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. NSCLC encompasses a heterogeneous group of histologies, with adenocarcinoma, squamous cell carcinoma, and large cell carcinoma being the most common subtypes. The complexity of NSCLC is further compounded by the presence of various genetic mutations that drive tumor growth, such as mutations in the epidermal growth factor receptor (EGFR) gene, anaplastic lymphoma kinase (ALK) rearrangements, and others.

Traditionally, the mainstay of NSCLC treatment has been surgery, radiation, and platinum-based chemotherapy. However, the last two decades have witnessed a paradigm shift with the introduction of targeted therapies and immunotherapies. These novel treatments have significantly improved outcomes for patients with advanced NSCLC, particularly those with specific genetic alterations. Targeted therapies, such as tyrosine kinase inhibitors (TKIs), are designed to attack cancer cells with particular genetic markers, while immunotherapies, including checkpoint inhibitors, aim to enhance the body's immune response against cancer cells.

Despite the promise of these new therapies, there is a growing recognition that clinical trial data may not fully capture the nuances of treatment effectiveness and safety in the broader, more heterogeneous real-world patient population. Clinical trials often have stringent inclusion criteria, which can exclude patients with comorbidities, older age, or varying performance statuses that are commonly seen in routine clinical practice. Consequently, there is a pressing need to examine the real-world evidence (RWE) to understand how these novel therapies perform outside the controlled environment of clinical trials.

Real-world evidence refers to the data regarding the use and potential benefits or risks of a medical product derived from analysis of real-world data (RWD), which includes a variety of data sources such as electronic health records (EHRs), claims and billing activities, product and disease registries, and patient-generated data. RWE can provide valuable insights into treatment outcomes, patient populations, and safety profiles in a more generalizable setting.

The rationale for conducting a systematic literature review (SLR) of RWE in NSCLC is to synthesize the existing evidence on the effectiveness, safety, and patient outcomes associated with the use of novel therapies in routine clinical practice. By systematically gathering and analyzing data from a range of studies, this SLR aims to provide a comprehensive overview of the current state of NSCLC treatment in the real-world context, thereby informing clinicians, patients, and healthcare decision-makers.

Given the rapid evolution of the treatment landscape in NSCLC and the importance of RWE in shaping clinical and policy decisions, this SLR is both timely and necessary. It will serve to bridge the gap between clinical research and everyday healthcare practice, ultimately contributing to improved patient care and outcomes in NSCLC.

# 1.3 Objectives

\*\*Objectives\*\*

The primary objectives of this systematic literature review (SLR) are to critically evaluate and synthesize the existing real-world evidence (RWE) on the effectiveness, safety, and patient outcomes of novel therapies for non-small cell lung cancer (NSCLC) in real-world clinical settings. The specific objectives are outlined as follows:

1. • To Evaluate the Effectiveness of Novel NSCLC Therapies in Real-World Settings:\*\*
2. • To systematically review and analyze RWE to determine the real-world effectiveness of targeted therapies and immunotherapies in the treatment of NSCLC.
3. • To compare the effectiveness of these novel therapies with standard chemotherapy treatments as reported in real-world studies.

2. \*\*To Assess Treatment Outcomes Among Various Sub-Populations within NSCLC:\*\*  
 - To identify and evaluate the treatment outcomes, including overall survival rates and progression-free survival, among different NSCLC patient sub-populations (e.g., based on genetic mutations, histological subtypes, and demographic factors).  
 - To explore the impact of novel therapies on the quality of life for NSCLC patients in the real-world setting.

3. \*\*To Analyze the Safety and Tolerability Profiles of New Therapies in Real-World NSCLC Populations:\*\*  
 - To review adverse events and safety data related to the use of targeted therapies and immunotherapies in real-world clinical practice.  
 - To assess the tolerability of these treatments across diverse patient populations, including those with comorbidities or varying performance statuses.

Through these objectives, the SLR aims to provide a comprehensive and updated synthesis of RWE that will contribute to the understanding of how novel NSCLC therapies are performing in routine clinical practice. This information is critical for healthcare providers, patients, and policy-makers to make informed decisions regarding NSCLC management and to identify areas where further research or improvement in care is needed.

# 1.4 Methods

\*\*Methods\*\*

\*\*Methodological Framework\*\*  
This systematic literature review (SLR) will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and reproducibility of the review process. The PRISMA statement will guide the identification, screening, eligibility assessment, and inclusion of studies relevant to the research questions.

\*\*Eligibility Criteria\*\*  
Studies will be selected according to the following criteria:

1. • Population\*\*: Adults diagnosed with non-small cell lung cancer (NSCLC).
2. • Interventions\*\*: Real-world application of targeted therapies, immunotherapies, and standard chemotherapy treatments.
3. • Comparators\*\*: Any other standard of care or placebo treatments as reported in the studies.
4. • Outcomes\*\*: Primary outcomes will include overall survival, progression-free survival, quality of life, and adverse events. Secondary outcomes may include treatment adherence and cost-effectiveness.
5. • Study Design\*\*: Observational studies, registry analyses, retrospective and prospective cohort studies, case-control studies, and cross-sectional studies providing real-world evidence will be included. Randomized controlled trials (RCTs) will be excluded as they do not reflect real-world settings.
6. • Time Frame\*\*: No restrictions on publication date will be applied to capture the full range of available RWE.
7. • Language\*\*: Studies published in English will be included.

\*\*Information Sources and Search Strategy\*\*  
A comprehensive literature search will be conducted across multiple electronic databases, including PubMed, EMBASE, and the Cochrane Library. The search strategy will employ a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to NSCLC, real-world evidence, treatment outcomes, and safety. The search will be supplemented by hand-searching reference lists of included studies and relevant review articles. A draft search strategy will be peer-reviewed by experts in the field to ensure comprehensiveness.

\*\*Study Selection\*\*  
All identified records will be collated and uploaded into a reference management software where duplicates will be removed. Two independent reviewers will screen titles and abstracts against the inclusion criteria. The full texts of potentially eligible studies will be retrieved and assessed for eligibility by the same reviewers. Any disagreements will be resolved through discussion or consultation with a third reviewer if necessary.

\*\*Data Extraction\*\*  
Data extraction will be performed independently by two reviewers using a standardized data extraction form. Extracted information will include study characteristics (authors, year of publication, country), study design, participant demographics, details of interventions and comparators, outcomes, and key findings. Any discrepancies in data extraction will be resolved through discussion or by involving a third reviewer.

\*\*Quality Assessment\*\*  
The quality of included studies will be appraised using appropriate tools based on study design. For observational studies, the Newcastle-Ottawa Scale (NOS) will be used to assess the risk of bias. The quality assessment will be conducted independently by two reviewers, with disagreements resolved by consensus or third-party adjudication.

\*\*Data Synthesis and Analysis\*\*  
A narrative synthesis of the findings from the included studies will be provided, structured around the effectiveness, safety, and patient outcomes of NSCLC therapies in real-world settings. If data permits, a meta-analysis will be conducted to pool quantitative data using appropriate statistical techniques. Heterogeneity will be assessed using the I^2 statistic, and publication bias will be evaluated through funnel plot analysis and Egger's test, where applicable.

\*\*Expected Outcomes\*\*  
The SLR will result in a comprehensive synthesis of RWE on the effectiveness, safety, and patient outcomes of novel therapies for NSCLC in real-world clinical settings. This will provide valuable insights for healthcare providers, patients, and policymakers.

\*\*Timeline\*\*  
The review process is expected to be completed within 6 months from the commencement of the literature search, with interim milestones for study selection, data extraction, and analysis to ensure timely progress.

\*\*Ethical Considerations\*\*  
As this SLR will utilize publicly available data from previously conducted studies, ethical approval is not required. However, the review will be conducted with strict adherence to ethical standards of reporting and data usage.

# 1.5 Search Strategy

\*\*Search Strategy\*\*

\*\*Database Selection\*\*  
To ensure a comprehensive literature search, we will conduct a systematic search across multiple electronic databases known for their extensive coverage of medical and health sciences literature. The databases to be searched include:

1. • PubMed/MEDLINE\*\*: A primary resource for biomedical literature, providing access to a vast array of journals and articles in the field of medicine and healthcare.
2. • EMBASE\*\*: A database renowned for its extensive coverage of drug research, pharmacology, and toxicology literature, including conference abstracts and European literature not always indexed in PubMed.
3. • The Cochrane Library\*\*: A collection of high-quality databases, including the Cochrane Database of Systematic Reviews, which is essential for identifying systematic reviews and meta-analyses relevant to our research question.

\*\*Search Terms and String Construction\*\*  
The search strategy will be developed using a combination of Medical Subject Headings (MeSH) terms and free-text keywords. The search terms will be related to non-small cell lung cancer, real-world evidence, treatment outcomes, and safety. The search will be designed to capture a wide range of studies providing real-world data on the effectiveness and safety of NSCLC therapies.

A preliminary set of search terms will include:

1. • "Non-Small Cell Lung Carcinoma" OR "NSCLC"
2. • "Real-World Evidence" OR "Real-Life Data" OR "Observational Data"
3. • "Treatment Outcomes" OR "Survival" OR "Progression-Free Survival"
4. • "Safety" OR "Adverse Events" OR "Tolerability"
5. • "Targeted Therapies" OR "Immunotherapies" OR "Chemotherapy"

The search strings will be constructed by combining these terms using the Boolean operators "AND" and "OR" to ensure a thorough search. An example search string for PubMed/MEDLINE might look like this:

("Non-Small Cell Lung Carcinoma" [MeSH] OR "NSCLC") AND ("Real-World Evidence" [Title/Abstract] OR "Real-Life Data" [Title/Abstract] OR "Observational Data" [Title/Abstract]) AND ("Treatment Outcomes" [Title/Abstract] OR "Survival" [Title/Abstract] OR "Progression-Free Survival" [Title/Abstract]) AND ("Safety" [Title/Abstract] OR "Adverse Events" [Title/Abstract] OR "Tolerability" [Title/Abstract]) AND ("Targeted Therapies" [Title/Abstract] OR "Immunotherapies" [Title/Abstract] OR "Chemotherapy" [Title/Abstract])

\*\*Search Refinement\*\*  
The search strategy will be peer-reviewed by experts in the field of oncology and information science to ensure comprehensiveness and relevance. Adjustments will be made based on their feedback.

\*\*Supplementary Search Methods\*\*  
In addition to database searches, we will hand-search the reference lists of included studies and relevant review articles to identify additional studies that may not be indexed in the selected databases. We will also search for grey literature, such as conference abstracts and clinical trial registries, to identify unpublished studies and ongoing research.

\*\*Search Limits\*\*  
The search will not be limited by publication date to capture the full range of available RWE. However, we will restrict the search to studies published in English due to resource constraints.

\*\*Documentation of Search Strategy\*\*  
All search activities, including the search date, database, search terms used, and the number of records retrieved, will be documented in detail to ensure reproducibility. This documentation will be included in the final report of the systematic literature review.

# 1.6 Selection Criteria

\*\*Selection Criteria\*\*

\*\*Inclusion Criteria\*\*

To be included in this systematic literature review, studies must meet the following criteria:

1. • Population\*\*: Studies must focus on adults diagnosed with non-small cell lung cancer (NSCLC). There will be no restrictions on NSCLC subtypes, stages, or genetic mutations.

2. \*\*Interventions\*\*: The review will include studies that report on the real-world application of targeted therapies, immunotherapies, and standard chemotherapy treatments for NSCLC.

3. \*\*Outcomes\*\*: Studies must report on at least one of the following outcomes: overall survival, progression-free survival, quality of life, and adverse events. Studies that provide additional relevant outcomes such as treatment adherence and cost-effectiveness will also be considered.

4. \*\*Study Design\*\*: Observational studies, including registry analyses, retrospective and prospective cohort studies, case-control studies, and cross-sectional studies, will be included. These studies should provide real-world evidence on the use and outcomes of NSCLC treatments.

5. \*\*Language\*\*: Studies must be published in English to be included in the review.

\*\*Exclusion Criteria\*\*

Studies will be excluded based on the following criteria:

1. • Population\*\*: Studies focusing on pediatric populations, small cell lung cancer, or other types of cancers will be excluded.

2. \*\*Interventions\*\*: Clinical trials, including randomized controlled trials (RCTs), will be excluded as they do not reflect real-world settings.

3. \*\*Outcomes\*\*: Studies that do not report on the specified outcomes of interest (survival rates, progression-free survival, quality of life, and adverse events) will be excluded.

4. \*\*Study Design\*\*: Case reports, editorials, commentaries, and reviews will be excluded. Studies with insufficient data or lacking methodological details will also be excluded.

5. \*\*Language\*\*: Non-English language studies will be excluded due to resource constraints.

\*\*Screening Process\*\*

The screening process will be conducted in two stages:

1. • Title and Abstract Screening\*\*: Two independent reviewers will screen the titles and abstracts of identified records for relevance based on the inclusion and exclusion criteria. Records that do not meet the criteria will be excluded. Any discrepancies between reviewers will be resolved through discussion or by consulting a third reviewer.

2. \*\*Full-Text Screening\*\*: Full texts of the selected abstracts will be retrieved and independently assessed by the two reviewers. Studies that meet all the inclusion criteria will be included in the review. Reasons for exclusion of full-text studies will be documented. Disagreements will be resolved through discussion or by consulting a third reviewer.

All screening decisions and the reasons for exclusion at the full-text stage will be recorded to ensure transparency and reproducibility of the review process. The PRISMA flow diagram will be used to map out the number of studies included and excluded at each stage of the screening process.

# 1.7 Data Extraction

Data Extraction

\*\*Data Collection Form\*\*

For the purpose of this systematic literature review (SLR) on real-world evidence in non-small cell lung cancer (NSCLC), a standardized data extraction form will be developed to systematically capture all relevant information from the included studies. The form will be designed to collect the following data:

1. • General Study Information\*\*: Study title, authors, year of publication, journal, and country of origin.
2. • Study Design\*\*: Type of observational study, study period, data sources, and follow-up duration.
3. • Population Characteristics\*\*: Sample size, age, sex, NSCLC subtype, stage at diagnosis, genetic mutations, and any other relevant demographic or clinical characteristics.
4. • Interventions\*\*: Specifics of targeted therapies, immunotherapies, and chemotherapy regimens used in the real-world setting.
5. • Comparators\*\*: Details of any standard care or other treatments against which the primary interventions were compared.
6. • Outcomes\*\*: Data on primary outcomes such as overall survival, progression-free survival, quality of life, and adverse events. Secondary outcomes may include treatment adherence and cost-effectiveness.
7. • Key Findings\*\*: Summary of the main results, including statistical significance and relevance to the study objectives.
8. • Quality Assessment\*\*: Risk of bias and quality of the study as assessed by standardized tools.

The form will be piloted on a small number of studies to ensure its comprehensiveness and functionality. Necessary adjustments will be made before proceeding with the full-scale data extraction.

\*\*Extraction Process\*\*

Data extraction will be conducted by two independent reviewers to minimize bias and errors. Each reviewer will extract data from the included studies using the data collection form. The following steps will outline the process:

1. • Preliminary Training\*\*: Reviewers will undergo training to familiarize themselves with the data extraction form and the specific information to be extracted.
2. • Independent Extraction\*\*: Each reviewer will independently extract data from assigned studies, ensuring that all relevant information is captured accurately and consistently.
3. • Cross-Verification\*\*: Upon completion of the independent data extraction, reviewers will compare their forms to identify any discrepancies or missing data.
4. • Resolution of Discrepancies\*\*: In cases of disagreement, reviewers will discuss to reach a consensus. If a consensus cannot be reached, a third reviewer will be consulted to make the final decision.
5. • Finalization of Data\*\*: Once all discrepancies have been resolved, the data will be finalized and prepared for analysis.

Throughout the extraction process, reviewers will maintain detailed notes on any challenges or ambiguities encountered, which will be discussed and resolved collectively. This will ensure a transparent and replicable data extraction process.

\*\*Data Management\*\*

All extracted data will be entered into a secure, electronic database. The database will be backed up regularly to prevent data loss. Access to the database will be restricted to the review team members to maintain data confidentiality and integrity.

The data extraction section of the SLR protocol will be documented in detail, including the design of the data collection form, the extraction process, and the data management strategy. This documentation will ensure that the data extraction process is transparent, systematic, and replicable for future research endeavors.

# 2.1 Quality Assessment

Quality Assessment

\*\*Overview\*\*

The quality assessment of studies included in this systematic literature review (SLR) on real-world evidence in non-small cell lung cancer (NSCLC) is a critical component of the review process. It ensures that the conclusions drawn are based on high-quality and reliable evidence. This section outlines the tools and processes that will be used to assess the methodological quality and risk of bias in the studies selected for inclusion in the review.

\*\*Quality Assessment Tools\*\*

Given the focus on observational studies in this SLR, the Newcastle-Ottawa Scale (NOS) will be employed as the primary tool for quality assessment. The NOS is specifically designed for evaluating the quality of non-randomized studies, such as cohort and case-control studies, in meta-analyses. It assesses three broad perspectives:

1. • Selection\*\*: Includes the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study.
2. • Comparability\*\*: Evaluates the comparability of cohorts based on the design or analysis, controlling for confounding factors.
3. • Outcome\*\*: Concerns the assessment of the outcome, the length and adequacy of the follow-up period, and the adequacy of follow-up of cohorts.

Each study will be judged on these criteria, and a star system will be used to provide an overall score for quality.

\*\*Quality Assessment Process\*\*

1. • Training\*\*: Reviewers will be trained in the application of the NOS to ensure consistency in the evaluation of study quality.
2. • Independent Assessment\*\*: Two independent reviewers will assess the quality of each included study. This dual assessment aims to minimize bias and enhance the reliability of the quality appraisal.
3. • Scoring\*\*: Each study will be awarded stars according to the NOS criteria. Studies will be categorized as 'high', 'moderate', or 'low' quality based on their star count.
4. • Discrepancy Resolution\*\*: Any discrepancies in quality assessment between reviewers will be discussed to reach a consensus. If consensus cannot be achieved, a third reviewer will be consulted to resolve the disagreement.
5. • Documentation\*\*: The quality assessment process and results for each study will be thoroughly documented, including the rationale for the number of stars awarded.

\*\*Risk of Bias Assessment\*\*

In addition to the NOS, a risk of bias assessment will be conducted to identify potential sources of bias within each study. This assessment will consider factors such as:

1. • Confounding variables
2. • Selection bias
3. • Information bias
4. • Reporting bias

\*\*Incorporation into Synthesis\*\*

The quality and risk of bias assessments will inform the synthesis of evidence. Studies with high risk of bias or low-quality scores may be given less weight in the analysis, or their results may be discussed separately to ensure that the conclusions of the SLR are based on the most robust evidence available.

\*\*Reporting\*\*

The results of the quality assessment will be reported in the SLR according to the PRISMA guidelines. A table summarizing the quality scores and risk of bias for each study will be included, providing transparency and allowing readers to critically appraise the robustness of the evidence base.

\*\*Continuous Monitoring\*\*

The quality assessment process will be subject to continuous monitoring and refinement. If any new quality assessment tools become relevant or if methodological advancements occur during the review process, the protocol may be updated to incorporate these changes, ensuring the highest standard of evidence appraisal.

By rigorously assessing the quality of the included studies, this SLR will provide a comprehensive and reliable synthesis of real-world evidence on the effectiveness, safety, and patient outcomes of novel therapies for NSCLC in real-world clinical settings.

# 3.1 Statistical

Statistical Analysis

\*\*Meta-analysis Methodology\*\*

If the data extracted from the included studies are sufficiently homogeneous and reported in a manner that allows for quantitative synthesis, a meta-analysis will be conducted. The meta-analysis will pool effect sizes from individual studies to estimate the overall effect of novel NSCLC therapies in real-world settings. We will use a random-effects model to account for potential heterogeneity across studies. The choice of effect measure (e.g., hazard ratio, odds ratio, mean difference) will be based on the type of outcome data reported in the studies.

\*\*Statistical Methods for Data Synthesis\*\*

For continuous outcomes such as progression-free survival, we will calculate the weighted mean difference or standardized mean difference if different scales are used. For dichotomous outcomes such as the incidence of adverse events, we will calculate the pooled odds ratio. Confidence intervals will be set at 95% for all effect measures. Statistical analyses will be performed using statistical software such as RevMan or STATA.

\*\*Heterogeneity Assessment Approach\*\*

Heterogeneity among the included studies 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 in the Chi-square test will indicate significant heterogeneity. Sources of heterogeneity will be explored through subgroup analyses and meta-regression if appropriate and if data are available.

\*\*Subgroup Analysis Plans\*\*

Subgroup analyses will be conducted to explore the potential sources of heterogeneity and to assess the consistency of treatment effects across different patient subpopulations. Subgroups may be defined by factors such as age, sex, NSCLC subtype, stage of disease, genetic mutations, and type of therapy (targeted therapies, immunotherapies, chemotherapy). The interaction between treatment effects and subgroup characteristics will be tested statistically.

\*\*Sensitivity Analysis Methods\*\*

Sensitivity analyses will be conducted to assess the robustness of the meta-analysis results. This will involve repeating the analysis using different methodological assumptions, such as excluding studies with a high risk of bias, using alternative statistical models (fixed-effect vs. random-effects), or excluding outliers. The impact of individual studies on the overall effect estimate will also be examined by omitting one study at a time.

\*\*Publication Bias Assessment\*\*

Publication bias will be assessed by visually inspecting funnel plots for asymmetry and by conducting Egger's regression test if there are a sufficient number of studies (typically at least 10). If publication bias is detected, we will use statistical methods such as trim-and-fill analysis to adjust for it.

\*\*Reporting of Statistical Analysis\*\*

The 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 heterogeneity assessments, the findings from subgroup and sensitivity analyses, and the conclusions drawn from the publication bias assessment. Forest plots will be used to graphically present the results of the meta-analyses, and tables will summarize the findings of the subgroup and sensitivity analyses.

\*\*Ethical Considerations\*\*

As this systematic literature review will be based on published data, there are no additional ethical considerations for the statistical analysis beyond the ethical conduct of research, such as avoiding data manipulation and ensuring accurate reporting of results.

\*\*Conclusion\*\*

The statistical analysis section of this systematic literature review protocol outlines the planned methodologies for synthesizing and interpreting the real-world evidence on the effectiveness, safety, and patient outcomes of novel therapies for NSCLC. By adhering to these rigorous statistical methods, we aim to provide a comprehensive and reliable synthesis of the available data.