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[Intervention Protocol]

Nirmatrelvir combined with ritonavir for preventing and treating COVID-19

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the efficacy and safety of nirmatrelvir/ritonavir (Paxlovid®) plus standard of care compared to standard of care with or without placebo, or any other proven intervention for treating COVID-19 and for preventing SARS-CoV-2 infection.

BACKGROUND

Description of the condition

Having been declared the sixth public health emergency of international concern by the World Health Organization (WHO), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting outbreak of coronavirus disease 2019 (COVID-19) has caused a pandemic that has accelerated at an unprecedented scale. As of February 2022, more than 2 years after the first reported SARS-CoV-2 case, there have been over 400 million confirmed cases of COVID-19, including nearly 6 million deaths in 222 countries and territories (WHO 2021a).

COVID-19 is a rapidly spreading infectious disease caused by SARS-CoV-2 (WHO 2020). SARS-CoV-2 is a positive-sense, double-stranded ribonucleic acid (RNA) virus that belongs to the *Coronaviridae* family (Kumar 2020).

SARS-CoV-2 uses its spike glycoprotein-S to bind to an angiotensin-converting enzyme 2 (ACE2) receptor on a host cell surface to initiate the infection process. Angiotensin-converting enzyme 2 receptors are expressed in lung, heart, kidney, intestine, and endothelium in the human body. The main expression site that is central to the pathophysiology of COVID-19 is respiratory epithelium of the nasopharynx. SARS-CoV-2 genes can then enter the human cell to begin viral replication and shedding. The process of viral replication is mediated by, and depends on, viral proteolytic enzymes (proteases), including main protease (M^{pro}, also known as 3C-like protease, $3CL^{pro}$) (Amin 2021; Anand 2003). Viral variants mainly present mutational changes in the spike glycoprotein (Harvey 2021). The spike glycoprotein is recognized by the immune system and is the main target of vaccines against SARS-CoV-2 (Salvatori 2020; Walls 2020). In contrast, the M^{pro} active binding site is highly conserved between different virus variants and less affected by mutations.

Most individuals with COVID-19 are either asymptomatic or develop mild symptoms not requiring hospitalizations (approximately 80% to 90%), depending on the time of the investigation, the cohort investigated, and the virus variant (Chen 2010; Funk 2021; Wu 2020). A smaller proportion is affected by severe (approximately 11% to 20%) or critical (approximately 1% to 5%) disease with hospitalization and intensive care unit (ICU) admittance due to respiratory failure, septic shock, or multiple organ dysfunction syndrome (Funk 2021; Wu 2020). Risk for severe disease, hospitalization, and mortality is higher for individuals aged 65 years or older, males, smokers, and individuals with certain underlying medical conditions, such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, moderate-to-severe asthma, immunocompromised state, obesity, sickle cell disease, or type 2 diabetes mellitus (Booth 2021; Huang 2020; Karagiannidis 2020; Petrilli 2020; Williamson 2020). Most common symptoms and signs of acute infection include fever, cough, fatigue, and shortness of breath (Grant 2020). Infection with SARS-CoV-2 may also lead to long-term health conditions including persistent fatigue, cognitive dysfunction, and post-exertional malaise (Huang 2021).

The gold standard for confirming a SARS-CoV-2 infection is the reverse transcription polymerase chain reaction (RT-PCR)-based detection of viral RNA from a nasopharyngeal swab test, anterior nares swab test, sputum, or tracheal secretion, with a sensitivity ranging from 70% to 98%, depending on pretest probability (Watson 2020). Offering lower sensitivity but greater practicality and accessibility, antigen tests have received increased attention, especially in point-of-care diagnostics of COVID-19 (Dinnes 2021; WHO 2020a).

Viral transmission is typically inferred from population-level information. Inherent properties of virus variants of concern, and individual differences in infectiousness among individuals or groups, and differences in local herd immunity make it difficult to contain its spread in the community (WHO 2021a). Currently, the most effective strategy to combat the pandemic is vaccination. COVID-19 vaccines are effective and can reduce the risk of getting SARS-CoV-2 and decrease hospitalization rates (CDC 2021; Juthani 2021). However, vaccination can fail to produce a sufficiently robust immune response, and the response it does elicit can wane over time and be less effective against new variants (Lin 2022). Furthermore, some people cannot get a COVID-19 vaccine for medical reasons, such as anaphylaxis, or may not develop sufficient immunogenicity following vaccination (NHS 2021). Others are hesitant to get vaccinated due to concerns about vaccine side effects and safety (Altulahi 2021; Wang 2021). The major obstacle in overcoming this pandemic, however, is vaccine inequity in different regions of the world (WHO 2021). Additionally, emerging new virus variants can increase the risk of infection in all countries, including the vaccinated population if vaccines become less effective due to viral immune escape mutations as could be seen with the recent Omicron variant (Ren 2022). Therefore, research on pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection and treatment of COVID-19 is still of high relevance and is being carried out under great pressure worldwide.

Description of the intervention

Pfizer's new drug combination nirmatrelvir/ritonavir (Paxlovid®) aims to avoid severe COVID-19 in asymptomatic people or those with mild symptoms, thereby decreasing hospitalization and death. Nirmatrelvir/ritonavir is a combination of the SARS-CoV-2 protease inhibitor nirmatrelvir, and ritonavir, a CYP3A4 inhibitor used in the treatment of HIV to enhance HIV protease inhibitors. Nirmatrelvir blocks the activity of the SARS-CoV-2-$3CL^{pro}$ protease, an enzyme needed for viral replication. In humans nirmatrelvir is metabolized by the P450 cytochrome enzyme CYP3A4. In order to remain active in the body for longer periods of time, nirmatrelvir is co-administered with low dose ritonavir, to slow down the breakdown of nirmatrelvir (Pfizer 2021). Nirmatrelvir/ritonavir is to be administered orally within 5 days of symptom onset and taken twice daily for 5 days. Given the inactivation of CYP3A4 by ritonavir, a common enzyme in drug metabolism, ritonavir interferes with the metabolism of many drugs, can alter their plasma concentrations, and increase drug-related adverse effects. The applicability of nirmatrelvir/ritonavir may thus be limited in some populations at high risk of severe COVID-19, such as those with comorbidities requiring medications metabolized using the CYP3A4 enzyme. As $3CL^{pro}$, the substrate-binding site is highly conserved among all coronaviruses and shares no homology with human proteases, a SARS-CoV-2-$3CL^{pro}$ antagonist will be highly specific to SARS-CoV-2 and less affected by virus mutations (Dai 2020) compared to antivirals binding to other sites, more prone to mutation.

Therapeutic options for treatment of COVID-19 in the outpatient setting or for prevention of a SARS-CoV-2 infection in close

contacts of infected people are still limited. In September 2021, the WHO gave the conditional recommendation to use a combination of neutralizing monoclonal antibodies (mAbs) (casirivimab and imdevimab) in non-severe COVID-19 patients at the highest risk of severe disease, and in seronegative patients with severe or critical COVID-19 (WHO 2021b). A recommendation for sotrovimab, another mAb in high-risk outpatients followed in January 2022 (WHO 2021b). Accurate clinical prediction guides to establish individual patient risk and benefit from monoclonal antibodies are lacking, and the current usual care for non-hospitalized COVID-19 patients varies greatly between countries. Unfortunately, contrary to sotrovimab, the combination of casirivimab and imdevimab has not retained neutralizing activity against the Omicron variant (Takashita 2022). Remdesivir, originally developed to treat hepatitis C, has proven to decrease hospitalization rates in unvaccinated COVID-19 patients and is currently recommended in several countries for outpatient treatment of infected patients with high risk of disease progression (Gottlieb 2022; NICE 2021; NIH 2021). However, the WHO advises against the use of remdesivir in hospitalized COVID-19 patients (WHO 2021b). To date only one direct oral antiviral treatment, molnupiravir, has been authorized by the Medicines and Healthcare products Regulatory Agency (MHRA) for infected, non-hospitalized individuals with at least one risk factor for severe disease (Merck 2021; NCT04575597) and international guidelines are being constantly updated (NICE 2021; WHO 2021b). However, clinical data on molnupiravir regarding efficacy and safety are currently limited. Other strategies to treat COVID-19 have included re-purposing existing drugs for an antiviral intention, including ivermectin. However, so far there is no proven effect for ivermectin (Popp 2021a) and, therefore, it should not be used for treatment of COVID-19 outside well-designed clinical trials (WHO 2021b). Experimental antivirals being studied include umifenovir (Deng 2020) and favipiravir (Cai 2020), and the antiretroviral protease inhibitor combination lopinavir/ritonavir (Cao 2020).

How the intervention might work

Viral non-structural proteins are important for replication and transcription of SARS-CoV-2. The SARS-CoV-2-3CL^{pro} plays a key role in the production of 16 non-structural proteins of SARS-CoV-2. Inhibition of 3CL^{pro} by nirmatrelvir blocks the release of these non-structural proteins, thereby suppressing further maturation and replication of SARS-CoV-2 (Zhang 2021). Boosting with ritonavir, a CYP3A4 inhibitor, is required to increase nirmatrelvir to a concentration that is effective against SARS-CoV-2 (Pfizer 2021). There is reason to presume that viral load, infectivity, and disease severity are positively correlated (Fajnzylber 2020; Kawasuji 2020; Liu 2020). Decreasing the viral load by blocking viral replication could thereby prevent disease progression and limit the infectivity of COVID-19 patients.

Nirmatrelvir (PF-07321332), the protease inhibitor agent in nirmatrelvir/ritonavir, was developed by modification of an earlier clinical candidate PF-00835231, originally developed as a potent inhibitor of recombinant SARS-CoV-1-3CL^{pro} during the SARS-CoV-1 pandemic in 2002/03. SARS-CoV-1-3CL^{pro} and SARS-CoV-2-3CL^{pro} share 96% sequence homology (Zhang 2020). However, PF-00835231 needs to be administered intravenously, limiting its application mainly to hospital settings. Stepwise modification led to the new substance nirmatrelvir, with increased oral bioavailability. To date, nirmatrelvir has shown potent inhibition of 3CL^{pro} from all coronavirus types known to infect humans, as well as favourable selectivity profiles against mammalian proteases (Owen 2021).

Lufotrelvir, the phosphate prodrug of PF-00835231, with a similar mechanism of action to nirmatrelvir but with intravenous administration is currently studied for safety and efficacy in the treatment of hospitalized COVID-19 patients, including trials in conjunction with remdesivir, as in vitro data showed synergistic effects (de Vries 2020; NCT04501978; NCT04535167).

Why it is important to do this review

Current treatment for hospitalized patients includes mAbs (casirivimab and imdevimab) and supportive care with oxygen in moderate cases, systemic corticosteroids, baricitinib, IL-6 blockers, and non-invasive ventilation or invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO) in severe or critical cases (WHO 2021b). Overall, data from randomized controlled trials (RCTs) with exception to the aforementioned treatments do not demonstrate a clear, major clinical benefit with most drugs evaluated so far. Therapeutic options for treatment of COVID-19 in the outpatient setting or for prevention of a SARS-CoV-2 infection in close contacts of infected people or in people at risk are still limited. In light of the ongoing potential for evolving virus variants, scarcity of effective treatments, and global vaccination coverage issues, the role of effective oral therapies for patients at high risk of severe disease is of utmost interest for reducing morbidity and mortality secondary to COVID-19.

The COVID-19 pandemic has brought social and racial injustice and health inequity in the spotlight of public health. The impact of COVID-19 disproportionally affects elderly, poor, racial and ethnic minorities, as well as a broad range of vulnerable populations, putting them at increased risk of illness and death (Killerby 2020). Reasons include, but are not limited to, inequitable viral spread in areas of dense population, and limited mitigation capacity due to a higher prevalence of chronic conditions or poor access to high-quality medical care (Shadmi 2020).

Prevention of COVID-19 in people at high risk for developing severe disease requiring hospital level treatment is critical, especially from a global perspective considering limited hospital capacity in low- and middle-income countries (LMICs). Antiviral drugs such as nirmatrelvir/ritonavir might therefore be of vital importance in the global fight against SARS-CoV-2. It is however yet to be determined whether the fact that nirmatrelvir/ritonavir has to be administered within 5 days of symptom onset may decrease its applicability due to inadequate healthcare infrastructure and lack of access to public health and medical care in LMICs, in elderly, and in racial and ethnic minority populations.

To allow equity of access across countries, Pfizer has signed a voluntary licence agreement for nirmatrelvir/ritonavir with the Medicines Patent Pool (MPP), a United Nations-backed public health organization working to increase access to life-saving medicines for low- and middle-income countries (MPP 2021a; Pfizer 2021). With the MPP having a licence on ritonavir for many years, the agreement will enable MPP to facilitate additional production and distribution of both ritonavir and nirmatrelvir by granting sublicenses to qualified generic medicine manufacturers (MPP 2021b). Pfizer further aims to offer a tiered pricing approach based on the income level of a country, with high- and upper-middle

income countries paying more than lower-income countries, which will pay a not-for-profit price (Pfizer 2021).

Pfizer has ongoing trials for nirmatrelvir/ritonavir on clinical outcomes for patients with COVID-19 at high and standard risk, and for post-exposure prophylaxis (Pfizer 2021). We expect that many new studies investigating nirmatrelvir/ritonavir will be initiated in hospitals worldwide after Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA). This review is designed as a living systematic review with continuous monitoring of new and ongoing studies. We aim to keep the evidence based on clinical studies investigating nirmatrelvir/ritonavir for COVID-19 up to date.

Nirmatrelvir/ritonavir is designed by Pfizer to reduce the viral load early after infection preventing replication of the virus and disease development including hospital admission. Following this rationale studies should mainly focus on ambulatory managed individuals and studies investigating nirmatrelvir/ritonavir in hospitalized patients with moderate to severe COVID-19 should not be considered. However, we do not know whether nirmatrelvir/ritonavir might be a valuable antiviral option for COVID-19 patients at high risk who are hospitalized early after infection. Therefore, all COVID-19 patients independent of disease severity will be considered for this review.

This review will provide a complete evidence profile, based on current Cochrane standards, for nirmatrelvir/ritonavir with regard to efficacy and safety for pre- and post-exposure prophylaxis and treatment of COVID-19.

OBJECTIVES

To assess the efficacy and safety of nirmatrelvir/ritonavir (Paxlovid®) plus standard of care compared to standard of care with or without placebo, or any other proven intervention for treating COVID-19 and for preventing SARS-CoV-2 infection.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) only.

We will include full-text journal articles published in PubMed-indexed and non-indexed journals, preprint articles, results published in trials registers, clinical study reports (CSRs), and abstract publications. We will apply no restrictions on the language of published articles.

We will screen all studies for research integrity using a tool developed by our group to deal with problematic studies (see Selection of studies).

Types of participants

Treating COVID-19

We will include studies investigating participants with confirmed SARS-CoV-2 infection (RT-PCR or antigen testing), regardless of age, gender, ethnicity, serology status, vaccination status, previous SARS-CoV-2 infection, and risk factors for developing severe COVID-19. If studies included participants with a confirmed or suspected COVID-19 diagnosis, we will use only the data for the patient population with confirmed COVID-19 diagnosis.

In cases where data have not been reported separately for people with confirmed or suspected COVID-19 diagnosis, we will exclude the study.

Preventing SARS-CoV-2 infection

We will synthesize evidence for both, post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) scenarios. For post-exposure prophylaxis, we will include studies investigating participants who were not infected with SARS-CoV-2 at enrolment (negative RT-PCR), but were at high risk of developing the infection following exposure to infected people or infectious viral particles.

For pre-exposure prophylaxis, we will include studies investigating participants who were not infected with SARS-CoV-2 at enrolment (negative RT-PCR) and were not yet exposed to infected people or infectious viral particles but are at increased risk of contacting the disease (e.g. healthcare workers). Participants in both settings would be eligible regardless of age, gender, ethnicity, serology status, vaccination status, previous SARS-CoV-2 infection, and risk factors for developing severe COVID-19. Eligible trials must report the history of previous SARS-CoV-2 infection or serological evidence and the vaccination status of included participants. A history of SARS-CoV-2 infection or vaccination will not be an exclusion criterion.

Types of interventions

All doses and regimens of nirmatrelvir/ritonavir will be eligible for the systematic review. Nirmatrelvir/ritonavir is authorized and approved by the US Food and Drug Administration (FDA) (EUA for Paxlovid) at a dose of 300 mg (as two 150 mg tablets) of nirmatrelvir with one 100 mg tablet of ritonavir, given twice-daily for 5 days.

Types of outcome measures

We will evaluate core outcomes in accordance with the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for COVID-19 patients (COMET 2020; Marshall 2020), and additional outcomes that have been prioritized by consumer representatives and the German guideline panel for treatment of people with COVID-19 (German AWMF Guideline 2021).

We will use different outcome sets for the use of nirmatrelvir/ritonavir for treating people with COVID-19 in the outpatient setting and for preventing SARS-CoV-2 infection. Following the rational from Pfizer that nirmatrelvir/ritonavir is developed to manage outpatients with COVID-19, an outcome set for inpatients is not yet included in the protocol avoiding the impression that studies for this population are needed. However, we do not know whether nirmatrelvir/ritonavir might be a valuable antiviral option for COVID-19 patients at high risk who are hospitalized early after infection. Therefore, if we identify inpatient studies we will include them and use the outcome set for hospitalized COVID-19 patients published elsewhere (Popp 2021b). If studies are eligible for inclusion regarding study design, population, intervention, and comparator, but did not report outcomes of interest, they will not be included for meta-analysis. However, we will summarize reported outcomes for all included studies in the 'Characteristics of included studies' table. We will not exclude studies if they do not report outcomes of interest.

Primary outcomes

Nirmatrelvir/ritonavir for treating COVID-19 in outpatient settings with asymptomatic or mild disease

- All-cause mortality at day 28, day 60, time-to-event, and up to the longest follow-up.
- Worsening of clinical status within 28 days.
  - Admission to hospital or death.
  - Admission to intensive care unit (ICU) or death.
- Improvement of clinical status.
  - All initial symptoms resolved (asymptomatic) at day 14, day 28, and up to the longest follow-up.
  - Time to symptom resolution.
- Quality of life, including fatigue and neurological status, assessed with standardized scales (e.g. WHOQOL-100) at up to 7 days, up to 28 days, and longest follow-up available.
- Serious adverse events during the study period, defined as number of participants with any event.
- Adverse events during the study period, defined as number of participants with any event.
  - Any grade treatment-emergent adverse events (any TEAE).
  - Any grade treatment-related adverse events (TRAE).
  - Discontinuation of study drug due to adverse events.
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, and 3, 7, and 14 days.

Nirmatrelvir/ritonavir for preventing SARS-CoV-2 infection (PrEP and PEP)

We will use the same outcome set for PEP and PrEP scenarios, but with different time frames for the outcome assessment. For PEP studies, the relevant period is 14 to 28 days and for PrEP studies, a longer period of up to 6 months is relevant.

- SARS-CoV-2 infection (confirmed by RT-PCR or antigen testing) at 14 days (PEP) and 6 months (PrEP).
- Development of clinical COVID-19 symptoms up to 28 days (PEP) and 6 months (PrEP); e.g. assessed in accordance with individual items of the WHO scale (Marshall 2020) or any other standardized scale. If the study did not use the standardized WHO scale to assess the status of the participants, we would categorize their status according to the WHO scale with the information provided by the study.
  - Uninfected (WHO scale 0).
  - Ambulatory mild disease (WHO scale 1 to 3).
  - Hospitalized with moderate disease (WHO scale 4 to 5).
  - Hospitalized with severe disease (WHO scale 7 to 9).
  - Mortality (WHO scale 10).
- All-cause mortality up to the longest follow-up.
- Admission to hospital or death within 28 days (PEP) and 6 months (PrEP).
- Quality of life assessed with the standardized scale, WHOQOL-100, up to 28 days (PEP) and 6 months (PrEP), and at longest follow-up available.
- Serious adverse events during the study period, defined as number of participants with any event.
- Adverse events during the study period, defined as number of participants with any event.
  - Any grade treatment-emergent adverse events (any TEAE).
  - Any grade treatment-related adverse events (TRAE).
  - Discontinuation of study drug due to adverse events.

Timing of outcome measurement

We will collect information on outcomes from all time points reported in the publications and study reports. If only a few studies contribute data to an outcome, we will pool different time points, provided the studies produced valid data and pooling was clinically reasonable.

In case of time-to-event analysis, e.g. for time to death, we will use the longest follow-up time measured from randomization.

We will report time points of outcome measurement in the footnotes of the forest plots. We will include serious adverse events and adverse events occurring during the study period, including adverse events during active treatment and long-term adverse events. If sufficient data are available, we will group the measurement time points of eligible outcomes into those measured directly after treatment (up to 7 days), medium-term outcomes (up to 14 days), and longer-term outcomes (28 days or more).

Secondary outcomes

This review protocol specifies no secondary outcomes. All outcomes will be treated as a primary outcome set which will inform the summary of findings tables.

Search methods for identification of studies

Electronic searches

Our Information Specialist (Maria-Inti Metzendorf) will conduct systematic searches in the following sources from the inception of each database to the date of search and will not place restrictions on the language of publication.

- Cochrane COVID-19 Study Register (CCSR) (www.covid-19.cochrane.org), comprising:
  - MEDLINE (PubMed), daily updates;
  - Embase, weekly updates;
  - US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov), daily updates;
  - World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch), weekly updates;
  - medRxiv (www.medrxiv.org), weekly updates;
  - Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates.
- Scopus.
- WHO COVID-19 Global literature on coronavirus disease (search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/).

For detailed search strategies, see Appendix 1. As this review is planned as a living systematic review (LSR), we will conduct monthly update searches. See section 'Methods for future updates' on specific LSR methodology.

We will not conduct separate searches of the databases required by the Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards (Higgins 2021), since these databases are being regularly searched for the production of the CCSR.

Searching other resources

We will identify other potentially eligible studies or ancillary publications by searching the reference lists of included studies, systematic reviews, and meta-analyses.

In addition, we will contact the manufacturer (Pfizer Inc.) through their dedicated website (www.pfizer.com/science/clinical_trials/trial_data_and_results/data_requests) to obtain access to individual de-identified participant data and related study documents, e.g. protocol, statistical analysis plan (SAP), clinical study report (CSR).

Data collection and analysis

Selection of studies

Inclusion criteria

We will perform study selection in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2022). Two review authors (Stefanie Reis (SR) and Stephanie Weibel (SW)) will independently screen titles and abstracts of identified records. We will retrieve full-text articles and independently assess eligibility of the remaining records against the predefined eligibility criteria. We will resolve discrepancies through discussion between the review authors. We will include studies irrespective of whether measured outcome data were reported in a 'usable' way. We will collate multiple reports of the same study, so that the study, rather than the report, will be the unit of interest in the review.

Research integrity screening

Early in this pandemic several studies were identified as unsuitable for public use and were either retracted, withdrawn, or noted with concern (Bramstedt 2020). Current standard tools for systematic reviews do not systematically consider issues of research integrity. However, there are useful tools available such as the 'REAPPRAISED' checklist for evaluation of publication integrity (Grey 2020) or the data extraction sheet from the Cochrane Pregnancy and Childbirth Group that addresses scientific integrity and trustworthiness (Data extraction template 2021). We modified these existing tools and developed a specific tool for studies in this pandemic. This tool along with detailed methodological instructions and critical and important signalling questions to key aspects (domains), is available elsewhere (10.5281/zenodo.6389649). Briefly, all trials fulfilling the PIC (patient, intervention, and comparator) eligibility criteria will be checked for issues with research integrity, such as retraction notices, prospective trial registration, ethics approval, plausible study authorship, sufficient reporting of methods regarding relevant eligibility criteria (e.g. randomization), and plausibility of study results. Studies are only eligible for the review if they meet critical aspects assuring research integrity. Studies will be excluded if they were retracted or if they were not prospectively registered in a national or international studies' registry according to the WHO guidelines for clinical trial registration (WHO 2018). All potentially eligible studies with disparities in the reporting of the methods and results will be hold in 'awaiting classification' until the study authors clarify certain questions upon request. The process will be documented and decisions will be transparently reported.

We will document the study selection process in a PRISMA flow diagram with the total number of studies included, excluded, awaiting classification, and ongoing. We will list the reasons for exclusion and awaiting classification in the 'Characteristics of excluded studies' and 'Characteristics of studies awaiting classification' tables.

Data extraction and management

Four review authors (SR, Maria Popp (MP), Rebecca Kuehn (RK), and SW) in teams of two will independently extract data using a standardized data extraction form, including details of the study, participants, intervention, comparator, and outcomes. If necessary, we will try to obtain missing data by contacting the authors of relevant articles. At each step of data extraction, we will resolve any discrepancies through discussion between the review authors.

We will extract the following information, if reported.

- General information: author, trial name, title, source, country, language, type of publication/report, and publication date.
- Study characteristics: setting and dates, inclusion/exclusion criteria, number of study arms, comparability of groups, length of follow-up, and funding.
- Participant characteristics: number of participants randomized/received intervention/analyzed, COVID-19 diagnostics, severity of disease, age, gender, race, ethnicity, comorbidities (e.g. diabetes, immunosuppression, obesity), concurrent interventions, time since symptom onset, vaccination status (e.g. type of vaccine, number of doses), serology status, and history of SARS-CoV-2 infection.
- Intervention: dose, frequency, time from symptom onset to treatment initiation, and duration and route of administration.
- Control intervention: type of control, dose and frequency, and duration and route of administration.
- Outcomes: as specified under Types of outcome measures.

To address health equity, we will consider the following population characteristics and report them per outcome on the study-level in an additional table.

- Elderly people (older than 65 years). People of advanced age are at increased risk for severe disease. The intervention (nirmatrelvir/ritonavir) could potentially have greater impact in the elderly.
- Persons at social disadvantage due to the number of comorbid health conditions. The intervention (nirmatrelvir/ritonavir) is aimed at persons with at least one risk factor for severe disease. Risk factors include individuals with a comorbid health condition, or multimorbidity, the presence of which is associated with social disadvantage (multimorbidity is associated with a reduction in quality of life, increased disability and premature mortality). The intervention could potentially have greater impact for persons with comorbid health conditions, promoting health equity.
- Populations from low-income countries (LICs), lower and upper middle-income countries (LMICs and UMICs), and high-income countries (HICs) as defined by the World Bank 2022 (studies were categorized based on the date of first participant enrolment).

Differences exist in access to care and the quality of care across LICs, LMICs, UMICs, and HICs. People from LICs and LMICs may not have access to the intervention within 5 days of onset of symptoms of COVID-19. Use of diagnostic tools in LICs and LMICs is also limited. In this context, nirmatrelvir/ritonavir could then be seen to have a potentially greater effectiveness for people from UMICs and HICs.

- People from different ethnic and racial backgrounds, including minorities. Differences exist in access to care and the quality of care across different ethnic and racial minority groups who may not have access to the intervention within 5 days of symptom onset of a SARS-CoV-2 infection. Nirmatrelvir/ritonavir could therefore be seen as having a lower impact in these population groups.

Assessment of risk of bias in included studies

We will assess the risk of bias in the included studies using RoB 2 (Higgins 2022a; Sterne 2019). The effect of interest is the effect of assignment at baseline, regardless of whether the interventions were received as intended (the 'intention-to-treat effect'). We will assess the risk of bias for all results (outcomes) reported in the included studies that we specified as outcomes for the review and that contribute to the review's summary of findings table.

Four review authors (SR, MP, RK, SW) in teams of two will independently assess the risk of bias of all results. We will resolve any disagreements through discussion with a third review author.

The RoB 2 tool considers the following domains:

- bias arising from the randomization process;
- bias due to deviations from the intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

We will assess the RoB 2 domains using the recommended signalling questions and the following response options:

- yes;
- probably yes;
- probably no;
- no; or
- no information.

RoB 2 algorithms map responses to signalling questions. We will use the proposed algorithm after verification to reach a risk of bias judgement, and assign one of three levels to each domain:

- low risk of bias;
- some concerns; or
- high risk of bias.

Similarly, we will reach an overall risk of bias judgement for a specific outcome by considering all domains resulting in one of the three judgement options described above. Overall low risk of bias of the trial result is assumed when all domains are at low risk; some concerns of bias is assumed when the trial result is judged to raise some concerns in at least one domain for this result, but not at high risk of bias for any domain; overall high risk of bias of the trial result is assumed when the trial is at high risk of bias in at least one domain for this result or when it is judged to have some concerns for multiple domains in a way that substantially lowered confidence in the result (Higgins 2022a).

We will use the RoB 2 Excel tool to implement RoB 2 (available at www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2). We will store the full RoB 2 data (e.g. completed Excel tool) in an online repository.

Measures of treatment effect

For dichotomous outcomes, we will record the number of events and the number of analyzed participants in the intervention and control groups. We will use the risk ratio (RR) with 95% confidence interval (CI) as effect measure.

For continuous outcomes, we will record the mean, the standard deviation (SD), and the number of analyzed participants in the intervention and control groups. If the standard deviation is not reported, we will use standard errors, CIs, or P values to calculate the SD with the formulas described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b). If studies have reported data as median with interquartile range (IQR), we assume that the median is similar to the mean when the distribution of the outcome is similar to the normal distribution (e.g. symmetric IQR). In these cases, the width of the IQR is approximately 1.35 SDs (Higgins 2022b). We will use the MD with 95% CI as effect measure.

If available, we will extract and report hazard ratios (HRs) for time-to-event outcomes (e.g. time to death). If HRs are not available, we will make every effort to estimate the HR as accurately as possible from available data using the methods proposed by Parmar and Tierney (Parmar 1998; Tierney 2007). If sufficient studies provide HRs, we plan to use HRs rather than RRs or MDs in a meta-analysis, as they provide more information.

We will consider effect estimates of dichotomous outcomes with the range of the 95% CIs not crossing 1 (the lines of null effect) and continuous outcomes with the range of the 95% CIs not crossing 0 as statistically significant effect estimates. A statistically significant effect does not necessarily mean that the estimated effect is clinically relevant. Clinical experts will assess the clinical relevance of the effects based on anticipated absolute effects separately, and we will report this transparently.

Unit of analysis issues

The unit of analysis for this review is the individually randomized participant.

In studies with multiple intervention groups, we will combine groups if reasonable (e.g. study arms with different doses of nirmatrelvir/ritonavir). If it is not reasonable to pool the groups, we plan to split the 'shared' comparator group to avoid double-counting of participants.

Dealing with missing data

There are many potential sources of missing data in a systematic review or meta-analysis, which can affect the level of studies, outcomes, summary data, individuals, or study-level characteristics (Deeks 2022). Incomplete data can introduce bias into the meta-analysis, if they are not missing at random. We will address all sources of missing data. Missing studies may be the result of reporting bias, and we will address this as described

in the Assessment of reporting biases section. Missing outcomes and summary data may be the result of selective reporting bias; missing individuals may be the result of attrition from the study or lack of intention-to-treat analysis. We will address these sources of missing data using the RoB 2 tool (Assessment of risk of bias in included studies). If data are incompletely reported, we will contact the study authors to request additional information.

Assessment of heterogeneity

We will use the descriptive statistics reported in the 'Characteristics of included studies' table to assess whether the studies within each pairwise comparison are homogeneous enough, with respect to study and intervention details and population baseline characteristics, that the assumption of homogeneity might be plausible. In case of excessive clinical heterogeneity, we will not pool the findings of included studies.

We will measure statistical heterogeneity using the Chi^2 test and the I^2 statistic (Deeks 2022), and the 95% prediction interval (PI) for random-effects meta-analysis (IntHout 2016). The prediction interval helps in the clinical interpretation of heterogeneity by estimating what true treatment effects can be expected in future settings (IntHout 2016). We will restrict the calculation of a 95% PI to meta-analyses with four or more studies (200 participants or more), since the interval is imprecise when a summary estimate is based on only a few small studies. We plan to use the open-source statistical software R package meta to calculate 95% PIs in review updates (Meta 2022). We declare statistical heterogeneity if the P value is less than 0.1 for the Chi^2 statistic, or the I^2 statistic is equal to or greater than 40% (40% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; and 75% to 100%: considerable heterogeneity; Deeks 2022), or the range of the 95% PI reveal a different clinical interpretation of the effect estimate compared to the 95% CI.

Assessment of reporting biases

We will try to identify all research that meets our predefined eligibility criteria. Missing studies can introduce bias to the analysis. We will search for completed non-published trials in trial registers, contact authors to seek assurance that results will be made available, and classify them as 'awaiting classification' until the results are reported. We will report the number of completed non-published trials.

When there are 10 or more relevant studies pooled in a meta-analysis, we plan to investigate risk of reporting bias (publication bias) in pairwise meta-analyses using contour-enhanced funnel plots. If funnel plot asymmetry is suggested by a visual assessment, we plan to perform exploratory analyses (e.g. Rücker's arcsine test for dichotomous data and Egger's linear regression test for continuous data) to further investigate funnel plot asymmetry. A P value of less than 0.1 will be considered as the level of statistical significance. We will analyze reporting bias using the open-source statistical software R package meta (Meta 2022).

Data synthesis

If necessary, dosing schemes will be considered and categorized into recommended (300 mg nirmatrelvir/100 mg ritonavir, twice-daily for 5 days), low (< recommended dose), and high doses (> recommended dose). We plan to analyze different doses in subgroup analyses, if sufficient studies are available.

We will compare nirmatrelvir/ritonavir plus standard of care to standard of care with or without placebo, or to any active comparator with proven efficacy. Co-interventions (standard of care) must have been comparable between the study arms. Active comparators with proven efficacy are defined as those recommended by the WHO living guideline (WHO 2021b). For patients that qualify for a proven active intervention, it would be unethical to further conduct trials that use placebo only. In contrast, studies using comparators with proven ineffectiveness (e.g. azithromycin, Popp 2021b) may confound the assessment of the efficacy or safety of nirmatrelvir/ritonavir and are not eligible. From these comparisons, no reliable evidence can be obtained.

We will create the following comparisons:

- nirmatrelvir/ritonavir plus standard of care versus standard of care (plus/minus placebo); and
- nirmatrelvir/ritonavir versus active pharmacological intervention with proven efficacy.

We will analyze trials with different intentions of nirmatrelvir/ritonavir use separately, as follows.

- Treatment of COVID-19 in an outpatient setting: participants with confirmed SARS-CoV-2 infection.
- Prevention of SARS-CoV-2 infection (post-exposure prophylaxis): RT-PCR negative participants at baseline with a high risk of developing the infection following exposure to infected people or infectious viral particles.
- Prevention of SARS-CoV-2 infection (pre-exposure prophylaxis): RT-PCR negative participants at baseline not yet exposed to infected people or infectious viral particles but at increased risk of contacting the disease (e.g. healthcare workers).

We will perform meta-analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022). Forest plots will be used to visualize meta-analyses.

If clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will pool the data in meta-analyses. When meta-analysis are feasible, we will use the random-effects model as we assume that the intervention effects are related but are not the same for the included studies. For dichotomous outcomes, we will perform meta-analyses using the Mantel-Haenszel method under a random-effects model to calculate the summary (combined) intervention effect estimate as a weighted mean of the intervention effects estimated in the individual studies. For continuous outcomes, we will use the inverse-variance method.

We plan to present descriptive statistics only, if we deem meta-analysis inappropriate for a certain outcome because of heterogeneity or because of serious study limitations leading to considerably high risk of bias (e.g competing risk of death not taken into account in outcome measurement).

We will use RevMan Web software for meta-analyses (RevMan Web 2020).

Subgroup analysis and investigation of heterogeneity

We will report details of the intervention and population at baseline for each study in the footnotes of the forest plot. We will investigate heterogeneity by visual inspection of the forest plot.

If statistical heterogeneity is present, we plan to investigate heterogeneity by subgroup analysis to calculate RR or MD in conjunction with the corresponding CI for each subgroup, if sufficient studies are available. Statistical heterogeneity is defined as $P < 0.1$ for the Chi^2 test of heterogeneity, I^2 of 40% or greater, or a different clinical conclusion of 95% CI versus 95% PI.

Health equity considering elderly people, socially disadvantaged people with comorbidities, populations from LICs/LMICs, and people from different ethnic and racial backgrounds will be investigated using subgroup analysis independent of statistical heterogeneity.

We will perform subgroup analyses for the following characteristics.

- Nirmatrelvir/ritonavir used as treatment (outpatients):
  - studies including different populations regarding age of the population (children versus adults versus older adults (greater than 65 years));
  - studies including participants with different level of comorbidity (high-risk versus low-risk population);
  - studies including participants from high-, middle-, or low-income country settings and populations according to the World Bank classification (World Bank 2022) (LICs/LMICs versus UMICs/HICs);
  - studies including different racial and ethnic groups (Asian, Black, White, Hispanic, and minority ethnic groups);
  - studies including participants with different severities of condition at baseline (symptomatic versus asymptomatic);
  - studies including participants with a history of SARS-CoV-2 infection/vaccination versus participants with no history of infection/vaccination;
  - studies with different recruitment periods examining different dominant virus variants circulating at the time of the study (e.g. Alpha versus Beta versus Gamma versus Delta versus Omicron, etc.);
  - studies that started nirmatrelvir/ritonavir treatment early versus late (more than 5 days after symptom onset);
  - studies investigating different doses of nirmatrelvir/ritonavir (low versus recommended versus high).
- Nirmatrelvir/ritonavir used for prevention:
  - studies including different populations regarding age of the population (children versus adults versus older adults (greater than 65 years));
  - studies including participants with different level of comorbidity (high-risk versus low-risk population);
  - studies including participants from high-, middle-, or low-income country settings and populations according to the World Bank classification (World Bank 2022) (LICs/LMICs versus UMICs/HICs);
  - studies including different racial and ethnic groups (Asian, Black, White, Hispanic, and minority ethnic groups);
  - studies including participants with a history of SARS-CoV-2 infection/vaccination versus participants with no history of infection/vaccination;
  - studies investigating different modes of exposure (e.g. working place, nursing home) and burden of exposure (e.g. living in a high-risk area, high-risk medical contact) in prevention studies;
  - studies with different recruitment periods examining different dominant virus variants circulating at the time of the study (e.g. Alpha versus Beta versus Gamma versus Delta versus Omicron, etc.);
  - studies investigating different doses of nirmatrelvir/ritonavir (low versus recommended versus high).

Sensitivity analysis

We will conduct sensitivity analyses to test the robustness of the meta-analyses. We will exclude:

- studies with overall high risk of bias;
- non-peer reviewed studies (including preprint articles);
- studies reporting data as median instead of mean for continuous outcomes;
- studies using no treatment in the comparator arm for patient-reported outcomes such as symptom resolution.

Summary of findings and assessment of the certainty of the evidence

We will present the main results of the review in summary of findings tables, including a rating of the certainty of evidence based on the GRADE approach. We will follow current GRADE guidance as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022).

Two review authors (SR, SW) will assess the certainty of evidence, considering risk of bias, inconsistency, imprecision, indirectness, and publication bias. We will use the overall RoB 2 assessment and RoB sensitivity analysis to inform the risk of bias judgement underlying the assessment of the certainty of evidence.

We will create separate summary of findings tables for the use of nirmatrelvir/ritonavir with different intentions (e.g. treatment of people with COVID-19 in outpatient settings, prevention of SARS-CoV-2 infection as PEP, and prevention as PrEP), and for different comparisons with regard to the intervention and comparator. The summary of findings tables will include the following outcomes.

For use of nirmatrelvir/ritonavir with intention to treat COVID-19 in an outpatient setting.

- All-cause mortality; all-cause mortality at longest follow-up and > 60 days most favourable; if not reported all-cause mortality day 60, followed by day 28, or time-to-event estimate, will be included in the summary of findings table.
- Admission to hospital or death within 28 days.
- Symptom resolution.
  - All initial symptoms resolved (asymptomatic) at day 14.
  - Time to symptom resolution.
- Quality of life at longest follow-up available.
- Serious adverse events during the study period.
- Adverse events during the study period.
  - Any grade treatment-emergent adverse events (any TEAE).
  - Any grade treatment-related adverse events (TRAE).
- Viral clearance at 7 days.

For use of nirmatrelvir/ritonavir with intention to prevent SARS-CoV-2 infection (PEP).

- SARS-CoV-2 infection (confirmed by RT-PCR or antigen testing) at 14 days.
- Development of clinical COVID-19 symptoms up to 28 days.
- All-cause mortality up to the longest follow-up.
- Admission to hospital or death within 28 days.
- Quality of life at longest follow-up available.
- Serious adverse events during the study period.
- Adverse events during the study period.
  - Any grade treatment-emergent adverse events (any TEAE).
  - Any grade treatment-related adverse events (TRAE).

For use of nirmatrelvir/ritonavir with intention to prevent SARS-CoV-2 infection (PrEP).

- SARS-CoV-2 infection (confirmed by RT-PCR or antigen testing) at 6 months.
- Development of clinical COVID-19 symptoms up to 6 months.
- All-cause mortality up to the longest follow-up.
- Admission to hospital or death within 6 months.
- Quality of life at longest follow-up available.
- Serious adverse events during the study period.
- Adverse events during the study period.
  - Any grade treatment-emergent adverse events (any TEAE).
  - Any grade treatment-related adverse events (TRAE).

The GRADE assessment result in one of four levels of certainty and these express our confidence in the estimate of effect (Balshem 2011).

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We will address equity for all outcomes presented in summary of findings tables. Interpretation of evidence will occur for the specific populations (see Data extraction and management) which are defined as important recipients of the intervention.

- Elderly people.
- People at social disadvantage due to the number of comorbid health conditions.
- People from LICs/LMICs.
- People from different ethnic and racial backgrounds, including minorities.

Interpretation considers the questions, whether findings likely to be applicable in those populations, even if they did not make up a large proportion of the participant populations in included studies.

We will report inequities in the footnotes of the summary of findings tables.

We will use the MAGICapp to create summary of findings tables (MAGICapp), and incorporate the results into RevMan Web manually (RevMan Web 2020).

Methods for future updates - Living systematic review considerations

Our information specialist (MIM) will provide us with new search records each month, which two review authors will screen, extract, evaluate, and integrate following the guidance for Cochrane living systematic reviews (Cochrane LSR). We will create and maintain monthly an Excel list of new studies potentially to be included. This list will be publicly available and implemented by including a link to an open science framework (OSF) in the review and maintaining this list in OSF monthly.

We will manually check platform trials for new treatment arms investigating nirmatrelvir/ritonavir.

We will wait until the accumulating evidence changes our conclusions of the implications of research and practice before republishing the review. We will consider one or more of the following components to inform this decision.

- The findings of one or more prioritized outcomes.
- The credibility (e.g. GRADE rating) of one or more prioritized outcomes.
- New settings, populations, interventions, comparisons, or outcomes studied.

In the case of emerging policy relevance due to global controversies regarding the intervention, we will consider republishing an updated review even though our conclusions remain unchanged. We will review the review scope and methods approximately monthly, or more frequently if appropriate, in light of potential changes in COVID-19 research (e.g. when additional comparisons, interventions, subgroups, or outcomes, or new review methods become available).

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- Contact Editor: Professor George Rutherford;
- Sign-off Editor (final editorial decision): Professor Paul Garner;
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Dr Deirdre Walshe;
- Copy Editor (copy editing and production): Luisa M Fernandez Mauleffinch, Cochrane Copy Edit Support;
- Peer-reviewers (provided comments and recommended an editorial decision):
  - protocol stage: Dr Paul Hine, Liverpool, UK (clinical content peer review); Dr Marty Chaplin, Cochrane Infectious Diseases Group (CIDG) Statistical Editor (statistical peer review); Dr Vittoria Lutje, CIDG Information Specialist (search peer review); Maria Rosaria Cozzolino, RN MSN, Emergency

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Emma Sydenham (Co-ordinating Editor, Cochrane Injuries) advised on trial regulatory compliance.

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APPENDICES

Appendix 1. Search strategies

Cochrane COVID-19 Study Register (CCSR)
Search string**:** "PF-07321332" OR "PF 07321332" OR "PF07321332" or paxlovid* or nirmatrelvir*

Study characteristics:
1) "Intervention assignment": “Randomised” OR
2) "Study design": "Parallel/Crossover" AND "Unclear" OR
3) "Study type": "Adaptive/Platform"

Scopus
TITLE-ABS-KEY ("PF-07321332" OR "PF 07321332" OR "PF07321332" OR paxlovid* OR nirmatrelvir*)

WHO COVID-19 Global literature on coronavirus disease
Title, abstract, subject: "PF-07321332" OR "PF 07321332" OR "PF07321332" or paxlovid* or nirmatrelvir*

CONTRIBUTIONS OF AUTHORS

- Stefanie Reis (SR): methodological expertise, and writing the protocol.
- Maria Popp (MP): methodological expertise and proofreading the protocol.
- Rebecca Kuehn (MS): methodological expertise and writing the protocol.
- Maria-Inti Metzendorf (MIM): search strategy design and writing the protocol.
- Ildikó Gágyor (IG): methodological expertise and proofreading the protocol.
- Peter Kranke (PK): clinical expertise and advice, and proofreading the protocol.
- Patrick Meybohm (PM): clinical expertise and advice, and proofreading the protocol.
- Nicole Skoetz (NS): methodological expertise and advice, and proofreading the protocol.
- Stephanie Weibel (SW): methodological expertise, conception, and writing the protocol.

DECLARATIONS OF INTEREST

- Stefanie Reis (SR) has no known conflicts of interest to declare.
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