# INPLASY PROTOCOL

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**Support:** **None.**

**Review Stage at time of this submission:** **The review has not yet started.**

**Conflicts of interest:**
**The authors have no conflicts of interest to disclose.**

# Efficacy and safety of Cinobufacini injection combined with vinorelbine and cisplatin regimen chemotherapy for stage III/IV non-small cell lung cancer A protocol for systematic review and meta-analysis of randomized controlled trials

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**Review question / Objective:** **Cinobufacini injection is a traditional Chinese medicine extract, which has a long-term adjuvant effect on chemotherapy in patients with non-small cell lung cancer (NSCLC). Cinobufacini injection is often used in combination with vinorelbine cisplatin chemotherapy in the treatment of stage III / IV non-small cell lung cancer. However, the efficacy and safety of this combination therapy are still unclear.Since there is no systematic review of cinobufacin injection combined with vinorelbine cisplatin in the treatment of stage III / IV non-small cell lung cancer, this systematic review and Meta analysis will conduct a high-quality comprehensive evaluation of its efficacy according to the PRISMA statement.**

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 June 2020 and was last updated on 24 June 2020 (registration number INPLASY202060091).

## INTRODUCTION

**Review question / Objective:** **Cinobufacini injection is a traditional Chinese medicine extract, which has a long-term adjuvant effect on chemotherapy in patients with non-small cell lung cancer (NSCLC). Cinobufacini injection is often used in**

combination with vinorelbine cisplatin chemotherapy in the treatment of stage III / IV non-small cell lung cancer. However, the efficacy and safety of this combination therapy are still unclear.Since there is no systematic review of cinobufacin injection combined with vinorelbine cisplatin in the treatment of stage III / IV non-small cell lung cancer, this systematic review and Meta analysis will conduct a high-quality comprehensive evaluation of its efficacy according to the PRISMA statement.

**Condition being studied:** As the first-line treatment of unresectable advanced non-small cell lung cancer, vinorelbine (NVB) and cisplatin (DDP) may have side effects such as myelosuppression and gastrointestinal disorders. Traditional Chinese medicine injection has the advantages of fast absorption, quick effect, convenient clinical application and so on. In recent years, it has been reported that cinobufacin injection combined with vinorelbine + cisplatin (NP) regimen in the treatment of of III / IV non-small cell lung cancer, but the clinical trial methods, clinical efficacy and side effects of each study are different.

## METHODS

**Search strategy:** We built the retrieval strategy using MeSH and free words. The retrieval form was (Cinobufacini injection OR huachansu OR huachansu injection ) AND ("Lung Neoplasms"[MeSH] OR Non-small cell lung cancer OR Non-small cell lung carcinoma OR NSCLC OR Pulmonary Neoplasms OR Lung Neoplasm OR Pulmonary Neoplasm OR Lung Cancer OR Lung Cancers OR Pulmonary Cancer OR Pulmonary Cancers OR Lung carcinoma OR Pulmonary carcinoma) AND (vinorelbine AND cisplatin).

**Participant or population:** Inclusion criteria include the following: (1) types of studies: randomized clinical trials (RCTs); (2) participants: adult human populations (≥18 years old) who were pathologically diagnosed as NSCLC with clinical stages III (unresectable) and IV.The sex of the patient is not limited; Exclusion criteria:(1) studies such as reviews, animal researches; (2) participants who had nonpathological diagnosis, previously subjected to chemotherapy, radiotherapy or surgery, concurrent infection, or other malignancies or severe illnesses; (3) repeatedly published literature or reviews.

**Intervention:** Cinobufacin injection combined with vinorelbine cisplatin chemotherapy.

**Comparator:** Vinorelbine cisplatin chemotherapy.

**Study designs to be included:** Randomized controlled trials (RCTs) will be included.

**Eligibility criteria:** Two reviewers will independently evaluate the included RCTs and extract the data.The following data will be extracted: author, year of publication, country in which the study was conducted, study cycle, original selection criteria, total number and age of participants in the study, course of disease, intervention measures, outcome indicators, and adverse events.Disagreements will be resolved by discussion or consensus with a 3rd reviewer.

**Information sources:** Two independent reviewers will carry out a comprehensive search of the PubMed, Web of Science, Cochrane Library, EMBASE, Weipu database(VIP), China National Knowledge Infrastructure(CNKI), Wanfang Databases, :China Biology Medicine (CBM).There will be no language restrictions and no year restriction.

**Main outcome(s):** The main efficacy indicators were based on the objective efficacy evaluation criteria of WHO antineoplastic drugs or the objective efficacy evaluation criteria of solid tumors established by RECIST.

**Additional outcome(s):** Secondary criteria KPS score, pain efficacy criteria, side effects of chemotherapy such as myelosuppression and gastrointestinal symptoms.

**Data management:** All retrieved studies will be managed with Endnote X9, and repetitive studies will be filtered.Two reviewers will independently screen the studies by titles and abstracts according to the predefined inclusion criteria.The two reviewers will then download the full text of all possible relevant studies and further review the full report independently.Two reviewers will cross check the included studies.Disagreements will be resolved by discussion or consensus with a 3rd reviewer.

**Quality assessment / Risk of bias analysis:** Two reviewers will cross check the included studies. Disagreements will be resolved by discussion or consensus with a 3rd reviewer . Adopt the evaluation criteria in the Cochrane Handbook 5.1 manual.

**Strategy of data synthesis:** RevMan 5.3 software provided by the Cochrane collaboration will be used to perform a meta-analysis.If heterogeneity is minor, a fixed-effects model will be used to estimate the summary OR ,and their 95% CIs, and meta-analysis will be carried out; if heterogeneity is substantial, a random-effects model will be used for data pooling, and meta-analysis will be conducted.To check the robustness of pooled outcome results, we will carry out sensitivity analysis to evaluate the impact of studies with high risk of bias.

**Subgroup analysis:** In order to study heterogeneity, we will conduct a subgroup analysis based on age, sex, drug dose and treatment time.

**Sensibility analysis:** In order to determine the robustness of the results of Meta analysis, we will conduct sensitivity analysis by excluding randomized controlled trials with high risk of deviation or randomized controlled trials with missing data.

**Language:** No language restrictions.

**Country(ies) involved:** No countries involved.

**Other relevant information:** If the included research data are insufficient or unclear, the original author will be contacted by email for more information.If there is no reply from the original author, we will only analyze the existing data.To investigate whether these missing data will affect the results of the meta analysis, we will analyze the existing data and discuss the potential impact of the missing data.

**Keywords:** vinorelbine and cisplatin; non-small cell lung cancer; Cinobufacini injection; Meta-Analysis; Randomized controlled trial.

**Dissemination plans:** The results of this systematic review will be disseminated through peer reviewed journal.It is hoped that this result will help to establish a better method for the treatment of stageIII/IVnon-small cell lung cancer and provide reliable evidence for its wide application.

**Contributions of each author:**
Author 1 - Qian Li - The author will draft the protocol and the manuscript. Contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. The referred author developed the search strategy and provided statistical expertise. The risk of bias assessment and screening of search studies against eligibility.
Author 2 - Hua Xiao - The author will provide a methodology. The risk of bias assessment and screening of search studies against eligibility criteria. The author will read, provided feedback, and approved the final manuscript.
Author 3 - Ren-long Liang - The author will provide data curation.The author will read, perform the risk of bias assessment, supervise, provided feedback, and approved the final manuscript.
Author 4 - Qian-ru Yu - The author will provide data curation.The author will read, perform the risk of bias assessment, supervise, provided feedback, and approved the final manuscript.
Author 5 - De-qing Tian - The authors will read, supervise, provided feedback, and approved the final manuscript.

**Author 6 - Li-na Zhao - The author will provide data curation.The author will read, perform the risk of bias assessment, supervise, provided feedback,and approved the final manuscript.**
**Author 7 - Wen-wen Wang - The authors will read, supervise, provided feedback, and approved the final manuscript.**
**Author 8 - Xiao-jia Yong - The author will provide a methodology.The risk of bias assessment and screening of search studies against eligibility criteria. The author will read, provided feedback, and approved the final manuscript.**