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Task force report

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Management of Hospitalised Adults with Coronavirus Disease-19 (COVID-19) : A European Respiratory Society Living Guideline

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Abstract

Introduction: Hospitalised patients with coronavirus disease 19 (COVID-19) as a result of SARS-CoV-2 infection have a high mortality rate and frequently require non-invasive respiratory support or invasive ventilation. Optimising and standardizing management through evidence-based guidelines may improve quality of care and therefore patient outcomes.

Methods: A task force from the European Respiratory Society and endorsed by the Chinese Thoracic Society identified priority interventions (pharmacological and non-pharmacological) for the initial version of this "living guideline" using the PICO (population, intervention, comparator, outcome) format. The GRADE approach was used for assessing the quality of evidence and strength of recommendations. Systematic literature reviews were performed, and data pooled by meta-analysis where possible. Evidence tables were presented and evidence to decision frameworks were used to formulate recommendations.

Results: Based on the available evidence at the time of guideline development (20th February 2021) the panel makes a strong recommendation in favour of the use of systemic corticosteroids in patients requiring supplementary oxygen or ventilatory support, and for the use of anticoagulation in hospitalised patients. The panel makes a conditional recommendation for IL-6 receptor antagonist monoclonal antibody treatment and high flow nasal oxygen or continuous positive airway pressure in patients with hypoxaemic respiratory failure. The panel make strong recommendations against the use of hydroxychloroquine and lopinavir-ritonavir. Conditional recommendations are made against the use of azithromycin, hydroxychloroquine and azithromycin, colchicine, and remdesivir, in the latter case specifically in patients requiring invasive mechanical ventilation. No recommendation was made for remdesivir in patients requiring supplemental oxygen. Further recommendations for research are made.

Conclusion: The evidence base for management of COVID-19 now supports strong recommendations in favour and against specific interventions. These guidelines will be regularly updated as further evidence becomes available.

Introduction

COVID-19 (Coronavirus Disease 2019) is the disease resulting from infection by the SARS-CoV-2 virus. First identified in Wuhan, China in November 2019, the disease rapidly developed into a global pandemic with over 62.2 million infections and more than 1.4 million deaths recorded worldwide as of the end of November 2020.[1–3] The onset of symptoms occurs around 3-5 days from initial infection, with fever, new continuous cough, dyspnoea, anosmia, ageusia and fatigue being amongst the most frequently experienced symptoms.[3–5] Pre-symptomatic transmission has been suggested as one of the features that promote the widespread transmission of the virus.[1,6] The spectrum of disease is remarkably broad, ranging from true asymptomatic or paucisymptomatic infection to fatal acute respiratory distress syndrome.[4,7–9] The case fatality rate of COVID-19 is debated but appears to be lower than MERS and SARS, with an estimated 5% of those experiencing symptoms requiring hospitalisation. The mortality rate in those requiring hospitalisation ranges from 5-25%.[2,10,11] Risk factors for hospitalisation and mortality have been defined.[12–15] In hospitalised patients, the ISARIC risk prediction tool incorporates increased age, male sex, number of co-morbidities, increased respiratory rate, oxygen saturations, Glasgow coma scale, urea and C-reactive protein as risk factors for mortality.[12] Risk of hospitalisation and mortality is most strongly associated with age, and therefore SARS-CoV-2 infection rarely results in hospitalisation or mortality in children.[16]

COVID-19 is often described as a biphasic illness with distinct stages.[17] The initial stage of infection with fever, cough and other symptoms is associated with the highest viral loads which peak in the first seven days of illness.[18] Live virus remains detectable in the respiratory tract for up to 9 days and in the majority of individuals symptoms start to improve after the first week of symptoms.[18] In a proportion of patients, however, a second phase characterized by a dysfunctional host inflammatory response and the development of lung inflammation and lung injury follows.[19–23] The inflammatory response in moderate and severe COVID-19 has been variously described as a pro-inflammatory cytokine storm or a manifestation of profound immunosuppression.[22–24] There is, nevertheless, clear evidence of increased systemic inflammatory markers including IL-6, IL-8, IL-1β, activation of coagulation pathways with increased markers such as D-dimer, neutrophil recruitment, activation and extracellular trap formation, deficient production in some patients of antiviral defence mediators such as IFN-α and -β, autoimmunity and T-cell activation among multiple other mechanisms.[4,19,25–28]

In view of the involvement of both the viral load and host inflammatory response in the disease, repurposing and development of new therapies in COVID-19 has focussed primarily on anti-viral, immunosuppressive and immunomodulatory treatments.[18,29–32] Randomized clinical trials have been

conducted at an unprecedented rate to generate evidence for specific interventions.[33] During the early stages of the pandemic in particular, empirical use of antiviral and anti-inflammatory drugs such as hydroxychloroquine, lopinavir-ritonavir, remdesivir and monoclonal antibodies was widespread globally in the absence of formal guidelines or randomized trial evidence.[34–37] It is therefore important to have both recommendations in favour of successful interventions but also evidence to avoid certain therapies if their benefit-risk balance is unfavourable.[34]

Scope and objectives of the guideline

The objective of these guidelines is to provide evidence-based recommendations primarily related to the management of hospitalised adults with COVID-19. This guideline does not address in detail the management of COVID-19 in the community, as the majority of evidence obtained relates to hospitalised patients. In addition, management in children is not addressed. A guideline cannot address the full complexity of a disease; hence all recommendations should be interpreted considering the clinical circumstances and patients' perceptions, values and preferences.

The evidence for the management of COVID-19 is accumulating at an unprecedented rate with new trials published every day. The formal literature review and evidence synthesis process of these guidelines, and the lag to publication, mean that all guidelines will be "out of date" at the point that they are published. Consequently, the present document represents the first European Respiratory Society Guideline on this topic and is therefore the starting point. It is intended to be continuously updated as a "living guideline" with rapid literature searches and updated grading and recommendations as new evidence emerges published as rapid guideline updates on specific topics in the ERS journals.

The target audience for this guideline comprises all stakeholders involved in the care of patients with COVID-19 in hospital. This includes specialists in respiratory medicine, infectious diseases, general internal medicine and multiple other medical and surgical specialities in view of the high prevalence of COVID-19. Allied health professionals, including but not limited to, pharmacists and nurses; regulatory authorities; pharmaceutical companies, policy makers, patients and their families.

Table 1 provides a framework to interpret the recommendations made in this document

Target group	Strong recommendations[#]	Conditional (weak) recommendations
Patients	All or almost all informed	Most informed people would choose the

Target group	Strong recommendations[#]	Conditional (weak) recommendations
	people would choose the recommended choice for or against an intervention.	recommended course of action, but a substantial number would not.
Clinicians	Most patients should receive the recommended course of action.	Recognise that different choices will be appropriate for different patients. Clinicians and other healthcare providers need to devote more time to the process of shared decision making by which they ensure that the informed choice reflects individual values and preferences; decision aids and shared decision making are particularly useful.
Policy makers	The recommendation can be adopted as a policy in most situations.	Policy making will require substantial debate and involvement of many stakeholders.

[#]: strong recommendations based on high quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all conditions; no recommendation can take into account all of the unique features of individual patients and clinical circumstances.[38,39]

Methods

Guideline development

This guideline was developed by a European Respiratory Society COVID-19 task force chaired by J.D. Chalmers (UK) and N. Roche (France) and utilised the GRADE methodology.[38] The task force included specialists in respiratory medicine, infectious diseases, guideline methodology, an allied health professional and a patient representative. The task force recommendations have been endorsed by the Chinese Thoracic Society (CTS) and 3 members of CTS participated as full members of the task force panel.

Due to the COVID-19 pandemic, all panel meetings were held online via teleconference and email, with the initial meeting on 26th June 2020 to identify and prioritise the key topics with the most important associated endpoints. From this meeting, the steering group were divided into working groups to focus on specific topics including anti-virals, anti-inflammatories, anti-coagulants and ventilation strategies. The patient representative was involved in all discussions with the guideline panel providing input into the final recommendations and will be involved in developing a lay version of the guideline.[40]

A total of eleven clinical questions were generated using the PICO format (Patients, Intervention, Comparison, Outcomes) and systematic reviews were conducted to answer these specific questions. The cut-off date for literature searches was 31st October 2020, with updates performed to identify key studies in November 2020 and again in February 2021. Further details of the literature review process are described below.

Disclosure of potential conflicts of interest

Committee members disclosed all potential conflicts of interest according to ERS policy. Conflicted members were asked to abstain from discussions and voting on recommendations in which they were considered to have potential conflicts. Compliance with the conflict of interest policy was monitored by the chairs. The methodologists were non-voting members of the panel.

Systematic review

Two experienced external librarians from KU Leuven libraries (Belgium) designed and ran search strategies using MeSH terms and keywords for each clinical question, in collaboration with the methodology working group (PCG, MLC, JDC, TT). More details of the search strategy are shown in the supplementary material. The search focused on identifying studies that included hospitalised patients or outpatients with confirmed or highly suspected COVID-19 which included a treatment group and control group that could be used to establish the efficacy and safety of the intervention being studied. The search retrieved 14,851 articles; after removal of duplicates and exclusion of citations that did not meet the established inclusion criteria, a total of 44 references were included in the initial evidence summaries.

The ERS methodology approach allows for results of existing systematic review and meta-analyses, when conducted to a high methodological standard, to be used for evidence synthesis and grading. If existing systematic reviews are not identified, then randomized controlled trials were identified and data extracted as described in the online supplement. Observational studies are only considered for

inclusion in the evidence tables if randomized controlled trials were not available. The results of randomized trials and observational studies are not pooled together but are considered separately.

Assessment of the level of evidence and degree of recommendations

The panel selected outcomes of interest for each clinical question *a priori*, based on their relative importance to adult patients with COVID-19 and to clinical decision making (supplementary material). The importance of outcomes was rated on a 9-point scale (ranging from "not important" to "critical") and only outcomes rated as important or critical for clinical decision making were included in the evidence tables. We followed the GRADE approach to assess the confidence in the evidence (quality) and the degree of recommendations. The GRADE methodology was used to rate the body of evidence at the outcome level rather than the study level with assessment of risk of bias at study level performed as described.[41] One recommendation (on ventilatory support) was addressed using a narrative format due to the lack of homogeneous literature.

Recommendations are reported as strong or conditional after considering the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the relative importance of outcomes, the implications for resource use, and the acceptability and feasibility of implementation. The quality of evidence was rated on 4 levels (high, moderate, low or very low) based on the GRADE methodology.[39] The overall quality of evidence is then rated as the lowest of the critical outcomes, except where the evidence for all of the critical outcomes favours the same alternative and where the quality of evidence for outcomes that are considered key to clinical decision takes precedence.[42] Evidence summary of findings tables and evidence to decisions frameworks were generated for each clinical question (supplementary material). Based on these formats, the panel formulated the clinical recommendations and decided on their strength by consensus, or, if required, by voting. Following the GRADE approach, strong recommendations are worded as "we recommend", while conditional recommendations are worded as "we suggest".[43]

Guideline

Table 2 summarises the 14 formal, graded recommendations made within the guideline. In each of the following sections we include a discussion of the underlying evidence and the rationale for the

recommendations made. Further details are provided in the evidence tables and evidence to decision frameworks provided online.

Summary of recommendations

Therapy	Recommendations	Recommendation	Quality of Evidence
Corticosteroids	1. The panel recommends offering treatment with corticosteroids for patients with COVID-19 requiring oxygen, non-invasive ventilation or invasive mechanical ventilation **2.** The panel recommends NOT to offer treatment with corticosteroids for patients with COVID-19 requiring hospitalisation but not requiring supplementary oxygen or ventilatory support	Strong Strong	Moderate Moderate
IL-6 receptor antagonist monoclonal antibody	3. The panel suggests offering IL-6 receptor antagonist monoclonal antibody therapy to hospitalised patients with COVID-19 requiring oxygen or ventilatory support 4. The panel suggests NOT to offer IL-6 receptor antagonist monoclonal antibody to patients not requiring supplementary oxygen	Conditional Conditional	Low Low
Hydroxychloroquine	5. The panel recommends NOT to offer hydroxychloroquine to patients with COVID-19, including hospitalised patients and outpatients	Strong	Moderate
Azithromycin	6. The panel suggests NOT to offer azithromycin to hospitalised patients with COVID-19 in the absence of	Conditional	Very low

	bacterial infection		
Azithromycin and Hydroxychloroquine	7. The panel suggests NOT to offer hydroxychloroquine and azithromycin in combination to patients with COVID-19	Conditional	Moderate
Colchicine	8. The panel suggests NOT to offer colchicine for hospitalised patients with COVID-19	Conditional	Very Low
Lopinavir-ritonavir	9. The panel recommends NOT to offer lopinavir-ritonavir to hospitalised patients with COVID-19	Strong	Low
Remdesivir	10. No recommendation is made regarding the use of remdesivir in patients hospitalised with COVID-19 and not requiring invasive mechanical ventilation 11. The panel suggests not to offer remdesivir to patients hospitalised with COVID-19 infection who require invasive mechanical ventilation	None Conditional	Moderate Moderate
Interferon beta	12. The panel suggests NOT to offer Interferon beta to hospitalised patients with COVID-19	Conditional	Very low
Anticogulation	13. The panel recommends offering a form of anticoagulation to hospitalised patients with COVID-19	Strong	Very low
Non-invasive ventilatory support	14. We suggest HFNC or non-invasive CPAP delivered through either a helmet or a face-mask for patients with COVID-19 and hypoxaemic acute respiratory failure without an	Conditional	Very low

	immediate indication for invasive mechanical ventilation.		

Table 2. Summary of recommedations in this guideline. In the document, high-flow nasal cannula oxygen therapy (HFNC) is integrated in the term "non-invasive ventilatory support".

PICO 1: In patients hospitalised with COVID-19, should systemic corticosteroids be used compared to usual care (placebo or background therapy)?

Recommendations:

The panel recommends offering treatment with corticosteroids to patients with COVID-19 requiring oxygen, non-invasive ventilation or invasive mechanical ventilation (strong recommendation, moderate quality of evidence)

The panel recommends NOT to offer corticosteroids to patients with COVID-19 requiring hospitalisation but not requiring supplementary oxygen or ventilatory support (strong recommendation, moderate quality of evidence)

Summary of evidence: It is clear that excessive inflammation and a dysregulated immune response play an important role in the progression of severe COVID-19, and therefore there is a strong scientific rationale for the use of anti-inflammatory treatments, particularly in patients with the most severe disease.[20,21,44,45] We reviewed data for 6 randomized trials and one existing meta-analysis.[31,46–49] The majority of evidence in support of the use of corticosteroids comes from the UK RECOVERY trial which randomized 2104 patients to dexamethasone 6mg daily and 4321 patients to standard care in a pragmatic, non-blinded controlled trial.[47] The results demonstrated a statistically significant reduction in mortality with corticosteroid treatment in patients receiving invasive mechanical ventilation at randomization (41.4% vs 29.3% in standard care vs dexamethasone respectively) and a lesser but still statistically significant mortality benefit in those requiring supplementary oxygen at randomization (26.2% vs 23.3% in standard care and dexamethasone respectively).[47] There was no mortality benefit evident in patients that did not require supplementary oxygen (14.0% vs 17.8% in standard care and dexamethasone respectively).[47] The pooled odds ratio in the evidence table which includes all patient subgroups, for mortality was 0.70 95% CI 0.48-1.01) when including all patients. A systematic review and meta-analysis of critically ill patients with COVID-19, which included data from 7 trials, confirms the benefit of corticosteroids on mortality in this population and included data for hydrocortisone and methylprednisolone

suggesting a class effect of steroids (odds ratio 0.70 95% CI 0.48-1.01,p=0.053 in random effects meta-analysis).[48]

The review of the data identified limited evidence on adverse events, and in particular the RECOVERY trial did not report detailed information on safety of the intervention.[47] Data from 4 trials did not show a significant increase in adverse events with OR 1.09 95% CI 0.37-3.18.[31,46,49,50] Nevertheless, the adverse event profile of corticosteroids is well known, and these trials have not identified major safety signals to date. Evidence was rated as moderate or high quality for all of the outcomes except for adverse events

Justification of the recommendation: The overall risk *versus* benefit for corticosteroids is favourable. Corticosteroids have been shown to significantly reduce mortality in a large-scale randomized trial and the consistency of results from other trials is reassuring that these data are generalizable. Results were significantly different between subgroups based on the requirement for oxygen, or requirement for mechanical ventilation, with clear absence of benefit in patients not requiring oxygen justifying different recommendations for different subgroups of patients.

Research Recommendations: Dexamethasone 6mg daily for 10 days was the regimen selected for RECOVERY and is therefore the regimen that is used as standard.[47] Unanswered questions regarding corticosteroids include the optimal molecule, the optimal timing, dose and scheme as well as the optimal duration of treatment, long term side effects and whether other subgroups of patients, such as those not requiring oxygen but with evidence of increased systemic inflammation or radiographic changes, would benefit.

PICO 2: In patients hospitalised with COVID-19, should IL-6 receptor antagonist monoclonal antibodies be used versus usual care (placebo or background therapy)?

Recommendation: The panel suggests offering IL-6 receptor antagonist monoclonal antibody therapy to hospitalised patients with COVID-19 requiring oxygen or ventilatory support (conditional recommendation, low quality of evidence)

The panel suggests NOT to offer IL-6 receptor antagonist monoclonal antibody therapy to patients not requiring supplementary oxygen (conditional recommendation, low quality of evidence)

Notes:

- All patients eligible for IL-6 receptor antagonist monoclonal antibody treatment should have already received or should be receiving treatment with corticosteroids, unless contraindicated.
- The patients most likely to benefit are those:
    - in the first 24 hours after receiving non-invasive or invasive ventilatory support
    - patients receiving supplementary oxygen and who are progressing despite corticosteroid treatment or who are considered at high risk of future requirement for ventilatory support.

Summary of evidence: Observational studies in severe COVID-19 found elevated levels of IL-6 that were associated with increased mortality.[20,25,51] Several uncontrolled trials suggested benefit of treatment with anti IL-6 receptor monoclonal antibodies with tocilizumab being among the most widely used and studied, with improvements in disease severity and recovery of inflammatory markers reported.[52–54]

The panel assessed eight randomized, controlled studies comparing the IL-6 receptor antagonist monoclonal antibody treatment (a total of 3,309 patients), to usual care (UC) (3,038 patients).[55–62] The vast majority of studies utilized tocilizumab, but sarilumab was also studied.[62] Patient populations varied but the majority of subjects were either hospitalised with severe COVID-19 requiring oxygen treatment but not mechanical ventilation, with evidence for increased inflammatory markers, or were requiring ventilatory support.

Our meta-analysis identified no significant effect of anti-IL-6 receptor monoclonal antibody treatment on mortality (820/3309- 24.8% with active treatment vs 893/3038- 29.4% with usual care, odds ratio 0.90 95% CI 0.73-1.12, from 8 studies with only limited heterogeneity I^2=28%).[55-62] It was noted that the two largest studies, RECOVERY and REMAP-CAP both demonstrated significant reductions in mortality.[61,62] RECOVERY enrolled patients admitted with hospital with COVID-19 who required oxygen and had a C-reactive protein level in blood greater than 75mg/L. REMAP-CAP enrolled patients within the first 24 hours of requiring non-invasive or invasive ventilatory support. Mechanical ventilation was significantly reduced by 25% (280/2161-13% vs 322/2038- 15.8%, OR 0.75 95%CI 0.63-0.90, from 4 studies). The combined endpoint of requirement for mechanical ventilation or death was also reduced OR 0.74 (95%CI 0.72-0.88, from 6 studies). Adverse events and serious adverse events were not increased.

Justification of the recommendation: Anti-IL-6 receptor monoclonal antibody treatment reduces the risk of mechanical ventilation or death in hospitalised COVID-19 patients. No major safety concerns were identified. The panel considers that currently it is hard to identify the optimal patient population to benefit from this treatment, but RECOVERY found a benefit in addition to treatment with corticosteroids. As corticosteroids are also recommended for patients requiring oxygen and ventilatory support, anti-IL-6 monoclonal antibody treatment would be expected to be given to patients also receiving corticosteroids in nearly all cases. Anti-IL-6 receptor therapy is relatively expensive, but it is expected the benefits will outweigh the costs. Patient populations most likely to benefit include those meeting the inclusion criteria for REMAP-CAP (within 24 hours of requirement for non-invasive or invasive ventilatory support) and hospitalised patients requiring oxygen who are considered at high risk of requiring mechanical ventilation or who have progressed despite treatment with corticosteroids, which is consistent with patients enrolled in RECOVERY and other trials included in our analysis.

Research recommendations: Further research is needed to identify the optimal patient population for treatment with IL-6 receptor antagonist monoclonal antibody treatment, including whether biomarkers of inflammatory are useful to identify responders.

PICO 3: ***In patients hospitalised with COVID-19 should hydroxychloroquine be used versus standard of care (defined as no treatment, placebo or background therapy according to local practice)?***

Recommendation: The panel recommends NOT to offer hydroxychloroquine to patients with COVID-19, including hospitalised patients and outpatients

Summary of evidence: Chloroquine and hydroxychloroquine are 4-aminoquinoline drugs primarily used for the treatment of malaria. These agents have immunomodulatory properties and also have in vitro activity against a variety of viruses, including SARS-CoV-2.[63] Early observational studies of these repurposed medications (alone or in combination with azithromycin) have given divergent results in patients with mild to severe COVID-19.[34] Despite the preliminary nature of these studies, the reported results have led to confusion about the usefulness of this treatment and widespread empirical use in some parts of the world.[37] Large randomized controlled studies have now been

performed allowing robust analysis of key outcomes in groups of patients with COVID-19 of diverse severity. Our evidence review included 11 randomized studies.[10,30,72,64–71] The results were heavily influenced by the two largest studies performed by the UK RECOVERY group and WHO SOLIDARITY trial.[10,30] In RECOVERY, participants who received hydroxychloroquine did not have a lower incidence of death at 28 days than those who received usual care.[10] This is in agreement with the interim results of the WHO SOLIDARITY trial, showing no apparent effect of hydroxychloroquine on mortality, irrespective of disease severity at study entry.[30] Our pooled estimate for mortality from 9 trials was 1.08 95% CI 0.97-1.19, which effectively excludes a meaningful beneficial effect. Besides the absence of a survival benefit, currently available evidence does not show significant positive trends in terms of clinical outcomes, including time to clinical improvements, clinical resolution, deterioration, hospitalisation, ICU admission, non-invasive or invasive ventilation. Moreover, hydroxychloroquine did not substantially reduce symptom severity in outpatients with early COVID-19. Regarding safety, there is an increased risk of adverse events with hydroxychloroquine, such as gastro-intestinal, ocular, liver and cardiac toxicity. Our pooled estimate for adverse effects was OR 4.23 95% CI 3.30-5.42, indicating a substantial increase in adverse effects in participants receiving hydroxychloroquine compared to those randomized to the control. Among Brazilian patients hospitalised with mild-to-moderate COVID-19, prolongation of the QT interval was more frequent in patients receiving hydroxychloroquine (alone or with azithromycin), than in those who were not receiving these drugs.[64] In the RECOVERY study, there was a small absolute excess of cardiac mortality of 0.4 percentage points in the hydroxychloroquine group on the basis of very few events.[10]

Justification of the recommendation: There is no evidence of significant clinical benefits associated with hydroxychloroquine, as compared to standard of care, while there is an increased risk of adverse events. Where there is no benefit and evidence of potential harm, a strong recommendation against the intervention is justified.

Future research: The panel considers that a sufficient number of studies have been performed to conclusively recommend not using hydroxychloroquine in COVID-19 patients. Several institutions, including the WHO and the NIH have ceased trials of its use in hospitalised patients on the ground of lack of efficacy. The US Food and Drug Administration has revoked the Early Use Authorization for chloroquine and hydroxychloroquine. Future studies on this repurposed agent should not be encouraged. The committee recommends studying other antiviral options in well-designed studies of repurposed or SARS-CoV-2 specific medications.

PICO 4: ***In patients hospitalised with COVID-19 should azithromycin be used versus standard of care (defined as no treatment, placebo or background therapy according to local practice)?***

Recommendation:

The panel suggests NOT to offer azithromycin to hospitalised patients with COVID-19 in the absence of bacterial infection (conditional recommendation, very low quality of evidence).

Summary of evidence:

Azithromycin is a macrolide antibiotic with reported antiviral and immunomodulatory activities, and also a well-documented effect on exacerbation rate in patients with chronic lung diseases, including asthma and bronchiectasis.[73,74] It is one of the most popular antibiotics used in inpatients and outpatients with acute respiratory infections worldwide.[75] Azithromycin is widely available and has a well-established safety profile.

The literature search identified three randomized studies which investigated azithromycin. One study, from Brazil COALITION 1, examined azithromycin plus hydroxychloroquine vs hydroxychloroquine alone.[64] Since hydroxychloroquine has been shown to have no beneficial effect and was regarded as standard of care in many parts of the world during the early part of the pandemic, the panel judged that this data could be used to infer the efficacy of azithromycin. Two studies were identified that examined the effect of azithromycin alone in hospitalised patients, COALITION 2, also performed in Brazil[76] and an open label trial performed by Sekhavati et al.[77]

These individual trials, and the pooled data from these three trials demonstrate no difference in mortality odds ratio 1.02 (0.69-1.49), length of hospital stay, clinical status or deterioration.

Justification of the recommendation:

Bacterial co-infection is reported infrequently in COVID-19 patients, with a systematic review suggestion <10% of patients isolate a bacterial pathogen[78] but there may still be a role for antibiotics in selected patients with proven or strongly suspected bacterial co-infection. The authors therefore recommend against routine use specifically for COVID-19 but acknowledge use for other indications outside the scope of this guideline. Although adverse events were not increased in COVID-19

patients in these 3 trials, long term concerns such as antimicrobial resistance that may result from widespread use of azithromycin should be considered.[75]

Future research:

The panel is aware at the time of writing that results of the azithromycin treatment arm of RECOVERY have been announced indicating no benefit of azithromycin in COVID-19.[79] These were not included in our meta-analysis but support our recommendation.

The panel recommends studies into the frequency of bacterial co-infection in COVID-19 patients utilising molecular techniques and/or biomarkers in view of the outstanding question over the use of antibiotics in this disease.

PICO 5: ***In patients hospitalised with COVID-19 should hydroxychloroquine and azithromycin be used in combination versus standard of care (defined as no treatment, placebo or background therapy according to local practice)?***

Recommendation: The panel recommends NOT to offer hydroxychloroquine and azithromycin in combination for hospitalised patients with COVID-19 (conditional recommendation, moderate quality of evidence).

Summary of evidence: The potential antiviral and anti-inflammatory effects of azithromycin and hydroxychloroquine are discussed in separate sections above. The use of azithromycin in combination with hydroxychloroquine has been tested in a Brazilian multicentre, randomized, open-label, controlled trial, involving hospitalised patients who were receiving a maximum of 4 litres per minute of supplemental oxygen.[64] The use of hydroxychloroquine with azithromycin in this population did not improve clinical status at 15 days, as compared with standard care. There was an increased number of adverse events in patients receiving hydroxychloroquine plus azithromycin (39.3%) or hydroxychloroquine alone (33.7%) than in those receiving none of the trial drugs (22.6%).[64]

Justification of the recommendation: No clinical benefits were noted in a single randomized, open label study where azithromycin was combined with hydroxychloroquine. The panel notes that azithromycin has a well-established safety profile, but that antibiotic use promotes antibiotic resistance. Despite the limited data, the absence of any clinically relevant benefits of hydroxychloroquine or azithromycin alone argues against any benefit of the combination treatment.

Future research: Despite limited data for the combination therapy, the lack of benefit of hydroxychloroquine alone suggests no further trials of a combination treatment containing hydroxychloroquine are justified, particularly in light of potential serious cardiac adverse events and other side effects.[80] The committee recommends studying other antiviral options in well-designed studies of repurposed or SARS-CoV-2 specific medications.

PICO 6: In patients hospitalised with COVID-19, should colchicine be used versus usual care (placebo or background therapy?)

Recommendation: The panel suggests NOT to offer colchicine to patients hospitalised with COVID-19 (conditional recommendation, very low quality of evidence).

Summary of evidence: The intense inflammatory response following a SARS-CoV-2 infection prompted the investigation of other possible anti-inflammatory therapies which do not show similar adverse effects as seen with corticosteroid or other non-steroidal anti-inflammatory treatments. Colchicine is considered to have anti-inflammatory properties through targeting IL-1 and IL-6 in hyperinflammatory syndromes and blocking the inflammasome as well as having in-vitro evidence for blocking the coagulation pathway and thrombosis.[81–83] One case-control analysis in COVID-19 suggested survival benefit in patients treated with colchicine as compared to standard of care (84.2% vs 63.6%).[84] Two randomized controlled trials in COVID-19 were identified in the literature search. In one small randomized trial with 38 patients, Lopes *et al*. found a better evolution in terms of need for supplemental oxygen in the colchicine group (median: 7 vs 3; p=0.02) while also demonstrating a significant reduction in length of hospital stay versus standard of care (median: 8.5 vs 6.0; p=0.03).[85] This was in contrast with a second and earlier analysis on 100 randomized patients, where no difference in hospitalisation length was seen (median: 12 vs 13; p=0.91).[86] Deftereos *et al*.

did however show a significant improvement in time to clinical deterioration in participants receiving colchicine (cumulative event-free 10-day survival of 83% in the control vs 93% in the colchicine group; p=0.03). The confidence intervals of these effects estimates are wide due to the low number of patients studied to date.[86]

The benefit of colchicine is uncertain as both trials had a small sample size. There is no consistency in the reported effect on length of hospital stay. The effect of colchicine in the GRECCO-19 trial on a lower risk of deterioration was also based on a small number of events and is therefore uncertain in nature. Other important endpoints such as ICU admission (OR 1.06 95% CI 0.06-18.45) and mortality (OR 0.21 95% 0.02- 1.97) were not significantly reduced with therapy, and the studies were underpowered to address these endpoints. Moreover, a significant increase in adverse events (mainly diarrhea) was noted with the administration of colchicine (OR 3.96 95% CI 1.72-9.12), which may be expected based longstanding experience with this drug.

Justification of the recommendation: The lack of clear benefits with an increase in adverse events results in a recommendation against use while awaiting further data.

Research recommendations: Colchicine should be evaluated in large randomized controlled trials and at the time of writing it has been added to the large pragmatic RECOVERY trial.

PICO 7: In patients hospitalised with COVID-19 should Lopinavir-ritonavir be used versus standard of care (defined as no treatment, placebo or background therapy according to local practice)?

Recommendation:

The panel recommends NOT to offer Lopinavir-ritonavir to hospitalised patients with COVID-19 (strong recommendation, low quality of evidence).

Summary of evidence:

Lopinavir is a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor, which is usually combined to ritonavir to increase its plasma half-life through inhibition of cytochrome P450.[87] These drugs are widely available as a drug in clinical use for HIV. The combination was shown to reduce the risk of adverse clinical outcomes and viral load among patients with SARS as compared to historical controls.[88] Our evidence review included 3 randomized trials, including the previous

mentioned RECOVERY and SOLIDARITY platform trials, plus a Chinese trial by Cao and colleagues.[30,89,90] No effect on mortality was observed (OR 1.02 95% CI 0.90-1.15). No other clinical benefits were evident on endpoints including time to clinical improvement, viral load, viral clearance, discharge from hospital within 28 days and invasive mechanical ventilation. Adverse events and serious adverse events were not increased.

Justification of the recommendation:

Lopinavir-ritonavir has a known adverse event profile and significant drug-drug interactions which present potential for patient harm.[91,92] Therefore, clear evidence of efficacy would be required to recommend its use. The literature review found no evidence of benefit across 3 randomized controlled trials. As the drug is not effective and may theoretically be harmful, this justifies a strong recommendation against its use even considering the low quality of available evidence.

Future research:

As two very large trials show no benefit, no further trials of lopinavir-ritonavir in this population are justified.

PICO 8: ***In patients hospitalised with COVID-19 should remdesivir be used versus standard of care (defined as no treatment, placebo or background therapy according to local practice)?***

Recommendation:

The panel makes no recommendation regarding the use of remdesivir in patients hospitalised with COVID-19 and not requiring invasive mechanical ventilation (no recommendation, moderate quality of evidence)

The panel suggests NOT to offer remdesivir to patients hospitalised with COVID-19 who require invasive mechanical ventilation (conditional recommendation, moderate quality of evidence)

Summary of evidence:

Remdesivir is an inhibitor of the viral RNA-dependent RNA polymerase. It has proven effective in-vitro against SARS-CoV-1, MERS-CoV and SARS-CoV-2.[93,94] A reduction in time to recovery and length of hospital stay was demonstrated for remdesivir in one trial (ACTT1).[95] This trial randomized 1062 patients (541 to remdesivir and 521 to placebo).[95] The primary outcome of recovery time was reduced from 15 days to 10 days (rate ratio for recovery 1.29 95% CI 1.12-1.48,p<0.001). Length of hospital stay was also reduced from a median of 17 days to 12 days, and other secondary endpoints showed positive benefits.[95] In contrast, no clinical benefits were demonstrated in the other trials including the large SOLIDARITY trial which found no evidence of a mortality benefit. The SOLIDARITY analysis of Remdesivir included 2743 receiving active treatment and 2708 controls. Mortality was not impacted with a rate ratio of 0.95 95% CI 0.81-1.11,p=0.50.[30] The SOLIDARITY group also included an updated meta-analysis of existing trials including ACTT1, SOLIDARITY and additional trials that randomized patients 2:1, and concluded there was no mortality benefit of remdesivir (RR 0.91 95% CI 0.79-1.05).[30] Our review identified very similar results with an odds ratio for mortality of 0.92 95% CI 0.79-1.07 with no increase in adverse events OR 1.05 95% CI 0.71-1.55 from 3 studies.

In ACTT1 no benefit on the primary outcome of clinical recovery (Recovery rate ratio 0.98 95% CI 0.70-1.36) was observed in patients who started remdesivir when they were already on mechanical ventilation or extracorporeal membrane oxygenation.[95] If treatment is given it should be given for 5 days based on evidence that this is at least as effective as 10 days administration.[96] Liver function tests should be checked prior to administration of remdesivir and checked while patients are on treatment, remdesivir should not be prescribed in patients with severe renal dysfunction (GFR <30ml/min).

Justification of the recommendation: The panel considers that time to recovery and length of hospital stay are relevant clinical endpoints in the absence of a mortality benefit of remdesivir. Nevertheless, these benefits have been demonstrated in only one randomized trial. The reported benefits are regarded by the panel as modest. The lack of significant adverse effects means that the balance of benefit *versus* risk was considered marginally in favour of the intervention by some members of the panel but not by others. The panel discussed this topic extensively, and voted on the final recommendation resulting in no majority favouring a recommendation for or a recommendation against remdesivir use. The panel therefore makes no recommendation regarding remdesivir in patients not requiring invasive mechanical ventilation. In GRADE methodology this is referred to as a condition recommendation for the intervention OR the alternative. This recommendation does not indicate that clinicians should use remdesivir routinely or that clinicians

should avoid use of remdesivir in all cases. Rather it indicates that the balance of risks and benefits is uncertain and its use by patients should ideally be in the context of a randomized clinical study, or where patients have been fully informed of the risks and benefits.

Subgroup effects were observed with no benefit on the primary outcome evident in patients requiring invasive mechanical ventilation or extracorporeal membrane oxygenation. As this outcome is the main benefit supporting any use of remdesivir, the panel considers it appropriate to make a subgroup recommendation against remdesivir use in these patients where clear absence of benefit has been demonstrated. Availability and cost are important considerations for some healthcare systems.

Future research: As the benefit is unclear, further large studies including endpoints such as clinical improvement, clinical deterioration and length of stay should be performed to confirm the results of ACTT1. Identifying subgroups of patients who benefit is a priority, based on timing of administration and requirement for oxygen. The benefit of remdesivir on top of systemic corticosteroids, which are now regarded as standard of care for COVID-19, requires to be established. There are strong theoretical reasons to believe anti-viral treatments will be more effective when given earlier in the disease course and future studies should consider whether earlier administration would be beneficial. At the time of writing the guideline, the panel is aware of recently published data suggesting that the Janus Kinase inhibitor baricitinib in combination with remdesivir decreases time to recovery in hospitalised patients in another study (ACTT2).[97] Further data on remdesivir, with or without additional therapies, against standard of care will be required to conclusively demonstrate clinical benefit.

PICO 9: In hospitalised patients with COVID-19 should interferon-β be used versus standard of care (defined as no treatment, placebo or background therapy according to local practice)?

Recommendation: The panel suggests NOT to offer Interferon-β to hospitalised patients with COVID-19 (conditional recommendation, very low quality of evidence).

Summary of evidence: Interferons are signaling proteins released by host cells as a component of innate immune system in response to viral infections.[7,98] Type 1 interferons have in-vitro activity against coronaviruses[99], and in-vivo promoted improved symptoms and viral clearance as part of a

triple therapy regimen also containing lopinavir-ritonavir and ribavirin compared to lopinavir-ritonavir alone.[100] There is evidence that SARS-CoV-2 suppresses innate interferon release and the extent of this is linked to disease severity.[98] All of this provides a sound rationale for evaluating interferon as a therapy for COVID-19.

Our literature review identified three trials.[30,101,102] Two small proof of concept trials showed large benefits including reduced mortality[101,102] but a much larger trial (the WHO SOLIDARITY trial) suggests no evidence of benefit and potential harm (rate ratio 1.16 95% CI 0.96-1.39,p=0.11). Our pooled estimate of these three trials showed no statistically significant mortality benefit or benefit on clinical deterioration. The quality of evidence was rated as very low.

Justification of the recommendation: Clinical benefit has not been clearly demonstrated for systemic interferon treatment. The largest trial on this drug showed no effect on mortality and a trend towards an increase in mortality. Safety data is incompletely reported across all trials. In the absence of clear benefit or safety, a recommendation for use cannot be made. The conditional recommendation is based on very low quality of evidence.

Future research: A recent trial published after the systematic review was completed demonstrated a significant benefit of inhaled interferon β-1a in 101 patients conducted in the UK.[103] While small trials should be treated with caution, this suggests the possibility that inhaled delivery has a different effect to systemic delivery of interferon. Further studies to investigate the efficacy of inhaled interferon beta are justified.

PICO 10: In hospitalised patients with COVID-19 should anticoagulants be used versus no anticoagulant?

Recommendation: The panel recommends offering a form of anticoagulation for hospitalised patients with COVID-19 (Strong recommendation, very low quality of evidence)

Notes accompanying this recommendation: The panel are unable to make a recommendation regarding the dose of anticoagulation (prophylactic, high dose prophylactic or therapeutic) or the preferred type of anticoagulant medication.

Summary of evidence: SARS-CoV-2 infection has been associated with an increased risk of venous thromboembolism (VTE) attributed to features of coagulopathy.[4,104] The incidence of VTE is highly variable, ranging from 0% to 85% in reported studies. This variability likely relates to differences in populations' characteristics (especially regarding severity, age, comorbidities, setting) and diagnostic procedures. Pooled estimates of incidence recently reported in a systematic review of 48 studies were 17.0% for VTE, 7.1% for pulmonary embolism and 12.1% for deep vein thrombosis.[105] This high incidence is associated with a pro-thrombotic state characterised by increased D-dimer levels, associated with the hyperinflammatory state triggered by the host's immune response against SARS-CoV.[106]

To date, no results from randomised controlled trials have been published although several such studies are ongoing based on registrations in clinicaltrials.gov and similar registries. Therefore, available evidence is restricted to data from observational studies.[107] Altogether, 19 studies were analysed, 16 retrospective cohorts and 3 prospective cohorts, 8 of which were considered of good or fair quality following risk of bias assessment. Anticoagulants used were low molecular weight heparin, unfractionated heparin and direct oral anticoagulants. In 5 studies, the adjusted mortality rate ratio was 0.56, 95% CI 0.36-0.92, p=0.0218 comparing patients with and without receipt of anticoagulation.[107] This result remained stable after elimination of outliers and restriction to studies of good and fair quality. Risk reduction was significant with both prophylactic and therapeutic anticoagulation therapy, but these options could be compared in only three studies providing adjusted estimates, which significantly favoured therapeutic doses but needs to be weighed against potential harm (i.e., bleeding events).[107]

The panel notes that the high frequency of pulmonary embolism in patients hospitalised with COVID-19 justifies a low threshold for investigation e.g with CT pulmonary angiogram in severe patients or those that experience a deterioration in oxygenation [105] as a diagnosis of VTE will impact on the indicated dose and length of anticoagulation.

Justification of the recommendation: Although the quality of evidence is very low, prophylactic anticoagulation is routine practice for hospitalised patients at risk of thromboembolic complications

in hospitals in many countries and the existing evidence and existing practice makes this an intervention that can be strongly advocated. The panel are unable to determine whether the benefit-risk balance is superior for prophylactic vs therapeutic dose anticoagulation nor to identify subgroups with different benefit-risk ratios, and therefore rather than recommending one or the other, the panel makes clear that this is a matter for clinical judgement while awaiting randomised clinical trials.

Future research: The panel considers that randomised controlled trials comparing various modalities of prophylactic, prophylactic-high and therapeutic anticoagulation are needed. In addition to the dosing issue, questions to address include the duration and type of agent. It is crucial to consider subgroups based on severity and biomarkers of inflammation and/or coagulation.

PICO 11: In patients with hospitalised COVID-19 should continuous positive airway pressure or high flow nasal cannula oxygen with or without adjunctive strategies such as prone positioning be used versus standard of care (defined as the absence of these interventions or invasive mechanical ventilation)?

Recommendation: We suggest high flow nasal cannula oxygen (HFNC) or non-invasive continuous positive airway pressure (CPAP) delivered through either a helmet or a face-mask for patients with COVID-19 and hypoxaemic acute respiratory failure in the absence of immediate indications for invasive mechanical ventilation (conditional recommendation, very low quality of evidence)

Notes accompanying this recommendation: HFNC and non-invasive CPAP are classified as aerosol generating and should therefore be delivered in a safe environment with staff wearing appropriate personal protecting equipment

HFNC and non-invasive CPAP should not delay mechanical ventilation in patients who are not responding to treatment

Prone positioning may improve oxygenation in non-intubated patient with acute hypoxaemic respiratory failure and is widely used for mechanically ventilated patients with COVID-19.

Summary of evidence: This question was addressed in a narrative format due to the identification of heterogeneous observational studies that could not be pooled for meta-analysis.

High flow nasal cannula therapy and non-invasive continuous positive airway pressure have been used in patients with hypoxemic acute respiratory failure (hARF) due to COVID-19 pneumonitis.[108–111] HFNC delivers a high flow of humidified heated gas at 30-60 l/min with a controlled oxygen concentration, via a nasal interface. Compared to standard oxygen therapy, HFNC therapy reduced 90-day mortality and increased the number of ventilator free days, in hARF due to non-COVID-19 causes.[112] Small case series suggest HFNC may decrease the need for intubation in COVID-19 patients more effectively than standard oxygen therapy, and large uncontrolled case series of application outside the ICU suggests HFNC and CPAP have similar efficacy, but these results are unconfirmed and patient groups may not be comparable.[108,109,113,114]

The role of CPAP mainly delivered through either helmet or facemask has been explored in more than 1,100 patients with ARF/ARDS due to COVID-19 pneumonia, also outside of the ICU.[108,109,122,111,115–121] The majority of studies were either case-series or retrospective, single centre observational studies. Only three studies were prospectively designed and only two were multicenter.[109,123,124] A large heterogeneity can be identified in terms of number of patients enrolled [median (IQR): 31 (17-71)] patients' selection (PaO2/FiO2 ratio ranging from less than 100 to 211), CPAP generators, interface used, initial PEEP pressure and FiO2 values. Some papers also evaluated prone positioning as an additional intervention.[121,123,125,126] The intubation rate for those undergoing CPAP ranged from 4% to 51% [median (IQR): 22% (20%-38%)] and a death rate from 0% to 52% [median (IQR): 20% (5%-34%)].

Prone positioning (PP) of non-intubated patients with hARF due to COVID-19 pneumonia has been recently tested across different settings including emergency departments, hospital wards, or in ICUs as an adjunct to conventional oxygen therapies.[118,120,131,121,123,125–130] A large heterogeneity across these experiences can be recognized. They differ in terms of patients' selection, type of oxygen therapy support used, setting, timing and duration of the intervention and therefore provide variable results. Despite this heterogeneity, reports document a significant improvement in oxygenation and respiratory rate upon prone positioning, and the majority were able to tolerate the procedure.

COVID-19-induced acute respiratory distress syndrome (ARDS) is a heterogeneous condition and the presence of specific phenotypes defined by physiological and biochemical markers is debated.[7,132–135] There is no RCT on timing of intubation in COVID-19 induced ARDS. A review of the evidence around invasive ventilatory strategies is beyond the scope of the present guideline. Low tidal volume

ventilation unless contraindicated, prone positioning and corticosteroid therapy as described elsewhere reduces mortality in patients receiving invasive ventilation.[49,136,137]

Venous-venous extracorporeal membrane oxygenation (ECMO) is used in patients with refractory hypoxemia despite optimal conventional ventilation and adjunctive interventions.[138] Case series show encouraging results but there has been no RCT. ECMO is both staffing and resource intensive.

Justification of the recommendation:

There are no RCTs completed yet comparing either HFNC or CPAP or NIV with standard oxygen therapy, or the three interventions in COVID-19 patients with hARF. However, reducing the need for invasive ventilation and pressure on ICU healthcare resources would be highly advantageous.

The application of CPAP and HFNC should not delay intubation and mechanical ventilation in patients who fail to respond to a non-invasive approach. CPAP and HFNC therapy are classified as aerosol generating procedures and should be used with healthcare professionals in full personal protective equipment (PPE).[113,139] The nature of aerosol generation or dispersion when using CPAP and HFNC has been explored using a range of imaging, particle sizing and virus sampling studies producing mixed results.[110,140–142] Benefits of CPAP and HFNC should be balanced against risks.

Research recommendations: Randomized studies addressing the optimal mode of ventilation in patients with acute hypoxaemic respiratory failure and COVID-19 are required. The Recovery–RS RCT (ISRCTN16912075), comparing standard oxygen therapy with CPAP and HFNC in COVID-19 patients is currently recruiting. This trial includes patients who fail to achieve arterial oxygen saturation of 94% and above on an FiO2 40% or above and the trial has a composite primary end-point of intubation or death at 30 days.

Summary and further considerations

The guideline recommendations are summarised in figure 2. The overall aim of management of hospitalised patients with COVID-19 is to reduce mortality and preventing complications including requirement for intensive care unit admission and prolonged length of hospital stay. This guideline indicates that with the exception of corticosteroids and IL-6 receptor antagonists there is limited evidence to support that any other antiviral or antiinflammatory treatment achieves these objectives with a high level of confidence. This confirms the need for further research. The majority of repurposed therapies have failed to reduce mortality or improve other clinical outcomes which emphasises the need to develop specific therapies directly targeting SARS-CoV-2 and the associated inflammatory response.

The recommendations in this guideline are derived from a systematic literature review and standardised GRADE methodology. This is distinct from a recent American Thoracic Society/European Respiratory Society consensus document which utilised the CORE process which requires 70% agreement on a topic among survey respondants without a systematic literature review.[143] There are similarities between the recommendations of that previous document and the current guideline, particularly the recommendation to use corticosteroids. There are however, large differences in that the ATS led document recommended remdesivir use in patients requiring supplemental oxygen, where the present guideline now does not recommend routine remdesivir use, and the previous document recommended remdesivir in mechanically ventilated patients where this document now suggests against its use in this group.[143] A previous version of the ATS led document also suggested the use of hydroxychloroquine.(https://www.thoracic.org/covid/COVID-19-guidance.pdf) This illustrates how differences in guideline methodology can lead to different conclusions as well as the need to continuously update recommendations based on emerging data.

Nevertheless demonstrating that many drugs should not be used in clinical practice is also important for patient care, particularly in the context of COVID-19 where clinicians worldwide have used many unproven therapies particularly in the early stages of the pandemic. The purpose of guidelines is to improve the quality of care that patients receive and to standardise care across different healthcare settings and systems. This guideline should be used as a starting point for treatment algorithms which have to be modified as additional data accumulates.

This is a living guideline with the panel continuously reviewing new evidence as it arises. Recommendations for additional therapies not addressed in this guideline such as convalescent plasma, monoclonal antibodies directed against SARS-CoV-2 and other therapies will be added in future versions, along with updates on the therapies already reviewed once new data are available.

ERS Guideline statement

The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription

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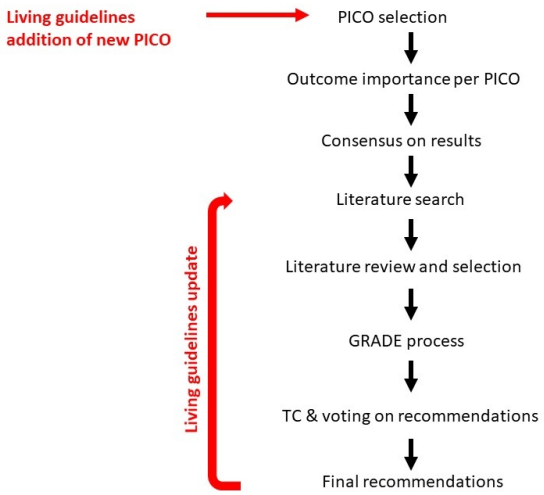
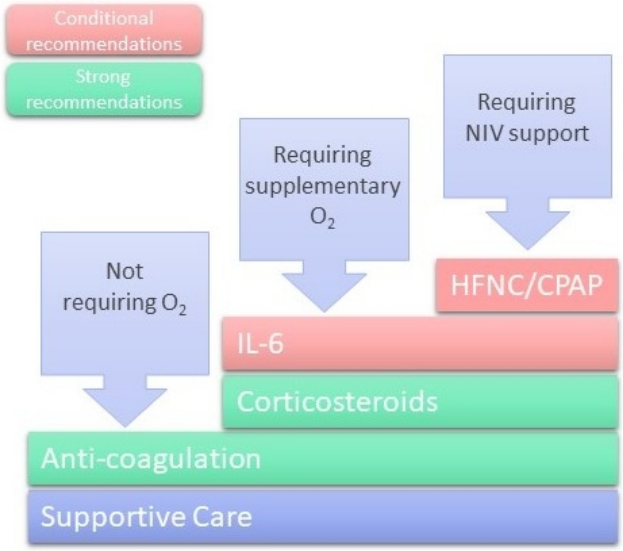


Figure 1. Process of guideline development. Abbreviations PICO= population, intervention, comparator, outcome. EtD= evidence to decision framework.



Summary of the ERS guideline for management of hospitalised patients with COVID-19. Abbreviations HFNC= high flow nasal cannula oxygen, CPAP= continuous positive airway pressure.

Supplementary material

Systematic review

Two experienced external librarians (TV, KT) designed and ran a search strategy using MeSH terms and keywords for each clinical question, in collaboration with the methodologists (PCG, MLC, JDC).

The PubMed platform was used to search MEDLINE. EMBASE, International Clinical Trials Registry Platform (ICTRP) and CDC were also searched.

The search was initially limited to randomised clinical trials published in English language. In the absence of clinical trials, we subsequently searched for observational studies. All searches were performed systematically through October 2020.

The search retrieved 11,343 records after removal of duplicates with a further 11,316 citations excluded through title and abstract screening. A search of MedRxiv database identified 10 further preprints. For the anti-coagulation data, 1 meta-analysis detailing 3 studies was identified. A total of 40 references were included in the evidence summaries and all were assessed in full text by at least two authors who determined inclusion by consensus; disagreements were resolved by consultation to guideline panel chairs. All authors monitored the literature up to October 2020.

Assessment of the level of evidence and degree of recommendations

The panel selected outcomes of interest for each clinical question a priori, based on their relative importance to adult patients with COVID-19 and to clinical decision making. Following the GRADE approach, outcomes were rated as "not important", "important" or "critical" for clinical decision making through an online vote of the entire panel. Only outcomes that were considered important or critical were subsequently used to formulate recommendations.

A methodology group composed of one chair (JDC) and two members (PCG and MLC) extracted the data in duplicate from relevant publications reporting important or critical outcomes and pooled them, whenever applicable, using RevMan 5 software version 5.3. The process of literature search, data extraction and reporting were supervised by an experienced ERS methodologist (TT).

We followed the GRADE approach to assess the confidence in the evidence (quality) and the degree of recommendations. This approach specifies four categories of quality (high, moderate, low and very low) that are applied to a body of evidence and not on individual studies. The body of evidence was evaluated based primarily on risk of bias, precision, consistency, directness of evidence and risk of publication bias.

Recommendations are graded as strong or conditional after considering the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the relative importance of outcomes, the implications for resource use, and the acceptability and feasibility of implementation.

Evidence summaries of findings (SoF tables) and Evidence to Decisions (EtD) frameworks were generated by the methodology group for each clinical question using the GRADEpro Guideline Development Tool. Based on these formats, the panel formulated the clinical recommendations and decided on their strength by consensus and, if required, by voting. Following the GRADE approach, strong recommendations are worded as "we recommend", while conditional recommendations are worded as "we suggest".

Evidence summaries of findings (SoF tables)

PICO Question 1: Are Corticosteroids, in comparison to standard care (defined as control, placebo or normal background therapy), beneficial in the treatment for COVID-19?

Setting: Hospitalised patients

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Mortality												
6	randomised trials	not serious	not serious	not serious	serious [a]	none	633/2558 (24.7%)	1271/4700 (27.0%)	OR 0.74 (0.53 to 1.04)	**65 fewer per 1,000** (from 120 fewer to 2 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospital length of stay (days)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	2104	4321	-	median **1 day lower**	⨁⨁⨁◯ MODERATE	IMPORTANT
Need for ICU admission												
2	randomised trials	not serious	not serious	not serious	serious [b]	none	116/1836 (6.3%)	296/3667 (8.1%)	OR 0.70 (0.56 to 0.88)	**23 fewer per 1,000** (from 34 fewer to 9 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Adverse effects												
4	randomised trials	not serious	not serious	not serious	serious [b]	none	14/398 (3.5%)	12/350 (3.4%)	OR 1.09 (0.37 to 3.18)	**3 more per 1,000** (from 21 fewer to 67 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Mortality- mechanical ventilation subgroup												
7	randomised trials	not serious	not serious	not serious	serious [c]	none	222/678 (32.7%)	425/1025 (41.5%)	OR 0.70 (0.48 to 1.01)	**83 fewer per 1,000** (from 161 fewer to 2 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Mortality - oxygen use												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [c]	none	298/1279 (23.3%)	682/2604 (26.2%)	OR 0.86 (0.73 to 1.00)	**28 fewer per 1,000** (from 56 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

Mortality- hospitalised no oxygen

1	randomised trials	not serious	not serious	not serious	serious [b]	none	89/501 (17.8%)	145/1034 (14.0%)	OR 1.32 (0.99 to 1.77)	**37 more per 1,000** (from 1 fewer to 84 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. No statistically significant difference. Confidence intervals not provided by likely to include both beneficial and detrimental effect of treatment

b. wide confidence interval that includes both beneficial and detrimental effect

c. Wide confidence interval includes the possibility of no effect of treatment

N.B. Mortality, Mortality (mechanical ventilation subgroup), Mortality (oxygen use), Mortality (hospitalised no oxygen), Hospital length of stay, Need for ICU admission and Adverse events were the measurable endpoints found for corticosteroids.

Additional endpoints not included in the evidence table which were searched for but were either not studied or data was not found in an extractable format were; Clinical resolution or cure (also includes the reverse i.e patients not cured); Time to clinical improvement or resolution on an ordinal scale; Requirement for oxygen; Hospital admission; Ordinal scale or clinical status at day 28; ICU length of stay; Need for non-invasive ventilation; Deterioration in those not requiring ventilation at start of treatment; DLCO and HRCT at 28 days and 3 months (and 6months); Severity of symptoms; Improvement in oxygen saturations or arterial blood gases; Relapse; Viral clearance (negative SARS-CoV-2 test) and Duration of fever.

PICO Question 2: Is anti-IL-6 or IL-6 receptor monoclonal antibody, in comparison to standard care (defined as control, placebo or normal background therapy), beneficial in the treatment for COVID-19?

Setting: Hospitalised patients

Bibliography:

1. Tocilizumab in Hospitalised Patients With COVID-19 Pneumonia. Rosas I, *et al*. medRxiv 2020.08.27.20183442; doi: https://doi.org/10.1101/2020.08.27.20183442
2. Effect of Tocilizumab vs standard care on clinical worsening in patients hospitalised with COVID-19 Pneumonia A randomised controlled trial. Salvarani C, *et al*. JAMA Intern Med. Doi:10.1001/jamainternmed.2020.6615 Published online October 20, 2020.
3. Effect of Tocilizumab vs Usual Care in Adults Hospitalised With COVID-19 and Moderate or Severe Pneumonia A Randomised Clinical Trial. Hermine *et al*. JAMA Intern Med.

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7. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. Salama et al N Engl J Med. 2021 Jan 7;384(1):20-30
8. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. Veiga et al. BMJ 2021 Jan 20;372:n84. doi: 10.1136/bmj.n84.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-IL-6 or IL-6 receptor monoclonal antibody	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Adverse events												
5	randomised trials	not serious	serious [a]	not serious	serious [b]	none	426/733 (58.1%)	247/464 (53.2%)	OR 1.03 (0.71 to 1.49)	**7 more per 1,000** (from 85 fewer to 97 more)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events												
7	randomised trials	serious [c]	not serious	not serious	serious [b]	none	210/1289 (16.3%)	141/942 (15.0%)	OR 0.86 (0.66 to 1.10)	**18 fewer per 1,000** (from 46 fewer to 13 more)	⨁⨁◯◯ LOW	CRITICAL
Mortality												
8	randomised trials	serious [c]	not serious	not serious	serious [b]	none	820/3309 (24.8%)	893/3038 (29.4%)	OR 0.90 (0.73 to 1.12)	**21 fewer per 1,000** (from 61 fewer to 24 more)	⨁⨁◯◯ LOW	CRITICAL
time to hospital discharge												
3	randomised trials	not serious	not serious	not serious	serious [b]	none	-/0	-/0	HR 1.19 (1.02 to 1.39)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
ICU admission												
3	randomised trials	not serious	not serious	not serious	not serious	none	47/247 (19.0%)	53/191 (27.7%)	OR 0.53 (0.31 to 0.91)	**108 fewer per 1,000** (from 171 fewer to 19 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Deterioration (time to clinical failure defined as death, mechanical ventilation or transfer to ICU)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-IL-6 or IL-6 receptor monoclonal antibody	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	not serious	not serious	none	-/0	-/0	HR 0.59 (0.42 to 0.82)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT
Mechanical ventilation												
4	randomised trials	serious [c]	not serious	not serious	not serious	none	280/2161 (13.0%)	322/2038 (15.8%)	OR 0.75 (0.63 to 0.90)	**35 fewer per 1,000** (from 52 fewer to 14 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
TIme to improvement on ordinal scale												
2	randomised trials	not serious	not serious	not serious	not serious	none	-/0	-/0	HR 1.20 (1.00 to 1.44)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Mechanical ventilation OR death												
6	randomised trials	serious [c]	not serious	not serious	not serious	none	760/2571 (29.6%)	897/2413 (37.2%)	OR 0.74 (0.62 to 0.88)	**67 fewer per 1,000** (from 103 fewer to 29 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical Worsening												
2	randomised trials	not serious	not serious	not serious	serious [b]	none	48/221 (21.7%)	31/144 (21.5%)	OR 1.11 (0.66 to 1.87)	**18 more per 1,000** (from 62 fewer to 124 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical Improvement on WHO ordinal scale												
1	randomised trials	not serious	not serious	not serious	very serious [d]	none	147/161 (91.3%)	72/81 (88.9%)	OR 1.31 (0.54 to 3.18)	**24 more per 1,000** (from 77 fewer to 73 more)	⨁⨁◯◯ LOW	CRITICAL
Proportion discharged from hospital												
4	randomised trials	serious [c]	not serious	not serious	serious [b]	none	1346/2306 (58.4%)	1169/2305 (50.7%)	OR 1.31 (1.17 to 1.48)	**67 more per 1,000** (from 39 more to 96 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio

Explanations

a. Significant heterogeneity between studies

b. wide confidence interval that includes both beneficial and detrimental effect

c. Inclusion of data from pre-prints

d. Very wide confidence intervals that includes the potential for substantial benefit and harm.

N.B. Mortality, Time to clinical improvement (on an ordinal scale), Clinical improvement on WHO ordinal scale, Clinical worsening, Deterioration (time to clinical failure defined as death, mechanical ventilation or transfer to ICU), Need for mechanical ventilation, Mechanical ventilation OR death, Need for ICU admission; Discharge from hospital (days), Proportion discharged from hospital, Adverse events and Serious adverse events were the measurable endpoints found for anti-IL-6 or IL-6 receptor.

Additional endpoints not included in the evidence table which were searched for but were either not studied or data was not found in an extractable format were; Clinical resolution or cure (also includes the reverse i.e patients not cured); Requirement for oxygen; Hospital admission; Hospital length of stay; Need for non-invasive ventilation; Ordinal scale or clinical status at day 28; ICU length of stay; DLCO and HRCT at 28 days and 3 months (and 6months); Severity of symptoms; Improvement in oxygen saturations or arterial blood gases; Relapse; Duration of fever; Viral load and Viral clearance.

PICO Question 3: Is Hydroxychloroquine, in comparison to standard care (defined as control, placebo or normal background therapy), beneficial in the treatment for COVID-19?
Setting: Hospitalised patients or outpatients
Bibliography:

1. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate COVID-19. Cavalcanti AB, *et al*. N Engl J Med. 2020 Jul 23:NEJMoa2019014. doi: 10.1056/NEJMoa2019014. Online ahead of print.
2. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. Tang W, *et al*. BMJ. 2020 May 14;369:m1849. doi: 10.1136/bmj.m1849
3. Hydroxychloroquine in Nonhospitalised Adults With Early COVID-19 : A Randomised Trial. Skipper CP, *et al*. Ann Intern Med. 2020 Jul 16:M20-4207. doi: 10.7326/M20-4207. Online ahead of print.
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6. [A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19]. Chen J, *et al*. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2020 May 25;49(2):215-219. doi: 10.3785/j.issn.1008-9292.2020.03.03.
7. Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomised controlled study. Chen L, *et al*. medRxiv 2020.06.19.20136093; doi: https://doi.org/10.1101/2020.06.19.20136093
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9. A Multicenter, randomised, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate Coronavirus disease 2019 (COVID-19) Chen CP, *et al*. medRxiv 2020.07.08.20148841; doi: https://doi.org/10.1101/2020.07.08.20148841
10. Hydroxychloroquine for Early Treatment of Adults with Mild COVID-19: A Randomised-Controlled Trial. Mitjà O, *et al*. Clin Infect Dis. 2020 Jul 16:ciaa1009. doi: 10.1093/cid/ciaa1009. Online ahead of print.
11. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. WHO Solidarity trial consortium. Pan H, *et al*. medRxiv preprint doi: https://doi.org/10.1101/2020.10.15.20209817

Certainty assessment	№ of patients	Effect	Certainty	Importanc

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxychloroquine	standard care (defined as no treatment, placebo or background therapy according to local practice)	Relative (95% CI)	Absolute (95% CI)		
Time to clinical improvement (days)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	-/0	-/0	**1.01** (0.59 to 1.74)	**-- per 1,000** (from -- to --)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical Resolution												
3	randomised trials	not serious	not serious	serious [b]	not serious	none	176/227 (77.5%)	201/249 (80.7%)	**RR 0.99** (0.91 to 1.07)	**8 fewer per 1,000** (from 73 fewer to 57 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Deterioration												
3	randomised trials	serious [c]	serious [c]	not serious	serious [a]	none	2/116 (1.7%)	4/126 (3.2%)	**OR 0.65** (0.17 to 2.50)	**11 fewer per 1,000** (from 26 fewer to 44 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Hospitalization												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	12/348 (3.4%)	21/368 (5.7%)	**RR 0.62** (0.31 to 1.24)	**22 fewer per 1,000** (from 39 fewer to 14 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Non-invasive ventilation												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	17/159 (10.7%)	16/173 (9.2%)	**OR 1.17** (0.57 to 2.41)	**14 more per 1,000** (from 38 fewer to 105 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Viral load												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	136	157	-	MD **0.07 lower** (0.11 lower to 0.03 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Adverse Events												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxychloroquine	standard care (defined as no treatment, placebo or background therapy according to local practice)	Relative (95% CI)	Absolute (95% CI)		
7	randomised trials	serious [d]	serious [d]	not serious	not serious	none	316/714 (44.3%)	109/710 (15.4%)	**OR 4.23** (3.30 to 5.42)	**281 more per 1,000** (from 221 more to 342 more)	⨁⨁◯◯ LOW	CRITICAL
Mortality - all patients												
9	randomised trials	serious [e]	not serious	not serious	not serious	none	536/3226 (16.6%)	894/4798 (18.6%)	**RR 1.08** (0.97 to 1.19)	**15 more per 1,000** (from 6 fewer to 35 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Invasive ventilation												
4	randomised trials	not serious	not serious	not serious	serious [f]	none	134/1692 (7.9%)	232/3050 (7.6%)	**OR 1.11** (0.88 to 1.38)	**8 more per 1,000** (from 9 fewer to 26 more)	⨁⨁⨁◯ MODERATE	CRITICAL
ICU admission												
1	randomised trials	not serious	not serious	not serious	serious [g]	none	11/97 (11.3%)	13/97 (13.4%)	**OR 0.83** (0.35 to 1.95)	**20 fewer per 1,000** (from 83 fewer to 98 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Cannot exclude a large beneficial or large deleterious effect of treatment

b. Mild COVID-19 disease only included in the dominant study (Mitja et al) therefore data may not be fully applicable to patients with more severe disease

c. One trial with a small sample size suggests a large effect and is inconsistent with the effect seen in the other 2 trials.

d. Inconsistent reporting of AEs across different studies. Studies used different doses of HCQ. Overall confidence in individual study reports is low. In addition, may get increased AE reporting in unblinded studies.

e. Includes data from a preprint which has not been peer reviewed

f. Confidence interval cross 1

g. small sample size, more data needed

N.B. Time to clinical improvement, Clinical resolution, Mortality, Deterioration, Hospitalisations, Invasive ventilation, Non-invasive ventilation, Viral load, ICU admission and adverse events were the only measurable endpoints found for hydroxychloroquine.

Additional endpoints not included in the evidence table which were searched for but were either not studied or data was not found in an extractable format were; Requirement for oxygen; Ordinal scale or clinical status at day 28; ICU length of stay; DLCO and HRCT at 28 days and 3 months (and 6months); Hospital length of stay; Severity of symptoms; Improvement in oxygen saturations or arterial blood gases; Relapse; Viral clearance (negative SARS-CoV-2 test) and Duration of fever.

PICO Question 4: Is azithromycin, in comparison to standard care (defined as control, placebo or normal background therapy), beneficial in the treatment for COVID-19?
Setting: Hospitalised patients
Bibliography:

1. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate COVID-19. Cavalcanti AB, *et al*. N Engl J Med. 2020 Jul 23:NEJMoa2019014. doi: 10.1056/NEJMoa2019014. Online ahead of print.
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3. Safety and effectiveness of azithromycin in patients with COVID-19: An open-label randomised trial. Sekhavati E, *et al*. Int J Antimicrob Agents. 2020 Oct;56(4):106143. doi: 10.1016/j.ijantimicag.2020.106143. Epub 2020 Aug 25.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	93/442 (21.0%)	84/570 (14.7%)	**OR 1.02** (0.69 to 1.49)	**3 more per 1,000** (from 41 fewer to 57 more)	⨁◯◯◯ VERY LOW	CRITICAL
Clinical Status measured by WHO Score on ordinal scale at day 15												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	-/0	-/0	**OR 0.99** (0.57 to 1.73)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Required ICU admission (deterioration)												
1	randomised trials	not serious	not serious	not serious	very serious [c]	none	2/56 (3.6%)	7/55 (12.7%)	**OR 0.25** (0.05 to 1.28)	**92 fewer per 1,000** (from 120 fewer to 30 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Hospital length of stay (days)												
2	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	228	214	-	MD **0.37 lower** (2.47 lower to 1.72 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events												
2	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	107/480 (22.3%)	79/574 (13.8%)	**OR 1.25** (0.86 to 1.81)	**29 more per 1,000** (from 17 fewer to 86 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. One study had several amendments to the protocol. All studies had high background use of additional therapies such as hydroxychloroquine.

b. one included trial did not aim to directly evaluate azithromycin, but was evaluating azithromycin plus hydroxychloroquine vs hydroxychloquine or standard care

c. wide confidence interval that includes both beneficial and detrimental effect

N.B. Mortality, Hospital length of stay, Need for ICU admission, Clinical status measured by WHO score on ordinal scale at day 15; and Serious adverse events were the measurable endpoint found for azithromycin. Additional endpoints not included in the evidence table which were searched for but were either not studied or data was not found in an extractable format were; Clinical resolution or cure (also includes the reverse i.e patients not cured); Time to clinical improvement or resolution on an ordinal scale; Requirement for oxygen; Adverse events; Hospital admission; ICU length of stay; Need for non-invasive ventilation; Deterioration in those not requiring ventilation at start of treatment; DLCO and HRCT at 28 days and 3 months (and 6months); Severity of symptoms; Improvement in oxygen saturations or arterial blood gases; Relapse; Viral clearance (negative SARS-CoV-2 test) and Duration of fever.

PICO Question 5: Is Hydroxychloroquine and azithromycin, in comparison to standard care (defined as control, placebo or normal background therapy), beneficial in the treatment for COVID-19?
Setting: Hospitalised patients
Bibliography:

1. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate COVID-19. Cavalcanti AB, *et al*. N Engl J Med. 2020 Jul 23:NEJMoa2019014. doi: 10.1056/NEJMoa2019014. Online ahead of print.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxychloroquine and azithromycin	Standard care (defined as control, placebo or background therapy according to local practice)	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	5/172 (2.9%)	6/173 (3.5%)	**OR 0.83** (0.25 to 2.78)	**6 fewer per 1,000** (from 26 fewer to 56 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical Status measured on the WHO Ordinal scale at day 15												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	-/0	-/0	**OR 0.99** (0.57 to 1.73)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Non-invasive ventilation												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	16/172 (9.3%)	16/173 (9.2%)	**OR 1.01** (0.49 to 2.08)	**1 more per 1,000** (from 45 fewer to 82 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Mechanical ventilation												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	19/172 (11.0%)	12/173 (6.9%)	**OR 1.67** (0.78 to 3.55)	**41 more per 1,000** (from 14 fewer to 140 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Duration of hospital stay (days)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	172	173	-	MD **0.8 higher** (0.85 lower to 2.45 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Adverse events												
1	randomised trials	serious [b]	not serious	not serious	not serious	none	94/239 (39.3%)	40/177 (22.6%)	**OR 2.22** (1.43 to 3.44)	**167 more per 1,000** (from 69 more to 275 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations
a. wide confidence interval that includes both beneficial and detrimental effect

b. Not blinded, higher propensity to report adverse events in active treatment arms

N.B. Mortality, Time to clinical improvement (measured on the WHO ordinal scale at day 15), Need for non-invasive ventilation, need for mechanical ventilation, Hospital length of stay and Adverse events were the measurable endpoint found for hydroxychloroquine and azithromycin combination treatment.
Additional endpoints not included in the evidence table which were searched for but were either not studied or data was not found in an extractable format were; Need for ICU admission (incorporating mechanical ventilation/shock/ARDS); Clinical resolution or cure (also includes the reverse i.e patients not cured); Requirement for oxygen; Hospital admission; Ordinal scale or clinical status at day 28; ICU length of stay; Deterioration in those not requiring ventilation at start of treatment; DLCO and HRCT at 28 days and 3 months (and 6months); Severity of symptoms; Improvement in oxygen saturations or arterial blood gases; Relapse; Viral clearance (negative SARS-CoV-2 test) and Duration of fever.

PICO Question 6: Is colchicine, in comparison to standard care (defined as control, placebo or normal background therapy), beneficial in the treatment for COVID-19?
Setting:
Bibliography:

1. Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalised with Coronavirus Disease 2019 The GRECCO-19 Randomised Clinical Trial. Deftereos S, *et al*. JAMA Network Open. 2020;3(6):e2013136. doi:10.1001/jamanetworkopen.2020.13136
2. Beneficial effects of colchicine for moderate to severe COVID-19: an interim analysis of a randomised, double-blinded, placebo controlled clinical trial. Lopes *et al*. medRxiv preprint doi: https://doi.org/10.1101/2020.08.06.20169573;

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Deterioration (defined as 2 points worsening on the WHO ordinal scale)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	1/55 (1.8%)	7/50 (14.0%)	**OR 0.11** (0.01 to 0.96)	**122 fewer per 1,000** (from 138 fewer to 5 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
Mortality												
2	randomised trials	serious [b]	not serious	not serious	serious [c]	none	1/72 (1.4%)	4/68 (5.9%)	**OR 0.21** (0.02 to 1.97)	**46 fewer per 1,000** (from 58 fewer to 51 more)	⨁⨁◯◯ LOW	CRITICAL
ICU admission												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	not serious	very serious [c]	none	1/17 (5.9%)	1/18 (5.6%)	**OR 1.06** (0.06 to 18.45)	**3 more per 1,000** (from 52 fewer to 465 more)	⨁◯◯◯ VERY LOW	CRITICAL

Adverse effect- Diarrhoea

2	randomised trials	serious [b]	not serious	not serious	not serious	none	29/72 (40.3%)	10/68 (14.7%)	**OR 3.96** (1.72 to 9.12)	**259 more per 1,000** (from 82 more to 464 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations
a. Single centre, open label trial, suboptimal reporting of outcomes

b. Suboptimal reporting. One trial has multiple primary endpoints without control for multiple statistical comparisons.

c. wide confidence interval that includes both beneficial and detrimental effect

N.B. Mortality, Deterioration (defined as 2 points worsening on the WHO ordinal scale), ICU admission and adverse effect (diarrhoea) were the only measurable endpoints found for colchicine.

Additional endpoints not included in the evidence table which were searched for but were either not studied or data was not found in an extractable format were; Clinical resolution or cure (also includes the reverse i.e patients not cured); Time to clinical improvement or resolution on an ordinal scale; Requirement for oxygen; Hospital admission; Ordinal scale or clinical status at day 28; ICU length of stay; Need for non-invasive ventilation; DLCO and HRCT at 28 days and 3 months (and 6months); Hospital length of stay; Severity of symptoms; Improvement in oxygen saturations or arterial blood gases; Relapse; Viral clearance (negative SARS-CoV-2 test) and Duration of fever.

PICO Question 7: Is Lopinavir-Ritonavir, in comparison to standard care (defined as control, placebo or normal background therapy), beneficial in the treatment for COVID-19?
Setting: Hospitalised patients
Bibliography:

1. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. RECOVERY Collaborative Group. Lancet. 2020 Oct 5:S0140-6736(20)32013-4. doi: 10.1016/S0140-6736(20)32013-4. Online ahead of print.
2. A Trial of Lopinavir-Ritonavir in Adults Hospitalised with Severe COVID-19. Cao B, *et al*. N Engl J Med. 2020 May 7;382(19):1787-1799. doi: 10.1056/NEJMoa2001282. Epub 2020 Mar 18.

3. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. WHO Solidarity trial consortium. Pan H, *et al*. medRxiv preprint doi: https://doi.org/10.1101/2020.10.15.20209817

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lopinavir-Ritonavir	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
time to clinical improvement (days)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	-/0	-/0	**HR 1.31** (0.95 to 1.80)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Improvement in clinical status on the WHO ordinal scale												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	78/99 (78.8%)	70/100 (70.0%)	**OR 1.59** (0.84 to 3.03)	**88 more per 1,000** (from 38 fewer to 176 more)	⨁⨁◯◯ LOW	CRITICAL
Mortality												
3	randomised trials	serious [b]	not serious	not serious	serious [a]	none	541/3114 (17.4%)	938/4896 (19.2%)	**OR 1.02** (0.90 to 1.15)	**3 more per 1,000** (from 16 fewer to 23 more)	⨁⨁◯◯ LOW	CRITICAL
Viral load												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	59	71	-	MD **7.6 higher** (0.49 lower to 15.69 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Viral clearance												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	35/59 (59.3%)	41/71 (57.7%)	**OR 1.07** (0.53 to 2.15)	**16 more per 1,000** (from 157 fewer to 169 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Adverse events												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	46/95 (48.4%)	49/99 (49.5%)	**OR 0.96** (0.55 to 1.68)	**10 fewer per 1,000** (from 145 fewer to 127 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	19/95 (20.0%)	32/99 (32.3%)	**OR 0.52** (0.27 to 1.01)	**124 fewer per 1,000** (from 209 fewer to 2 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lopinavir-Ritonavir	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Discharge from hospital within 28 days												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	1113/1616 (68.9%)	2382/3424 (69.6%)	**OR 0.97** (0.85 to 1.10)	**6 fewer per 1,000** (from 35 fewer to 20 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Invasive mechanical ventilation												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	152/1556 (9.8%)	279/3280 (8.5%)	**OR 1.16** (0.95 to 1.43)	**12 more per 1,000** (from 4 fewer to 32 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio; **MD:** Mean difference

Explanations
a. Confidence intervals include the possibility of both beneficial and deleterious effects on outcomes

b. One study is published only in the form of a pre-print

N.B. Mortality, Time to clinical improvement (days), Time to clinical improvement on the WHO ordinal scale; Viral load and Viral clearance, Need for invasive mechanical ventilation, Discharge from hospital within 28days, Adverse events and Serious adverse events were the measurable endpoints found for Lopinavir-Ritonavir.

Additional endpoints not included in the evidence table which were searched for but were either not studied or data was not found in an extractable format were; Need for ICU admission (incorporating mechanical ventilation/shock/ARDS); Clinical resolution or cure (also includes the reverse i.e patients not cured); Requirement for oxygen; Hospital admission; Hospital length of stay; Need for non-invasive ventilation; Ordinal scale or clinical status at day 28; ICU length of stay; Deterioration in those not requiring ventilation at start of treatment; DLCO and HRCT at 28 days and 3 months (and 6months); Severity of symptoms; Improvement in oxygen saturations or arterial blood gases; Relapse; and Duration of fever.

PICO Question 8: Is Remdesivir, in comparison to standard care (defined as control, placebo or normal background therapy), beneficial in the treatment for COVID-19?
Setting: Hospitalised patients
Bibliography:

1. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomised Clinical Trial. Spinner CD, *et al*. JAMA. 2020 Sep 15;324(11):1048-1057. doi: 10.1001/jama.2020.16349.

2. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Wang Y, *et al*. Lancet. 2020 May 16;395(10236):1569-1578. doi: 10.1016/S0140-6736(20)31022-9. Epub 2020 Apr 29.
3. Remdesivir for the Treatment of COVID-19 - Final Report. Beigel JH, *et al*. N Engl J Med. 2020 Oct 8:NEJMoa2007764. doi: 10.1056/NEJMoa2007764. Online ahead of print.
4. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. WHO Solidarity trial consortium. Pan H, *et al*. medRxiv preprint doi: https://doi.org/10.1101/2020.10.15.20209817

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Time to Clinical improvement on the WHO ordinal scale												
1	randomised trials	not serious	not serious	not serious	not serious	none	-/0	-/0	**Rate ratio 1.29** (1.12 to 1.49)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁⨁ HIGH	CRITICAL
Proportion of patients with improvement on ordinal scale at designated time point												
1	randomised trials	not serious	not serious	not serious	not serious	none	-/0	-/0	**OR 1.50** (1.18 to 1.91)	**2 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Clinical recovery												
1	randomised trials	not serious	not serious	not serious	not serious	none	399/541 (73.8%)	352/521 (67.6%)	**OR 1.35** (1.03 to 1.76)	**62 more per 1,000** (from 6 more to 110 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Mortality												
4	randomised trials	serious [b]	not serious	not serious	serious [a]	none	387/3826 (10.1%)	394/3507 (11.2%)	**OR 0.92** (0.79 to 1.07)	**8 fewer per 1,000** (from 21 fewer to 7 more)	⨁⨁◯◯ LOW	CRITICAL
Conversion to negative viral detection												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	99/131 (75.6%)	54/65 (83.1%)	**OR 0.63** (0.29 to 1.35)	**75 fewer per 1,000** (from 243 fewer to 38 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Adverse events												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	618/1071 (57.7%)	466/794 (58.7%)	**OR 1.05** (0.71 to 1.55)	**7 more per 1,000** (from 92 fewer to 101 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events												
3	randomised trials	not serious	not serious	not serious	not serious [a]	none	178/1071 (16.6%)	201/794 (25.3%)	**OR 0.67** (0.53 to 0.85)	**68 fewer per 1,000** (from 101 fewer to 29 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Time to clinical recovery- requiring mechanical ventilation or ECMO												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	-/0	-/0	**Rate ratio 0.98** (0.70 to 1.36)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁◯ MODERATE	CRITICAL
Time to clinical recovery- requiring oxygen												
1	randomised trials	not serious	not serious	not serious	not serious	none	-/0	-/0	**Rate ratio 1.45** (1.18 to 1.79)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁⨁ HIGH	CRITICAL
time to clinical recovery- receiving high flow oxygen or NIV												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	-/0	-/0	**Rate ratio 1.09** (0.76 to 1.57)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁◯ MODERATE	CRITICAL
time to clinical recovery- not receiving oxygen												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	-/0	-/0	**Rate ratio 1.29** (0.91 to 1.83)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁◯ MODERATE	CRITICAL
time to clinical recovery - symptoms less than 10 days												
1	randomised trials	not serious	not serious	not serious	not serious	none	-/0	-/0	**Rate ratio 1.37** (1.14 to 1.64)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁⨁ HIGH	CRITICAL
time to clinical recovery- symptoms more than 10 days												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [a]	none	-/0	-/0	**Rate ratio 1.20** (0.94 to 1.52)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio

Explanations
a. wide confidence interval that includes both beneficial and detrimental effect

b. Includes data from a pre-print manuscript which has not been peer reviewed

N.B. Time to clinical improvement or resolution on an ordinal scale, Time to clinical improvement on the WHO ordinal scale, proportion of patients with improvement on ordinal scale at designated time point, Clinical recovery, Mortality, Viral clearance (negative SARS-CoV-2 test), Adverse events, serious adverse events, Time to clinical recovery – requiring mechanical ventilation or ECMO, Time to clinical recovery – requiring oxygen and Time to clinical recovery – receiving high flow oxygen or NIV were the measurable endpoints found for remdesivir.

Additional endpoints not included in the evidence table which were searched for but were either not studied or data was not found in an extractable format were; Deterioration in those not requiring ventilation at start of treatment; Requirement for oxygen; Hospital admission; ICU length of stay; Need for non-invasive ventilation; DLCO and HRCT at 28 days and 3 months (and 6months); Hospital length of stay; Severity of symptoms; Improvement in oxygen saturations or arterial blood gases; Relapse and Duration of fever.

PICO Question 9: Is Interferon -β, in comparison to standard care (defined as control, placebo or normal background therapy), beneficial in the treatment for COVID-19?
Setting: Hospitalised patients
Bibliography:

1. Efficacy and safety of interferon β-1a in treatment of severe COVID-19: A randomised clinical trial. Davoudi-Monfared E, *et al*. medRxiv preprint doi: https://doi.org/10.1101/2020.05.28.20116467
2. Interferon β-1b in treatment of severe COVID-19: A randomised clinical trial. Ramani H, *et al*. Int. Immunopharmacology 88 (2020) 106903 https://doi.org/10.1016/j.intimp.2020.106903
3. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. WHO Solidarity trial consortium. Pan H, *et al*. medRxiv preprint doi: https://doi.org/10.1101/2020.10.15.20209817

Certainty assessment	№ of patients	Effect	Certainty	Importance

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon beta	Standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	randomised trials	very serious [a]	very serious [b]	not serious	very serious [c]	none	253/2125 (11.9%)	239/2122 (11.3%)	**OR 0.55** (0.18 to 1.63)	**47 fewer per 1,000** (from 90 fewer to 59 more)	⨁◯◯◯ VERY LOW	CRITICAL
Deterioration (defined as requirement for mechanical ventilation or ICU admission)												
2	randomised trials	very serious [a]	not serious	not serious	very serious [d]	none	29/75 (38.7%)	39/72 (54.2%)	**OR 0.53** (0.27 to 1.04)	**157 fewer per 1,000** (from 300 fewer to 10 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations
a. Single centre trials with small sample size, unblinded/open label

b. Highly discordant results between two trials from Iran and the Solidarity trial

c. Wide confidence intervals include a large benefit and large harm

d. Wide confidence intervals include the possibility of no meaningful effect of treatment

N.B. Mortality and Deterioration (defined as need for ventilation or ICU admission) were the only measurable endpoints found for interferon-β.
Additional endpoints not included in the evidence table which were searched for but were either not studied or data was not found in an extractable format were; Clinical resolution or cure (also includes the reverse i.e patients not cured); Time to clinical improvement or resolution on an ordinal scale; Adverse events; Requirement for oxygen; Hospital admission; Ordinal scale or clinical status at day 28; ICU length of stay; Need for non-invasive ventilation; DLCO and HRCT at 28 days and 3 months (and 6months); Hospital length of stay; Severity of symptoms; Improvement in oxygen saturations or arterial blood gases; Relapse; Viral clearance (negative SARS-CoV-2 test) and Duration of fever.

PICO Question 10: Is Anticoagulation, in comparison to no anticoagulation, beneficial in the treatment for COVID-19?
Setting: Hospitalised patients
Bibliography:

1. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia Tang N, Li D, Wang X, Sun Z.. *J Thromb Haemost*. 2020;18(4):844- 847. https://doi.org/10.1111/jth.14768.
2. Risk factors for systemic and venous thromboembolism, mortality and bleeding risks in 1125 patients with COVID- 19: relationship to anticoagulation status Li W, Xiong J, Guo Y, Lip GYH.. 2020.

3. The association between treatment with heparin and survival in patients with Covid- 19. Ayerbe L, Risco C, Ayis S. *J Thromb Thrombolysis*. 2020;50(2):298- 301. https://doi.org/10.1007/s11239-020-02162-z
4. D- Dimers, LDH and absence of anticoagulation are independently associated with one- month mortality in older inpatients with Covid- 19. Bousquet G, Falgarone G, Deutsch D, et al. *Aging (Albany NY)*. 2020;12(12):11306- 11313. https://doi.org/ 10.18632/aging.103583.
5. Low molecular weight heparin in adults inpatient COVID- 19 Gonzalez- Porras JR, Belhassen- Garcia M, Bernus AL, Vaquero- Roncero LM. . https://doi.org/10.2139/ssrn.3586665.
6. Anticoagulation outcomes in hospitalised COVID-19 patients. A systematic review and meta-analysis of case control and cohort studies Kamel AM, Sobhy M, Magdy N et al. *Rev Med Virol.* 2020;e2180.

Certainty assessment							Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)		
3	observational studies	very serious [a]	very serious [b]	not serious	not serious	publication bias strongly suspected	**RR 0.57** (0.35 to 0.94)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations
a. Clear differences in the propensity to prescribe anticoagulation which are partially but not fully adjusted for.

b. Heterogeneity statistic (I2=87%) and visual inspection of funnel plots shows major inconsistency between studies with some suggesting a beneficial effect and one suggesting a detrimental effect.

N.B. Mortality was the only measurable endpoint found for anti-coagulants.
Additional endpoints not included in the evidence table which were searched for but were either not studied or data was not found in an extractable format were; Need for ICU admission (incorporating mechanical ventilation/shock/ARDS); Clinical resolution or cure (also includes the reverse i.e patients not cured); Time to clinical improvement or resolution on an ordinal scale; Adverse events; Requirement for oxygen; Hospital admission; Ordinal scale or clinical status at day 28; ICU length of stay; Need for non-invasive ventilation; Deterioration in those not requiring ventilation at start of treatment; DLCO and HRCT at 28 days and 3 months (and 6months); Hospital length of stay; Severity of symptoms; Improvement in oxygen saturations or arterial blood gases; Relapse; Viral clearance (negative SARS-CoV-2 test) and Duration of fever.

PubMed search strings

Concept 1: COVID	("COVID-19"[Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR nCoV[all] OR 2019nCoV[all] OR COVID[all] OR COVID19[all] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All] OR "sars cov 2"[All] OR SARS2[all] OR "sars coronavirus 2"[all] OR "cov 2"[all] OR cov2[all] OR ((wuhan[all] OR novel[all] OR 19[tiab] OR 2019[tiab] OR epidem*[tiab] OR epidemy[all] OR epidemic*[all] OR pandem*[all] OR outbreak[all] OR new[tiab]) AND ("coronavirus"[MeSH Terms] OR "Coronavirus Infections"[Mesh:NoExp] OR coronavirus*[all] OR corona-virus*[all] OR pneumonia-virus*[tiab] OR cov[tiab] OR hcov[tiab])) AND 2019/12[PDAT]:2030[PDAT])
AND	
Concept 2: Corticosteroids	"Glucocorticoids"[Mesh] OR glucocorticoid*[tiab] OR corticosteroid*[tiab] OR corticoid*[tiab] OR steroid*[tiab] OR "Prednisolone"[Mesh] OR prednisolon[tiab] OR prednisolon[tiab] OR Methylprednisolone[tiab] OR "Dexamethasone"[Mesh] OR dexamethasone[tiab] OR dexamethason[tiab] OR "Hydrocortisone"[Mesh] OR hydrocortisone[tiab] OR hydrocortison[tiab] OR glucocorticoidsteroid[tiab] OR glucocorticosteroid[tiab] OR glucocortoid[tiab] OR glycocorticoid[tiab] OR glycocorticosteroid[tiab] OR adelcort[tiab] OR antisolon[tiab] OR antisolone[tiab] OR aprednislon[tiab] OR aprednislone[tiab] OR benisolon[tiab] OR benisolone[tiab] OR berisolon[tiab] OR berisolone[tiab] OR caberdelta[tiab] OR capsoid[tiab] OR “co hydeltra”[tiab] OR codelcortone[tiab] OR compresolon[tiab] OR cortadeltona[tiab] OR cortadeltone[tiab] OR cortalone[tiab] OR cortelinter[tiab] OR cortisolone[tiab] OR cotolone[tiab] OR dacortin[tiab] OR dacrotin[tiab] OR decaprednil[tiab] OR “decortin h”[tiab] OR decortril[tiab] OR “dehydro cortex”[tiab] OR dehydrocortex[tiab] OR dehydrocortisol[tiab] OR dehydrocortisole[tiab] OR dehydrohydrocortison[tiab] OR dehydrohydrocortisone[tiab] OR delcortol[tiab] OR “delta cortef”[tiab] OR “delta cortril”[tiab] OR “delta ef cortelan”[tiab] OR “delta f”[tiab] OR “delta hycortol”[tiab] OR “delta ophticor”[tiab] OR “delta stab”[tiab] OR “delta1 dehydrocortisol”[tiab] OR “delta1 dehydrohydrocortisone”[tiab] OR deltacortef[tiab] OR deltacortenolo[tiab] OR deltacortil[tiab] OR deltacortoil[tiab] OR deltacortril[tiab] OR deltaderm[tiab] OR deltaglycortril[tiab] OR deltahycortol[tiab] OR deltahydrocortison[tiab] OR deltahydrocortisone[tiab] OR deltaophticor[tiab] OR deltasolone[tiab] OR deltastab[tiab] OR deltidrosol[tiab] OR deltisilone[tiab] OR deltisolon[tiab] OR deltisolone[tiab] OR deltolasson[tiab] OR deltolassone[tiab] OR deltosona[tiab] OR deltosone[tiab] OR “depo-predate”[tiab] OR dermosolon[tiab] OR dhasolone[tiab] OR “di adreson f”[tiab] OR “di adresone f”[tiab] OR “diadreson f”[tiab] OR “diadresone f”[tiab] OR dicortol[tiab] OR domucortone[tiab] OR encortelon[tiab] OR encortelone[tiab] OR encortolon[tiab] OR equisolon[tiab] OR “fernisolone-p”[tiab] OR glistelone[tiab] OR hefasolon[tiab] OR “hostacortin h”[tiab] OR hydeltra[tiab] OR hydeltrone[tiab] OR hydrelta[tiab] OR hydrocortancyl[tiab] OR hydrocortidelt[tiab] OR hydrodeltalone[tiab] OR hydrodeltisone[tiab] OR hydroretrocortin[tiab] OR hydroretrocortine[tiab] OR inflanefran[tiab] OR insolone[tiab] OR “keteocort h”[tiab] OR “key-pred”[tiab] OR lenisolone[tiab] OR leocortol[tiab] OR liquipred[tiab] OR “lygal kopftinktur n”[tiab] OR mediasolone[tiab] OR meprisolon[tiab] OR meprisolone[tiab] OR metacortalon[tiab] OR metacortalone[tiab] OR metacortandralon[tiab] OR metacortandralone[tiab] OR metacortelone[tiab] OR “meti derm”[tiab] OR meticortelone[tiab] OR metiderm[tiab] OR morlone[tiab] OR mydrapred[tiab] OR “neo delta”[tiab] OR nisolon[tiab] OR nisolone[tiab] OR “nsc 9120”[tiab] OR nsc9120[tiab] OR opredsone[tiab] OR panafcortelone[tiab] OR panafcortolone[tiab] OR panafort[tiab] OR paracortol[tiab] OR phlogex[tiab] OR “pre cortisyl”[tiab] OR preconin[tiab] OR precortalon[tiab] OR precortancyl[tiab] OR precortisyl[tiab] OR “pred-ject-50”[tiab] OR “predacort 50”[tiab] OR “predaject-50”[tiab] OR “predalone 50”[tiab] OR predartrina[tiab] OR predartrine[tiab] OR predate[tiab] OR predeltilone[tiab] OR predisole[tiab] OR predisyr[tiab] OR "predne dome"[tiab] OR prednecort[tiab] OR prednedome[tiab] OR prednelan[tiab] OR “predni coelin”[tiab] OR “predni h tablinen”[tiab] OR “predni-helvacort”[tiab] OR prednicoelin[tiab] OR prednicort[tiab] OR prednicortelone[tiab] OR “prednifor drops”[tiab] OR predniment[tiab] OR predniretard[tiab] OR prednis[tiab] OR prednisil[tiab] OR prednisolona[tiab] OR prednivet[tiab] OR prednorsolon[tiab] OR prednorsolone[tiab] OR predonine[tiab] OR predorgasolona[tiab] OR predorgasolone[tiab] OR prelon[tiab] OR prelone[tiab] OR prenilone[tiab] OR prenin[tiab] OR prenolone[tiab] OR preventan[tiab] OR prezolon[tiab]

	OR rubycort[tiab] OR scherisolon[tiab] OR scherisolona[tiab] OR serilone[tiab] OR solondo[tiab] OR solone[tiab] OR solupren[tiab] OR soluprene[tiab] OR spiricort[tiab] OR spolotane[tiab] OR sterane[tiab] OR sterolone[tiab] OR supercortisol[tiab] OR supercortizol[tiab] OR taracortelone[tiab] OR walesolone[tiab] OR wysolone[tiab] OR "adlone-40"[tiab] OR "adlone-80"[tiab] OR "dep medalone"[tiab] OR depmedalone[tiab] OR "depoject-80"[tiab] OR depopred[tiab] OR esametone[tiab] OR firmacort[tiab] OR "med-jec-40"[tiab] OR medixon[tiab] OR mednin[tiab] OR "medralone 80"[tiab] OR medrate[tiab] OR Medrol[tiab] OR medrone[tiab] OR meprednisolone[tiab] OR meprelon[tiab] OR mesopren[tiab] OR "methacort 40"[tiab] OR "methacort 80"[tiab] OR methylcotol[tiab] OR methylcotolone[tiab] OR "methylpred dp"[tiab] OR methylsterolone[tiab] OR metidrol[tiab] OR metrisone[tiab] OR metycortin[tiab] OR metypred[tiab] OR metypresol[tiab] OR neomedrone[tiab] OR "nsc 19987"[tiab] OR "nsc19987"[tiab] OR prednol[tiab] OR solomet[tiab] OR "solu decortin"[tiab] OR urbason[tiab] OR adrecort[tiab] OR adrenocot[tiab] OR "aeroseb dex"[tiab] OR aflucoson[tiab] OR aflucosone[tiab] OR alfalyl[tiab] OR anaflogistico[tiab] OR arcodexan[tiab] OR arcodexane[tiab] OR artrosone[tiab] OR azium[tiab] OR bidexol[tiab] OR calonat[tiab] OR cebedex[tiab] OR cetadexon[tiab] OR colofoam[tiab] OR corsona[tiab] OR cortastat[tiab] OR cortidex[tiab] OR cortidexason[tiab] OR cortidrona[tiab] OR cortidrone[tiab] OR cortisumman[tiab] OR "dacortina fuerte"[tiab] OR "dacortine fuerte"[tiab] OR dalalone[tiab] OR danasone[tiab] OR "de-sone la"[tiab] OR decacortin[tiab] OR decadeltosona[tiab] OR decadeltosone[tiab] OR decaderm[tiab] OR decadion[tiab] OR decadran[tiab] OR decadron[tiab] OR decadronal[tiab] OR decadrone[tiab] OR decaesadril[tiab] OR decaject[tiab] OR decamethasone[tiab] OR decasone[tiab] OR decaspray[tiab] OR decasterolone[tiab] OR decdan[tiab] OR decilone[tiab] OR decofluor[tiab] OR dectancyl[tiab] OR dekacort[tiab] OR delladec[tiab] OR deltafluoren[tiab] OR deltafluorene[tiab] OR dergramin[tiab] OR deronil[tiab] OR desacort[tiab] OR desacortone[tiab] OR desadrene[tiab] OR desalark[tiab] OR desameton[tiab] OR desametone[tiab] OR desigdron[tiab] OR "dexa cortisyl"[tiab] OR "dexa dabrosan"[tiab] OR "dexa korti"[tiab] OR "dexa scherosan"[tiab] OR "dexa scherozon"[tiab] OR "dexa scherozone"[tiab] OR "dexa-p"[tiab] OR "dexacen 4"[tiab] OR dexachel[tiab] OR dexacort[tiab] OR dexacortal[tiab] OR dexacorten[tiab] OR dexacortin[tiab] OR dexacortisyl[tiab] OR dexadabroson[tiab] OR dexadecadrol[tiab] OR dexadrol[tiab] OR dexagel[tiab] OR dexagen[tiab] OR dexahelvacort[tiab] OR dexakorti[tiab] OR dexalien[tiab] OR dexalocal[tiab] OR dexame[tiab] OR dexamecortin[tiab] OR dexameson[tiab] OR dexamesone[tiab] OR dexametason[tiab] OR dexametasone[tiab] OR dexameth[tiab] OR dexamethason[tiab] OR dexamethazon[tiab] OR dexamethazone[tiab] OR dexamethonium[tiab] OR dexamonozon[tiab] OR dexan[tiab] OR dexane[tiab] OR dexano[tiab] OR dexapot[tiab] OR dexascheroson[tiab] OR dexascherozon[tiab] OR dexascherozone[tiab] OR dexason[tiab] OR dexasone[tiab] OR dexinoral[tiab] OR dexionil[tiab] OR dexmethsone[tiab] OR dexona[tiab] OR dexone[tiab] OR dexpak[tiab] OR dextelan[tiab] OR dextenza[tiab] OR dextrasone[tiab] OR dexycu[tiab] OR dezone[tiab] OR dibasona[tiab] OR doxamethasone[tiab] OR esacortene[tiab] OR "ex s1"[tiab] OR exadion[tiab] OR exadione[tiab] OR firmalone[tiab] OR fluormethylprednisolon[tiab] OR fluormethylprednisolone[tiab] OR fluormone[tiab] OR fluorocort[tiab] OR fluorodelta[tiab] OR fluoromethylprednisolone[tiab] OR fortecortin[tiab] OR gammacorten[tiab] OR gammacortene[tiab] OR grosodexon[tiab] OR grosodexone[tiab] OR hemady[tiab] OR hexadecadiol[tiab] OR hexadecadrol[tiab] OR hexadiol[tiab] OR hexadrol[tiab] OR isnacort[tiab] OR "isopto dex"[tiab] OR "isopto maxidex"[tiab] OR isoptodex[tiab] OR isoptomaxidex[tiab] OR "lokalison f"[tiab] OR loverine[tiab] OR luxazone[tiab] OR marvidione[tiab] OR maxidex[tiab] OR mediamethasone[tiab] OR megacortin[tiab] OR mephameson[tiab] OR mephamesone[tiab] OR metasolon[tiab] OR metasolone[tiab] OR "methazon ion"[tiab] OR "methazone ion"[tiab] OR methazonion[tiab] OR methazonione[tiab] OR "metisone lafi"[tiab] OR mexasone[tiab] OR millicorten[tiab] OR millicortenol[tiab] OR "mk 125"[tiab] OR mk125[tiab] OR mymethasone[tiab] OR neoforderx[tiab] OR neofordex[tiab] OR nisomethasona[tiab] OR novocort[tiab] OR "nsc 34521"[tiab] OR nsc34521[tiab] OR oftan-dexa[tiab] OR opticorten[tiab] OR opticortinol[tiab] OR oradexan[tiab] OR oradexon[tiab] OR oradexone[tiab] OR orgadrone[tiab] OR ozurdex[tiab] OR pidexon[tiab] OR policort[tiab] OR posurdex[tiab] OR predni-f[tiab] OR prodexona[tiab] OR prodexone[tiab] OR sanamethasone[tiab] OR santenson[tiab] OR santeson[tiab] OR sawasone[tiab] OR solurex[tiab] OR spoloven[tiab] OR sterasone[tiab] OR thilodexine[tiab] OR triamcimetil[tiab] OR vexamet[tiab] OR visumetazone[tiab] OR visumethazone[tiab] OR Methylfluorprednisolone[tiab] OR methylfluorprednisolon[tiab] OR decameth[tiab] OR acticort[tiab] OR "aeroseb hc"[tiab] OR "ala-cort"[tiab] OR "ala-scalp"[tiab] OR alfacort[tiab] OR algicortis[tiab] OR alkindi[tiab] OR "alpha derm"[tiab] OR alphaderm[tiab] OR "anucort-hc"[tiab] OR "anumed-hc"[tiab] OR "anutone-hc"[tiab] OR "aquanil hc"[tiab] OR "balneol-hc"[tiab] OR "barseb hc"[tiab] OR "beta-hc"[tiab] OR biacort[tiab] OR cetacort[tiab] OR cobadex[tiab] OR colocort[tiab]

	OR “compound f”[tiab] OR “cordicare lotion”[tiab] OR coripen[tiab] OR “cort dome”[tiab] OR cortef[tiab] OR cortenema[tiab] OR cortibel[tiab] OR corticorenol[tiab] OR cortifan[tiab] OR cortiphate[tiab] OR cortisol[tiab] OR cortisole[tiab] OR cortispray[tiab] OR cortoderm[tiab] OR cortril[tiab] OR cotacort[tiab] OR covocort[tiab] OR “cremicort-h”[tiab] OR cutaderm[tiab] OR “derm-aid cream”[tiab] OR “dermacrin hc lotion”[tiab] OR dermaid[tiab] OR dermocare[tiab] OR dermocortal[tiab] OR dermolate[tiab] OR dioderm[tiab] OR eczacort[tiab] OR “ef cortelan”[tiab] OR efcortelan[tiab] OR egocort[tiab] OR eksalb[tiab] OR eldecort[tiab] OR “emo-cort”[tiab] OR epicort[tiab] OR ficortril[tiab] OR filocot[tiab] OR flexicort[tiab] OR “gly-cort”[tiab] OR glycort[tiab] OR “h-cort”[tiab] OR hc[tiab] OR hebcort[tiab] OR “hemril-30”[tiab] OR “hemril-hc uniserts”[tiab] OR “hi-cor”[tiab] OR hidrotisona[tiab] OR hycor[tiab] OR hycort[tiab] OR hydracort[tiab] OR hydrasson[tiab] OR “hydro ricortex”[tiab] OR “hydro-rx”[tiab] OR hydrocort[tiab] OR hydrocorticosteroid[tiab] OR hydrocortisate[tiab] OR hydrocortison[tiab] OR hydrocortisonum[tiab] OR hydrocortisyl[tiab] OR hydrocortone[tiab] OR hydrogalen[tiab] OR hydrokort[tiab] OR hydrokortison[tiab] OR hydrotopic[tiab] OR hysone[tiab] OR hytisone[tiab] OR hytone[tiab] OR “incortin h”[tiab] OR “instacort 10”[tiab] OR kyypakkaus[tiab] OR “lacticare-hc”[tiab] OR lenirit[tiab] OR “medihaler cort”[tiab] OR “medihaler duo”[tiab] OR medrocil[tiab] OR mildison[tiab] OR “mildison-fatty”[tiab] OR “mitocortyl demangeaisons”[tiab] OR munitren[tiab] OR novohydrocort[tiab] OR “nsc 10483”[tiab] OR “nsc 741”[tiab] OR “nsc10483”[tiab] OR nutracort[tiab] OR optef[tiab] OR “otosone f”[tiab] OR penecort[tiab] OR plenadren[tiab] OR prepcort[tiab] OR “pro cort”[tiab] OR procort[tiab] OR “procto-kit”[tiab] OR proctocort[tiab] OR “proctosol-hc”[tiab] OR proctosone[tiab] OR procutan[tiab] OR “rectasol-hc”[tiab] OR rectocort[tiab] OR rederm[tiab] OR sanatison[tiab] OR “scalp-aid”[tiab] OR schericur[tiab] OR “scherosone f”[tiab] OR “sistral hydrocort”[tiab] OR skincalm[tiab] OR “stie-cort”[tiab] OR “substance m”[tiab] OR synacort[tiab] OR texacort[tiab] OR “triburon-hc”[tiab] OR unicort[tiab] OR vasocort[tiab] OR Epicortisol[tiab]
Concept 3: Hydroxychloroquin	Hydroxychloroquin*[tiab] OR "Chloroquine"[Mesh] OR chloroquin*[tiab] OR oxychlorochin*[tiab] OR oxychloroquin*[tiab] OR hydroxychlorochin*[tiab] OR plaquenil[tiab] OR HCQ[tiab] OR CQ[tiab] OR Chlorochi[tiab] OR Chingamin*[tiab] OR Khingamin*[tiab] OR Nivaquin*[tiab] OR Aralen[tiab] OR Arequin[tiab] OR Arechin*[tiab] OR ercoquin*[tiab] OR hydrocloroquin*[tiab] OR quensyl[tiab] OR “sn 8137”[tiab] OR a-cq[tiab] OR amokin*[tiab] OR anoclor[tiab] OR aralan[tiab] OR aralen[tiab] OR aralene[tiab] OR arechin*[tiab] OR arequin*[tiab] OR arthrochin*[tiab] OR arthroquin*[tiab] OR artrichin*[tiab] OR artriquin*[tiab] OR avloclor[tiab] OR avoclor[tiab] OR bemaphata[tiab] OR bemaphate[tiab] OR bemasulph[tiab] OR bipiquin*[tiab] OR cadiquin*[tiab] OR chemochin*[tiab] OR chingamin*[tiab] OR chingaminum[tiab] OR chloraquin*[tiab] OR chlorochin*[tiab] OR chlorochin*[tiab] OR chlorofoz[tiab] OR chloroquin*[tiab] OR chloroquinesulphate[tiab] OR “chloroquini diphosphas”[tiab] OR “chloroquinum diphosphoricum”[tiab] OR chlorquin*[tiab] OR choloquin*[tiab] OR cidanchin*[tiab] OR “clo-kit junior”[tiab] OR clorichin*[tiab] OR cloriquin*[tiab] OR clorochin*[tiab] OR delagil[tiab] OR delagyl[tiab] OR dichinalex[tiab] OR diclokin*[tiab] OR diquinalex[tiab] OR diroquin*[tiab] OR emquin*[tiab] OR genocin*[tiab] OR gontochin*[tiab] OR gontoquin*[tiab] OR heliopar[tiab] OR imagon[tiab] OR iroquin*[tiab] OR klorokin*[tiab] OR klorokin*[tiab] OR klorokinfosfat[tiab] OR lagaquin*[tiab] OR malaquin*[tiab] OR malarex[tiab] OR malarivon[tiab] OR malaviron[tiab] OR maliaquin*[tiab] OR maquin*[tiab] OR mesylith[tiab] OR mexaquin*[tiab] OR mirquin*[tiab] OR nivachin*[tiab] OR nivaquin*[tiab] OR nivaquin*[tiab] OR “p roquin*”[tiab] OR quinachlor[tiab] OR quingamin*[tiab] OR repal[tiab] OR resochen*[tiab] OR resochin*[tiab] OR resoquin*[tiab] OR reumachlor[tiab] OR roquin*[tiab] OR “rp 3377”[tiab] OR rp3377[tiab] OR sanoquin*[tiab] OR silbesan[tiab] OR siragan[tiab] OR sirajan[tiab] OR “sn 7618”[tiab] OR sn7618[tiab] OR solprin*[tiab] OR tresochin*[tiab] OR tresoquin*[tiab] OR trochin*[tiab] troquin*[tiab] OR “w 7618”[tiab] OR w7618[tiab] OR “win 244”[tiab] OR win244[tiab] OR Chlorochi[tiab] OR hydroxychloroquin*[tiab] OR dolquin*[tiab] OR reuquinol[tiab] OR hidroxicloroquin*[tiab] OR dimard[tiab] OR oxiklorin*[tiab] OR quineprox[tiab]
Concept 4: Azithromycin	"Azithromycin"[Mesh] OR Azithromycin[tiab] OR Azythromycin[tiab] OR Sumamed[tiab] OR Toraseptol[tiab] OR Vinzam[tiab] OR "CP-62993"[tiab] OR CP62993[tiab] OR Zithromax[tiab] OR Azitrocin[tiab] OR Azadose[tiab] OR Ultreon[tiab] OR Zitromax[tiab] OR Goxal[tiab] OR Zentavion[tiab] OR Aruzilina[tiab] OR atizor[tiab] OR azasite[tiab] OR azatril[tiab] OR azenil[tiab] OR azibiot[tiab] OR azimin[tiab] OR azithral[tiab] OR Azitromax[tiab] OR azitromicin[tiab] OR azitromicina[tiab] OR aziwok[tiab] OR azomyne[tiab] OR aztrin[tiab] OR azydrop[tiab] OR azyter[tiab] OR bazyt[tiab] OR "cp 62933"[tiab] OR cp62933[tiab] OR forcin[tiab] OR inedol[tiab] OR infectoazit[tiab] OR "isv 401"[tiab] OR isv401[tiab] OR kromicin[tiab] OR

	macrozit[tiab] OR mezatrin[tiab] OR octavax[tiab] OR ordipha[tiab] OR ribotrex[tiab] OR sunamed[tiab] OR tobyl[tiab] OR tromix[tiab] OR trozocina[tiab] OR xithrone[tiab] OR "xz 450"[tiab] OR xz450[tiab] OR zaret[tiab] OR zarom[tiab] OR zetamax[tiab] OR zeto[tiab] OR zibramax[tiab] OR zifin[tiab] OR zimericina[tiab] OR zistic[tiab] OR zithrox[tiab] OR zitinn[tiab] OR zitrim[tiab] OR zitrobifan[tiab] OR zitrocin[tiab] OR zmax[tiab]
Concept 5: Lopinavir-Ritonavir	"Lopinavir"[Mesh] OR lopinavir[tiab] OR "A-157378"[tiab] OR "A157378"[tiab] OR "ABT 378"[tiab] OR ABT378[tiab] OR "Ritonavir"[Mesh] OR ritonavir[tiab] OR ritovir[tiab] OR "ABT 538"[tiab] OR ABT538[tiab] OR Norvir[tiab] OR "a 84538"[tiab] OR "a84538"[tiab] OR "abt 84538"[tiab] OR "abt84538"[tiab] OR Kaletra[tiab] OR Lopimune[tiab] OR Aluvia[tiab]
Concept 6: Remdesevir	"remdesivir" [Supplementary Concept] OR remdesivir[tiab] OR "GS-5734"[tiab] OR "GS5734"[tiab]
Concept 7: Anti-coagulants	"Heparin, Low-Molecular-Weight"[Mesh] OR heparin*[tiab] OR LMWH[tiab] OR dalteparin*[tiab] OR tedelparin*[tiab] OR FR-860[tiab] OR FR860[tiab] OR Kabi-2165[tiab] OR Kabi2165[tiab] OR fragmin*[tiab] OR enoxaparin*[tiab] OR PK-10-169[tiab] OR PK-10169[tiab] OR PK10169[tiab] OR EMT-967[tiab] OR lovenox[tiab] OR clexan*[tiab] OR EMT-966[tiab] OR nadroparin*[tiab] OR fraxiparin*[tiab] OR CY-216[tiab] OR CY216[tiab] OR Tinzaparin*[tiab] OR 3-phenyl-2-propenoic-acid[tiab] OR innohep[tiab] OR "Anticoagulants" [Pharmacological Action] OR anticoagula*[tiab] OR “anti coagula*”[tiab] OR "Anticoagulants"[Mesh:NoExp] OR bm-2123[tiab] OR bm2123[tiab] OR choay[tiab] OR ebpm*[tiab] OR ff1034[tiab] OR ff-1034[tiab] OR gag-869[tiab] OR gag869[tiab] OR pk-007[tiab] OR pk007[tiab] OR “sandoz 5100”[tiab] OR “sandoz 6700”[tiab] OR traxyparin*[tiab] OR adomiparin*[tiab] OR m118[tiab] OR m-118[tiab] OR antixarin*[tiab] OR ardeparin*[tiab] OR normifio[tiab] OR normiflo[tiab] OR wy-90493[tiab] OR wy90493[tiab] OR bemiparin*[tiab] OR entervit[tiab] OR hepadren*[tiab] OR hibor[tiab] OR ivor[tiab] OR ivorat[tiab] OR ivormax[tiab] OR phivor[tiab] OR zibor[tiab] OR certoparin*[tiab] OR arteven[tiab] OR badyket[tiab] OR “einecs 232-681-7”[tiab] OR eparina[tiab] OR “mono embolex”[tiab] OR monoembolex[tiab] OR op-622[tiab] OR op622[tiab] OR op-386[tiab] OR op386[tiab] OR pabyrin*[tiab] OR pulari[tiab] OR sandoparin*[tiab] OR sublingula[tiab] OR troparin*[tiab] OR “vitrum a”[tiab] OR cy-222[tiab] OR cy222[tiab] OR k-2165[tiab] OR k2165[tiab] OR “low liquemin*”[tiab] OR danaparoid[tiab] OR danaproid[tiab] OR kb-101[tiab] OR kb101[tiab] OR lomoparan[tiab] OR lomoparin*[tiab] OR mucoglucuronan[tiab] OR org-10172[tiab] OR org10172[tiab] OR orgaran[tiab] OR deligoparin*[tiab] OR op-2000[tiab] OR op2000[tiab] OR embolex[tiab] OR inhixa[tiab] OR klexane[tiab] OR ledraxen[tiab] OR neoparin*[tiab] OR “qualiop klinik”[tiab] OR thorinane[tiab] OR fondaparin*[tiab] OR arixtra[tiab] OR ic-851589[tiab] OR ic851589[tiab] OR org-31540[tiab] OR org31540[tiab] OR quixidar[tiab] OR sr-90107[tiab] OR sr-90107a[tiab] OR sr90107[tiab] OR sr90107a[tiab] OR idrabiotaparinux[tiab] OR ssr-126517[tiab] OR ssr-126517-e[tiab] OR ssr126517[tiab] OR ssr126517e[tiab] OR idraparinux[tiab] OR org-34006[tiab] OR org34006[tiab] OR “sanorg 34006”[tiab] OR sanorg34006[tiab] OR sr-34006[tiab] OR sr34006[tiab] OR “livaraparin calcium”[tiab] OR minolteparin*[tiab] OR cy-216d[tiab] OR cy216d[tiab] OR fraxodi[tiab] OR seledie[tiab] OR seleparin*[tiab] OR tedegliparin*[tiab] OR necuparanib[tiab] OR df-01[tiab] OR df01[tiab] OR m-402[tiab] OR m402[tiab] OR tafoxiparin*[tiab] OR parnaparin*[tiab] OR fluxum[tiab] OR lohepa[tiab] OR lowhepa[tiab] OR minidalton[tiab] OR op-2123[tiab] OR op2123[tiab] OR parvoparin*[tiab] OR rd-11885[tiab] OR rd11885[tiab] OR reviparin*[tiab] OR clivarin*[tiab] OR clivarodi[tiab] OR lomorin*[tiab] OR lu-47311[tiab] OR lu47311[tiab] OR semuloparin*[tiab] OR ave-5026[tiab] OR ave5026[tiab] OR mulsevo[tiab] OR visamerin*[tiab] OR sevuparin*[tiab] OR lhn1[tiab] OR lhn-1[tiab] OR logiparin*[tiab]

Concept 8: CPAP	"Continuous Positive Airway Pressure"[Mesh] OR “continuous positive airway pressure”[tiab] OR CPAP[tiab] OR nCPAP[tiab] OR “airway pressure release ventilation”[tiab] OR APRV[tiab] OR “positive end expiratory pressure”[tiab] OR “constant positive pressure breathing”[tiab] OR “continuous positive airway pressure”[tiab] OR “continuous positive pressure breathing”[tiab] OR cppb[tiab] OR cppv[tiab] OR “hyperbaric respiration”[tiab] OR (hyperbaric[tiab] AND ventilation[tiab]) OR PEEP[tiab] OR “positive end expiratory pressure breathing”[tiab]
Concept 9: Anti-IL-6 therapy	"IL-6 receptor"[tiab] OR "IL-6"[tiab] OR "IL6"[tiab] OR "Tocilizumab"[tiab] OR "siltuximab"[tiab] OR "olokizumab"[tiab] OR "sarilumab"[tiab] OR "clazakizumab"[tiab] OR "olokizumab"[tiab] OR "sirukumab"[tiab] OR "Sirukumab"[tiab]

Searches for Interferon and Colchicine were conducted using these individual search terms PLUS the COVID-19 concept using PUBMED only. ERS rules allow searches of one database only. As it was expected that searches for hydroxychloroquine and Azithromycin individually would capture trials in which both drugs were used in combination, no repeat searches were performed and trials were selected from the hydroxychloroquine and azithromycin search results for inclusion in the evidence tables.

EMBASE search strings

Concept 1: COVID	('coronavirus disease 2019'/exp OR nCoV:ti,ab,kw,ff OR 2019nCoV:ti,ab,kw,ff OR COVID:ti,ab,kw,ff OR COVID19:ti,ab,kw,ff OR 'Severe acute respiratory syndrome coronavirus 2'/exp OR 'severe acute respiratory syndrome coronavirus 2':ti,ab,kw,ff OR 'sars cov 2':ti,ab,kw,ff OR SARS2:ti,ab,kw,ff OR 'sars coronavirus 2':ti,ab,kw,ff OR 'cov 2':ti,ab,kw,ff OR cov2:ti,ab,kw,ff OR ((wuhan:ti,ab,kw,ad,ff OR novel:ti,ab,kw,ff OR 19:ti,ab,kw OR 2019:ti,ab,kw OR epidem*:ti,ab,kw OR epidemy:ti,ab,kw,ff OR epidemic*:ti,ab,kw,ff OR pandem*:ti,ab,kw,ff OR outbreak:ti,ab,kw,ff OR new:ti,ab,kw) AND ('Coronavirinae'/exp OR 'Coronavirus infection'/de OR coronavirus*:ti,ab,kw,ff OR 'corona virus*':ti,ab,kw,ff OR 'pneumonia virus*':ti,ab,kw OR cov:ti,ab,kw OR hcov:ti,ab,kw))) AND [2019-2020]/py
AND	
Concept 2: Corticosteroids	'glucocorticoid'/exp OR glucocorticoid*:ti,ab,kw OR glucocorticoidsteroid:ti,ab,kw OR glucocorticosteroid:ti,ab,kw OR glucocortoid:ti,ab,kw OR glycocorticoid:ti,ab,kw OR glycocorticosteroid:ti,ab,kw OR corticosteroid*:ti,ab,kw OR corticoid*:ti,ab,kw OR steroid*:ti,ab,kw OR 'prednisolone'/exp OR prednisolone:ti,ab,kw OR adelcort:ti,ab,kw OR antisolon:ti,ab,kw OR antisolone:ti,ab,kw OR aprednislon:ti,ab,kw OR aprednislone:ti,ab,kw OR benisolon:ti,ab,kw OR benisolone:ti,ab,kw OR berisolon:ti,ab,kw OR berisolone:ti,ab,kw OR caberdelta:ti,ab,kw OR capsoid:ti,ab,kw OR ‘co hydeltra’:ti,ab,kw OR codelcortone:ti,ab,kw OR compresolon:ti,ab,kw OR cortadeltona:ti,ab,kw OR cortadeltone:ti,ab,kw OR cortalone:ti,ab,kw OR cortelinter:ti,ab,kw OR cortisolone:ti,ab,kw OR cotolone:ti,ab,kw OR dacortin:ti,ab,kw OR dacrotin:ti,ab,kw OR decaprednil:ti,ab,kw OR ‘decortin h’:ti,ab,kw OR decortril:ti,ab,kw OR ‘dehydro cortex’:ti,ab,kw OR dehydrocortex:ti,ab,kw OR dehydrocortisol:ti,ab,kw OR dehydrocortisole:ti,ab,kw OR dehydrohydrocortison:ti,ab,kw OR dehydrohydrocortisone:ti,ab,kw OR delcortol:ti,ab,kw OR ‘delta cortef’:ti,ab,kw OR ‘delta cortril’:ti,ab,kw OR ‘delta ef cortelan’:ti,ab,kw OR ‘delta f’:ti,ab,kw OR ‘delta hycortol’:ti,ab,kw OR ‘delta ophticor’:ti,ab,kw OR ‘delta stab’:ti,ab,kw OR ‘delta1 dehydrocortisol’:ti,ab,kw OR ‘delta1 dehydrohydrocortisone’:ti,ab,kw OR deltacortef:ti,ab,kw OR deltacortenolo:ti,ab,kw OR deltacortil:ti,ab,kw OR deltacortoil:ti,ab,kw OR deltacortril:ti,ab,kw OR deltaderm:ti,ab,kw OR deltaglycortril:ti,ab,kw OR deltahycortol:ti,ab,kw OR deltahydrocortison:ti,ab,kw OR deltahydrocortisone:ti,ab,kw OR deltaophticor:ti,ab,kw OR deltasolone:ti,ab,kw OR deltastab:ti,ab,kw OR deltidrosol:ti,ab,kw OR deltisilone:ti,ab,kw

	OR deltisolon:ti,ab,kw OR deltisolone:ti,ab,kw OR deltolasson:ti,ab,kw OR deltolassone:ti,ab,kw OR deltosona:ti,ab,kw OR deltosone:ti,ab,kw OR 'depo-predate':ti,ab,kw OR dermosolon:ti,ab,kw OR dhasolone:ti,ab,kw OR 'di adreson f':ti,ab,kw OR 'di adresone f':ti,ab,kw OR 'diadreson f':ti,ab,kw OR 'diadresone f':ti,ab,kw OR dicortol:ti,ab,kw OR domucortone:ti,ab,kw OR encortelon:ti,ab,kw OR encortelone:ti,ab,kw OR encortolon:ti,ab,kw OR equisolon:ti,ab,kw OR 'fernisolone-p':ti,ab,kw OR glistelone:ti,ab,kw OR hefasolon:ti,ab,kw OR 'hostacortin h':ti,ab,kw OR hydeltra:ti,ab,kw OR hydeltrone:ti,ab,kw OR hydrelta:ti,ab,kw OR hydrocortancyl:ti,ab,kw OR hydrocortidelt:ti,ab,kw OR hydrodeltalone:ti,ab,kw OR hydrodeltisone:ti,ab,kw OR hydroretrocortin:ti,ab,kw OR hydroretrocortine:ti,ab,kw OR inflanefran:ti,ab,kw OR insolone:ti,ab,kw OR 'keteocort h':ti,ab,kw OR 'key-pred':ti,ab,kw OR lenisolone:ti,ab,kw OR leocortol:ti,ab,kw OR liquipred:ti,ab,kw OR 'lygal kopftinktur n':ti,ab,kw OR mediasolone:ti,ab,kw OR meprisolon:ti,ab,kw OR meprisolone:ti,ab,kw OR metacortalon:ti,ab,kw OR metacortalone:ti,ab,kw OR metacortandralon:ti,ab,kw OR metacortandralone:ti,ab,kw OR metacortelone:ti,ab,kw OR 'meti derm':ti,ab,kw OR meticortelone:ti,ab,kw OR metiderm:ti,ab,kw OR morlone:ti,ab,kw OR mydrapred:ti,ab,kw OR 'neo delta':ti,ab,kw OR nisolon:ti,ab,kw OR nisolone:ti,ab,kw OR 'nsc 9120':ti,ab,kw OR nsc9120:ti,ab,kw OR opredsone:ti,ab,kw OR panafcortelone:ti,ab,kw OR panafcortolone:ti,ab,kw OR panafort:ti,ab,kw OR paracortol:ti,ab,kw OR phlogex:ti,ab,kw OR 'pre cortisyl':ti,ab,kw OR preconin:ti,ab,kw OR precortalon:ti,ab,kw OR precortancyl:ti,ab,kw OR precortisyl:ti,ab,kw OR 'pred-ject-50':ti,ab,kw OR 'predacort 50':ti,ab,kw OR 'predaject-50':ti,ab,kw OR 'predalone 50':ti,ab,kw OR predartrina:ti,ab,kw OR predartrine:ti,ab,kw OR predate:ti,ab,kw OR predeltilone:ti,ab,kw OR predisole:ti,ab,kw OR predisyr:ti,ab,kw OR 'predne dome':ti,ab,kw OR prednecort:ti,ab,kw OR 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	p’:ti,ab,kw OR ‘dexacen 4’:ti,ab,kw OR dexachel:ti,ab,kw OR dexacort:ti,ab,kw OR dexacortal:ti,ab,kw OR dexacorten:ti,ab,kw OR dexacortin:ti,ab,kw OR dexacortisyl:ti,ab,kw OR dexadabroson:ti,ab,kw OR dexadecadrol:ti,ab,kw OR dexadrol:ti,ab,kw OR dexagel:ti,ab,kw OR dexagen:ti,ab,kw OR dexahelvacort:ti,ab,kw OR dexakorti:ti,ab,kw OR dexalien:ti,ab,kw OR dexalocal:ti,ab,kw OR dexame:ti,ab,kw OR dexamecortin:ti,ab,kw OR dexameson:ti,ab,kw OR dexamesone:ti,ab,kw OR dexametason:ti,ab,kw OR dexametasone:ti,ab,kw OR dexameth:ti,ab,kw OR dexamethason:ti,ab,kw OR dexamethazon:ti,ab,kw OR dexamethazone:ti,ab,kw OR dexamethonium:ti,ab,kw OR dexamonozon:ti,ab,kw OR dexan:ti,ab,kw OR dexane:ti,ab,kw OR dexano:ti,ab,kw OR dexapot:ti,ab,kw OR dexascheroson:ti,ab,kw OR dexascherozon:ti,ab,kw OR dexascherozone:ti,ab,kw OR dexason:ti,ab,kw OR dexasone:ti,ab,kw OR dexinoral:ti,ab,kw OR dexionil:ti,ab,kw OR dexmethsone:ti,ab,kw OR dexona:ti,ab,kw OR dexone:ti,ab,kw OR ‘dexpak’:ti,ab,kw OR 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OR visumethazone:ti,ab,kw OR Methylfluorprednisolone:ti,ab,kw OR methylfluorprednisolon:ti,ab,kw OR decameth:ti,ab,kw OR 'hydrocortisone'/exp OR hydrocortisone:ti,ab,kw OR acticort:ti,ab,kw OR ‘aeroseb hc’:ti,ab,kw OR ‘ala-cort’:ti,ab,kw OR ‘ala-scalp’:ti,ab,kw OR alfacort:ti,ab,kw OR algicortis:ti,ab,kw OR alkindi:ti,ab,kw OR ‘alpha derm’:ti,ab,kw OR alphaderm:ti,ab,kw OR ‘anucort-hc’:ti,ab,kw OR ‘anumed-hc’:ti,ab,kw OR ‘anutone-hc’:ti,ab,kw OR ‘aquanil hc’:ti,ab,kw OR ‘balneol-hc’:ti,ab,kw OR ‘barseb hc’:ti,ab,kw OR ‘beta-hc’:ti,ab,kw OR biacort:ti,ab,kw OR cetacort:ti,ab,kw OR cobadex:ti,ab,kw OR colocort:ti,ab,kw OR ‘compound f’:ti,ab,kw OR ‘cordicare lotion’:ti,ab,kw OR coripen:ti,ab,kw OR ‘cort dome’:ti,ab,kw OR cortef:ti,ab,kw OR cortenema:ti,ab,kw OR cortibel:ti,ab,kw OR corticorenol:ti,ab,kw OR cortifan:ti,ab,kw OR cortiphate:ti,ab,kw OR cortisol:ti,ab,kw OR cortisole:ti,ab,kw OR cortispray:ti,ab,kw OR cortoderm:ti,ab,kw OR cortril:ti,ab,kw OR cotacort:ti,ab,kw OR covocort:ti,ab,kw OR ‘cremicort-h’:ti,ab,kw OR cutaderm:ti,ab,kw OR ‘derm-aid cream’:ti,ab,kw OR ‘dermacrin hc lotion’:ti,ab,kw OR dermaid:ti,ab,kw OR dermocare:ti,ab,kw OR dermocortal:ti,ab,kw OR dermolate:ti,ab,kw OR dioderm:ti,ab,kw OR eczacort:ti,ab,kw OR ‘ef cortelan’:ti,ab,kw OR efcortelan:ti,ab,kw OR egocort:ti,ab,kw OR eksalb:ti,ab,kw OR eldecort:ti,ab,kw OR ‘emo-cort’:ti,ab,kw OR epicort:ti,ab,kw OR ficortril:ti,ab,kw OR filocot:ti,ab,kw OR flexicort:ti,ab,kw OR ‘gly-cort’:ti,ab,kw OR glycort:ti,ab,kw OR ‘h-cort’:ti,ab,kw OR hc:ti,ab,kw OR hebcort:ti,ab,kw OR ‘hemril-30’:ti,ab,kw OR ‘hemril-hc uniserts’:ti,ab,kw OR ‘hi-cor’:ti,ab,kw OR hidrotisona:ti,ab,kw OR hycor:ti,ab,kw OR hycort:ti,ab,kw OR hydracort:ti,ab,kw OR hydrasson:ti,ab,kw OR ‘hydro ricortex’:ti,ab,kw OR ‘hydro-rx’:ti,ab,kw OR hydrocort:ti,ab,kw OR hydrocorticosteroid:ti,ab,kw OR hydrocortisate:ti,ab,kw OR hydrocortison:ti,ab,kw OR hydrocortisonum:ti,ab,kw OR hydrocortisyl:ti,ab,kw OR hydrocortone:ti,ab,kw OR 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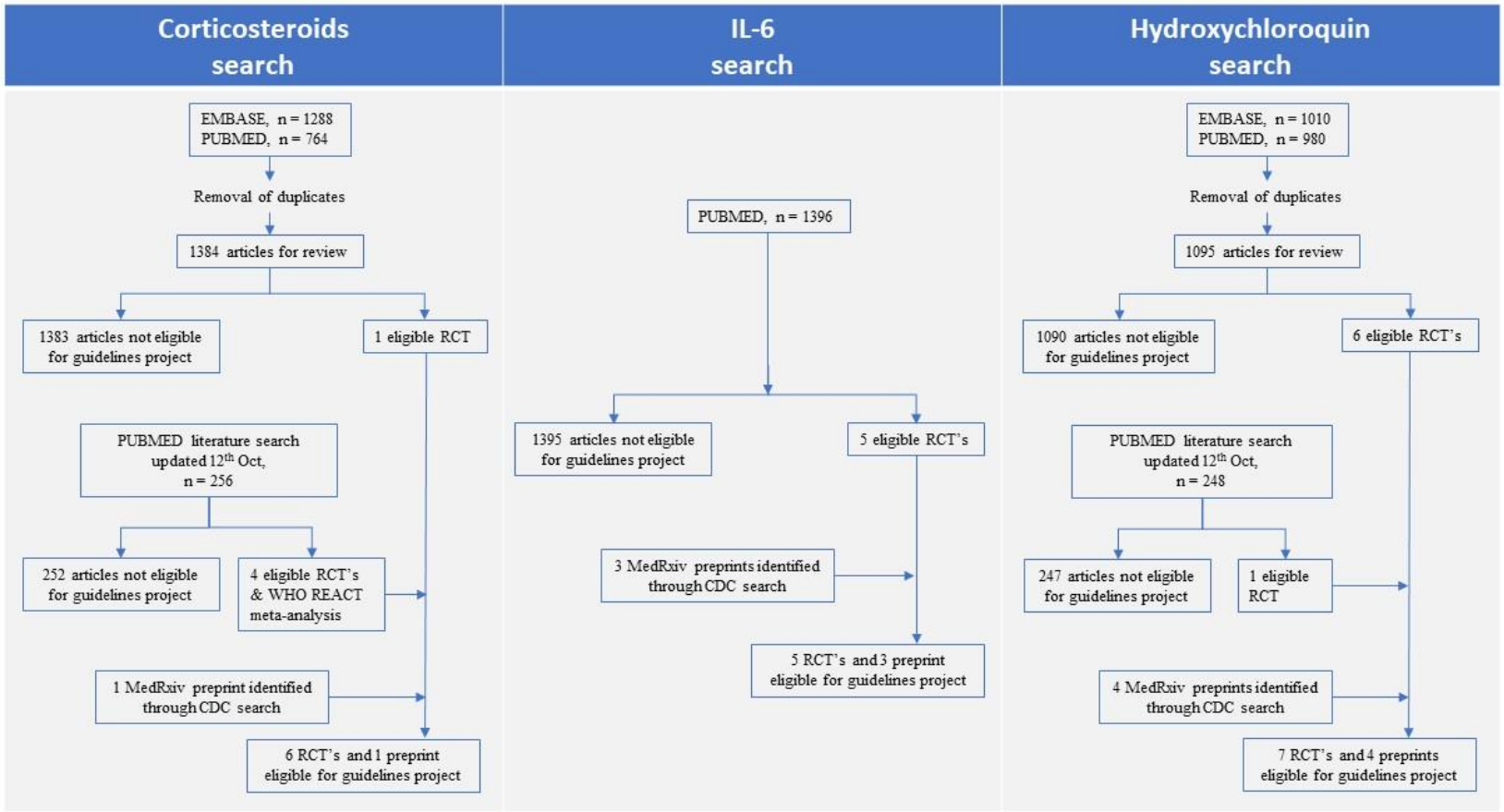
	‘nsc10483’:ti,ab,kw OR nutracort:ti,ab,kw OR optef:ti,ab,kw OR ‘otosone f’:ti,ab,kw OR penecort:ti,ab,kw OR plenadren:ti,ab,kw OR prepcort:ti,ab,kw OR ‘pro cort’:ti,ab,kw OR procort:ti,ab,kw OR ‘procto-kit':ti,ab,kw OR proctocort:ti,ab,kw OR ‘proctosol-hc’:ti,ab,kw OR proctosone:ti,ab,kw OR procutan:ti,ab,kw OR ‘rectasol-hc’:ti,ab,kw OR rectocort:ti,ab,kw OR rederm:ti,ab,kw OR sanatison:ti,ab,kw OR ‘scalp-aid’:ti,ab,kw OR schericur:ti,ab,kw OR ‘scherosone f’:ti,ab,kw OR ‘sistral hydrocort’:ti,ab,kw OR skincalm:ti,ab,kw OR ‘stie-cort’:ti,ab,kw OR ‘substance m’:ti,ab,kw OR synacort:ti,ab,kw OR texacort:ti,ab,kw OR ‘triburon-hc’:ti,ab,kw OR unicort:ti,ab,kw OR vasocort:ti,ab,kw OR Epicortisol:ti,ab,kw OR cortifair:ti,ab,kw
Concept 3: Hydroxychloroquin	'hydroxychloroquine'/exp OR ‘hydroxychloroquin*’:ti,ab,kw OR ‘chloroquin*’:ti,ab,kw OR ‘ercoquin*’:ti,ab,kw OR ‘hydrocloroquin*’:ti,ab,kw OR ‘oxychloroquin*’:ti,ab,kw OR ‘quensyl’:ti,ab,kw OR ‘sn 8137’:ti,ab,kw OR ‘oxychlorochin*’:ti,ab,kw OR ‘hydroxychlorochin*’:ti,ab,kw OR ‘plaquenil’:ti,ab,kw OR ‘HCQ’:ti,ab,kw OR ‘CQ’:ti,ab,kw OR 'chloroquine'/exp OR 'a-cq':ti,ab,kw OR amokin*:ti,ab,kw OR anoclor:ti,ab,kw OR aralan:ti,ab,kw OR aralen:ti,ab,kw OR aralene:ti,ab,kw OR arechin*:ti,ab,kw OR arequin*:ti,ab,kw OR arthrochin*:ti,ab,kw OR arthroquin*:ti,ab,kw OR artrichin*:ti,ab,kw OR artriquin*:ti,ab,kw OR avloclor:ti,ab,kw OR avoclor:ti,ab,kw OR bemaphata:ti,ab,kw OR bemaphate:ti,ab,kw OR bemasulph:ti,ab,kw OR bipiquin*:ti,ab,kw OR cadiquin*:ti,ab,kw OR chemochin*:ti,ab,kw OR chingamin*:ti,ab,kw OR chingaminum:ti,ab,kw OR chloraquin*:ti,ab,kw OR chlorochin*:ti,ab,kw OR chlorochin*:ti,ab,kw OR chlorofoz:ti,ab,kw OR chloroquin*:ti,ab,kw OR chloroquinesulphate:ti,ab,kw OR ‘chloroquini diphosphas’:ti,ab,kw OR ‘chloroquinum diphosphoricum’:ti,ab,kw OR chlorquin*:ti,ab,kw OR choloquin*:ti,ab,kw OR cidanchin*:ti,ab,kw OR ‘clo-kit junior’:ti,ab,kw OR clorichin*:ti,ab,kw OR cloriquin*:ti,ab,kw OR clorochin*:ti,ab,kw OR delagil:ti,ab,kw OR delagyl:ti,ab,kw OR dichinalex:ti,ab,kw OR diclokin*:ti,ab,kw OR diquinalex:ti,ab,kw OR diroquin*:ti,ab,kw OR emquin*:ti,ab,kw OR genocin*:ti,ab,kw OR gontochin*:ti,ab,kw OR gontoquin*:ti,ab,kw OR heliopar:ti,ab,kw OR imagon:ti,ab,kw OR iroquin*:ti,ab,kw OR klorokin*:ti,ab,kw OR klorokin*:ti,ab,kw OR klorokinfosfat:ti,ab,kw OR lagaquin*:ti,ab,kw OR malaquin*:ti,ab,kw OR malarex:ti,ab,kw OR malarivon:ti,ab,kw OR malaviron:ti,ab,kw OR maliaquin*:ti,ab,kw OR maquin*:ti,ab,kw OR mesylith:ti,ab,kw OR mexaquin*:ti,ab,kw OR mirquin*:ti,ab,kw OR nivachin*:ti,ab,kw OR nivaquin*:ti,ab,kw OR nivaquin*:ti,ab,kw OR ‘p roquin*’:ti,ab,kw OR quinachlor:ti,ab,kw OR quingamin*:ti,ab,kw OR repal:ti,ab,kw OR resochen*:ti,ab,kw OR resochin*:ti,ab,kw OR resoquin*:ti,ab,kw OR reumachlor:ti,ab,kw OR roquin*:ti,ab,kw OR ‘rp 3377’:ti,ab,kw OR rp3377:ti,ab,kw OR sanoquin*:ti,ab,kw OR silbesan:ti,ab,kw OR siragan:ti,ab,kw OR sirajan:ti,ab,kw OR ‘sn 7618’:ti,ab,kw OR sn7618:ti,ab,kw OR solprin*:ti,ab,kw OR tresochin*:ti,ab,kw OR tresoquin*:ti,ab,kw OR trochin*:ti,ab,kw troquin*:ti,ab,kw OR ‘w 7618’:ti,ab,kw OR w7618:ti,ab,kw OR ‘win 244’:ti,ab,kw OR win244:ti,ab,kw OR Chlorochi:ti,ab,kw OR hydroxychloroquin*:ti,ab,kw OR dolquin*:ti,ab,kw OR reuquinol:ti,ab,kw OR hidroxicloroquin*:ti,ab,kw OR dimard:ti,ab,kw OR oxiklorin*:ti,ab,kw OR quineprox:ti,ab,kw
Concept 4: Azithromycin	'azithromycin'/exp OR Azithromycin:ti,ab,kw OR Azythromycin:ti,ab,kw OR Sumamed:ti,ab,kw OR Toraseptol:ti,ab,kw OR Vinzam:ti,ab,kw OR 'CP 62993':ti,ab,kw OR CP62993:ti,ab,kw OR Zithromax:ti,ab,kw OR Azitrocin:ti,ab,kw OR Azadose:ti,ab,kw OR Ultreon:ti,ab,kw OR Zitromax:ti,ab,kw OR Goxal:ti,ab,kw OR Zentavion:ti,ab,kw OR Aruzilina:ti,ab,kw OR atizor:ti,ab,kw OR azasite:ti,ab,kw OR azatril:ti,ab,kw OR azenil:ti,ab,kw OR azibiot:ti,ab,kw OR azimin:ti,ab,kw OR azithral:ti,ab,kw OR Azitromax:ti,ab,kw OR azitromicin:ti,ab,kw OR azitromicina:ti,ab,kw OR aziwok:ti,ab,kw OR azomyne:ti,ab,kw OR aztrin:ti,ab,kw OR azydrop:ti,ab,kw OR azyter:ti,ab,kw OR bazyt:ti,ab,kw OR 'cp 62933':ti,ab,kw OR cp62933:ti,ab,kw OR forcin:ti,ab,kw OR inedol:ti,ab,kw OR infectoazit:ti,ab,kw OR 'isv 401':ti,ab,kw OR isv401:ti,ab,kw OR kromicin:ti,ab,kw OR macrozit:ti,ab,kw OR mezatrin:ti,ab,kw OR octavax:ti,ab,kw OR ordipha:ti,ab,kw OR ribotrex:ti,ab,kw OR sunamed:ti,ab,kw OR tobyl:ti,ab,kw OR tromix:ti,ab,kw OR trozocina:ti,ab,kw OR xithrone:ti,ab,kw OR 'xz 450':ti,ab,kw OR xz450:ti,ab,kw OR zaret:ti,ab,kw OR zarom:ti,ab,kw OR zetamax:ti,ab,kw OR zeto:ti,ab,kw OR zibramax:ti,ab,kw OR zifin:ti,ab,kw OR zimericina:ti,ab,kw OR zistic:ti,ab,kw OR zithrox:ti,ab,kw OR zitinn:ti,ab,kw OR zitrim:ti,ab,kw OR zitrobifan:ti,ab,kw OR zitrocin:ti,ab,kw OR zmax:ti,ab,kw
Concept 5: Lopinovir-Ritonavir	'lopinavir'/exp OR lopinavir:ti,ab,kw OR 'A-157378':ti,ab,kw OR 'A157378':ti,ab,kw OR 'ABT 378':ti,ab,kw OR ABT378:ti,ab,kw OR 'ritonavir'/exp OR ritonavir:ti,ab,kw OR ritovir:ti,ab,kw OR 'ABT 538':ti,ab,kw OR ABT538:ti,ab,kw OR Norvir:ti,ab,kw OR 'a 84538':ti,ab,kw OR 'a84538':ti,ab,kw OR 'abt 84538':ti,ab,kw OR 'abt84538':ti,ab,kw OR 'lopinavir plus ritonavir'/exp OR 'lopinavir ritonavir drug combination'/exp OR Kaletra:ti,ab,kw OR Lopimune:ti,ab,kw OR Aluvia:ti,ab,kw

Concept 6: Remdesevir	'remdesivir'/exp OR ‘remdesivir’:ti,ab,kw OR ‘GS-5734’:ti,ab,kw OR ‘GS5734’:ti,ab,kw
Concept 7: Anit-coagulants	'low molecular weight heparin'/exp OR ‘heparin*’:ti,ab,kw OR ‘LMWH’:ti,ab,kw OR ‘bm 2123’:ti,ab,kw OR ‘bm2123’:ti,ab,kw OR ‘choay’:ti,ab,kw OR ‘ebpm*’:ti,ab,kw OR ‘ff1034’:ti,ab,kw OR ‘ff 1034’:ti,ab,kw OR ‘fr 860’:ti,ab,kw OR ‘fr860’:ti,ab,kw OR ‘gag 869’:ti,ab,kw OR ‘gag869’:ti,ab,kw OR ‘pk 007’:ti,ab,kw OR ‘pk007’:ti,ab,kw OR ‘sandoz 5100’:ti,ab,kw OR ‘sandoz 6700’:ti,ab,kw OR ‘traxyparin*’:ti,ab,kw OR ‘adomiparin*’:ti,ab,kw OR ‘m118’:ti,ab,kw OR ‘m 118’:ti,ab,kw OR ‘antixarin*’:ti,ab,kw OR ‘ardeparin*’:ti,ab,kw OR ‘normifio’:ti,ab,kw OR ‘normiflo’:ti,ab,kw OR ‘wy 90493’:ti,ab,kw OR ‘wy90493’:ti,ab,kw OR ‘bemiparin*’:ti,ab,kw OR ‘entervit’:ti,ab,kw OR ‘hepadren’:ti,ab,kw OR ‘hibor’:ti,ab,kw OR ‘ivor’:ti,ab,kw OR ‘ivorat’:ti,ab,kw OR ‘ivormax’:ti,ab,kw OR ‘phivor’:ti,ab,kw OR ‘zibor’:ti,ab,kw OR ‘certoparin*’:ti,ab,kw OR ‘arteven’:ti,ab,kw OR ‘badyket’:ti,ab,kw OR ‘einecs 232-681-7’:ti,ab,kw OR ‘eparina’:ti,ab,kw OR ‘mono$embolex’:ti,ab,kw OR ‘op 622’:ti,ab,kw OR ‘op622’:ti,ab,kw OR ‘op 386’:ti,ab,kw OR ‘op386’:ti,ab,kw OR ‘pabyrin*’:ti,ab,kw OR ‘pulari’:ti,ab,kw OR ‘sandoparin*’:ti,ab,kw OR ‘sublingula’:ti,ab,kw OR ‘troparin*’:ti,ab,kw OR ‘vitrum a’:ti,ab,kw OR ‘cy 222’:ti,ab,kw OR ‘cy222’:ti,ab,kw OR ‘dalteparin*’:ti,ab,kw OR ‘fragmin*’:ti,ab,kw OR ‘k 2165’:ti,ab,kw OR ‘k2165’:ti,ab,kw OR ‘kabi 2165’:ti,ab,kw OR ‘low liquemin*’:ti,ab,kw OR ‘danap$roid’:ti,ab,kw OR ‘kb 101’:ti,ab,kw OR ‘kb101’:ti,ab,kw OR ‘lomopar?n’:ti,ab,kw OR ‘mucoglucuronan’:ti,ab,kw OR ‘org 10172’:ti,ab,kw OR ‘org10172’:ti,ab,kw OR ‘orgaran’:ti,ab,kw OR ‘deligoparin*’:ti,ab,kw OR ‘op 2000’:ti,ab,kw OR ‘op2000’:ti,ab,kw OR ‘embolex’:ti,ab,kw OR ‘enoxaparin*’:ti,ab,kw OR ‘clexan*’:ti,ab,kw OR ‘inhixa’:ti,ab,kw OR ‘klexane’:ti,ab,kw OR ‘ledraxen’:ti,ab,kw OR ‘lovenox’:ti,ab,kw OR ‘neoparin*’:ti,ab,kw OR ‘pk 10169’:ti,ab,kw OR ‘pk10169’:ti,ab,kw OR ‘qualiop klinik’:ti,ab,kw OR ‘thorinane’:ti,ab,kw OR ‘fondaparin*’:ti,ab,kw OR ‘arixtra’:ti,ab,kw OR ‘ic 851589’:ti,ab,kw OR ‘ic851589’:ti,ab,kw OR ‘org 31540’:ti,ab,kw OR ‘org31540’:ti,ab,kw OR ‘quixidar’:ti,ab,kw OR ‘sr 90107’:ti,ab,kw OR ‘sr 90107a’:ti,ab,kw OR ‘sr90107’:ti,ab,kw OR ‘sr90107a’:ti,ab,kw OR ‘idrabiotaparinux’:ti,ab,kw OR ‘ssr 126517’:ti,ab,kw OR ‘ssr 126517 e’:ti,ab,kw OR ‘ssr126517’:ti,ab,kw OR ‘ssr126517e’:ti,ab,kw OR ‘idraparinux’:ti,ab,kw OR ‘org 34006’:ti,ab,kw OR ‘org34006’:ti,ab,kw OR ‘sanorg 34006’:ti,ab,kw OR ‘sanorg34006’:ti,ab,kw OR ‘sr 34006’:ti,ab,kw OR ‘sr34006’:ti,ab,kw OR ‘livaraparin* calcium’:ti,ab,kw OR ‘minolteparin*’:ti,ab,kw OR ‘nadroparin*’:ti,ab,kw OR ‘cy 216’:ti,ab,kw OR ‘cy 216d’:ti,ab,kw OR ‘cy216’:ti,ab,kw OR ‘cy216d’:ti,ab,kw OR ‘fraxiparin*’:ti,ab,kw OR ‘fraxodi’:ti,ab,kw OR ‘seledie’:ti,ab,kw OR ‘seleparin*’:ti,ab,kw OR ‘tedegliparin*’:ti,ab,kw OR ‘necuparanib’:ti,ab,kw OR ‘df 01’:ti,ab,kw OR ‘df01’:ti,ab,kw OR ‘m 402’:ti,ab,kw OR ‘m402’:ti,ab,kw OR ‘tafoxiparin*’:ti,ab,kw OR ‘parnaparin*’:ti,ab,kw OR ‘fluxum’:ti,ab,kw OR ‘lo$hepa’:ti,ab,kw OR ‘minidalton’:ti,ab,kw OR ‘op 2123’:ti,ab,kw OR ‘op2123’:ti,ab,kw OR ‘parvoparin*’:ti,ab,kw OR ‘rd 11885’:ti,ab,kw OR ‘rd11885’:ti,ab,kw OR ‘reviparin*’:ti,ab,kw OR ‘clivarin*’:ti,ab,kw OR ‘clivarodi’:ti,ab,kw OR ‘lomorin*’:ti,ab,kw OR ‘lu 47311’:ti,ab,kw OR ‘lu47311’:ti,ab,kw OR ‘semuloparin*’:ti,ab,kw OR ‘ave 5026’:ti,ab,kw OR ‘ave5026’:ti,ab,kw OR ‘mulsevo’:ti,ab,kw OR ‘visamerin*’:ti,ab,kw OR ‘sevuparin*’:ti,ab,kw OR ‘tedelparin*’:ti,ab,kw OR ‘tinzaparin*’:ti,ab,kw OR ‘innohep’:ti,ab,kw OR ‘lhn1’:ti,ab,kw OR ‘lhn 1’:ti,ab,kw OR ‘logiparin*’:ti,ab,kw OR 'anticoagulant agent'/de OR ‘anticoagula*’:ti,ab,kw OR ‘anti coagula*’:ti,ab,kw OR ‘PK-10 169’:ti,ab,kw OR ‘EMT-967’:ti,ab,kw OR ‘EMT-966’:ti,ab,kw OR ‘3-phenyl-2-propenoic-acid’:ti,ab,kw
At the end of the search strategy add: NOT ‘conference abstract’:it	

Flow charts – outcomes from the systematic reviews


Corticosteroids search
EMBASE, n = 1288
PUBMED, n = 764
Removal of duplicates
1384 articles for review
1383 articles not eligible for guidelines project
1 eligible RCT
PUBMED literature search updated 12th Oct, n = 256
252 articles not eligible for guidelines project
4 eligible RCT's & WHO REACT meta-analysis
1 MedRxiv preprint identified through CDC search
6 RCT's and 1 preprint eligible for guidelines project
IL-6 search
PUBMED, n = 1396
1395 articles not eligible for guidelines project
5 eligible RCT's
3 MedRxiv preprints identified through CDC search
5 RCT's and 3 preprint eligible for guidelines project
Hydroxychloroquin search
EMBASE, n = 1010
PUBMED, n = 980
Removal of duplicates
1095 articles for review
1090 articles not eligible for guidelines project
6 eligible RCT's
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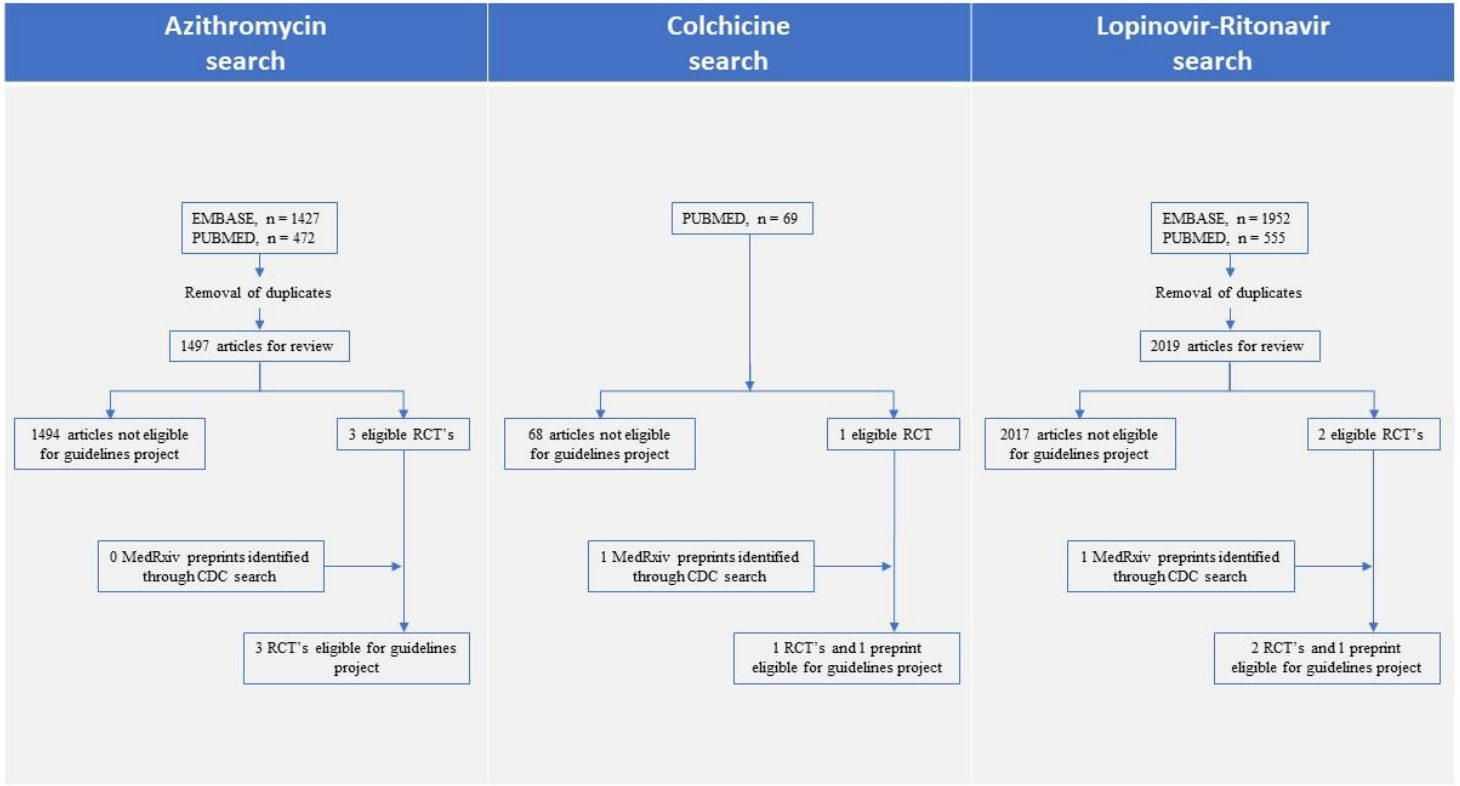
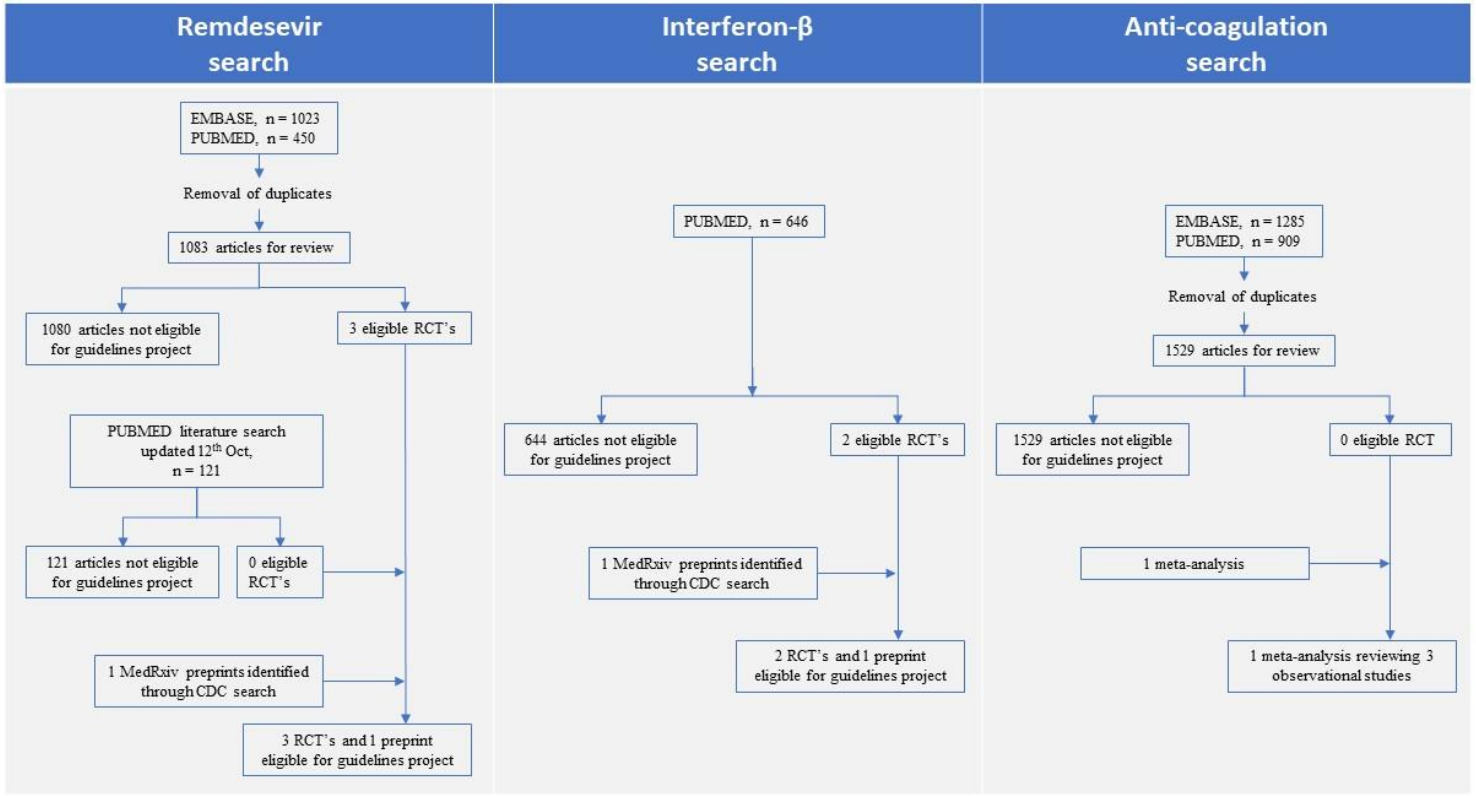
247 articles not eligible for guidelines project
1 eligible RCT
4 MedRxiv preprints identified through CDC search
7 RCT's and 4 preprints eligible for guidelines project


Azithromycin search
EMBASE, n = 1427
PUBMED, n = 472
Removal of duplicates
1497 articles for review
1494 articles not eligible for guidelines project
3 eligible RCT's
0 MedRxiv preprints identified through CDC search
3 RCT's eligible for guidelines project
Colchicine search
PUBMED, n = 69
68 articles not eligible for guidelines project
1 eligible RCT
1 MedRxiv preprints identified through CDC search
1 RCT's and 1 preprint eligible for guidelines project
Lopinovir-Ritonavir search
EMBASE, n = 1952
PUBMED, n = 555
Removal of duplicates
2019 articles for review
2017 articles not eligible for guidelines project
2 eligible RCT's
1 MedRxiv preprints identified through CDC search
2 RCT's and 1 preprint eligible for guidelines project


Remdesevir search
EMBASE, n = 1023
PUBMED, n = 450
Removal of duplicates
1083 articles for review
1080 articles not eligible for guidelines project
3 eligible RCT's
PUBMED literature search updated 12th Oct, n = 121
121 articles not eligible for guidelines project
0 eligible RCT's
1 MedRxiv preprints identified through CDC search
3 RCT's and 1 preprint eligible for guidelines project
Interferon-β search
PUBMED, n = 646
644 articles not eligible for guidelines project
2 eligible RCT's
1 MedRxiv preprints identified through CDC search
2 RCT's and 1 preprint eligible for guidelines project
Anti-coagulation search
EMBASE, n = 1285
PUBMED, n = 909
Removal of duplicates
1529 articles for review
1529 articles not eligible for guidelines project
0 eligible RCT
1 meta-analysis
1 meta-analysis reviewing 3 observational studies

Evidence to decision frameworks

PICO 1: CORTICOSTEROIDS

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate X Large ○ Varies ○ Don't know	The analysis shows a clinically meaningful reduction in mortality. This effect is even greater in the mechanical ventilation subgroup. The effect in the mechanically ventilated subgroup has been confirmed in a meta-analysis of all trials in critically ill patients with a rate ratio of 0.70. The magnitude of benefit may be smaller in those requiring oxygen without mechanical ventilation but remains clinically meaningful.

UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large X Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Adverse events were not reported in the largest trial, but smaller trials show few safety concerns. There is a well-known safety profile for corticosteroids with adverse effects including hyperglycaemia, bruising, confusion and secondary infections.
	What is the overall certainty of the evidence of effects? ○ Very low ○ Low X Moderate ○ High ○ No included studies	The certainty of the most critical endpoint, mortality is high, however adverse events are rated as low. As the majority of endpoints that are important for clinical decision making are rated as high to moderate according to GRADE methodology, the overall quality is regarded as moderate. The consistency of benefit in the meta-analysis for critically ill patients increases certainty that the effect seen in the largest trial (RECOVERY) is generalizable.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X No important uncertainty or	There is no uncertainty or variability about how clinicians and patients value mortality.

	variability ○ No known undesirable outcomes	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention X Favours the intervention ○ Varies ○ Don't know	Corticosteroids are currently the only therapy proven to reduce mortality in COVID-19. The balance of benefits and risks from the published trials to date clearly favours the intervention. Further data on safety would be desirable but is highly unlikely to change the evaluation of risk versus benefit.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings X Large savings ○ Varies ○ Don't know	Dexamethasone and other corticosteroids are inexpensive and widely available and therefore resource requirements are low. Savings in terms of reduced mortality, and potentially length of stay or ICU length of stay are likely to off-set any costs although a formal economic evaluation has not been performed.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased X Increased ○ Varies ○ Don't know	As a cheap and widely available therapy that can be implemented in low resource settings this treatment should have a positive effect on health equity.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	The treatment is widely used and is acceptable to patients and clinicians.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes X Yes ○ Varies	There are no implementation concerns as this therapy is widely used.

	○ Don't know	

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention X
RECOMMENDATION	The panel recommends treatment with corticosteroids for patients with COVID-19 infection requiring oxygen, non-invasive mechanical ventilation or invasive mechanical ventilation (strong recommendation, moderate quality of overall evidence) The panel recommends NOT to offer corticosteroids to patients with COVID-19 infection requiring hospitalisation but not requiring supplementary oxygen or ventilatory support (strong recommendation, moderate quality of evidence)				
JUSTIFICATION	The overall risk versus benefit for corticosteroids is favourable with a clear reduction in mortality and improvement in other clinically relevant endpoints. The consistent results across all trials is reassuring that				

	the data from the largest trial is generalizable.
SUBGROUP CONSIDERATIONS	Recommendations based on subgroups are justified as there is no evidence of benefit in the subgroup of patients without requirement for oxygen.
IMPLEMENTATION CONSIDERATIONS	The largest trial used dexamethasone 6mg daily for 10 days and so it is reasonable to suggest this regimen is implemented where possible. The meta-analysis in critically ill patients suggests a similar trend with other corticosteroids and so where dexamethasone is not available it is reasonable to use alternative steroids.
MONITORING AND EVALUATION	Although not reported in trials, care should be taken with patients at higher risk of steroid related adverse effects such as patients with diabetes mellitus. Steroids can exacerbate delirium in elderly patients who are also the population most at risk of severe COVID-19.
RESEARCH PRIORITIES	Further data on adverse effects and to identify the optimal patient population and treatment duration would be welcome.

PICO 2: IL-6 receptor antagonists

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small X Moderate ○ Large ○ Varies ○ Don't know	A reduction in patients requiring intensive care unit admission or mechanical ventilation was observed in the pooled analysis. No reduction in mortality was demonstrated in the pooled analysis, but the two largest studies showed an overall reduction in mortality in patients in the intensive care unit, and in the RECOVERY trial with requirement for oxygen and raised C-reactive protein. In the RECOVERY trial the effect appears to be greatest when added to corticosteroids. The benefit was otherwise similar across a number of different subgroups of patients.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small X Trivial ○ Varies ○ Don't know	No increase in adverse events or serious adverse events were noted. Anti-IL-6 therapy can increase the risk of infections and it was noted that reporting of adverse effects was incomplete in the largest trials included.

	What is the overall certainty of the evidence of effects? ○ Very low X Low ○ Moderate ○ High ○ No included studies	The reduced risk of ICU admission and mechanical ventilation is highly consistent across trials giving high confidence that this is generalizable. The mortality results are inconsistent and suggest different effects in different patient populations.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X No important uncertainty or variability ○ No known undesirable outcomes	The outcomes were all rated important or critical. Patient feedback confirmed all of these outcomes are considered important.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative X Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	There are demonstrated clinical benefits in terms of reduced ICU admission and requirement for mechanical ventilation, with possible reductions in mortality in specific patient populations are demonstrated in two randomized trials. Important uncertainty includes the optimal patient population to maximise clinical benefit.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings X Varies ○ Don't know	This was not formally assessed in any of the trials. However, reductions in ICU admissions may be associated with savings. The balance between the cost of the drug and savings in ICU costs may differ between health care systems.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased X Varies ○ Don't know	This has not been formally assessed. As there is significant uncertainty about the benefits and risks of this treatment, it is hard to estimate any effect on health equity.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	The treatment has been used in rheumatoid arthritis, is relatively easy to administer and is therefore likely to be acceptable.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no X Probably yes ○ Yes ○ Varies	Yes, the treatment is relatively easy to administer to hospitalised patients.

	○ Don't know	

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention X	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	The panel suggests to offer IL-6 receptor antagonist monoclonal antibody to hospitalised patients with COVID-19 requiring oxygen or ventilatory support (conditional recommendation, low quality of evidence) The panel suggests NOT to offer IL-6 receptor antagonist monoclonal antibody to patients not requiring supplementary oxygen (conditional recommendation, low quality of evidence) Notes: - All patients eligible for anti-IL-6 receptor monoclonal antibody treatment should have already				

	received or should be receiving treatment with corticosteroids, unless contraindicated. - The patients most likely to benefit are those in the first 24 hours after receiving non-invasive or invasive ventilatory support - Patients receiving supplementary oxygen and who are progressing despite corticosteroid treatment or who are considered at high risk of future requirement for ventilatory support.
JUSTIFICATION	Anti-IL-6 receptor monoclonal antibody treatment reduces the risk of mechanical ventilation or death in hospitalised COVID-19 patients. No major safety concerns were identified. The panel considers that currently it is hard to identify the optimal patient population to benefit from this treatment, but RECOVERY found a benefit in addition to treatment with corticosteroids. As corticosteroids are also recommended for patients requiring oxygen and ventilatory support, anti-IL-6 monoclonal antibody treatment would be expected to be given to patients also receiving corticosteroids in nearly all cases. Anti-IL-6 receptor therapy is relatively expensive but it is expected the benefits will outweigh the costs. Patient populations most likely to benefit include those meeting the inclusion criteria for REMAP-CAP (within 24 hours of requirement for non-invasive or invasive ventilatory support) and hospitalised patients requiring oxygen who are considered at high risk of requiring mechanical ventilation or who have progressed despite treatment with corticosteroids, which is consistent with patients enrolled in RECOVERY and other trials included in our analysis.
SUBGROUP	RECOVERY found no difference in the treatment effect between patients requiring oxygen treatment and

CONSIDERATIONS	those requiring additional ventilatory support. Therefore, the panel decided not to make different recommendations for patients requiring different levels of oxygen or ventilatory support. There is no evidence to support the use of anti-IL-6 receptor monoclonal antibody therapy in patients with COVID-19 infection and not requiring oxygen or ventilatory support.
IMPLEMENTATION CONSIDERATIONS	RECOVERY showed an additive benefit of tocilizumab on top of corticosteroids and no evidence of benefit in the small group of patients who did not receive corticosteroids. Therefore IL-6 receptor monoclonal antibody therapy should be used in addition to corticosteroids unless corticosteroids are contraindicated. The median time from admission to treatment in RECOVERY was 2 days and in REMAP-CAP patients were treated within 24 hours of requirement for ventilatory support. Therefore, the strongest evidence supports administration of treatment as early in the hospital course as possible.
MONITORING AND EVALUATION	No adverse events or serious adverse events were observed. Nevertheless IL-6 receptor monoclonal antibody therapy carries a risk of increased infections and should be used with caution in patients with known or strongly suspected bacterial infection.
RESEARCH PRIORITIES	Further research is needed to identify the optimal patient population for treatment with anti-IL-6 receptor monoclonal antibody treatment.

PICO 3: hydroxychloroquine

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** X Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No clinical endpoints showed significant benefits.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** X Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	A large increase in adverse effects was demonstrated in the meta-analysis (44.3% vs 15.4%)

	What is the overall certainty of the evidence of effects? ○ Very low ○ Low X Moderate ○ High ○ No included studies	Moderate
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X No important uncertainty or variability ○ No known undesirable outcomes	The endpoints evaluated are those such as mortality, ICU admission and adverse events which are considered highly important by clinicians and patients.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** X Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	As there are no clinical benefits and a significant increase in adverse events this would not favour the intervention.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs X Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Hydroxychloroquine is widely available and not expensive but more importantly not recommended. In the absence of clinical benefit it is unlikely to be cost-effective.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced X Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Hydroxychloroquine is not recommended for the treatment of COVID-19 and therefore should not have an impact on health equity.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know	Hydroxychloroquine is acceptable to stakeholders for appropriate use but it is not recommended for COVID-19 due to safety reasons.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no X Probably yes ○ Yes ○ Varies	Hydroxychloroquine is widely available for appropriate use but is not recommended for COVID-19 due to safety reasons.

	○ Don't know	

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention X	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	The panel recommends NOT to offer hydroxychloroquine to patients with COVID-19 infection (strong recommendation, moderate evidence)				
JUSTIFICATION	The strongest evidence is for an increase in adverse events with no evidence of clinical benefit.				
SUBGROUP CONSIDERATIONS	No subgroup analyses were performed.				

IMPLEMENTATION CONSIDERATIONS	Implementation would be easy if it were to be approved for COVID-19 use.
MONITORING AND EVALUATION	n/a as not recommended for use.
RESEARCH PRIORITIES	Due to negative health impact, future studies on this repurposed agent should not be encouraged.

PICO 4: azithromycin

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** X Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No beneficial effects were noted in the meta-analysis
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large X Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	No significant increase in adverse events was noted in the included trials, however the panel notes that antibiotic use promotes antibiotic resistance and azithromycin has a well-established safety profile.
	What is the overall certainty of the evidence of effects? X Very low ○ Low ○ Moderate	Very low

	○ High ○ No included studies	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X No important uncertainty or variability ○ No known undesirable outcomes	No important uncertainty. All outcomes rated important or critical and are considered important by clinicians and patients.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative X Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention	Azithromycin is generally safe to use, however as no beneficial evidence for its use in COVID-19 has been found its use would promote unnecessary side effects or risk of promoting antibiotic resistance when no underlying bacterial infection is present.

	○ Favours the intervention ○ Varies ○ Don't know	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs X Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Azithromycin is inexpensive and widely used. Therefore, the cost is not large, but in the absence of clinical benefits there are no cost savings through its use.
EQUITY	**What would be the impact on health equity?** ○ Reduced X Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	If shown to be beneficial, azithromycin is widely available and may increase health equity. Uncertain currently due to lack of data.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know	Yes, the treatment is widely used.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	Yes, azithromycin is widely used and available.

TYPE OF RECOMMENDATION	

	Strong recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention X	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	The panel suggests that patients hospitalised with COVID-19 should NOT be offered azithromycin in the absence of bacterial infection (conditional recommendation, very low quality of evidence)				
JUSTIFICATION	No clinical benefits have been clearly demonstrated for use of azithromycin as an anti-inflammatory drug for COVID-19. It is acknowledged that the prevalence of secondary bacterial infection in COVID-19 is not fully established and that azithromycin may be used for its antibacterial effect in this context. Antimicrobial resistance may result from widespread use of azithromycin if used unnecessarily.				
SUBGROUP CONSIDERATIONS	No subgroups have been examined				
IMPLEMENTATION CONSIDERATIONS	It is not recommended that this intervention is implemented at present.				
MONITORING AND EVALUATION	As above				

RESEARCH PRIORITIES	A large-scale study of azithromycin in COVID-19; RECOVERY, has recently reported but after the completion of our literature search and grading. Research priorities will be reassessed based on the published results of this trial.

PICO 5- azithromycin and hydroxychloroquine

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** X Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No clinical benefits demonstrated were demonstrated for any of the endpoints.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large X Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	A significant increase in adverse events (39.3% vs 22.6%) was demonstrated. Azithromycin also runs a risk of increased antimicrobial resistance which was not actively studied but is nevertheless a known effect of the drug. Cardiovascular side effects including prolonged QT interval are potential side effects of this combination.

	What is the overall certainty of the evidence of effects? ○ Very low ○ Low X Moderate ○ High ○ No included studies	Moderate
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X No important uncertainty or variability ○ No known undesirable outcomes	The main outcomes studied are considered clinically relevant by patients and clinicians.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative X Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No clinical benefits and an increase in adverse events suggests an unfavourable balance between benefits and risks.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs X Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Both drugs are inexpensive so unlikely to result in a major increase in healthcare costs. Nevertheless as neither drug alone or in combination provides clinical benefits there will be no cost savings.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced X Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	As the treatment has not been shown to have effectiveness it will not have an effect on health equity.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know	Both drugs are widely available and used for other indications and therefore likely to be accepted if proven in future to have benefit.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes X Yes	Both drugs are widely available.

	○ Varies ○ Don't know	

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention X	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	The panel suggests NOT to offer hydroxychloroquine and azithromycin for hospitalised patients with COVID-19 (conditional recommendation, moderate quality of evidence).				
JUSTIFICATION	Azithromycin administration was not associated with improved clinical status in a single randomized, open label study where azithromycin was combined with hydroxychloroquine. The panel notes that azithromycin has a well-established safety profile but that that antibiotic use promotes antibiotic resistance. The conditional recommendation against azithromycin use is based on a limited dataset summarized in the online				

	supplement. Despite the limited data, the absence of any clinically relevant benefits of hydroxychloroquine or azithromycin alone argues against any benefit of the combination treatment.
SUBGROUP CONSIDERATIONS	No subgroup analyses were performed.
IMPLEMENTATION CONSIDERATIONS	As no clinical benefits were demonstrated there are no subgroup considerations.
MONITORING AND EVALUATION	As we are not recommending that the treatments are used, no monitoring or evaluation is required.
RESEARCH PRIORITIES	Despite limited data for the combination therapy, the lack of benefit of hydroxychloroquine alone suggests no further trials of a combination treatment containing hydroxychloroquine are justified, particularly in light of potential serious cardiac adverse events and other side effects. The committee recommends studying other antiviral options in well-designed studies of repurposed or SARS-CoV-2 specific medications.

PICO 6: Colchicine

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial X Small ○ Moderate ○ Large ○ Varies ○ Don't know	Significant benefit demonstrated in one trial where patients had a lower risk of deterioration on the World Health Organisation scale. This is based on small number of events and is therefore uncertain. Other relevant endpoints are not affected such as mortality or ICU admission.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large X Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Significant increase in diarrhoea demonstrated. Insufficient data reported to pool for other adverse events.

	What is the overall certainty of the evidence of effects? X Very low ○ Low ○ Moderate ○ High ○ No included studies	All data come from studies with a small sample size and methodological limitations and therefore the quality of evidence and therefore the certainty is very low.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X No important uncertainty or variability ○ No known undesirable outcomes	Outcomes such as mortality and ICU admissions are recognised as important to both patients and clinicians.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** X Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	The benefit is uncertain as the trials performed to date are not large enough to conclusively demonstrate benefit. There is also a significant increase in adverse events. The balance of the effects, therefore, does not favour the intervention.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs X Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Colchicine is cheap and widely available and therefore resource requirements are small or negligible

EQUITY	**What would be the impact on health equity?** ○ Reduced X Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	If shown to be beneficial. Colchicine is widely available and may increase health equity. Uncertain currently due to lack of data.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	Yes, widely used drug without issues around acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes X Yes ○ Varies	Yes, this is a widely available medication given orally.

	○ Don't know	

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention X	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	The panel suggests NOT to offer colchicine to hospitalised patient with COVID-19 infection (conditional recommendation, very low quality of evidence)				
JUSTIFICATION	As the strongest evidence is for an increase in adverse events and the clinical benefit is uncertain or not established, this would support only using colchicine in the context of a randomized controlled trial				
SUBGROUP CONSIDERATIONS	None, the trials to date are not large enough to perform subgroup analyses.				

IMPLEMENTATION CONSIDERATIONS	Straightforward to implement if colchicine was shown to be beneficial.
MONITORING AND EVALUATION	n/a as not recommended for use
RESEARCH PRIORITIES	Colchicine should be evaluated in large randomized controlled trials and at the time of writing it has been added to the large pragmatic RECOVERY trial.

PICO 7: Lopinavir-ritonavir

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** X Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No evidence of clinical benefits demonstrated in the meta-analysis. In particularly there was no benefit on mortality, time to clinical improvement, improvement on the WHO ordinal scale or invasive mechanical ventilation.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small X Trivial ○ Varies ○ Don't know	Adverse events were not significantly increased, although there are well recognised issues with drug-drug interactions and adverse events which may not have been adequately detected in the trials.

	What is the overall certainty of the evidence of effects? ○ Very low X Low ○ Moderate ○ High ○ No included studies	Low
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X No important uncertainty or variability ○ No known undesirable outcomes	No, endpoints in clinical improvements are rated as important or critical for clinicians and patients.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** X Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	There are no demonstrated clinical benefits. Although increased adverse events were not identified the largest trials did not systematically collect adverse event data. Therefore there are important potential risks.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs X Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The drug is widely available in clinical use for HIV and is not prohibitively expensive.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced X Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	As the therapy has no clinical benefits it would not have a meaningful effect on health equity.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No X Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Physicians and patients find this therapy less acceptable than others due to large drug-drug interactions and risk of adverse events.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no X Probably yes ○ Yes ○ Varies	As above, drug-drug interactions make the drug more difficult to use than others, although if the benefit was meaningful it is likely this could be used in practice.

	○ Don't know	

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention X	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	The panel recommends that patients hospitalised with COVID-19 are NOT offered lopinavir-ritonavir (Strong recommendation, low quality of evidence)				
JUSTIFICATION	There is no evidence of benefit and while no evidence of harm was identified the treatment has a known adverse event profile and drug-drug interactions that would argue against use.				
SUBGROUP CONSIDERATIONS	No subgroups show any benefit and so the recommendation applies to all subgroups.				

IMPLEMENTATION CONSIDERATIONS	**N/A**
MONITORING AND EVALUATION	N/A
RESEARCH PRIORITIES	As two very large trials show clearly no benefit, no further trials of lopinavir-ritonavir in this population are justified.

PICO 8: Remdesivir

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial X Small ○ Moderate ○ Large ○ Varies ○ Don't know	A reduction in time to recovery and length of hospital stay was demonstrated in one trial (ACTT1). Little or no clinical benefits were demonstrated in the other trials including the large SOLIDARITY trial which found no evidence of a mortality benefit. The benefits demonstrated are therefore those from ACTT1 only. The desirable effects are absent in the subgroup of patients in ACTT1 requiring mechanical ventilation.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate X Small ○ Trivial ○ Varies ○ Don't know	No significant increase in adverse effects. Pooled estimate for serious adverse effects suggests fewer SAEs with treatment.

	What is the overall certainty of the evidence of effects? ○ Very low ○ Low X Moderate ○ High ○ No included studies	Moderate
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability X Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	The guideline panel and patient representative agreed that all of the included endpoints and outcomes are important or critical for clinical decision making. Reduced length of hospital stay, and more rapid recovery would still be considered clinically meaningful in the absence of a mortality benefit by many clinicians and patients, but not by all.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention ○ Favours the intervention X Varies ○ Don't know	The reported benefits are modest and are supported by only one randomized trial. A limitation of the data to date is a need to determine the additional benefit of remdesivir on top of corticosteroids now that corticosteroids are standard of care. The balance of effects is negative in the ICU population where no improvement in time to clinical recovery was demonstrated.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** X Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	This therapy is expensive and there have been shortages of the drug at some stages during the pandemic. The treatment has to be administered intravenously.

EQUITY	**What would be the impact on health equity?** ○ Reduced X Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	As the treatment is expensive and may not be available to all patients, this may have an impact on health equity.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	Antiviral treatment is an established concept in respiratory infections and so the treatment is acceptable to patients and clinicians.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes X Yes ○ Varies	Subject to the comments above regarding drug availability and cost, it is feasible to implement the treatment in a clinical setting and it has been used widely across Europe during the pandemic to date.

	○ Don't know	

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative X	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	The panel makes no recommendation on offering remdesivir to patients hospitalised with COVID-19 infection (conditional recommendation, moderate quality of evidence) The panel suggests not to offer remdesivir to patients hospitalised with COVID-19 infection who require invasive mechanical ventilation (conditional recommendation, moderate quality of evidence)				
JUSTIFICATION	The panel considers that time to recovery and length of hospital stay are relevant clinical endpoints in the absence of a mortality benefit of remdesivir. Nevertheless these benefits have been demonstrated in only one randomized trial. The reported benefits are regarded by the panel as modest. The lack of significant				

	adverse effects means that the balance of benefit versus risk was considered marginally in favour of the intervention by some members of the panel but not by others. The panel discussed this topic extensively, and voted on the final recommendation resulting in a majority in favour of a conditional recommendation for both the intervention or the alternative.
SUBGROUP CONSIDERATIONS	Subgroup effects were observed with no benefit on the primary outcome evident in patients requiring invasive mechanical ventilation. As this outcome is the main benefit on which the recommendation is based, the panel considers it appropriate to make a subgroup recommendation against remdesivir use in these patients where no benefit has been demonstrated.
IMPLEMENTATION CONSIDERATIONS	Treatment should be given for 5 days based on evidence that this is at least as effective as 10 days administration.
MONITORING AND EVALUATION	Liver function tests should be checked prior to administration of remdesivir and checked while patients are on treatment.
RESEARCH PRIORITIES	As the benefit is unclear, further large studies including endpoints such as clinical improvement, clinical deterioration and length of stay should be performed to confirm the results of ACTT1. Identifying subgroups of patients who benefit is a priority, based on timing of administration and requirement for oxygen for example.

PICO 9: Interferon beta

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** X Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Two small trials show large benefits but a trial with a much larger sample size (SOLIDARITY) shows no evidence of benefit and potential harm. The overall interpretation must be no evidence of benefit on mortality or risk of deterioration.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies X Don't know	Safety data are incompletely reported and therefore cannot be properly evaluated.

	What is the overall certainty of the evidence of effects? X Very low ○ Low ○ Moderate ○ High ○ No included studies	Very low
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X No important uncertainty or variability ○ No known undesirable outcomes	Mortality is valued by both patients and clinicians. The only other end point available is clinical deterioration which is also considered highly relevant and rated critical to clinical decision making.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative X Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Unclear, due to lack of safety data and imprecise estimates of benefit.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies X Don't know	None of the studies reported the costs associated with the intervention. In the absence of clinical benefit, it is unlikely to be cost-effective.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies X Don't know	Not known.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know	This is a therapy that is used in other indications and is therefore acceptable if it demonstrates clinical benefit. Patients indicate they would be willing to receive such a treatment if it demonstrated benefit.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes X Yes ○ Varies	This is an existing therapy that can be delivered in routine clinical practice. Therefore, there are unlikely to be many issues with implementation if it is shown to be an effective treatment.

	○ Don't know	

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention X	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	The panel suggests not to use interferon-β in patients hospitalised with COVID-19 infection (conditional recommendation, very low quality of evidence)				
JUSTIFICATION	In the absence of clear benefit or safety, a recommendation for use cannot be made.				
SUBGROUP CONSIDERATIONS	No subgroup effects are reported				

IMPLEMENTATION CONSIDERATIONS	None, the treatment should currently be reserved for use in clinical trials.
MONITORING AND EVALUATION	Not applicable.
RESEARCH PRIORITIES	A recent trial published after the systematic review demonstrated a significant benefit of inhaled interferon beta-1a in 101 patients conducted in the UK (https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30511-7/fulltext) . While small trials should be treated with caution, this suggests the possibility that inhaled delivery has a different effect to systemic delivery of interferon. Further studies to investigate the efficacy of inhaled interferon beta are justified.

PICO 10: Anticoagulation

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small X Moderate ○ Large ○ Varies ○ Don't know	Anticoagulation is associated with a significant reduction in mortality compared to no anticoagulation in the meta-analysis of observational studies. Allowing for the limitations of observational studies, there is a clinically important benefit evident which is biologically plausible given the known high incidence of thromboembolism in patients hospitalised with COVID-19.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate X Small ○ Trivial ○ Varies ○ Don't know	The studies performed do not identify any significant safety concerns, but reporting is incomplete and there are known complications particularly of high dose anticoagulation (bleeding) which the guideline panel acknowledges. It is likely there are some increased complications with high dose versus low dose anticoagulation.

	What is the overall certainty of the evidence of effects? X Very low ○ Low ○ Moderate ○ High ○ No included studies	As all of the data is derived from observational studies with a high likelihood of intrinsic biases the certainty is very low.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X No important uncertainty or variability ○ No known undesirable outcomes	Outcomes such as mortality are clearly recognised as important by patients and clinicians.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention X Favours the intervention ○ Varies ○ Don't know	The balance between desirable and undesirable effects is uncertain due to low quality of the evidence but the panel considers that it probably favours the intervention. There is insufficient data to say whether high or low dose anticoagulation should be preferred.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings X Moderate savings ○ Large savings ○ Varies ○ Don't know	Although not evaluated in the context of COVID-19, prophylactic anticoagulation is believed to be a cost-effective intervention in hospitalised patients generally, and the panel considers it is likely to be cost-effective in COVID-19 as well.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced X Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	none
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	Anticoagulation is widely used in hospitalised patients and is both available and acceptable. The patient representative confirms that this intervention is acceptable to patients.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes X Yes ○ Varies	Yes, the intervention of prophylactic anticoagulation is widely used in hospitalised patients worldwide.

	○ Don't know	

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention X
RECOMMENDATION	The panel recommends that patients hospitalised with COVID-19 should receive a form of anticoagulation (Strong recommendation, very low quality of evidence) We are unable to make a recommendation over the dose of anticoagulation.				
JUSTIFICATION	Although the quality of evidence is very low, prophylactic anticoagulation is routine practice for hospitalised patients at risk of thromboembolic complications in hospitals in many countries and the existing evidence and existing practice makes this an intervention that can be strongly advocated.				

	We are unable to determine whether prophylactic vs therapeutic dose anticoagulation is superior and therefore rather than recommending one or the other, we make clear that this is a matter for clinical judgement while awaiting randomized clinical trials.
SUBGROUP CONSIDERATIONS	None
IMPLEMENTATION CONSIDERATIONS	As this is widely used and inexpensive, implementation should be straightforward
MONITORING AND EVALUATION	Thromboembolic complications are common in COVID-19. In patients with respiratory deterioration particularly if receiving prophylactic anticoagulation, investigated for pulmonary embolism is indicated.
RESEARCH PRIORITIES	A randomized clinical trial of therapeutic vs prophylactic dose anticoagulation in hospitalised patients is recommended.

PICO 11: Ventilatory strategies

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small X Moderate ○ Large ○ Varies ○ Don't know	Invasive mechanical ventilation has well documented risks and long term adverse effects. Avoiding invasive mechanical ventilation is therefore highly desirable and there is evidence in other contexts that this can be achieved through the use of non-invasive ventilation. There is also evidence in other contexts of reduced 90-day mortality with the use of high flow nasal cannula oxygen in patients with acute hypoxaemic respiratory failure. Therefore, while data are limited in COVID-19, the indirect evidence suggests potential benefits could be clinically important. Proning appears to improve oxygen in COVID-19.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate X Small ○ Trivial ○ Varies ○ Don't know	There are theoretical concerns that delaying invasive mechanical ventilation could result in worse patient outcomes but there is no specific evidence in COVID-19 and limited evidence in other contexts that this is true. Non-invasive ventilation with or without awake proning may be uncomfortable but is well tolerated by most patients. There are theoretical concerns that protracted CPAP use could result in lung injury.

	What is the overall certainty of the evidence of effects? X Very low ○ Low ○ Moderate ○ High ○ No included studies	Data were derived from observational cohorts and case series only. Such studies are inherently at high risk of bias. Reports frequently arise from centres highly experienced in the delivery of non-invasive ventilation or HFNC and therefore results obtained in specialised centres may not be fully generalizable. Publication bias is a concern, if centres are motivated to report results where outcomes are better than expected.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X No important uncertainty or variability ○ No known undesirable outcomes	The guideline panel and patient representative agreed that all of the included endpoints and outcomes are important or critical for clinical decision making. Endpoints evaluated include mortality, intubation and mechanical ventilation, length of hospital stay and adverse effects.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative X Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	HFNC or non-invasive CPAP have both been reported to be associated with preventing requirement for mechanical ventilation in patients with COVID-19 associated acute hypoxaemic respiratory failure. There is limited comparative data and limited data on adverse effects, but as both are currently regarded as part of standard care in the management of acute hypoxaemic respiratory failure the panel considers it is likely the benefit outweighs any theoretical risks.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies X Don't know	This has not been formally established, but ICU care and subsequent rehabilitation is expensive and therefore an intervention that reduces the requirement for intensive care may be associated with significant cost savings. As the magnitude of benefit associated with HFNC and non-invasive CPAP have not been clearly established, any comment on relative costs is speculative

EQUITY	**What would be the impact on health equity?** ○ Reduced X Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	ICU beds are highly limited in most countries worldwide and ICU capacity was strained in many countries particularly during the first wave of the pandemic leading to rationing of resources. The use of HFNC and non-invasive CPAP can be conducted outside of an ICU environment in many countries which allows this intervention to be offered to a large number of people and also to populations who may otherwise have contraindications to invasive mechanical ventilation, which may have the effect of increasing health equity.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	HFNC and non-invasive CPAP are widely used. The main issue around acceptability is the aerosol generating nature of the intervention which puts staff and other patients at risk of infection with SARS-CoV-2. The intervention is therefore only acceptable when delivered in an appropriate environment with appropriate personal protective equipment.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes X Yes ○ Varies	The intervention is widely available worldwide. The main feasibility issue is around the appropriate environment, trained nursing resources and personal protective equipment to deliver the interventions.

	○ Don't know	

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention X	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	We suggest HFNC or non-invasive CPAP delivered through either a helmet or a face-mask for patients with COVID-19 and hypoxaemic acute respiratory failure (conditional recommendation, very low quality of evidence) Notes accompanying this recommendation: HFNC and non-invasive CPAP are classified as aerosol generating and should therefore be delivered in a safe environment with staff wearing appropriate personal protecting equipment				

	HFNC and non-invasive CPAP should not delay mechanical ventilation in patients who are not responding to treatment Prone positioning may improve oxygenation in non-intubated patient with acute hypoxaemic respiratory failure and is widely used for mechanically ventilated patients with COVID-19.
JUSTIFICATION	This is based on evidence that non-invasive ventilation with or without proning can improve oxygenation, prevent invasive mechanical ventilation and is associated with acceptable overall outcomes. The interventions appear to be well tolerated and acceptable to patients.
SUBGROUP CONSIDERATIONS	No subgroups were prespecified
IMPLEMENTATION CONSIDERATIONS	HFNC and non-invasive CPAP are aerosol generating and should therefore be delivered in a safe environment with staff wearing appropriate personal protecting equipment
MONITORING AND EVALUATION	Patients should be cared for in an environment with staff experienced in delivering HFNC or non-invasive CPAP with continuous monitoring of the patients' condition. In patients not responding to non-invasive ventilation it is important that this is recognised promptly, and invasive ventilation is not delayed.
RESEARCH PRIORITIES	Randomized studies comparing different ventilatory strategies are needed. There are no large RCTs completed yet comparing either HFNC or non-invasive CPAP or NIV with standard oxygen therapy, or the three interventions in COVID-19 patients with hARF. The Recovery–RS RCT (ISRCTN16912075), comparing standard oxygen therapy with CPAP and HFNC in COVID-19 patients is currently recruiting