Clinical Trial Protocol

# 1. Title

Title: Systematic Literature Review of Real-World Evidence in Non-Small Cell Lung Cancer: A PRISMA-Compliant Analysis of Treatment Effectiveness, Outcomes, and Safety Profiles

# 2. Background

Background

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases globally, making it a major public health concern. Despite advancements in early detection and treatment, lung cancer remains the leading cause of cancer-related mortality worldwide. Over the past decade, the treatment landscape for NSCLC has evolved significantly with the introduction of targeted therapies and immunotherapies, offering new hope for improved patient outcomes. These novel therapies have demonstrated promising results in clinical trials, leading to their approval and integration into clinical practice.

However, the controlled environment of clinical trials often does not fully represent the diverse patient populations encountered in real-world settings. Patients in clinical practice may have different demographic characteristics, comorbidities, and treatment histories compared to those in clinical trials. As such, there is a critical need to evaluate the effectiveness and safety of these therapies in real-world clinical settings to ensure that the benefits observed in trials are translated into everyday practice.

Real-world evidence (RWE) provides valuable insights into how treatments perform outside the confines of clinical trials. It encompasses data collected from various sources such as electronic health records, insurance claims, patient registries, and observational studies. RWE can help bridge the gap between clinical trial results and clinical practice by providing information on treatment outcomes, safety profiles, and the impact of therapies on different patient subgroups.

The primary aim of this systematic literature review (SLR) is to synthesize existing RWE on the effectiveness of novel NSCLC therapies, including targeted therapies and immunotherapies, in real-world settings. By systematically reviewing and analyzing the available literature, this study seeks to provide a comprehensive understanding of treatment outcomes such as survival rates and progression-free survival, as well as safety and tolerability profiles among various NSCLC sub-populations. This knowledge is crucial for informing clinical decision-making and optimizing treatment strategies for NSCLC patients.

In summary, this SLR will contribute to the growing body of evidence on the real-world application of novel NSCLC therapies, offering insights into their effectiveness and safety across diverse patient populations. The findings will be instrumental in guiding healthcare providers, policymakers, and researchers in their efforts to improve NSCLC management and patient care.

# 3. Objectives

Study Objectives

The primary objective of this systematic literature review (SLR) is to synthesize real-world evidence (RWE) on the effectiveness and safety of novel therapies for non-small cell lung cancer (NSCLC), including targeted therapies and immunotherapies, in clinical practice. This review will adhere to the PRISMA guidelines to ensure a comprehensive and transparent synthesis of the literature. The specific objectives are as follows:

1. To evaluate the real-world effectiveness of novel NSCLC therapies by analyzing treatment outcomes such as overall survival rates and progression-free survival across diverse patient populations.  
   
2. To assess the impact of these therapies on various NSCLC sub-populations, considering factors such as demographic characteristics, comorbidities, and treatment histories, to identify potential variations in treatment efficacy and outcomes.

3. To analyze the safety and tolerability profiles of new NSCLC therapies in real-world settings, focusing on the incidence and nature of adverse events and their management in routine clinical practice.

4. To provide a comprehensive synthesis of RWE that can inform clinical decision-making, optimize treatment strategies, and guide future research and policy development in NSCLC management.

By achieving these objectives, the study aims to bridge the gap between clinical trial results and real-world clinical practice, offering valuable insights into the application of novel NSCLC therapies in diverse patient populations.

# 4. Methods

Methods

Study Design

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 comprehensive and transparent synthesis of the literature. The study focused on evaluating real-world evidence (RWE) regarding the effectiveness, treatment outcomes, and safety profiles of novel therapies for non-small cell lung cancer (NSCLC), including targeted therapies and immunotherapies.

Eligibility Criteria

Inclusion criteria were defined as follows:  
• Population: Adults diagnosed with NSCLC.  
• Interventions: Studies examining targeted therapies, immunotherapies, and standard chemotherapy treatments.  
• Outcomes: Studies reporting on survival rates, progression-free survival, quality of life, and adverse events.  
• Study Design: Observational studies, cohort studies, case-control studies, and registry data providing real-world evidence.

Exclusion criteria included:  
• Studies not published in English.  
• Studies without available full-text.  
• Clinical trials or studies not providing real-world data.

Information Sources and Search Strategy

A comprehensive search strategy was developed and executed across multiple electronic databases, including PubMed, EMBASE, and the Cochrane Library. The search strategy incorporated a combination of Medical Subject Headings (MeSH) and free-text terms related to "non-small cell lung cancer," "real-world evidence," "treatment outcomes," and "safety." The search was limited to studies published up to October 2023.

Study Selection

Two independent reviewers screened the titles and abstracts of identified studies for eligibility. Full-text articles were then assessed for inclusion based on the predefined criteria. 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, and reported outcomes (e.g., survival rates, adverse events). Any disagreements were resolved through consensus or third-party adjudication.

Risk of Bias Assessment

The risk of bias in included studies was assessed using appropriate tools for observational studies, such as the Newcastle-Ottawa Scale. This assessment was conducted independently by two reviewers, with discrepancies resolved through discussion.

Data Synthesis and Analysis

A qualitative synthesis of the extracted data was conducted to summarize the findings across different treatment categories. Where feasible, a meta-analysis was performed to quantitatively synthesize data on treatment outcomes and safety profiles. Heterogeneity among studies was assessed using the I² statistic, and subgroup analyses were conducted to explore variations in treatment effects across different patient populations.

Ethical Considerations

As this study involved the synthesis of previously published data, no ethical approval was required. However, ethical guidelines for conducting systematic reviews were adhered to throughout the study process.

Timeline

The study was conducted over a period of six months, encompassing literature search, data extraction, synthesis, and manuscript preparation.

# 5. Search Strategy

Search Strategy

The search strategy for this systematic literature review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a comprehensive and transparent approach. The strategy was designed to identify relevant studies that provide real-world evidence (RWE) on the effectiveness, treatment outcomes, and safety profiles of novel therapies for non-small cell lung cancer (NSCLC).

Information Sources:  
The following electronic databases were searched to identify relevant studies:  
• PubMed  
• EMBASE  
• Cochrane Library

Search Terms:  
The search strategy incorporated a combination of Medical Subject Headings (MeSH) and free-text terms. The key search terms included:  
• "non-small cell lung cancer" OR "NSCLC"  
• "real-world evidence" OR "RWE"  
• "treatment outcomes" OR "survival" OR "progression-free survival"  
• "safety" OR "adverse events"  
• "targeted therapies" OR "immunotherapies" OR "chemotherapy"

Search Strategy:  
The search was conducted using a structured approach, combining the above terms with Boolean operators (AND, OR) to refine the search results. The search was limited to studies published up to October 2023 to ensure the inclusion of the most recent evidence.

Eligibility Criteria:  
Studies were included if they met the following criteria:  
• Population: Adults diagnosed with NSCLC.  
• Interventions: Targeted therapies, immunotherapies, and standard chemotherapy treatments.  
• Outcomes: Reported on survival rates, progression-free survival, quality of life, or adverse events.  
• Study Design: Observational studies, cohort studies, case-control studies, and registry data providing real-world evidence.

Exclusion Criteria:  
• Studies not published in English.  
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# 6. Data Extraction

Data Extraction

Data extraction for 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 comprehensive and systematic approach. The process involved the following steps:

1. Data Extraction Form: A standardized data extraction form was developed to capture relevant information from each included study. This form was designed to ensure consistency and comprehensiveness in data collection across all studies.

2. Data Extraction Process: Two independent reviewers conducted the data extraction process to minimize bias and errors. Each reviewer independently extracted data from the eligible studies, and any discrepancies were resolved through discussion or consultation with a third reviewer.

3. Extracted Data Elements: The following key 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, and relevant clinical characteristics of the NSCLC population.  
• Intervention Details: Type of therapy (e.g., targeted therapy, immunotherapy, chemotherapy), treatment regimens, and duration of treatment.  
• Outcomes: Primary and secondary outcomes reported in the studies, including overall survival, progression-free survival, quality of life measures, and incidence of adverse events.  
• Subgroup Analyses: Data on treatment outcomes and safety profiles in specific sub-populations, such as those with particular genetic mutations or comorbidities.

4. Data Management: Extracted data were entered into a secure database to facilitate organization and analysis. The database was regularly reviewed and updated to ensure accuracy and completeness.

5. Quality Assurance: To ensure the reliability of the extracted data, a random sample of studies was re-evaluated by a third reviewer. This quality check helped confirm the consistency and accuracy of the data extraction process.

6. Risk of Bias Assessment: As part of the data extraction process, the risk of bias in each study was assessed using the Newcastle-Ottawa Scale for observational studies. This assessment was conducted independently by two reviewers, with any disagreements resolved through consensus.

The extracted data provided the foundation for the subsequent synthesis and analysis phases of the SLR, enabling a comprehensive evaluation of real-world evidence on the effectiveness, outcomes, and safety profiles of novel therapies for non-small cell lung cancer (NSCLC).

# 7. Quality Assessment

Quality Assessment

The quality assessment of the included studies in this systematic literature review (SLR) adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring a rigorous evaluation of the methodological quality and risk of bias. The assessment process involved the following key elements:

1. Assessment Tool: The Newcastle-Ottawa Scale (NOS) was employed to evaluate the quality of observational studies included in the review. This tool assesses three main domains: selection of study groups, comparability of groups, and ascertainment of outcomes. Each study was scored based on these criteria to determine its overall quality.

2. Independent Review: Two independent reviewers conducted the quality assessment to minimize bias and ensure objectivity. Each reviewer independently evaluated the included studies using the NOS, and any discrepancies in scoring were resolved through discussion or consultation with a third reviewer.

3. Criteria for Quality Assessment:  
• Selection: Evaluated 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.  
• Comparability: Assessed the comparability of cohorts based on the design or analysis, specifically considering confounding factors.  
• Outcome: Examined the assessment of outcome, adequacy of follow-up duration, and completeness of follow-up.

4. Risk of Bias: The risk of bias was categorized as low, moderate, or high based on the NOS scores. Studies with higher scores were considered to have a lower risk of bias, while those with lower scores indicated a higher risk of bias.

5. Quality Assurance: To ensure the reliability of the quality assessment process, a random sample of studies was re-evaluated by a third reviewer. This step served as a quality check to confirm the consistency and accuracy of the assessments.

6. Reporting of Quality Assessment: The results of the quality assessment were systematically reported, highlighting the strengths and limitations of the included studies. This information was used to inform the synthesis and interpretation of the findings, ensuring that conclusions drawn from the SLR were based on high-quality evidence.

The quality assessment process was integral to the SLR, providing a foundation for evaluating the robustness of the real-world evidence on the effectiveness, outcomes, and safety profiles of novel therapies for non-small cell lung cancer (NSCLC). By adhering to PRISMA guidelines and employing a systematic approach, the review aimed to deliver reliable and comprehensive insights into the real-world application of these therapies.

# 8. Data Synthesis

Data Synthesis

The data synthesis for 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 comprehensive and transparent analysis of the real-world evidence (RWE) on novel therapies for non-small cell lung cancer (NSCLC). The synthesis process involved the following steps:

1. Qualitative Synthesis:   
• A narrative synthesis was performed to summarize the findings from the included studies. This involved organizing the data into thematic categories based on the type of intervention (e.g., targeted therapies, immunotherapies, chemotherapy) and key outcomes (e.g., overall survival, progression-free survival, quality of life, adverse events).  
• The synthesis highlighted the effectiveness of novel therapies in real-world settings, providing insights into how these treatments impact survival rates and progression-free survival across diverse NSCLC patient populations. The narrative also explored variations in treatment outcomes based on demographic characteristics, comorbidities, and genetic profiles.

2. Quantitative Synthesis:  
• Where feasible, a meta-analysis was conducted to quantitatively synthesize data on treatment outcomes and safety profiles. This involved pooling data from studies that reported similar outcomes and using statistical methods to estimate overall effect sizes.  
• The meta-analysis assessed heterogeneity among studies using the I² statistic, which quantifies the degree of variability in effect estimates that is due to heterogeneity rather than chance. Subgroup analyses were performed to explore potential sources of heterogeneity, such as differences in study design, patient characteristics, and treatment regimens.

3. Safety and Tolerability Profiles:  
• The synthesis included a detailed analysis of the safety and tolerability profiles of novel NSCLC therapies in real-world settings. This involved summarizing the incidence and nature of adverse events reported in the included studies, as well as strategies for managing these events in routine clinical practice.  
• The analysis provided a comprehensive understanding of the risk-benefit profiles of these therapies, highlighting any significant safety concerns and their implications for clinical decision-making.

4. Subgroup Analyses:  
• Subgroup analyses were conducted to examine treatment outcomes and safety profiles in specific NSCLC sub-populations, such as those with particular genetic mutations (e.g., EGFR, ALK) or comorbidities. These analyses aimed to identify potential variations in treatment efficacy and safety, offering insights into personalized treatment strategies.

5. Interpretation of Findings:  
• The findings from the qualitative and quantitative syntheses were interpreted in the context of existing literature and clinical practice. The synthesis aimed to bridge the gap between clinical trial results and real-world clinical practice, providing valuable insights into the application of novel NSCLC therapies in diverse patient populations.  
• The implications of the findings for clinical practice, policy development, and future research were discussed, emphasizing the need for ongoing evaluation of real-world treatment outcomes and safety profiles.

6. Limitations:  
• The synthesis acknowledged the limitations of the included studies, such as potential biases, variability in study designs, and differences in patient populations. These limitations were considered in the interpretation of the findings and the formulation of conclusions.

By adhering to PRISMA guidelines and employing a systematic approach to data synthesis, this SLR aimed to deliver reliable and comprehensive insights into the real-world effectiveness, outcomes, and safety profiles of novel therapies for NSCLC. The findings are intended to inform clinical decision-making, optimize treatment strategies, and guide future research and policy development in NSCLC management.