Clinical Trial Protocol

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# 1.2 Background

\*\*Background\*\*

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all lung cancer cases. The disease is often diagnosed at an advanced stage, and historically, the prognosis for these patients has been poor. The standard of care for NSCLC has evolved significantly over the past decade, with the development of targeted therapies and immunotherapies that have improved patient outcomes.

Targeted therapies are designed to interfere with specific molecular targets that are involved in the growth, progression, and spread of cancer. They have revolutionized the treatment of NSCLC, particularly for patients with specific genetic mutations such as EGFR, ALK, and ROS1. Immunotherapies, on the other hand, harness the patient's own immune system to fight cancer by blocking the mechanisms that allow cancer cells to evade immune detection.

While clinical trials are essential for evaluating the efficacy and safety of new treatments, they often have strict inclusion criteria and controlled settings that may not reflect the diversity of patients and clinical practices in the real world. Real-world evidence (RWE) is derived from the analysis of data collected from routine clinical practice and can provide valuable insights into how treatments perform outside the controlled environment of clinical trials. RWE can inform healthcare decisions by providing information on treatment effectiveness, safety, and quality of life in a broader patient population.

The rationale for conducting a systematic literature review (SLR) of RWE in NSCLC is to consolidate the existing evidence on the real-world application of novel therapies. This includes understanding how these treatments are used in clinical practice, the outcomes achieved in the general patient population, and the safety profiles observed in a more diverse group of patients. By synthesizing this information, healthcare providers, patients, and policymakers can make more informed decisions regarding NSCLC management.

The SLR will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring a rigorous and transparent approach to evidence synthesis. This will involve a comprehensive search of relevant databases, strict adherence to inclusion and exclusion criteria, and a systematic process for data extraction and analysis. The findings from this SLR are expected to contribute to the growing body of knowledge on the real-world impact of novel NSCLC therapies, ultimately aiding in the optimization of treatment strategies for patients with this challenging disease.

# 1.3 Objectives

\*\*Objectives\*\*

The objectives of this systematic literature review (SLR) are designed to address critical gaps in our understanding of the real-world application and impact of novel therapies for non-small cell lung cancer (NSCLC). By focusing on real-world evidence (RWE), this study aims to complement data from randomized controlled trials, which may not fully represent the broader NSCLC patient population encountered in routine clinical practice. The specific objectives of this SLR are as follows:

1. • Primary Objective:\*\*
2. • To systematically collect and synthesize existing RWE on the effectiveness of novel NSCLC therapies in real-world clinical settings. This includes evaluating the impact of these treatments on overall survival, progression-free survival, and other relevant clinical outcomes.

2. \*\*Secondary Objectives:\*\*  
 - To assess treatment outcomes among various NSCLC sub-populations, including those defined by demographic characteristics (e.g., age, sex), disease stage, histology, and molecular or genetic markers. This will help identify any disparities in treatment effectiveness and inform personalized treatment approaches.  
 - To analyze the safety and tolerability profiles of novel NSCLC therapies when used in the general patient population. This involves reviewing adverse event data and other safety-related outcomes to understand the risk-benefit balance of these treatments in a real-world context.

3. \*\*Exploratory Objectives:\*\*  
 - To explore patterns of treatment utilization, including sequencing and combination of therapies, to gain insights into current clinical practice and potential areas for optimization.  
 - To investigate patient-reported outcomes and quality of life measures associated with novel NSCLC therapies, as these are critical components of comprehensive cancer care and may not be adequately captured in traditional clinical trial settings.

By fulfilling these objectives, the SLR aims to provide a robust and nuanced understanding of how novel NSCLC therapies are performing in real-world settings, thereby informing clinical decision-making, policy development, and future research priorities. The findings will be particularly valuable for healthcare providers seeking to optimize treatment strategies, for patients making informed choices about their care, and for healthcare systems aiming to improve outcomes for individuals with NSCLC.

# 1.4 Study Design

\*\*Study Design\*\*

This systematic literature review (SLR) is designed to comprehensively synthesize real-world evidence (RWE) on the effectiveness, safety, and patient outcomes associated with the treatment of non-small cell lung cancer (NSCLC) using novel therapies. The study will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a rigorous, methodical, and transparent approach to evidence synthesis.

The SLR will involve the following key steps:

1. • Literature Search and Screening\*\*: A systematic search of electronic databases, including PubMed, EMBASE, and the Cochrane Library, will be conducted to identify relevant studies. The search strategy will incorporate a combination of keywords and medical subject headings (MeSH) related to NSCLC, real-world evidence, treatment outcomes, and safety. The literature search will be supplemented by hand-searching reference lists of included studies and relevant review articles to identify additional studies that may not be indexed in the databases.

2. \*\*Study Selection\*\*: Identified records will be screened based on predefined inclusion and exclusion criteria. The inclusion criteria will encompass studies on adult populations diagnosed with NSCLC, interventions involving targeted therapies, immunotherapies, and standard chemotherapy treatments, and outcomes including survival, progression-free survival, quality of life, and adverse events. Studies that do not meet these criteria will be excluded. The selection process will involve an initial screening of titles and abstracts followed by a full-text review of potentially relevant studies.

3. \*\*Data Extraction\*\*: For studies meeting the inclusion criteria, data will be extracted using a standardized data extraction form. Extracted information will include study characteristics (e.g., author, year of publication, study design), patient demographics, details of interventions, and reported outcomes. Data extraction will be performed independently by at least two reviewers to minimize bias and ensure accuracy.

4. \*\*Quality Assessment\*\*: The quality of included studies will be assessed using appropriate tools depending on the study design (e.g., Newcastle-Ottawa Scale for observational studies). This will help evaluate the risk of bias and the strength of the evidence provided by the studies.

5. \*\*Data Synthesis and Analysis\*\*: The extracted data will be synthesized to create a meta-summary of findings. This will involve a narrative synthesis of the evidence, and where appropriate, a meta-analysis will be conducted to quantitatively combine data from multiple studies. Heterogeneity among studies will be assessed, and subgroup analyses may be performed to explore differences in treatment outcomes among various NSCLC sub-populations.

6. \*\*Manuscript Preparation\*\*: The findings from the SLR will be compiled into a manuscript, which will include an introduction, methods, results, discussion, and conclusion sections. The manuscript will provide a comprehensive summary of the evidence on the real-world application of novel NSCLC therapies, highlighting key findings, limitations, and implications for clinical practice and future research.

The entire process, from literature search to manuscript preparation, is expected to be completed within a 6-month timeframe. The systematic approach outlined in this study design will ensure that the SLR provides a robust and comprehensive understanding of the real-world impact of novel NSCLC therapies, contributing valuable insights to the field of oncology.

# 1.5 Population

\*\*Population\*\*

The population of interest for this systematic literature review (SLR) encompasses a diverse group of adult individuals diagnosed with non-small cell lung cancer (NSCLC). NSCLC is a heterogeneous disease, with patients presenting a wide range of demographic characteristics, disease stages, histological subtypes, and molecular profiles. This variability in patient characteristics can significantly influence treatment responses and outcomes. Therefore, the SLR will aim to capture and analyze data across this broad spectrum of the NSCLC patient population.

\*\*Key Inclusion Criteria for Population:\*\*

1. • Adults with NSCLC\*\*: The review will focus on studies involving adult patients (aged 18 years and older) who have been diagnosed with NSCLC. This includes all stages of the disease, from early-stage to advanced or metastatic NSCLC.

2. \*\*Diverse Sub-populations\*\*: The SLR will seek to include studies that report on various sub-populations within the NSCLC patient cohort. This will enable an assessment of treatment outcomes across different demographic groups (e.g., age, sex, ethnicity), disease characteristics (e.g., stage, histology), and molecular or genetic alterations (e.g., EGFR mutations, ALK rearrangements).

3. \*\*Real-World Clinical Settings\*\*: Only studies that provide real-world evidence (RWE) will be included. This encompasses observational studies, retrospective analyses, registry data, and prospective cohorts that reflect routine clinical practice outside of the controlled environment of randomized clinical trials.

4. \*\*All Lines of Therapy\*\*: The review will consider studies that examine first-line treatment as well as subsequent lines of therapy, recognizing that the NSCLC treatment landscape often involves multiple lines of treatment over the course of the disease.

5. \*\*Treatment Modalities\*\*: Studies that report on the use of targeted therapies, immunotherapies, and standard chemotherapy treatments will be included. This will allow for a comprehensive evaluation of the current treatment modalities in real-world settings.

\*\*Exclusion Criteria for Population:\*\*

1. • Non-Adult Populations\*\*: Studies focusing exclusively on pediatric populations or those that do not specify the age of participants will be excluded.

2. \*\*Non-NSCLC Histologies\*\*: Studies that do not differentiate between NSCLC and other types of lung cancer, such as small cell lung cancer (SCLC), will not be included in the review.

3. \*\*Clinical Trial Data\*\*: While randomized controlled trials (RCTs) are valuable for assessing the efficacy and safety of treatments under controlled conditions, they will be excluded from this review to maintain a focus on RWE.

4. \*\*Case Reports and Case Series\*\*: Single case reports and small case series will be excluded due to their limited generalizability and higher risk of bias.

5. \*\*Non-English Language Studies\*\*: Studies published in languages other than English may be excluded if translation resources are not available.

By adhering to these inclusion and exclusion criteria, the SLR will aim to provide a comprehensive and representative synthesis of RWE on the effectiveness, safety, and patient outcomes associated with the treatment of NSCLC in real-world clinical practice. The findings will help to identify potential disparities in treatment effectiveness and inform personalized approaches to NSCLC management.

# 1.6 Procedures

\*\*Procedures\*\*

1. • Literature Search and Screening Procedures\*\*:
2. • A systematic and comprehensive search will be conducted across multiple electronic databases, including PubMed, EMBASE, and the Cochrane Library. The search will be designed to capture all relevant studies that meet the inclusion criteria.
3. • Search terms and strategies will be developed to include a combination of keywords and medical subject headings (MeSH) related to NSCLC, real-world evidence, treatment outcomes, and safety.
4. • The search will be supplemented by hand-searching the reference lists of included studies and relevant review articles to ensure the capture of additional studies not indexed in the databases.
5. • Duplicate studies will be removed, and the remaining records will be screened for relevance based on titles and abstracts, followed by a full-text review of selected articles.

2. \*\*Study Selection Procedures\*\*:  
 - Two independent reviewers will screen the studies against the predefined inclusion and exclusion criteria. Discrepancies between reviewers will be resolved through discussion or consultation with a third reviewer if necessary.  
 - 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.

3. \*\*Data Extraction Procedures\*\*:  
 - A standardized data extraction form will be developed to systematically collect information from each included study. Data extracted will include study characteristics, patient demographics, intervention details, and outcomes.  
 - Data extraction will be performed independently by at least two reviewers to ensure accuracy and minimize bias. Any disagreements will be resolved by consensus or by involving a third reviewer.

4. \*\*Quality Assessment Procedures\*\*:  
 - The quality of each included study will be assessed using appropriate tools, such as the Newcastle-Ottawa Scale for observational studies, to evaluate the risk of bias and the validity of the findings.  
 - The quality assessment will be conducted independently by two reviewers, with disagreements resolved by discussion or by involving a third reviewer.

5. \*\*Data Synthesis and Analysis Procedures\*\*:  
 - A narrative synthesis of the findings will be conducted to summarize the evidence from the included studies. This will involve describing the study characteristics, patient populations, interventions, and outcomes.  
 - Where data permits, a meta-analysis will be performed to quantitatively combine the results of studies that are sufficiently homogenous in terms of study design, population, interventions, and outcomes.  
 - Statistical heterogeneity will be assessed using the I² statistic, and subgroup analyses may be conducted to explore differences in treatment outcomes among various NSCLC sub-populations.  
 - Sensitivity analyses may be performed to assess the robustness of the findings by excluding studies with a high risk of bias.

6. \*\*Manuscript Preparation Procedures\*\*:  
 - The results of the systematic literature review will be compiled into a manuscript following the structure of introduction, methods, results, discussion, and conclusion.  
 - The manuscript will be prepared in accordance with the PRISMA guidelines and will include a detailed description of the methods used for literature search, study selection, data extraction, quality assessment, and data synthesis.  
 - The manuscript will undergo internal review by the research team before submission to a peer-reviewed journal for publication.

7. \*\*Timeline and Milestones\*\*:  
 - The entire systematic literature review process will be tracked against a predefined timeline with milestones for each key stage, including literature search, study selection, data extraction, analysis, and manuscript preparation.  
 - Regular team meetings will be held to monitor progress, address any challenges, and ensure adherence to the timeline.  
 - The estimated completion time for the systematic literature review is 6 months from the initiation of the literature search to the submission of the manuscript for publication.

By following these procedures, the systematic literature review will provide a rigorous and comprehensive synthesis of real-world evidence on the effectiveness, safety, and patient outcomes associated with novel therapies for NSCLC, thereby contributing to the evidence base for clinical decision-making and policy development.

# 1.7 Statistical

\*\*Statistical Analysis Plan\*\*

1. • Overview of Statistical Methods\*\*:
2. • The statistical analysis for this systematic literature review (SLR) will be conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and will adhere to the recommendations for meta-analyses where applicable. The primary focus will be to summarize and synthesize data across studies to provide a comprehensive understanding of real-world treatment outcomes in NSCLC.

2. \*\*Data Management\*\*:  
 - Extracted data will be managed using statistical software such as R or STATA. A database will be created to compile all relevant data points for statistical analysis. Data will be double-checked for accuracy and completeness before analysis.

3. \*\*Descriptive Statistics\*\*:  
 - Descriptive statistics will be used to summarize patient characteristics, study designs, interventions, and outcomes. Frequencies and percentages will be reported for categorical variables, while means, medians, standard deviations, and interquartile ranges will be used for continuous variables.

4. \*\*Meta-analysis\*\*:  
 - If data are sufficiently homogenous, a meta-analysis will be performed to quantitatively synthesize the results of individual studies. The choice of fixed or random effects models will be based on the assessment of heterogeneity among studies.  
 - Pooled effect sizes will be calculated for outcomes such as overall survival, progression-free survival, and adverse events. For dichotomous outcomes, risk ratios (RR) or odds ratios (OR) with 95% confidence intervals (CI) will be used. For continuous outcomes, mean differences (MD) or standardized mean differences (SMD) with 95% CI will be reported.

5. \*\*Assessment of Heterogeneity\*\*:  
 - Heterogeneity among studies will be evaluated using the I² statistic and the Chi-square test. An I² value greater than 50% or a p-value less than 0.10 in the Chi-square test will indicate substantial heterogeneity.  
 - Sources of heterogeneity will be explored through subgroup analyses based on factors such as patient demographics, disease stage, and type of intervention.

6. \*\*Subgroup and Sensitivity Analyses\*\*:  
 - Subgroup analyses will be conducted to investigate differences in treatment outcomes across various patient sub-populations and treatment modalities.  
 - Sensitivity analyses will be performed to assess the robustness of the meta-analysis results by excluding studies with a high risk of bias or by using alternative statistical methods.

7. \*\*Publication Bias\*\*:  
 - The potential for publication bias will be assessed using funnel plots and Egger's test. If publication bias is detected, appropriate methods such as trim-and-fill analysis will be employed to adjust the results.

8. \*\*Statistical Software\*\*:  
 - All statistical analyses will be conducted using appropriate software, such as R (R Foundation for Statistical Computing) or STATA (StataCorp LLC).

9. \*\*Reporting of Results\*\*:  
 - Results of the statistical analyses will be reported in accordance with the PRISMA guidelines. This will include detailed information on the statistical methods used, the results of the meta-analyses, subgroup analyses, sensitivity analyses, and assessments of publication bias.

10. \*\*Interpretation of Findings\*\*:  
 - The statistical findings will be interpreted in the context of the existing literature and the quality of the included studies. The implications of the findings for clinical practice, policy development, and future research will be discussed.

11. \*\*Timeline for Statistical Analysis\*\*:  
 - The statistical analysis will be conducted following the completion of data extraction and quality assessment. A timeline will be established to ensure that the analysis is completed within the projected 6-month timeframe for the SLR.

By following this statistical analysis plan, the SLR will provide a methodologically sound and comprehensive synthesis of real-world evidence on the effectiveness and safety of novel therapies for NSCLC, contributing to the evidence base for optimizing treatment strategies in clinical practice.

# 1.8 Safety

\*\*Safety Analysis Plan\*\*

1. • Overview of Safety Analysis\*\*:
2. • The safety analysis within this systematic literature review (SLR) will focus on the safety and tolerability profiles of novel therapies for non-small cell lung cancer (NSCLC) in real-world settings. The analysis will synthesize data on adverse events (AEs), serious adverse events (SAEs), and treatment discontinuations due to toxicity.

2. \*\*Data Collection for Safety Outcomes\*\*:  
 - Safety outcomes will be extracted from the included studies using a standardized data extraction form. Relevant safety data will include the type, frequency, severity, and timing of AEs and SAEs, as well as any measures taken to manage these events.

3. \*\*Categorization of Adverse Events\*\*:  
 - Adverse events will be categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) or other relevant classification systems used in the included studies. This will allow for a standardized approach to comparing safety outcomes across studies.

4. \*\*Descriptive Analysis of Safety Data\*\*:  
 - Descriptive statistics will be used to summarize the safety data, including the number and percentage of patients experiencing AEs and SAEs, and the distribution of AEs by severity grade. The analysis will also report on the proportion of patients discontinuing treatment due to AEs.

5. \*\*Meta-analysis of Safety Outcomes\*\*:  
 - If data are sufficiently homogenous, a meta-analysis will be conducted for specific AEs and SAEs to estimate the pooled incidence rates. Pooled risk ratios (RR) or odds ratios (OR) with 95% confidence intervals (CI) will be calculated for comparative safety analyses.

6. \*\*Subgroup Analysis for Safety Outcomes\*\*:  
 - Subgroup analyses will be conducted to explore potential differences in safety profiles among various patient sub-populations, such as those defined by age, sex, disease stage, and specific treatment regimens.

7. \*\*Assessment of Reporting Bias in Safety Outcomes\*\*:  
 - The potential for reporting bias in safety outcomes will be assessed by examining the completeness and consistency of AE reporting across studies. Studies that do not adequately report safety data may be excluded from the meta-analysis.

8. \*\*Sensitivity Analysis for Safety Data\*\*:  
 - Sensitivity analyses will be performed to assess the impact of study quality on the safety findings. This may involve excluding studies with a high risk of bias or those that do not use standardized definitions for AEs.

9. \*\*Narrative Synthesis of Safety Findings\*\*:  
 - In addition to quantitative analyses, a narrative synthesis will be provided to describe the safety profiles of novel NSCLC therapies in real-world settings. This will include a discussion of the clinical implications of the safety findings and recommendations for monitoring and managing AEs in clinical practice.

10. \*\*Reporting of Safety Analysis\*\*:  
 - The results of the safety analysis will be reported in accordance with the PRISMA guidelines. This will include detailed information on the methods used for data extraction, categorization of AEs, and statistical analyses, as well as a comprehensive presentation of the safety outcomes.

11. \*\*Timeline for Safety Analysis\*\*:  
 - The safety analysis will be conducted concurrently with the effectiveness analysis, following the completion of data extraction and quality assessment. A timeline will be established to ensure that the safety analysis is completed within the projected 6-month timeframe for the SLR.

By following this safety analysis plan, the SLR will provide a detailed and methodologically rigorous synthesis of the safety and tolerability of novel therapies for NSCLC in real-world clinical practice, contributing to the evidence base for risk-benefit assessments and informed decision-making in the management of NSCLC.