Clinical Trial Protocol

Title

Given the provided synopsis, the following content can be generated for the specified section titles:

1. Study Title
"Systematic Literature Review of Real-World Evidence in Non-Small Cell Lung Cancer"

2. Background & Rationale
Non-small cell lung cancer (NSCLC) accounts for the majority of lung cancer diagnoses worldwide. The landscape of NSCLC treatment has been transformed by the introduction of novel targeted therapies and immunotherapies. However, clinical trials often have stringent inclusion criteria, which may not reflect the broader NSCLC patient population encountered in routine clinical practice. Real-world evidence (RWE) provides insights into the effectiveness, safety, and patient-reported outcomes of treatments in a more diverse patient population. This systematic literature review (SLR) is designed to collect and synthesize RWE to enhance our understanding of the real-world impact of NSCLC treatments, thus informing clinical decision-making and potentially guiding future research and healthcare policies.

3. Study Objectives
The objectives of this systematic literature review are threefold:
- To evaluate the real-world effectiveness of novel NSCLC therapies, including targeted therapies and immunotherapies, as well as compare these with standard chemotherapy treatments.
- To assess treatment outcomes, such as overall survival and progression-free survival, among different sub-populations of patients with NSCLC, with a focus on demographic and clinical characteristics that may influence these outcomes.
- To analyze the safety and tolerability profiles of new NSCLC therapies in real-world populations, identifying any adverse events or patterns of toxicity that may differ from those reported in clinical trials.

4. Study Design
This study will be conducted as a systematic literature review, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review will include published studies that report on real-world data concerning the treatment of NSCLC.

5. Key Inclusion Criteria

Studies will be selected based on the following inclusion criteria:
- Population: The study population includes adults who have been diagnosed with non-small cell lung cancer.
- Interventions: The review will consider studies evaluating the effectiveness and safety of targeted therapies, immunotherapies, and standard chemotherapy treatments.
- Outcomes: The primary outcomes of interest are overall survival, progression-free survival, quality of life, and adverse events.

6. Literature Search Strategy
A comprehensive literature search will be performed using databases such as PubMed, EMBASE, and the Cochrane Library. Search terms will be carefully selected to encompass "non-small cell lung cancer," "real-world evidence," "treatment outcomes," and "safety." The search strategy will be designed to capture the most relevant and recent literature on the subject.

7. Data Extraction & Analysis
Data will be extracted from the selected studies by trained reviewers using a standardized form. Extracted data will include patient demographics, treatment regimens, outcomes of interest, and study design features. A qualitative and quantitative synthesis, including a meta-summary when appropriate, will be conducted to integrate findings across studies and to identify patterns and trends in the data.

8. Expected Outcomes
The systematic literature review is expected to yield:
- A consolidated body of evidence regarding the real-world efficacy of NSCLC treatments.
- Detailed insights into treatment outcomes for specific patient subgroups, potentially revealing differential responses to therapy.
- A comprehensive profile of the safety and tolerability of new NSCLC therapies in the real-world setting.

9. Timeline
The systematic literature review is anticipated to be completed within a 6-month timeframe. This period will encompass the literature search, data extraction, analysis, and synthesis of findings, followed by the preparation and submission of a manuscript for publication.

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 clinical management of NSCLC has evolved significantly over the past decade due to the development and approval of novel therapeutic agents, including targeted therapies and immunotherapies. These advancements have led to improved patient outcomes, particularly for those with specific genetic mutations or biomarkers that can be targeted by these new treatments.

Despite the promise shown in controlled clinical trial settings, there is a recognized gap between trial results and the effectiveness of treatments in real-world clinical practice. Clinical trial populations are often not fully representative of the patient population seen in routine clinical care due to stringent inclusion and exclusion criteria. As a result, the generalizability of trial findings to the broader NSCLC population can be limited.

Real-world evidence (RWE) is derived from the analysis of data collected outside the context of randomized controlled trials, such as electronic health records, insurance claims databases, patient registries, and observational studies. RWE can provide valuable insights into the effectiveness and safety of treatments as they are used in everyday clinical settings, encompassing a more diverse patient population with comorbidities, varying treatment adherence patterns, and different healthcare systems.

The systematic literature review (SLR) proposed here is crucial to consolidate the existing RWE on NSCLC treatments, which will help to bridge the knowledge gap between clinical research and clinical practice. By synthesizing data from a range of real-world studies, this SLR aims to provide a comprehensive overview of the effectiveness, safety, and patient-reported outcomes associated with novel NSCLC therapies in the populations that are actually receiving them.

The rationale for this SLR is underpinned by the need to inform clinicians, patients, healthcare policymakers, and other stakeholders about the real-world impact of NSCLC treatments. This information is essential for making informed treatment decisions, developing guidelines, and optimizing patient care pathways. Furthermore, the findings from this SLR may identify areas where additional research is needed, potentially influencing the design of future clinical studies and RWE initiatives.

In summary, this SLR will address a critical need for synthesized RWE on NSCLC treatments, offering a more nuanced understanding of their real-world effectiveness and safety, and providing a foundation for informed decision-making in the management of NSCLC.

Objectives

3. Study Objectives

The objectives of this systematic literature review (SLR) are to comprehensively evaluate and synthesize real-world evidence (RWE) related to the treatment of non-small cell lung cancer (NSCLC). The specific objectives are as follows:

1. **To Evaluate the Real-World Effectiveness of Novel NSCLC Therapies:** This objective aims to assess how new treatment options, such as targeted therapies and immunotherapies, perform in real-world clinical settings. The review will compare the effectiveness of these novel therapies with standard chemotherapy treatments to determine their impact on patient outcomes.

2. **To Assess Treatment Outcomes Among Various Sub-Populations within NSCLC:** Recognizing that NSCLC is a heterogeneous disease, this objective seeks to evaluate treatment outcomes, including overall survival and progression-free survival, among different patient subgroups. Factors such as demographic characteristics, genetic mutations, and biomarker status will be considered to understand how these variables may influence treatment responses.

3. **To Analyze the Safety and Tolerability Profiles of New Therapies in Real-World NSCLC Populations:** This objective involves a thorough investigation of the safety profiles of novel NSCLC therapies as used in the general patient population. It will identify adverse events and patterns of toxicity that may differ from those reported in controlled clinical trials, providing a more realistic picture of the risks associated with these treatments.

These objectives will be pursued through a methodical review of the literature, following the PRISMA guidelines, to ensure that the evidence gathered is robust, relevant, and can be used to inform clinical practice, policy-making, and future research directions in the treatment of NSCLC.

Methods

9. Methods

9.1 Literature Search Strategy

The literature search will be conducted following a predefined protocol to ensure comprehensive retrieval of relevant studies. The search strategy will include a combination of MeSH terms and free-text keywords to capture the broad spectrum of RWE in NSCLC. The databases to be searched will include PubMed, EMBASE, and the Cochrane Library. Additional sources such as conference abstracts, clinical trial registries, and grey literature databases will be considered to identify unpublished studies and ongoing research.

The search will be limited to studies published in English, with no date restrictions to capture the full range of available evidence. The search strategy will be peer-reviewed by an independent expert in systematic literature reviews to ensure its robustness and completeness.

9.2 Study Selection

Following the literature search, all identified citations will be collated and uploaded into a reference management software where duplicates will be removed. Titles and abstracts will be screened by two independent reviewers against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full and their citation details imported into a data management software.

The full texts of these potentially eligible studies will be assessed in detail against the inclusion criteria by two independent reviewers. Any disagreements between reviewers will be resolved through discussion or by consulting a third reviewer. Reasons for exclusion of studies will be recorded and a PRISMA flow diagram will be generated to summarize the study selection process.

9.3 Data Extraction

Data will be extracted from included studies using a standardized data extraction tool, which will be piloted on a small number of studies and refined as necessary. The data extraction tool will capture information on study characteristics (e.g., author, year of publication, study design), participant demographics, interventions, comparators, outcomes of interest, and key findings.

Two reviewers will independently extract data from each study, with discrepancies resolved through discussion or by involving a third reviewer. Extracted data will be entered into a database for further analysis.

9.4 Quality Assessment

The quality of included studies will be assessed using appropriate tools based on the study design. For observational studies, tools such as the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies may be used. The quality assessment will evaluate the risk of bias within studies, including selection bias, performance bias, detection bias, and reporting bias.

9.5 Data Synthesis and Analysis

The data will be synthesized to provide a narrative summary of the findings from the included studies. Where possible and appropriate, meta-analytic techniques will

be used to combine data and provide pooled estimates of treatment effectiveness and safety. Heterogeneity between studies will be assessed using the I^2 statistic, and subgroup analyses will be conducted to explore potential sources of heterogeneity.

The synthesis will also consider the quality of the evidence and the applicability of the study findings to real-world clinical practice. Any gaps in the literature or areas requiring further research will be identified.

9.6 Ethical Considerations

As this study is a systematic literature review of published data, ethical approval is not required. However, the review will be conducted in accordance with ethical principles for systematic reviews, ensuring respect for the original authors' work and intellectual property.

9.7 Timeline

The systematic literature review process, from the initial literature search to the final synthesis and manuscript preparation, is expected to be completed within a 6-month timeframe. This includes time allocated for potential revisions and peer review prior to submission for publication.

Search Strategy

6. Literature Search Strategy

The search strategy for this systematic literature review (SLR) on real-world evidence in non-small cell lung cancer (NSCLC) is designed to be comprehensive and systematic, ensuring the inclusion of relevant studies that meet the predefined inclusion criteria. The following steps outline the search strategy:

6.1 Database and Source Selection
The literature search will be conducted in the following electronic databases and sources:
- PubMed/MEDLINE
- EMBASE
- The Cochrane Library
Additional sources to be considered include:
- Conference proceedings and abstracts
- Clinical trial registries (e.g., ClinicalTrials.gov)
- Grey literature databases (e.g., OpenGrey)

6.2 Search Terms and Strategy

The search strategy will employ a combination of Medical Subject Headings (MeSH) and free-text terms to ensure a broad and thorough search. The search terms will include but are not limited to:
- "Non-Small Cell Lung Carcinoma" OR "NSCLC"
- "Real-World Evidence" OR "Real-World Data" OR "Observational Study"
- "Treatment Outcomes" OR "Survival" OR "Progression-Free Survival"
- "Safety" OR "Adverse Events" OR "Tolerability"
- "Targeted Therapy" OR "Immunotherapy" OR "Chemotherapy"

Boolean operators (AND, OR) will be used to combine search terms, and search filters will be applied to select studies involving human subjects and articles published in English. The search strategy will be adapted for each database to account for differences in indexing terms and search functionalities.

6.3 Search Limits
The search will not be restricted by publication date to capture the full extent of available evidence. However, studies will be limited to those published in English due to resource constraints.

6.4 Search Execution
The search will be executed by an experienced medical librarian or researcher with expertise in conducting systematic literature searches. The search strategy will be peer-reviewed by an independent expert to ensure its comprehensiveness and reproducibility.

6.5 Record Management
All records retrieved from the search will be imported into a reference management software (e.g., EndNote, Zotero) for deduplication and organization. The reference manager will be used to track the selection process and manage citations throughout the review.

6.6 Search Updates
To ensure the inclusion of the most recent literature, the search will be updated before the final analysis, and any new relevant studies will be incorporated into the review.

6.7 Documentation
The search process will be thoroughly documented, including the search strategy for each database, the number of records retrieved, and the date of the search. This documentation will be included in the final report to ensure transparency and reproducibility of the search strategy.

6.8 Supplementary Search Methods
Hand-searching of reference lists of included studies and relevant reviews will be

conducted to identify additional studies not captured by the electronic search. Experts in the field may also be consulted for potential additional sources of data.

By adhering to this rigorous and systematic search strategy, the SLR aims to provide a comprehensive synthesis of real-world evidence on the effectiveness and safety of treatments for NSCLC, addressing the study objectives and informing clinical practice and policy.

Selection Criteria

10. Selection Criteria

10.1 Inclusion Criteria

For a study to be included in this systematic literature review (SLR), it must meet the following criteria:

1. **Population**: The study must involve adults (18 years and older) who have been diagnosed with non-small cell lung cancer (NSCLC). Studies should clearly define diagnostic criteria and staging.

2. **Interventions**: Studies must evaluate the real-world use of targeted therapies, immunotherapies, or standard chemotherapy treatments for NSCLC. The intervention should be clearly described, including dosage, treatment regimen, and duration.

3. **Comparators**: If applicable, comparators should include other standard treatments, placebo, or no treatment. Studies with and without comparators will be considered.

4. **Outcomes**: The primary outcomes of interest for this review are overall survival, progression-free survival, quality of life, and adverse events. Studies must report on at least one of these outcomes to be included.

5. **Study Design**: Observational studies, including cohort studies, case-control studies, and cross-sectional studies, as well as registry analyses and retrospective studies that provide real-world evidence on the treatment of NSCLC.

6. **Publication Type**: Peer-reviewed full-text articles, conference abstracts, and grey literature that report primary data.

7. **Language**: Studies published in English.

10.2 Exclusion Criteria

Studies will be excluded based on the following criteria:

1. **Population**: Studies focusing on pediatric populations, non-NSCLC lung cancers, or lacking clear diagnostic criteria for NSCLC.

2. **Interventions**: Studies that do not focus on targeted therapies, immunotherapies, or standard chemotherapy treatments for NSCLC.

3. **Outcomes**: Studies that do not report on the predefined primary outcomes of interest.

4. **Study Design**: Randomized controlled trials (RCTs), case reports, editorials, commentaries, and reviews will be excluded, as the focus is on real-world evidence.

5. **Publication Type**: Abstracts or reports without sufficient data, unpublished data, or non-peer-reviewed literature.

6. **Language**: Non-English language studies, due to resource constraints.

10.3 Screening Process

The study selection process will involve two levels of screening:

1. **Initial Screening**: Titles and abstracts will be independently screened by two reviewers to identify studies that potentially meet the inclusion criteria. Any discrepancies at this stage will be resolved through discussion or by involving a third reviewer.

2. **Full-Text Screening**: Full-text articles of the selected abstracts will be retrieved and independently assessed for eligibility by two reviewers. Disagreements will be resolved through discussion or consultation with a third reviewer.

The reasons for excluding studies at the full-text screening stage will be documented, and a PRISMA flow diagram will be used to illustrate the study selection process.

10.4 Data Management

A reference management tool will be used to organize and manage all studies identified during the search process. This tool will facilitate the removal of duplicates, screening of studies, and documentation of the selection process.

10.5 Amendments to Selection Criteria

Any amendments to the selection criteria after the review process begins will be documented and published with the final review to ensure transparency and reproducibility of the methods.

Data Extraction

7. Data Extraction & Analysis

The data extraction and analysis process for this systematic literature review (SLR) on real-world evidence in non-small cell lung cancer (NSCLC) will be conducted in a structured and systematic manner to ensure the accurate and reliable synthesis of information from the included studies. The following steps outline the data extraction and analysis methodology:

7.1 Data Extraction Process

A standardized data extraction form will be developed and used to collect relevant information from each included study. This form will be designed to capture:

- Study identification details (author, year of publication, country)
- Study design and methodology
- Participant characteristics (sample size, age, sex, disease stage)
- Details of interventions (type of therapy, dosage, duration)
- Comparator groups, if applicable
- Outcomes measured (overall survival, progression-free survival, quality of life, adverse events)
- Key findings and conclusions

Data extraction will be performed independently by two reviewers to minimize the risk of bias and errors. Any discrepancies between reviewers will be resolved through discussion or by consulting a third reviewer. The data extraction form will be piloted on a subset of included studies and refined as necessary to ensure that it captures all relevant information.

7.2 Data Analysis Strategy

The extracted data will be analyzed to address the study objectives. The analysis will involve:

- Descriptive synthesis of study characteristics and patient demographics
- Comparative analysis of treatment outcomes across different therapies
- Subgroup analyses to explore outcomes among various NSCLC sub-populations

- Assessment of the safety and tolerability profiles of therapies based on reported adverse events

Where possible, meta-analytic techniques will be employed to combine quantitative data from multiple studies. This will include calculating pooled estimates of effect sizes for outcomes such as survival rates and progression-free survival, using random-effects or fixed-effects models depending on the level of heterogeneity observed.

Heterogeneity among studies will be assessed using statistical measures such as the I^2 statistic and explored through subgroup analyses and sensitivity analyses. Potential sources of heterogeneity, such as differences in study design, population characteristics, or intervention types, will be investigated.

7.3 Quality of Evidence Assessment

The quality of evidence from the included studies will be assessed using appropriate tools. For observational studies, the Newcastle-Ottawa Scale (NOS) may be used to evaluate the risk of bias. The quality assessment will inform the interpretation of the findings and the strength of the conclusions drawn from the review.

7.4 Reporting of Findings

The results of the data extraction and analysis will be reported in accordance with the PRISMA guidelines. A narrative summary, supplemented by tables and figures, will present the key findings related to the effectiveness and safety of NSCLC treatments in real-world settings. The synthesis will highlight patterns, trends, and gaps in the evidence.

7.5 Handling of Missing Data

In cases where data are missing or incomplete, the authors of the original studies will be contacted for additional information. If necessary, sensitivity analyses will be conducted to assess the impact of missing data on the overall findings.

7.6 Data Extraction & Analysis Timeline

The data extraction and analysis phase is expected to be completed within the specified 6-month timeframe of the SLR. This phase will follow the literature search and study selection processes and precede the synthesis and manuscript preparation stages.

By adhering to this rigorous data extraction and analysis protocol, the SLR aims to provide a comprehensive and reliable synthesis of real-world evidence on the

effectiveness and safety of NSCLC treatments, thereby contributing valuable insights to the field of oncology and informing clinical practice.

Quality Assessment

9.4 Quality Assessment

Quality assessment is a critical component of a systematic literature review (SLR), as it evaluates the validity and reliability of the included studies and the potential risk of bias that may affect the review's conclusions. The quality assessment process for this SLR on real-world evidence in non-small cell lung cancer (NSCLC) will be conducted following these steps:

9.4.1 Selection of Quality Assessment Tools

The selection of appropriate quality assessment tools will be based on the study designs of the included studies. For observational studies, such as cohort and case-control studies, the Newcastle-Ottawa Scale (NOS) will be used. This scale assesses the quality of non-randomized studies based on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest.

9.4.2 Assessment Process

Each study will be independently assessed by two reviewers to minimize the risk of subjective bias. The reviewers will score each study according to the criteria set out in the chosen assessment tools. Disagreements between reviewers will be resolved through discussion or by consulting a third reviewer.

9.4.3 Evaluation of Bias

The quality assessment will focus on identifying various types of bias, including:
- Selection bias: Were the study participants representative of the general NSCLC population?
- Performance bias: Were the interventions and exposure status reliably ascertained?
- Detection bias: Were the outcomes measured in a standard, reliable, and valid way for all participants?
- Attrition bias: Were follow-up periods sufficient and similar across study groups, and were dropouts accounted for?
- Reporting bias: Were all pre-specified outcomes reported in the study?

9.4.4 Grading the Quality of Evidence

After the assessment, each study will be assigned a quality grade that reflects the overall risk of bias. This grading will help in weighting the studies during the synthesis of results and in interpreting the findings.

9.4.5 Addressing Limitations in the Evidence

The quality assessment will also identify any limitations in the evidence base, such as the lack of control groups, small sample sizes, or short follow-up periods. These limitations will be discussed in the context of their potential impact on the review's conclusions.

9.4.6 Reporting of Quality Assessment

The results of the quality assessment will be reported in detail, providing transparency and allowing readers to evaluate the strength of the evidence. A summary table may be included to present the quality scores and comments on each study.

9.4.7 Use of Quality Assessment in Data Synthesis

The findings from the quality assessment will inform the data synthesis process. Studies with high risk of bias may be analyzed separately or given less weight in meta-analyses. The overall quality of the evidence will be considered when drawing conclusions and making recommendations based on the SLR findings.

9.4.8 Continuous Quality Monitoring

The quality assessment process will be an ongoing component throughout the SLR. Any new studies identified during the updated search will undergo the same rigorous quality assessment to ensure consistency and reliability of the review's outcomes.

By implementing a thorough and systematic quality assessment process, this SLR aims to provide a robust and credible synthesis of real-world evidence on the effectiveness and safety of treatments for NSCLC, ultimately contributing to improved patient care and informed decision-making in clinical practice.

Synthesis Methods

11. Synthesis Methods

11.1 Overview of Synthesis Approach

The synthesis of findings from the included studies will be conducted using a mixed-

methods approach, integrating both qualitative and quantitative data to provide a comprehensive understanding of the real-world evidence on the treatment of non-small cell lung cancer (NSCLC). The synthesis will be structured around the study objectives, focusing on the effectiveness of novel therapies, treatment outcomes among various sub-populations, and the safety profiles of treatments in real-world settings.

11.2 Qualitative Synthesis

A narrative synthesis will be employed to summarize and explain the findings from the included studies. This will involve organizing the studies into thematic categories based on the type of intervention, patient populations, outcomes reported, and study design. The narrative synthesis will highlight patterns, trends, and key insights that emerge from the data, providing context and interpretation of the quantitative results.

11.3 Quantitative Synthesis (Meta-Analysis)

Where data permit, a meta-analysis will be conducted to quantitatively combine the results of studies reporting similar outcomes. The meta-analysis will use random-effects or fixed-effects models as appropriate, based on the level of heterogeneity detected among the studies. Pooled estimates of effect sizes, such as hazard ratios for survival outcomes or odds ratios for adverse events, will be calculated along with 95% confidence intervals.

11.4 Assessment of Heterogeneity

Heterogeneity among studies will be assessed using the I^2 statistic and chi-square tests. Sources of heterogeneity will be explored through subgroup analyses based on factors such as patient demographics, disease stage, type of intervention, and study quality. Sensitivity analyses will be conducted to determine the robustness of the meta-analysis results by excluding studies with high risk of bias or other significant limitations.

11.5 Exploration of Publication Bias

Publication bias will be assessed using funnel plots and statistical tests such as Egger's test, where a sufficient number of studies are available. The potential impact of publication bias on the review's conclusions will be discussed.

11.6 Synthesis of Safety Data

Safety data will be synthesized to provide an overview of the adverse events associated with NSCLC treatments in real-world settings. This will include the

frequency, severity, and types of adverse events reported across studies. Meta-analytic techniques will be used to estimate the overall incidence of specific adverse events where data are available and sufficiently homogenous.

11.7 Grading the Strength of Evidence

The strength of the evidence will be graded based on factors such as study quality, consistency of results, directness of evidence, and precision of effect estimates. The GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) may be utilized to provide a systematic assessment of the quality of the evidence and the strength of recommendations that can be drawn from the synthesis.

11.8 Reporting of Synthesis Findings

The findings from the synthesis will be reported in a clear and structured manner, following the PRISMA guidelines. Tables, figures, and forest plots will be used to visually represent the data and facilitate the interpretation of results. A summary of evidence table will be included to provide an at-a-glance overview of the key findings related to each objective of the review.

11.9 Consideration of Real-World Implications

The synthesis will consider the real-world implications of the findings, discussing how the evidence can inform clinical decision-making, guideline development, and policy-making. The relevance of the findings to different healthcare settings and populations will be addressed, ensuring the applicability of the review's conclusions to a broad range of real-world contexts.

11.10 Timeline for Synthesis

The synthesis of data is expected to be completed within the 6-month timeline of the systematic literature review, following the data extraction and analysis phase. This will allow for the integration of findings, interpretation of results, and preparation of the final manuscript for dissemination.

By employing these synthesis methods, the systematic literature review will provide a rigorous and insightful analysis of the real-world evidence on NSCLC treatments, contributing to the body of knowledge and supporting the advancement of patient care in oncology.