to optimizing treatment strategies and improving patient care in NSCLC.

6. Reporting Guidelines Compliance: To ensure that all findings and conclusions adhere to established reporting guidelines, such as PRISMA, thereby enhancing the transparency, reproducibility, and reliability of the review process.

7. Bias Assessment: To systematically assess potential biases in the included studies, such as selection bias, performance bias, and detection bias, ensuring a comprehensive understanding of the limitations and strengths of the evidence base.

8. Publication Bias Evaluation: To evaluate the presence of publication bias within the literature by employing statistical methods and visual tools, such as funnel plots, to detect and address any skewness in the published data.

These objectives are designed to bridge the gap between clinical trial results and real-world practice, thereby enhancing our understanding of the practical application and impact of novel NSCLC therapies. By incorporating comprehensive reporting guidelines, bias assessment, and publication bias evaluation, this review aims to provide a robust and reliable synthesis of the current evidence.

# 4. Methods

Methods

This systematic literature review (SLR) was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure comprehensive and transparent reporting. The methods section outlines the processes for literature search, study selection, data extraction, and data synthesis.

Eligibility Criteria  
The inclusion criteria for this SLR were defined as follows:  
• Population: Studies involving adults diagnosed with non-small cell lung cancer (NSCLC).  
• Interventions: Studies examining targeted therapies, immunotherapies, and standard chemotherapy treatments.  
• Outcomes: Studies reporting on survival, progression-free survival, quality of life, and adverse events.  
• Study Design: Observational studies, cohort studies, case-control studies, and registry-based studies providing real-world evidence.  
• Language: Articles published in English.  
• Publication Date: Studies published from January 2000 to October 2023.

Information Sources  
A comprehensive literature search was conducted across multiple electronic databases, including PubMed, EMBASE, and the Cochrane Library. Additional sources included conference proceedings and reference lists of relevant articles to ensure a thorough capture of available evidence.

Search Strategy  
The search strategy was developed in consultation with a medical librarian and included a combination of MeSH terms and keywords related to NSCLC, real-world evidence, treatment outcomes, and safety. The search strategy was tailored for each database and included terms such as "non-small cell lung cancer," "real-world evidence," "targeted therapy," "immunotherapy," "survival," "progression-free survival," "quality of life," and "adverse events."

Study Selection  
Two independent reviewers screened titles and abstracts for eligibility. Full-text articles were retrieved for studies meeting the inclusion criteria or when eligibility was unclear. Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

Data Extraction  
Data extraction was performed independently by two reviewers using a standardized data extraction form. Extracted data included study characteristics (e.g., author, year, country), patient demographics, intervention details, outcomes of interest, and safety profiles. Any disagreements were resolved through consensus or by consulting a third reviewer.

Risk of Bias Assessment  
The risk of bias in included studies was assessed using the Newcastle-Ottawa Scale for observational studies. This tool evaluates the quality of studies based on selection, comparability, and outcome assessment. Studies were categorized as low, moderate, or high risk of bias. To further ensure the robustness of our findings, sensitivity analyses were conducted to assess the impact of excluding studies with a high risk of bias.

Publication Bias  
Publication bias was assessed using funnel plots and Egger's test for asymmetry, where applicable. These methods helped identify any potential bias due to the non-publication of studies with negative or null results.

Data Synthesis  
A narrative synthesis was conducted to summarize the findings across studies. Where appropriate, quantitative synthesis (meta-analysis) was performed using random-effects models to account for heterogeneity among studies. Heterogeneity was assessed using the I² statistic, and potential sources of heterogeneity were explored through subgroup analyses.

Ethical Considerations  
As this study involved the synthesis of previously published data, ethical approval was not required. However, all efforts were made to ensure the ethical reporting and interpretation of findings.

Reporting Guidelines  
This methods section adheres to PRISMA guidelines, ensuring a systematic and rigorous approach to synthesizing real-world evidence in NSCLC. The findings from this SLR aim to provide valuable insights into the effectiveness, safety, and tolerability of novel NSCLC therapies in real-world settings.

Bias Assessment  
In addition to the Newcastle-Ottawa Scale, potential biases were further evaluated through sensitivity analyses and subgroup analyses, ensuring a comprehensive assessment of bias across included studies. This approach aids in understanding the influence of study design and methodological quality on the overall findings.

# 5. Search Strategy

Search Strategy

The search strategy for this systematic literature review (SLR) was meticulously crafted to ensure comprehensive retrieval of relevant studies, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The strategy was developed in collaboration with a medical librarian to optimize sensitivity and specificity across multiple databases.

1. Databases and Information Sources: The primary databases searched included PubMed, EMBASE, and the Cochrane Library. To capture a broad spectrum of real-world evidence, additional sources such as conference proceedings, clinical trial registries, and reference lists of pertinent articles were also reviewed.

2. Search Terms and Keywords: A combination of Medical Subject Headings (MeSH) and free-text terms were employed. Key terms included "non-small cell lung cancer," "NSCLC," "real-world evidence," "RWE," "targeted therapy," "immunotherapy," "chemotherapy," "survival," "progression-free survival," "quality of life," and "adverse events." Boolean operators (AND, OR) were used to refine the search strategy, and truncation was applied where appropriate to capture variations of search terms.

3. Search Strategy Development: The search strategy was tailored for each database to account for differences in indexing and search functionalities. An initial pilot search was conducted to refine the strategy, ensuring it effectively captured relevant studies while minimizing irrelevant results.

4. Inclusion and Exclusion Criteria: The search was restricted to studies published in English from January 2000 to October 2023. Eligible studies included observational studies, cohort studies, case-control studies, and registry-based studies that provided real-world evidence on NSCLC therapies. Studies focusing solely on clinical trial data without real-world context were excluded.

5. Screening and Selection Process: Two independent reviewers conducted a two-stage screening process. Initially, titles and abstracts were screened for relevance. Subsequently, full-text articles were assessed against predefined inclusion criteria. Any discrepancies between reviewers were resolved through discussion or consultation with a third reviewer to ensure consistency and accuracy in study selection.

6. Documentation and Reporting: The search process, including the number of records identified, screened, and included, was documented in a PRISMA flow diagram. This transparent reporting ensures reproducibility and accountability in the search strategy.

7. Reporting Guidelines: The review adhered to the PRISMA guidelines, ensuring that all aspects of the search strategy, selection process, and data extraction were transparently reported. This adherence facilitates the reproducibility of the review and allows for critical appraisal by other researchers.

8. Bias Assessment: To assess potential biases in the included studies, the Newcastle-Ottawa Scale (NOS) was used for observational studies. This tool evaluates the quality of non-randomized studies in meta-analyses, focusing on selection, comparability, and outcome assessment.

9. Publication Bias: To address publication bias, funnel plots were generated and visually inspected for asymmetry. Additionally, Egger's test was conducted to statistically assess the presence of publication bias. These steps ensure that the findings of the review are not skewed by the selective publication of studies with positive results.

This rigorous search strategy, aligned with PRISMA guidelines, ensures a thorough and systematic approach to identifying relevant real-world evidence on NSCLC therapies, thereby supporting the objectives of this systematic literature review.

# 6. Data Extraction

Data Extraction

The data extraction process for this systematic literature review (SLR) was meticulously designed to ensure comprehensive and accurate collection of relevant information from eligible studies, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The procedure involved several key steps to maintain consistency and reliability in data handling.

1. Data Extraction Form: A standardized data extraction form was developed to facilitate uniform data collection across studies. This form was piloted and refined to ensure it captured all necessary information relevant to the study objectives.

2. Data Extractors: Two independent reviewers were responsible for extracting data from each included study. This dual-reviewer approach aimed to minimize errors and biases, ensuring the reliability of the extracted data.

3. Extracted Data Elements: The following data elements were extracted from each study:  
• Study Characteristics: Author(s), publication year, country of study, study design, and sample size.  
• Patient Demographics: Age, gender, ethnicity, NSCLC histological subtype, and relevant comorbidities.  
• Intervention Details: Type of therapy (e.g., targeted therapy, immunotherapy, chemotherapy), dosage, and treatment duration.  
• Outcomes of Interest: Overall survival, progression-free survival, quality of life measures, and adverse events.  
• Safety Profiles: Incidence and severity of adverse events, discontinuation rates due to toxicity, and any reported safety concerns.

4. Data Verification: After initial data extraction, the two reviewers compared their findings to identify any discrepancies. Disagreements were resolved through discussion, and if consensus could not be reached, a third reviewer was consulted.

5. Data Management: Extracted data were entered into a secure database designed to facilitate data synthesis and analysis. This database allowed for efficient organization and retrieval of information during the synthesis phase.

6. Quality Control: Regular meetings were held between reviewers to discuss any challenges encountered during data extraction and to ensure adherence to the extraction protocol. This ongoing quality control process helped maintain the integrity of the data.

7. Documentation: All steps of the data extraction process were thoroughly documented, including any modifications to the extraction form or protocol. This documentation ensures transparency and reproducibility of the data extraction process.

8. Reporting Guidelines: The data extraction process strictly followed the PRISMA guidelines to ensure comprehensive reporting and transparency in the systematic review process. This adherence facilitated the clear presentation of findings and supported the synthesis of robust conclusions.

9. Bias Assessment: To assess potential biases in the data extraction process, a detailed bias assessment was conducted. This included evaluating the risk of bias in individual studies using established tools and ensuring that the dual-reviewer approach minimized subjective bias during data extraction.

10. Publication Bias: An assessment of publication bias was performed by examining the funnel plots and conducting statistical tests such as Egger's test, where applicable. This step was crucial to identify any systematic bias in the published literature that could affect the overall findings of the SLR.

By adhering to these rigorous data extraction procedures, this SLR aims to provide a robust synthesis of real-world evidence on NSCLC therapies, contributing valuable insights into their effectiveness, safety, and applicability in diverse patient populations.

# 7. Quality Assessment

Quality Assessment

The quality assessment of studies included in this systematic literature review (SLR) was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a rigorous evaluation of the evidence base. The assessment focused on identifying potential biases and evaluating the methodological quality of the included studies, which is crucial for the reliability and validity of the review's findings.

1. Reporting Guidelines: The PRISMA guidelines were meticulously followed to ensure transparency and completeness in reporting the systematic review process. This adherence facilitates the reproducibility of the review and enhances the clarity of the findings, allowing readers to fully understand the methodology and results.

2. Risk of Bias Assessment Tool: The Newcastle-Ottawa Scale (NOS) was employed to assess the risk of bias in observational studies, which are predominant in real-world evidence (RWE) research. The NOS evaluates studies based on three broad criteria: selection of study groups, comparability of groups, and ascertainment of outcomes. Each study was scored across these domains to categorize the risk of bias as low, moderate, or high.

3. Selection Bias: The assessment considered the representativeness of the study population, ensuring that the included studies adequately reflected the broader NSCLC patient population. Studies were evaluated for potential selection bias, particularly in terms of how participants were recruited and whether inclusion criteria were clearly defined.

4. Comparability: The comparability of study groups was assessed by examining whether studies controlled for confounding variables, such as age, gender, comorbidities, and treatment history. The presence of appropriate control groups and statistical adjustments for confounders were key factors in this evaluation.

5. Outcome Assessment: The reliability of outcome measures, such as survival rates and adverse events, was scrutinized. Studies were evaluated based on the objectivity and consistency of outcome measurement, as well as the adequacy of follow-up duration to capture meaningful clinical outcomes.

6. Data Completeness: The completeness of data reporting was assessed, including the extent of missing data and how it was addressed in the analysis. Studies with high levels of missing data or inadequate handling of such data were considered to have a higher risk of bias.

7. Bias Assessment: A comprehensive bias assessment was conducted to identify and address potential biases in the studies. This included examining selection bias, performance bias, detection bias, and attrition bias, ensuring a thorough evaluation of the internal validity of the studies.

8. Publication Bias: While not directly assessed through the NOS, potential publication bias was considered by examining the diversity of publication sources and the inclusion of grey literature, such as conference abstracts and registry data, to mitigate the risk of over-representing positive findings. Funnel plots and statistical tests, such as Egger's test, were also utilized to detect asymmetry indicative of publication bias.

9. Quality Rating: Each study was independently assessed by two reviewers, and discrepancies in quality ratings were resolved through discussion or consultation with a third reviewer. This process ensured a consistent and unbiased evaluation of study quality.

10. Sensitivity Analysis: To assess the robustness of the findings, sensitivity analyses were conducted by excluding studies with a high risk of bias. This approach helped determine the impact of study quality on the overall conclusions of the review.

By implementing these comprehensive quality assessment procedures, this SLR aims to provide a credible synthesis of real-world evidence on NSCLC therapies, thereby supporting informed clinical decision-making and policy development. The rigorous evaluation of study quality enhances the reliability of the review's conclusions regarding the effectiveness, safety, and applicability of novel NSCLC treatments in diverse patient populations.

# 8. Data Synthesis

Data Synthesis

The data synthesis for this systematic literature review (SLR) was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring a comprehensive and systematic approach to summarizing the findings from included studies. The synthesis process involved both qualitative and quantitative methods to provide a robust overview of real-world evidence (RWE) on non-small cell lung cancer (NSCLC) therapies.

1. Narrative Synthesis:   
• A narrative synthesis was employed to qualitatively summarize the key findings across studies. This approach facilitated the integration of diverse study designs and outcomes, highlighting patterns and themes in treatment effectiveness, safety profiles, and patient characteristics.  
• The narrative synthesis focused on comparing the effectiveness of targeted therapies, immunotherapies, and standard chemotherapy in real-world settings, emphasizing differences in survival rates, progression-free survival, and quality of life among various NSCLC sub-populations.

2. Quantitative Synthesis (Meta-Analysis):  
• Where appropriate, a meta-analysis was conducted using random-effects models to quantitatively synthesize data on treatment outcomes. This approach accounted for heterogeneity among studies, providing pooled estimates of overall survival and progression-free survival.  
• The I² statistic was used to assess heterogeneity, with values above 50% indicating substantial heterogeneity. Subgroup analyses were performed to explore potential sources of heterogeneity, such as differences in patient demographics, treatment regimens, and study settings.

3. Safety and Tolerability:  
• Data on adverse events and safety profiles were synthesized to provide a comprehensive understanding of the risk-benefit profile of NSCLC therapies in real-world populations. The synthesis included the incidence and severity of adverse events, as well as treatment discontinuation rates due to toxicity.  
• Comparative analyses were conducted to identify differential safety outcomes between targeted therapies, immunotherapies, and chemotherapy, offering insights into the tolerability of these treatments across diverse patient groups.

4. Sub-Population Insights:  
• The synthesis explored treatment outcomes and safety profiles across different NSCLC sub-populations, including variations in histological subtypes, genetic mutations, and comorbidities. This analysis aimed to identify differential responses and guide personalized treatment approaches.  
• The findings highlighted the importance of tailoring treatment strategies to specific patient characteristics, supporting the optimization of therapeutic interventions in clinical practice.

5. Sensitivity Analysis:  
• Sensitivity analyses were performed to assess the robustness of the findings by excluding studies with a high risk of bias. This approach helped determine the impact of study quality on the overall conclusions of the review, ensuring the reliability of the synthesized evidence.

6. Bias Assessment:  
• A thorough bias assessment was conducted using established tools such as the Cochrane Risk of Bias tool for randomized studies and the ROBINS-I tool for non-randomized studies. This assessment helped identify potential biases in study design, conduct, and reporting, which were considered in interpreting the findings.

7. Publication Bias:  
• Publication bias was assessed using funnel plots and Egger's test, where applicable. These methods helped evaluate the potential for selective publication of studies with positive results, ensuring a balanced representation of the evidence.

8. Limitations and Implications:  
• The synthesis acknowledged potential limitations, such as variability in study designs, differences in data reporting, and the inherent challenges of synthesizing real-world evidence. These limitations were considered in the interpretation of the findings and their implications for clinical practice and policy development.

By adhering to these rigorous data synthesis procedures, this SLR provides valuable insights into the effectiveness, safety, and applicability of novel NSCLC therapies in real-world settings. The findings contribute to a deeper understanding of treatment outcomes across diverse patient populations, supporting informed clinical decision-making and the optimization of NSCLC management strategies.