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Favipiravir for treating COVID-19 (Protocol)

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[Intervention Protocol]

Favipiravir for treating COVID-19

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ABSTRACT

Objectives

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

To determine the efficacy and safety of favipiravir in patients with COVID-19 as compared to standard of care without favipiravir.

BACKGROUND

Description of the condition

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an infectious agent causing a potentially life-threatening respiratory tract infection. After the initial outbreak in Wuhan, China, the World Health Organization (WHO) designated the disease associated with the virus as coronavirus disease 2019, or COVID-19. Since then, the COVID-19 pandemic has been an unprecedented phenomenon with almost 423 million confirmed infections and nearly 5.8 million confirmed deaths as of 22 February 2022 (WHO 2022). The Americas account for almost 44% of the world's cumulative deaths, Europe about 31%, and the South-East Asia region 12% of cumulative global deaths (WHO 2022). New cases continue to rise in some parts of the world at the time of writing (WHO 2022).

In low- and middle-income countries (LMICs) there continue to be challenges with regard to hospitalizations and deaths owing to a lack of robust public health infrastructure and vaccine availability. Around the globe, there has been waxing and waning in the number of infections, morbidity, and mortality following COVID-19 infection due to circulating variants despite public health and social measures (PHSM) (WHO 2022). Thus, the global public health risk remains high according to the WHO's rapid risk assessments. Global efforts are ongoing to enhance infection control and vaccination (WHO 2021). Although vaccine efficacy has been established, most of the world's population still has difficulty in accessing vaccines which has been a major focus for international health bodies like WHO (CDC 2021). For countries with good vaccine access and availability, tackling vaccine hesitancy seems to be the challenge (WHO 2021). Infections in adolescents and children could be a potential challenge for health systems (Hashemian 2021) as the cost effectiveness of vaccinating this group is still unclear.

SARS-CoV-2 is a lipid membrane enveloped ribonucleic acid (RNA) virus distantly related to the Middle Eastern respiratory syndrome coronavirus (MERS-CoV) and perhaps more closely related to bat coronaviruses, suggesting bat to human transmission may have been the source of the outbreak (NIH 2021b). It is transmissible through the respiratory route in humans via respiratory particles. The virus has a droplet or an aerosol spread via talking, sneezing, and coughing in enclosed spaces. Entry into the host's respiratory tract appears to be through the binding of the virus's spike glycoprotein (S) to the host's angiotensin-converting enzyme-2 (ACE-2) receptors. The transmembrane serine protease 2 (TMPRSS2) of the host's cell also is thought to prime the spike protein for entry into the cell (NIH 2021a). Fusion of the virus membrane with the host cell membrane facilitates entry into the human cell.

With the ancestral strain, though some had asymptomatic disease, amongst those symptomatic, 80% were mild illness (no pneumonia, or mild pneumonia, with or without mild hypoxia). Around 15% had severe disease, with increasing requirement of oxygen and other respiratory support, and about 5% had critical disease often requiring ventilatory support (Chinese CDC 2020).

Common symptoms include fever, myalgia (muscle pain), headache, cough, sore throat, anosmia (loss of smell), and diarrhoea, and the symptomatology has varied slightly depending on the strain. Risk factors for severe or critical disease include the male sex, increasing age, and a number of pre-existing medical conditions (Hassanipour 2021; Thompson 2021). Involvement of the lower respiratory tract with the infection, and a secondary inflammatory response, results in acute respiratory distress syndrome (ARDS) in critically ill patients. The phenomenon of human hosts being infectious prior to the onset of symptoms has made the control of transmission particularly challenging. Mutations in the virus is an ongoing global issue, with some contributing to increased infections (even among vaccinated people), transmission, and even deaths (Kuehn 2021). The Delta variant in the last year (2021) and the Omicron variant this year (2022) have been the most prevalent globally, although data showing that vaccinated populations have a lower incidence of severe to critical disease seems encouraging despite these challenges (Hoffmann 2020; WHO 2022).

Finding optimal pharmacological agents and treatment strategies continues to be an important priority in tackling COVID-19. This is true as hospitals continue to have a steady influx of patients, despite reasonable vaccine coverage. It is likely that the disease may become endemic. The recent variants have reported a lower efficacy of vaccination, suggesting that we need to continue to explore therapeutic interventions, especially antivirals which may attenuate progression to severe disease (Bernal 2021).

Targets for therapeutic intervention include structural proteins involved in viral-host cell binding and fusion, or the non-structural proteins like RdRP (RNA-dependent RNA polymerase), 3C-like protease ($3CL^{pro}$), and papain-like proteases (PL^{pro}). Examples of drugs that target RdRP include remdesivir and favipiravir. Neutralizing antibodies from convalescent plasma or monoclonal antibodies could inhibit the ability of the virus to bind and fuse to the host cells but may have variable utility depending on the type of viral variant and absence of antibodies (Wu 2020). Modulation of the host response to the virus using anti-inflammatory agents such as steroids and interleukin (IL) inhibitors, antithrombotic and anticoagulant agents which mitigate the tendency for thrombosis secondary to the inflammatory response, seems to impact mortality and morbidity (Abou-Ismail 2020; Braz-de-Melo 2021; Horby 2020; Spyropoulos 2021).

The quest for an ideal therapeutic intervention that is easy to administer and prevents progression to severe or critical illness in those with mild symptomatic COVID-19, led to many irrational therapies being administered to patients based on anecdotal or even fraudulent evidence. Some of these include ivermectin, chloroquine/hydroxychloroquine (Singh 2021a), or antibiotics like azithromycin (Ayerbe 2022). Antivirals are hypothetically likely to have maximal benefit when used early in the disease course. Remdesivir was proven to have little utility when given in hospitalized patients with moderate to critical disease (Ansems 2021). However, it does lower risk of hospitalization or death (87%) in mild COVID-19 infection when used in early disease in non-hospitalized patients (Gottlieb 2022). Molnupiravir, by Ridgeback Biotherapeutics and Merck, is the first oral antiviral for COVID-19, and has demonstrated a marginal benefit of 33% in reducing hospitalization or death in mild infection in those with risk factors for severe disease (Singh 2021b). Paxlovid, an oral antiviral drug developed by Pfizer, is a combination of nirmatrelvir and ritonavir, and has been given emergency use authorization by the United States Food and Drug Administration (FDA) based on data from a phase II/III trial which demonstrated that Paxlovid reduced COVID-19 related hospitalizations and deaths by 88% (FDA 2021).

Description of the intervention

Historically, favipiravir (T-705) is a synthetic prodrug, discovered while assessing the antiviral activity of agents active against influenza (Furuta 2013). It was approved as a treatment for novel or re-emerging influenza viruses in Japan in 2014 based on clinical trial data (Shiraki 2020). It was also found to be effective for the prevention and treatment of Ebola virus infections in animal models (Oestereich 2014), and hence the drug was recommended as a possible treatment during the pandemic in Africa in 2014 since there were no other suitable alternatives available at that time (Bai 2016; Jacobs 2015). Similarly, this drug found a role in the treatment of Lassa fever (Raabe 2017) and norovirus infections (Ruis 2018).

Favipiravir is administered orally, has excellent bioavailability (~94%), and reaches maximum blood concentration within 2 hours after the first dose. Favipiravir has a short half-life (about 2.5 to 5 hours) with rapid renal elimination in a hydroxylated form (Hayden 2019). This drug needs to be given in relatively high doses to achieve an effect. However, the optimal dose and duration for favipiravir in the treatment of COVID-19 is still unknown. Most clinical trials related to COVID-19 have used favipiravir in varying doses ranging from 1.6 g twice daily on day 1, followed by 600 mg twice daily, for a total duration of 7 to 14 days (Cai 2020), or 0.8 g twice daily on day 1, followed by 800 mg twice daily, for a total duration of up to 14 days (Cai 2020; Ivashchenko 2021).

Safety data are limited. The most common adverse effects are chest pain, nausea, anorexia, hepatitis, and hyperuricaemia (raised uric acid level in the blood). Favipiravir is contraindicated in severe hepatic and renal impairment, pregnancy, and breastfeeding based on its association with embryonic deaths and possible teratogenicity (Hayden 2019).

Drug-drug interactions are possible. As a CYP2C8 inhibitor it may interfere with the metabolism, and therefore the concentrations, of various drugs, including repaglinide and theophylline (Fujifilm 2017; Hayden 2019). An additive effect of increasing serum uric acid concentrations may occur with drugs also increasing uric acid levels, such as pyrazinamide. In addition, the administration of this drug is contraindicated when inactivated influenza vaccine has been given in the last 2 weeks or is planned to be given (Hayden 2019).

How the intervention might work

The activity of the viral-RdRp of SARS-CoV-2 is 10 times more active than any other known viral-RdRp enzyme (Furuta 2013; Shannon 2020). Favipiravir acts by inhibiting RdRp, without affecting human DNA. Administered as a prodrug, after entering the cell it undergoes phosphorylation and is converted to favipiravir-RTP, which acts as a nucleotide leading to viral mutagenesis (Caroline 2014).

The optimal dose of favipiravir is not well-established. In treating Ebola virus disease, higher doses of favipiravir were used based on pre-clinical studies showing that the target concentrations needed to inhibit the Ebola virus were higher than that in influenza (Hashemian 2021). Thus, varying doses have been used in clinical trials related to COVID-19 (Joshi 2021). Even though uncertainties exist, the clinical dose of favipiravir in several countries is 1800 mg twice daily on day 1, followed by 800 mg twice daily on days 2 to 14 (Bhagat 2021).

Favipiravir being an antiviral, is postulated to be most effective in COVID-19 when given early in the disease course, by reducing viral replication (Agrawal 2020). This could reduce transmission of the virus as well as the risk of progression to severe disease (Joshi 2021). Being an oral drug, it may be most effective for outpatients or inpatients with early and mild or moderate disease (Udwadia 2021).

Why it is important to do this review

Despite the promise of vaccination, substantial numbers of people are still developing COVID-19 worldwide, with some requiring hospital admission. It is likely the virus will become endemic with intermittent surges affecting susceptible individuals (Telenti 2021). Thus, it is imperative to find pharmacological agents to effectively treat the virus. Re-purposing of an existing drug for the treatment of COVID-19 is an attractive option. Oral drugs like chloroquine, hydroxychloroquine, and ivermectin were previously considered to hold some promise, however, good randomized controlled trials and systematic reviews have concluded lack of efficacy (Popp 2021; Singh 2021a).

Early studies with favipiravir showed some promise as well, including an open-label, non-randomized study from China that reported significant improvement in chest computerized tomography (CT) scan appearances (Cai 2020), and a phase II/III clinical trial from Russia that showed significant improvement in clearance of SARS-CoV-2 from the nose and throat of COVID-19 patients (Ivashchenko 2021).

More recent trials from China showed the use of favipiravir had no significant benefit in clinical outcomes (Chen 2021). A recent trial from Japan reported that favipiravir shortens the time of clinical improvement by 3 days (Shinkai 2021).

Most existing systematic reviews of the safety and efficacy of favipiravir against standard of care or other antiviral agents included non-randomized studies in their analyses (Hassanipour 2021; Özlüşen 2021). Additionally, they did not assess certainty in the evidence using GRADE principles to provide a summary of findings.

Favipiravir is administered orally and has been used widely for influenza in some countries. With the widespread availability of rapid antigen and reverse transcription polymerase chain reaction (RT-PCR) tests for early diagnosis of SARS-CoV-2, favipiravir could make a difference when started early in the course of the disease. Some guidelines mention that it shows viral clearance in mild COVID-19 but do not make any recommendations (ESCMID 2021), while others recommend against its use in all COVID-19 severities (Covid Guidelines India 2021). The PRINCIPLE trial based in ambulatory settings announced their favipiravir arm in April 2021 (PRINCIPLE Trial 2021). There may also be scope for post-exposure prophylaxis with this drug, especially if early treatment is found to be promising (Caroline 2014; Furuta 2013).

The continuing need for evidence-based antiviral options for COVID-19 requires a well-conducted systematic review of the efficacy and safety of favipiravir in treating people with COVID-19. Moreover, one randomized controlled trial of significance has since been retracted (Dabbous 2021).

This is potentially a very important review given that COVID-19 may become more endemic with repeated viral mutations affecting the efficacy of available vaccines. Also, that the results of the review

would be important for patients and inform healthcare providers more distinctly, considering the countable antivirals available as therapeutic options since the commencement of COVID-19. It would add clarity to therapeutic strategies for COVID-19 for policy makers.

OBJECTIVES

To determine the efficacy and safety of favipiravir in patients with COVID-19 as compared to standard of care without favipiravir.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

Patients with confirmed COVID-19 as defined by the study authors.

Types of interventions

Intervention

Favipiravir (any dose, route, duration).

Control

No favipiravir (this could include standard care, placebo, or other experimental antiviral treatment).

Types of outcome measures

The following outcome sets were classified into two categories: primary outcome as critical and secondary outcomes as important.

Primary outcomes

- **All-cause mortality - at 28 to 30 days, or in-hospital.**

Secondary outcomes

All measurements are made at 28 to 30 days or in-hospital.

- **Progression to invasive mechanical ventilation.**
- **Need for admission to hospital (if ambulatory).**
- **Time to clinical improvement** (defined as time to a two-point reduction in patients' admission status on WHO's ordinal scale).
- **Progression to oxygen therapy.**
- Need for critical or intensive care (any reason).
- Progression to non-invasive ventilation.
- Duration of hospitalization.
- Time to negative PCR for SARS-CoV-2.
- Adverse events**.**
  - **All adverse events.**
  - **Serious adverse events attributable to the drug.**
  - Hyperuricaemia.

(Outcomes listed in bold will be included in the summary of findings table.)

Search methods for identification of studies

We will attempt to identify all relevant trials regardless of language or publication status.

Electronic searches

We will search the following databases.

- Cochrane COVID-19 Study Register (CCSR) (covid-19.cochrane.org/) comprising: Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates; 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 (WHO ICTRP) (www.who.int/trialsearch), weekly updates; medRxiv (www.medrxiv.org), weekly updates.
- Web of Science Clarivate: Science Citation Index Expanded; WHO COVID-19 Global literature on coronavirus disease (search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/).
- COVID Network Meta-Analysis (COVID-NMA) (www.covid-nma.com).
- Epistemonikos (www.epistemonikos.org/).

The strategy for the Cochrane COVID-19 Study register (CCSR) is presented in Appendix 1; all search terms used in the databases listed will be reported in the final review.

Searching other resources

We will attempt to 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 principal investigators of the included studies to obtain additional information on the retrieved studies if required.

Data collection and analysis

We will use the web-based software platform (Covidence) to help us screen and select studies, and to extract data.

Selection of studies

Three review authors (Pritish Korula (PK), Hanna Alexander (HA), and Jisha John (JJ)) will independently screen the titles and abstracts of the records retrieved by the search using Covidence to exclude duplicate publications. The authors will independently assess the abstracts of potentially relevant studies and the full papers against the eligibility criteria. We will seek clarifications from study authors, if needed. Disagreements will be resolved by discussion or by seeking the opinion of another author (Priscilla Rupali (PR)). All excluded studies will also be independently checked by other authors (PR and Prathap Tharyan (PT)) for appropriateness. We will describe the reasons for excluding studies in the 'Characteristics of excluded studies' table. We will present the search and selection process in a PRISMA flow diagram.

Research integrity screening

We will use a research integrity checklist (RICS) to screen for any problematic studies, that is "any published or unpublished study where there are serious questions about the trustworthiness of the data or findings" (Cochrane 2022). This includes six criteria:

whether retraction notices or notices of concern have been published; if the trial has been prospectively registered; if the trial has ethical approval; if the trial authorship is plausible; if the methods are reported in sufficient detail; and if the results are plausible. We are in touch with the innovators of this tool for support (Reis 2022).

Data extraction and management

Three review authors (PK, HA, and JJ) will extract data independently and in duplicate, using a piloted, customized data extraction form developed using the Covidence platform. We will contact study authors for any clarifications and for missing information. Any disagreements will be resolved through discussion or by consulting a fourth review author (PR).

The following data will be collected.

- General information: author, title, source, publication date, country, language, and duplicate publications.
- Study characteristics: trial design, setting, and dates, source of participants, inclusion/exclusion criteria, comparability of groups, treatment cross-overs, compliance with assigned treatment, and length of follow-up.
- Participant characteristics: age, gender, ethnicity, number of participants recruited/allocated/evaluated, additional diagnoses, the severity of disease, previous treatments, concurrent treatments, and co-morbidities (e.g. diabetes, respiratory disease, hypertension, immunosuppression, obesity, heart failure).
- Interventions: dosage, frequency, timing, duration and route of administration, setting, and duration of follow-up.
- Control interventions (placebo or standard care alone): dosage, frequency, timing, duration and route of administration, setting, and duration of follow-up.
- Outcomes: all the prespecified outcomes. For dichotomous outcomes, we will extract the number of events and the total number of participants in both the treatment and control groups. For continuous outcomes, we will extract the mean, standard deviation, and total number of participants in both the treatment and control groups. For time-to-event outcomes (e.g. time to hospital discharge), we will extract hazard ratios (HRs), if sufficient information is available. When HRs are not available, we will contact the authors for additional information.

We will describe these details for each included study in the 'Characteristics of included studies' table.

Assessment of risk of bias in included studies

We will assess the risk of bias in each included study using the RoB 2 tool (beta version 7) (Sterne 2019).

Three review authors (PK, HA, and JJ) will independently assess the risk of bias for each outcome using the RoB 2 tool to record assessments for each outcome. In case of discrepancies in judgements, a third review author will be consulted to reach a final decision. We will assess the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). The primary analysis for efficacy outcomes will be an available-case analysis where the denominator is the number of patients completing follow-up to the point of outcome assessment, where possible. Where this is not possible, we will perform an intention-to-treat analysis, with investigation of the effects of missing data. For safety outcomes, we plan to include all participants receiving at least one dose of the intervention drug or placebo.

- 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.
- Bias in selection of the reported result.

The algorithms proposed by RoB 2 assign each domain one of the following levels of bias.

- Low risk of bias.
- Some concerns.
- High risk of bias.

Subsequently, the overall risk of bias rating for each prespecified outcome in each study is in accordance with the following suggestions.

- 'Low risk of bias': we judge the trial to be at low risk of bias for all domains for the result.
- 'Some concerns': we judge the trial to raise some concerns in at least one domain for the result, but not to be at high risk of bias for any domain.
- 'High risk of bias': we judge the trial to be at high risk of bias in at least one domain for the result, or we judge the trial to have some concerns for multiple domains in a way that substantially lowers our confidence in the result.

Measures of treatment effect

Dichotomous data

We will use the risk ratio (RR) with its associated 95% confidence interval (CI), and risk difference (RD) with its associated 95% CI (Deeks 2021).

Continuous data

Where continuous outcomes used the same units or scale, we will use the mean difference (MD) with 95% CIs. For time-to-event outcomes (e.g. time to hospital discharge), we will use hazard ratios (HRs).

For continuous outcomes measured with different units or scales, we will pool the data using the standardized mean difference (SMD). While interpreting SMDs, we will use the methods described in Murad 2019 to convert and interpret the pooled SMDs as mean differences with 95% CIs in the original units of a scale with the most clinical relevance and impact.

Unit of analysis issues

If there are multi-arm trials encountered during the study, only the relevant arms would be included. If more than two treatment arms are considered relevant, we will combine data from the relevant arms in the meta-analysis, using the methods described in Higgins 2021b.

If cluster trials are encountered then the appropriate analysis would be conducted to adjust for the same. The intracluster

correlation coefficient (ICC) would be used for unadjusted data or we will attempt to obtain these data from study authors if needed. If there is a need to adjust for the ICC, then sensitivity analysis would be done for the same.

Dealing with missing data

For efficacy outcomes, we will perform intention-to-treat analysis where the denominator is the number of participants completing follow-up to the point of outcome assessment. Where this is not possible, we will perform an available-case analysis. For safety outcomes, the denominator will include all participants receiving at least one dose of favipiravir, where possible. If there was discrepancy in the numbers randomized and the numbers analyzed in each treatment group, we will calculate the percentage loss to follow-up in each group and report this information. We will use this information in making judgements about the risk of attrition bias and in making judgements about the overall certainty of the evidence when summarizing findings.

Assessment of heterogeneity

We will assess heterogeneity by visually inspecting the forest plots to determine the closeness of point estimates with each other and the overlap of CIs. We will use the Chi^2 test with a P value of 0.10 to indicate statistical significance, and the I^2 statistic to measure heterogeneity. We will use the following ranges outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* to interpret the I^2 statistic (Higgins 2019):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We will also consider the magnitude and direction of effects, and the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test), when determining the importance of the observed I^2 value.

Assessment of reporting biases

We will assess all included studies for adequacy of reporting of data for pre-stated outcomes and for selective reporting of outcomes. We will note judgements based on the risk of selective reporting in the domain 5 of the risk of bias tables for each included study.

Publication bias

We will perform a comprehensive search to identify completed trials that have not been published, to minimize publication bias or determine publication bias. We intend to explore potential publication bias for meta-analyses involving at least 10 trials by generating a funnel plot and using the Egger's test to assess asymmetry of the funnel plot (Sterne 2019).

Data synthesis

If the individual studies are clinically and methodologically homogeneous, we will pool the data in meta-analysis following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021).

We will use Review Manager Web (RevMan Web; RevMan Web 2020) for analyses. One review author will enter the data, and a second review author will check the data for accuracy.

We will synthesize dichotomous data with the Mantel-Haenszel method to derive pooled weighted risk ratios in fixed-effect meta-analyses.

Continuous data summarized by arithmetic means and standard deviations will be combined using the inverse variance method to derive the mean difference in fixed-effect meta-analyses. We will use the generic inverse variance method for continuous outcomes that include data from cluster-randomized controlled trials, or outcomes where hazard ratios were available.

For continuous outcomes measured with different units or scales, we will pool the data using the standardized mean difference (SMD). While interpreting SMDs, we will use the methods described in Murad 2019 to convert and interpret the pooled SMDs as mean differences with 95% confidence intervals in the original units of a scale with the most clinical relevance and impact.

We plan to combine the analysis for different control groups i.e. assess it as favipiravir versus no favipiravir (standard of care, placebo, or a comparator not considered efficacious for treatment of COVID-19).

We will start with a random-effects model as we anticipate that the sampling frame is likely to include populations of different severity, different countries, different standards of care, etc. We will not choose a model based on a test of heterogeneity. Only if we find that the true effect size does not vary from study to study, we will opt for or choose a fixed-effect model. We feel that this approach will not need us to undertake a sensitivity analysis but we will do so if required. If random-effects analyses are used, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 (an estimate of the between-study variance) and I^2. We will incorporate this information while grading the certainty of the evidence due to inconsistency in the summary tables.

Subgroup analysis and investigation of heterogeneity

We plan to assess for heterogeneity by performing subgroup analysis on patients with COVID-19 based on their:

- severity of illness: according to WHO criteria (WHO 2020);
- administration of intervention: ≤ 7 days of admission/symptoms versus > 7 days of admission/symptoms;
- dose: ≥ 1600 mg/day and < 1600 mg/day;
- duration of the intervention: < 7 days versus > 7 days of drug administration.

Sensitivity analysis

Sensitivity analysis will be performed to assess the effect of risk of bias on the outcomes prioritized for inclusion in the summary of findings table. Trials at high risk of bias will be removed from the meta-analysis for each of these outcomes to assess the robustness of the findings. A sensitivity analysis will also be performed to determine if the data available from pre-prints provide valid conclusions.

Summary of findings and assessment of the certainty of the evidence

We will use the GRADE approach to create a summary of findings table and to interpret the findings (Schünemann 2021a; Schünemann 2021b).

We will use an overall risk of bias from the Cochrane RoB2 tool in the GRADE output from each study to judge a cumulative risk of bias grade for each outcome.

The seven outcomes in bold type within the Types of outcome measures section have been prioritized for inclusion in this summary table. The table will include information concerning the relative and absolute effects for the selected outcomes along with our grading of the certainty of the evidence for each outcome. The GRADE framework would be used to evaluate the certainty of evidence as developed by the GRADE working group (GRADEpro GDT).

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.

- Contact Editor: Dr Eleanor Ochodo.
- 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 Kerry Dwan, Cochrane Methods Support Unit (statistical peer review); Dr Alice V Easton, NYC Health Department, New York, USA (clinical peer review); Dr Rebecca Kuehn, Liverpool School of Tropical Medicine (LSTM), Liverpool, UK (clinical peer review); Dr Joseph Okebe, LSTM, Liverpool, UK (methodological peer review); Jenny Negus, Public and Patient Involvement, UK (consumer peer review).

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APPENDICES

Appendix 1. Search strategy Cochrane COVID-19 Study Register

Search string: Favipiravir OR T-705 OR Avigan OR “6-FLUORO-3-HYDROXYPYRAZINE-2-CARBOXAMIDE” OR Avifavir OR Avipiravir OR Areplivir OR FabiFlu OR Favipira OR Reeqonus OR Qifenda

Study characteristics:
1) "Intervention assignment": “Randomised”

CONTRIBUTIONS OF AUTHORS

- Pritish Korula (PK), Hanna Alexander (HA), and Jisha John (JJ) prepared initial drafts of Background and Methods.
- Richard Kirubakaran (RK) helped complete the Methods.
- Bhagteshwar Singh (BS) and Priscilla Rupali (PR) helped complete the Background and Methods.
- Prathap Tharyan (PT) reviewed the Background and Methods.
- All authors read and approved the final version of the protocol.

DECLARATIONS OF INTEREST

- PK has no conflicts of interest to declare with respect to favipiravir for the management of COVID-19.
- HA has no conflicts of interest to declare with respect to favipiravir for the management of COVID-19.
- JJ has no conflicts of interest to declare with respect to favipiravir for the management of COVID-19.
- RK is employed as a consultant to India Covid guidelines, and has no conflicts of interest to declare with respect to favipiravir for the management of COVID-19.
- BS is a Clinical Research Fellow for the National Institute for Health Research (NIHR) Global Health Research Group on Brain Infections at the University of Liverpool (No. 17/63/110), the MRC-funded COVID-Neuro Global programme (project number MR/V033441/1) and in the NIHR Health Protection Research Unit on Emerging and Zoonotic Infections, and also works at the Royal Liverpool University Hospital, UK, and Christian Medical College, Vellore, India. He is a member of the Core Committee and Antiviral Working Group for the India Covid Guidelines Group. He has no known conflicts of interest to declare with respect to favipiravir for the management of COVID-19.
- PT has no conflicts of interest to declare with respect to favipiravir for the management of COVID-19.
- PR is leading an effort on India Covid guidelines which includes evidence synthesis on all therapeutic interventions including favipiravir. She is the coordinator of the core committee, leader of the scientific steering committee, and is a member of the antiviral working group. This was partly supported by the Research, Evidence and Development Initiative (READ-It). READ-It (project number 300342-104) is funded by UK aid from the UK Government. She has no conflicts of interest to declare with respect to favipiravir for the management of COVID-19.

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