

Nelfinavir, a Repurposed HIV Protease Inhibitor, as an Add-on to Chemotherapy Versus Chemotherapy Alone in the Treatment of Locally Advanced Pancreatic Cancer (LAPC): A Systematic Review Protocol

Title Identification:

This is a protocol for a systematic review, and it does not update a previously published review.

Background:

Pancreatic cancer remains one of the most devastating malignancies, with a dismal prognosis of 91% mortality rate and a 5 year overall-survival rate of 9% (Rawla, Sunkara and Gaduputi, 2019). Globally, approximately half a million new cases and another half a million deaths from pancreatic cancer are recorded annually (Ilic and Ilic, 2022; Li, Lin and Wang, 2025). Although pancreatic cancer accounts for 1.8% of all cancers, it disproportionally causes 3.9% of all cancer disability-adjusted life years (DALYs) and 4.6% of all cancer deaths (Lippi and Mattiuzzi, 2020).

Pancreatic cancer encompasses several neoplasms and carcinomas (Conroy et al., 2023). However, this review will focus on a very specific subtype, having the worst prognosis where new advancements in treatment are urgently needed: **Locally advanced pancreatic cancer (LAPC)**. LAPC is the least survivable form of pancreatic cancer and is defined as an unresectable tumour with extensive vascular involvement (Seufferlein et al., 2019). Currently, only 15–20% of patients are diagnosed with operable disease, while 40–50% are diagnosed with unresectable (LAPC) (van Veldhuisen et al., 2019). The ESMO clinical practice guidelines cite the barriers to surgery in LAPC, recommending an induction or neoadjuvant therapy to downsize the tumour before surgery (Conroy et al., 2023). A systematic review of 9 studies confirms that LAPC patients should undergo induction chemotherapy with the aim of tumour regression, enhancing the biological markers, and allowing surgical resection (He et al., 2024). Additionally, the REDISCOVER guidelines suggest chemo-radiotherapy as an escalation to standalone chemotherapy (Boggi et al., 2024).

A meta-analysis reveals that the latest chemotherapy approach comprising a combination of four agents called FOLFIRINOX improves the overall survival (OS) with a median survival time of 24.2 months (95% CI 21.7-26.8), however this remains unsatisfactory (Suker et al., 2016). The very low survival rates and median (OS) pose a significant demand for new interventions in clinical management of LAPC.

Nelfinavir (Viracept®) is an oral HIV-1 protease inhibitor formerly used to treat HIV at a daily dose of 2500 mg, however its use declined due to the availability of newer antiretrovirals, significant side effects, and a high pill burden (Perry et al., 2005). The early anti-cancer feasibility trials were limited to cell cultures, and tested several protease inhibitors, with nelfinavir found to have the highest potency on several cancer cell types (Gills et al., 2007). Follow-up research further documented nelfinavir's anti-cancer effects in several in-vitro studies, highlighting several mechanisms of action, including cell growth inhibition (He et al., 2021), and increased apoptosis, or programmed cell death (Koltai, 2015). Specifically, apoptosis and disruptions in cell life cycle have been reported in pancreatic cancer cells (Veschi et al., 2018). Moreover, evidence show that Nelfinavir sensitises in-vitro pancreatic cells to radiation and chemo-radiation, enhancing traditional treatment (Al-Assar et al., 2016).

While nelfinavir has been investigated for its anti-cancer effects in various in-vitro cell types such as breast (Besse et al., 2024), cervical (Reddy et al., 2025), and lung xenografts (Kawabata et al., 2021), only in LAPC has research progressed to human clinical trials (Mukherjee et al., 2024). This is due to LAPC's extremely poor prognosis and low survival rates, underscoring the urgent need for novel therapies.

To date, no systematic review has evaluated the effectiveness of add-on nelfinavir with chemotherapy in LAPC patients. This review aims to address that gap by synthesising evidence from eligible clinical trials to assess impact on overall survival (OS) measured from diagnosis, and progression-free survival (PFS) measured from randomisation (Gyawali et al., 2022). Given the clearly defined condition and analogous outcome measures, the available data could be meaningfully pooled to draw conclusions on clinical benefit of nelfinavir in LAPC.

Objectives:

The objective is to assess the effectiveness of **nelfinavir**, in combination with standard chemotherapy, in improving survival in patients with **locally advanced pancreatic cancer (LAPC)**, while gaining insight into tolerability profile and the general quality of life associated with the intervention. Preclinical and in-vitro evidence suggest that add-on nelfinavir to standard chemotherapy may improve overall survival (OS) and progression free survival (PFS).

Methodology:

This protocol is guided in development and structure by the PRIMSA-P statement (Moher et al., 2015)., and the systematic review will be reported according to the PRISMA-2020 statement (Page et al., 2021). To test the objectives above we use the **PICOS** framework:

- **Population:** Adults (≥ 18 years) with histologically or radiologically confirmed LAPC
- **Intervention:** Nelfinavir (Use of nelfinavir as an adjunct or component of therapy)
- **Comparator:** Standard treatment without nelfinavir
- **Outcomes:**
 - I. Primary: Overall survival (**OS**), progression-free survival (**PFS**),
 - II. Secondary: adverse drug reactions (**ADR**), quality of life (**QoL**)
- **Study Design:** clinical trials (RCTs, phase I, Phase II)

Eligibility Criteria:

Table 1. The inclusion and exclusion criteria, according to each frame of PICOS.

Frames	Inclusion Criteria	Exclusion Criteria
Population	• Humans with confirmed LAPC diagnosis • Adults, including all ages and genders	• Diagnosis with other cancers of the pancreas • Diagnosis with other cancers • Animals
Intervention	• Nelfinavir(NFV) as adjunct to standard chemo • Nelfinavir(NFV) add-on to chemo-radiotherapy	• Any other Protease Inhibitor • Add-ons other than standard radio-chemotherapy
Comparator	• Standard radio-chemotherapy without NFV	• Having placebo or no treatment
Outcomes	Primary outcomes: • Median Overall survival (OS) in months and Hazard ratios (HR) • Progression free survival (PFS) and (HR) Other outcomes: • Adverse events • Quality of Life (QoL)	• Mechanisms of action • Any other outcome • Studies with no relevant outcome
Study Design	• Randomised Clinical Trials • Phase I trials • Phase II trials	• Observational studies • Reviews • In-vitro studies • Animal studies

Search Strategy:

A comprehensive literature search will be conducted independently by two reviewers using the following databases: Ovid MEDLINE, Ovid EMBASE, Cochrane CENTRAL, Scopus, and PubMed. The search strategy will combine Medical Subject Headings (MeSH) and keywords, to be searched for in titles and abstracts using field tags (.ti.) and (.ab.), identifying relevant studies on the use of nelfinavir, as adjunct treatment of (LAPC). As demonstrated in **figure (1)** below, the search will begin with broader terms narrowing down to terms specific to LAPC. Nelfinavir's various chemical and brand names will also be included to ensure sensitivity. Synonyms, truncation symbols, Boolean operators (AND/OR), and proximity operators (*adj3*) will be applied where appropriate to enhance sensitivity and expand coverage. Terms to filter the results to randomized controlled trials and Phase I/II clinical trials will be used, such as (.pt.) as well as (.mp.). Animal-only studies will be excluded using the filter "not (animals.sh. not humans.sh.)". Publications will be limited to the English language; however, non-English studies may be considered later if translation resources are available.

For **data management** all retrieved results will be managed and screened using **Covidence** which would also be used for de-duplication, search results will then be exported as a .ris file to be used with **Covidence** (2025).

Fig.1. Exported search example on Ovid Medline, showing keywords, MeSH terms, field tags and operators that capture the intervention, cases and limit studies to human trials with valid comparators (chemotherapy).

Database: Ovid MEDLINE(R) <1946 to May 09, 2025>

Search Strategy:

- 1 HIV protease inhibitor.mp. or HIV Prote?se Inhibitors/ (779)
- 2 Nelfinavir*.ti,ab. (1641)
- 3 Viracept.ti,ab. (95)
- 4 Nelvir*.ti,ab. (1)
- 5 Nelfinavir Mesylate.ti,ab. (44)
- 6 HIV antiviral*.ti,ab. (85)
- 7 proteinase#inhibitor.ti,ab. (1)
- 8 (nelfinavir* adj3 chemotherapy).mp. (1)
- 9 (nelfinav?r* adj3 cancer*).mp. (17)
- 10 Pancreatic Neoplasms/ or pancre#tic cancer.mp. (103080)
- 11 exp Pancreatic Neoplasms/dt, rt, th [Drug Therapy, Radiotherapy, Therapy] (25271)
- 12 Locally Advanced Pancreatic Cancer.mp. or Carcinoma, Pancreatic Ductal/ (16082)
- 13 nonmetastasized pancreatic cancer.mp. (3)
- 14 (Neoadjuvant* adj3 pancreatic cancer).mp. (315)
- 15 (locally advanced pancreatic cancer* or LAPC).ti,ab. (1506)
- 16 unresectable pancreatic cancer.ti,ab. (834)
- 17 inoperable pancreatic cancer.ti,ab. (157)
- 18 Clinical Trials as Topic/ or Randomized Controlled Trials as Topic/ (383738)
- 19 randomised controlled trials.mp. (28538)
- 20 clinical trials , Phase I.mp. (6307)
- 21 clinical trials, phase II.mp. (9920)
- 22 randomized controlled trial.pt. (638591)
- 23 controlled clinical trial.pt. (95667)
- 24 clinical trial, phase I.pt. (27461)
- 25 clinical trial, phase II.pt. (43590)
- 26 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (2423)
- 27 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (104041)
- 28 19 or 20 or 21 or 22 or 23 or 24 or 25 (812501)
- 29 26 and 27 (16)
- 30 28 and 29 (9)
- 31 30 not (animals not humans).sh. (9)

Data Extraction:

Two reviewers will independently screen the title and abstract of all search results and decide on eligibility independently. Conflicts will be resolved by consultation with departmental research lead. After full text screening using a standardised tool, information of interest would be extracted, these include key study characteristics (citation, year of publication, and funding sources), patient demographics (sample size, age), and intervention details, specifically nelfinavir dosage, timing, and details on comparator treatment (chemotherapy or chemoradiotherapy alone) will also be recorded. Primary survival outcomes will include (OS) and (PFS), both recorded in months, also hazard ratios (**HRs**) maybe reported along with p values. Although not central to the study's primary aim, secondary outcomes such as adverse events, toxicity, and quality of life (QoL) scores will also be collected. Funding sources and any reported conflicts of interest will be noted.

Table 2. Data extraction form contents and details on what to include

Item	Details / Notes
Citation	Author(s), Year,
Study Design	RCT, Non-RCT, Phase I/II/III Trial,
Sample Size	Total number of participants included in the study
Mean Age	Mean or median age $\pm$ SD (if available)
NFV Dosage & Regimen	Dosage in mg/day, frequency
Chemotherapy Chemoradiotherapy (CRT)	Name(s) of agents used (e.g., gemcitabine, FOLFIRINOX), +/- radiotherapy
Overall Survival (OS)	Mean OS, HR (95% CI), p-values,
Progression-Free-Survival (PFS)	Mean PFS, HR (95% CI), p-values,
Adverse Events	Type, grade, frequency, treatment discontinued
Quality of Life (QoL)	Instrument used, score changes, time points
Funding	Source of funding, conflicts of interest
Remarks	Notes on study limitations, protocol deviations ...

Data extraction forms will be created using appropriate software and will include all previously stated data to be extracted, as shown in table 2. The two reviewers will agree upon a unified method of using a piloted data extraction form to ensure consistency and clarity based on the Cochrane Handbook recommendations (Higgins et al., 2019). The form will be refined following initial piloting on a sample of studies; an example is presented in table 3.

Risk of Bias Assessment:

The risk of bias for included studies will be assessed independently by two reviewers, using the Cochrane Risk of Bias 2.0 tool for randomized controlled trials (Higgins et al., 2019), and the ROBINS-I tool for non-randomized studies (Sterne et al., 2016). These tools will be used to evaluate risk of bias rating across domains such as selection, generation of sequence, allocation concealment, deviations from intended interventions, blinding of participants, and outcome reporting. The level of bias in studies will be accordingly rated as high, low, or unclear. Discrepancies will be resolved through discussion or consultation with departmental lead.

Data Synthesis and Assessment for Quantitative Analysis:

Extracted data will be summarised in structured tables and synthesized narratively, grouped by intervention types (add-on to chemo or chemo-radiotherapy), and key outcome measures. Descriptive synthesis will focus on intervention efficacy in primary outcome measures (OS) and (PFS). As these are survival measures, we expect outcomes to be reported using standardised methods as in **Hazard Ratios (HR)**, a ratio comparing the intervention and control groups, enhancing consistency of findings. Where HRs are not reported, they will be estimated from available data using the validated methods described by Tierney et al. (2007). Importance will be given to direction of effect in the intervention group, strength of evidence, risk of biases and the quality of each study. Secondary outcomes of adverse drug reactions (ADRs) and Quality of Life (QoL) will also be described separately with adequate reporting methodologies. ADRs will be reported according to the CONSORT-harms guidelines, and will include ADR types, severity and treatment discontinuation (Junqueira et al., 2023). ADRs could be reported quantitatively as risk ratios or incidence rates. However, if inconsistent across studies, a description of most common ADRs, tolerability, and bias due to underreporting will be provided, and a benefit-risk balance of nelfinavir use in LAPC will also be discussed. As for QoL data, reviewers would describe the tools used in measurement and analyse results.

Heterogeneity will be quantified using the **I² statistic**, and if studies are deemed sufficiently homogeneous in terms of population, intervention, comparator, and outcomes (PICO), and provide adequate statistical data, a quantitative meta-analysis will be

conducted. For survival outcomes (OS) and (PFS), (HRs) and the continuous survival time outcome, will be extracted along with confidence intervals. Corresponding log HRs and standard errors will also be calculated to enable meta-analysis.

Meta-analyses will be performed using the random-effects model, reflecting the expected variation across studies. Forest plots will be generated to visually summarise effect sizes and the weighted mean differences of the outcomes across studies. Visual inspection of forest plots will further support heterogeneity assessment. Clinical, methodological, and statistical sources of heterogeneity will be explored through subgroup analyses, stratified by nelfinavir dosage, chemo or radio-chemotherapy regimen, and risk of bias rating. If standard deviations are missing, study authors will be contacted. In the absence of a response, standard methods outlined in the Cochrane Handbook (Higgins et al., 2019) will be used to impute missing data. This, along with (HRs) estimation methods, sample size issues, and risk of bias scores will be addressed in study limitations.

Sensitivity analyses will be conducted to assess the robustness of findings. These will include creating subgroups of studies at high risk of bias, inclusion/exclusion of non-randomized studies, and testing the impact of different statistical models. Where at least 10 studies are included in a meta-analysis, publication bias will be evaluated using funnel plots and, if appropriate, Egger's test. All analyses will be conducted using **Stata (version 18)** (2025), and methods will adhere to PRISMA standards (Page et al., 2021).

If the included studies are too heterogeneous to permit valid statistical pooling, or if essential data are lacking, results will be synthesized narratively, coupled with tables and charts as mentioned earlier.

Confidence in Cumulative Evidence:

The **GRADE** approach will be used to rate the certainty of evidence for each outcome, specifically guidance 24 for synthesising evidence by integration of randomised and non-randomised studies (Cuello-Garcia et al., 2022). The certainty of evidence will be ranked as high, moderate, low, or very low based on study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias (Granholt et al., 2019). A Summary of Findings table will be created to describe level of certainty for each primary outcome, namely (OS) and (PFS) along with (HRs), as well as secondary outcomes, sample size, measures of effect and the GRADE level of certainty. Higher certainty publications will be prioritised, while those with lower certainty will be downgraded.

Dissemination Strategy:

Findings from this systematic review will be disseminated through omnichannel to reach a range of stakeholders. Peer-reviewed publication in oncology and public health journals (BMJ, Cancer Discovery, Lancet...) will target clinical and academic audiences. For patients and advocacy groups, we will produce an infographic to be shared via social media and patient networks such as Pancreatic Cancer UK (2025). Additionally, we will engage with policy stakeholders and decision makers by preparing a summary policy brief outlining potential implications for treatment funding, while highlighting importance of further research. These strategies aim to ensure that evidence on nelfinavir's potential role in LAPC treatment reaches those best positioned to translate knowledge into practice or further research.

Summary and Impact:

This systematic review investigates the feasibility of repurposing nelfinavir as an adjunct therapy for locally advanced pancreatic cancer (LAPC), a specific condition with limited treatment options and poor prognosis. The review is exploratory rather than definitive, given the novelty of intervention. By synthesising available clinical trial data, the review aims to evaluate whether nelfinavir enhances tumour sensitivity to standard treatment improving survival. As the first review of its kind, it lays the groundwork for future research and clinical decision-making, with the potential to influence treatment guidelines and improve outcomes in a highly challenging cancer population.

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