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,

The search was limited to randomised clinical trials published in English language. All searches were performed systematically through September 2021.

The search retrieved 6,337 records after removal of duplicates with a further 6,303 citations excluded through title and abstract screening. A search of MedRxiv database identified 11 further preprints. 10 citations were retained from the original guidelines. A total of 55 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 September 2021.

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
Bibliography:

1. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomised Clinical Trial. Tomazini BM, *et al*. JAMA. 2020 Sep 2;324(13):1-11. doi: 10.1001/jama.2020.17021. Online ahead of print.
2. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, *et al*. JAMA. 2020 Sep 2;324(13):1-13. doi: 10.1001/jama.2020.17023. Online ahead of print.
3. Dexamethasone in Hospitalised Patients with COVID-19 - Preliminary Report. RECOVERY Collaborative Group, Horby P, *et al*. N Engl J Med. 2020 Jul 17:NEJMoa2021436. doi: 10.1056/NEJMoa2021436. Online ahead of print.
4. Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomised Clinical Trial. Dequin PF, *et al*. JAMA. 2020 Sep 2;324(13):1-9. doi: 10.1001/jama.2020.16761. Online ahead of print.
5. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomised Clinical Trial. Writing Committee for the REMAP-CAP Investigators, Angus DC, *et al*. JAMA. 2020 Sep 2;324(13):1317-29. doi: 10.1001/jama.2020.17022. Online ahead of print.
6. GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalised with COVID-19 pneumonia Luis Corral, *et al*. medRxiv 2020.06.17.20133579; doi: https://doi.org/10.1101/2020.06.17.20133579
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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												

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)		
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

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 but 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

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1. Abani, O., Abbas, A., Abbas, F., Abbas, M., Abbasi, S., Abbass, H., … Zuriaga-Alvaro, A. (2021). "Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): arandomised, controlled, open-label, platform trial." The Lancet, 397(10285), 1637–1645. https://doi.org/10.1016/S0140-6736(21)00676-0

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6 receptor antagonists	standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Adverse events												
9	randomised trials	not serious	not serious	not serious	serious[a]	none	856/1559 (54.9%)	363/755 (48.1%)	OR 1.25 (0.90 to 1.75)	**56 more per 1,000** (from 26 fewer to 138 more)	⨁⨁⨁◯ Moderate	CRITICAL
Serious adverse events												
11	randomised trials	not serious	not serious	not serious	serious[a]	none	492/2121 (23.2%)	227/1238 (18.3%)	OR 0.91 (0.73 to 1.12)	**14 fewer per 1,000** (from 43 fewer to 18 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mortality												
12	randomised trials	not serious	not serious	not serious	serious[a]	none	1310/5188 (25.3%)	1068/3615 (29.5%)	OR 0.89 (0.78 to 1.01)	**24 fewer per 1,000** (from 49 fewer to 2 more)	⨁⨁⨁◯ Moderate	CRITICAL
time to hospital discharge												
5	randomised trials	not serious	not serious	not serious	not serious	none			HR 1.31 (1.15 to 1.48)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁⨁ High	IMPORTANT
ICU admission												
4	randomised trials	not serious	serious[b]	not serious	serious[a]	none	115/338 (34.0%)	114/279 (40.9%)	OR 0.74 (0.40 to 1.37)	**70 fewer per 1,000** (from 192 fewer to 78 more)	⨁⨁◯◯ Low	CRITICAL
Deterioration (time to clinical failure defined as death, mechanical ventilation or transfer to ICU)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	70/243 (28.8%)	55/153 (35.9%)	OR 0.68 (0.44 to 1.06)	**83 fewer per 1,000** (from 161 fewer to 14 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mechanical ventilation												
7	randomised trials	not serious	not serious	not serious	not serious	none	370/2561 (14.4%)	426/2317 (18.4%)	OR 0.75 (0.64 to 0.87)	**39 fewer per 1,000** (from 58 fewer to 20 fewer)	⨁⨁⨁⨁ High	IMPORTANT
TIme to improvement on ordinal scale												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6 receptor antagonists	standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	not serious	not serious	not serious	not serious	none			HR 1.15 (1.01 to 1.32)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁⨁ High	CRITICAL

Mechanical ventilation OR death

5	randomised trials	not serious	not serious	not serious	not serious	none	695/2292 (30.3%)	820/2140 (38.3%)	OR 0.76 (0.65 to 0.88)	**62 fewer per 1,000** (from 96 fewer to 30 fewer)	⨁⨁⨁⨁ High	CRITICAL

Clinical Worsening on OS scale

2	randomised trials	not serious	not serious	not serious	serious[a]	none	39/411 (9.5%)	20/208 (9.6%)	OR 0.97 (0.54 to 1.75)	**3 fewer per 1,000** (from 42 fewer to 61 more)	⨁⨁⨁◯ Moderate	IMPORTANT

Clinical Improvement on OS scale

2	randomised trials	not serious	not serious	not serious	serious[a]	none	361/528 (68.4%)	120/171 (70.2%)	OR 1.24 (0.82 to 1.87)	**43 more per 1,000** (from 43 fewer to 113 more)	⨁⨁⨁◯ Moderate	IMPORTANT

Proportion discharged from hospital

5	randomised trials	not serious	not serious	not serious	not serious	none	1666/2638 (63.2%)	1296/2389 (54.2%)	OR 1.29 (1.15 to 1.46)	**62 more per 1,000** (from 34 more to 91 more)	⨁⨁⨁⨁ High	CRITICAL

ICU length of stay

1	randomised trials	not serious	not serious	not serious	serious[a]	none	91	88	-	MD **0.2 lower** (2.06 lower to 1.66 higher)	⨁⨁⨁◯ Moderate	IMPORTANT

Non-invasive ventilation

2	randomised trials	not serious	not serious	not serious	serious[a]	none	289/998 (29.0%)	322/1000 (32.2%)	OR 0.85 (0.71 to 1.04)	**34 fewer per 1,000** (from 70 fewer to 9 more)	⨁⨁⨁◯ Moderate	IMPORTANT

Progression to MV, ECMO or death

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6 receptor antagonists	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	not serious	none	113/279 (40.5%)	144/273 (52.7%)	OR 0.61 (0.44 to 0.85)	**122 fewer per 1,000** (from 198 fewer to 41 fewer)	⨁⨁⨁⨁ High	CRITICAL

time to ICU discharge

2	randomised trials	not serious	not serious	not serious	not serious	none			HR 1.48 (1.26 to 1.73)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁⨁⨁⨁ High	CRITICAL

CI: confidence interval; **HR:** hazard Ratio; **MD:** mean difference; **OR:** odds ratio

Explanations

a. CI shows both beneficial and detrimental effects

b. Heterogeneity between studies

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:

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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)		
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												

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)		
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
Hospitalisation												
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												
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												

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)		
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. Abaleke, E., Abbas, M., Abbasi, S., Abbott, A., Abdelaziz, A., Abdelbadiee, S., … Zuriaga-Alvaro, A. (2021). "Azithromycin in patients admitted to hospital with COVID-19(RECOVERY): a randomised, controlled, open-label, platform trial." The Lancet, 397(10274), 605–612. https://doi.org/10.1016/S0140-6736(21)00149-5
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4. Hinks, T. S., Cureton, L., Knight, R., Wang, A., Cane, J. L., Barber, V. S., … Richards, D. (2021). "A Randomised Clinical Trial of Azithromycin Versus Standard Care inAmbulatory COVID-19 – The ATOMIC2 Trial." SSRN Electronic Journal, 1–22. https://doi.org/10.2139/ssrn.3827019
5. Sekhavati, E., Jafari, F., SeyedAlinaghi, S. A., Jamalimoghadamsiahkali, S., Sadr, S., Tabarestani, M., … Ghiasvand, F. (2020). "Safety and effectiveness of azithromycin inpatients with COVID-19: An open-label randomised trial." International Journal of Antimicrobial Agents, 56(4). https://doi.org/10.1016/j.ijantimicag.2020.106143

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												
5	randomised trials	not serious	not serious	not serious	serious[a]	none	657/3169 (20.7%)	1250/5898 (21.2%)	OR 0.97 (0.87 to 1.08)	**5 fewer per 1,000** (from 22 fewer to 13 more)	⨁⨁⨁◯ Moderate	CRITICAL
Score on ordinal scale at day 15												
3	randomised trials	not serious	not serious	not serious	serious[a]	none	-/0	-/0	OR 1.13 (0.87 to 1.46)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Required ICU admission (deterioration)												
1	randomised trials	not serious	not serious	not serious	serious[b]	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)	⨁⨁⨁◯ Moderate	CRITICAL
Hospital length of stay												

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)		
2	randomised trials	not serious	not serious	not serious	serious[a]	none	228	214	-	MD **0.37 lower** (2.47 lower to 1.72 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Serious adverse events												
3	randomised trials	not serious	not serious	not serious	serious[b]	none	107/625 (17.1%)	79/721 (11.0%)	OR 1.25 (0.86 to 1.81)	**24 more per 1,000** (from 14 fewer to 73 more)	⨁⨁⨁◯ Moderate	CRITICAL
Requiring Non-invasive ventilation												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	215/1513 (14.2%)	468/2852 (16.4%)	OR 0.89 (0.75 to 1.06)	**15 fewer per 1,000** (from 36 fewer to 8 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Requiring Invasive mechanical ventilation												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	57/1368 (4.2%)	115/2705 (4.3%)	OR 0.98 (0.71 to 1.35)	**1 fewer per 1,000** (from 12 fewer to 14 more)	⨁⨁⨁◯ Moderate	CRITICAL
Proportion discharged from hospital at 28days												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	1788/2582 (69.2%)	3525/5181 (68.0%)	OR 1.06 (0.96 to 1.17)	**13 more per 1,000** (from 9 fewer to 33 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. CI shows both beneficial and detrimental effects

b. CI shows possible 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												

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)		
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: hospital
Bibliography:

1. Deftereos, S. G., Giannopoulos, G., Vrachatis, D. A., Siasos, G. D., Giotaki, S. G., Gargalianos, P., … Stefanadis, C. (2020). "Effect of Colchicine vs Standard Care on Cardiacand Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalised with Coronavirus Disease 2019: The GRECCO-19 Randomised Clinical Trial." JAMA NetworkOpen, 3(6), 1–14. https://doi.org/10.1001/jamanetworkopen.2020.13136
2. Landray, M. (2021). "Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial." MedRxiv,2021.05.18.21257267. https://doi.org/10.1101/2021.05.18.21257267
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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 on ordinal scale)												
1	randomised trials	not serious	not serious	not serious	serious[a]	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												
3	randomised trials	not serious	not serious	not serious	serious[b]	none	1174/5701 (20.6%)	1196/5816 (20.6%)	OR 0.64 (0.22 to 1.89)	**64 fewer per 1,000** (from 152 fewer to 123 more)	⊕⊕◯ Moderate	CRITICAL
ICU admission												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	2/36 (5.6%)	4/36 (11.1%)	OR 0.47 (0.08 to 2.75)	**56 fewer per 1,000** (from 101 fewer to 145 more)	⊕⊕◯ Moderate	CRITICAL
Adverse effect- Diarrhoea												
2	randomised trials	not serious	not serious	not serious	serious[c]	none	31/91 (34.1%)	11/86 (12.8%)	OR 3.70 (1.68 to 8.16)	**224 more per 1,000** (from 70 more to 417 more)	⊕⊕◯ Moderate	CRITICAL
Proportion discharged from hospital at day28												

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	not serious	not serious	not serious	serious[b]	none	3901/5610 (69.5%)	4032/5730 (70.4%)	OR 0.96 (0.89 to 1.04)	**9 fewer per 1,000** (from 25 fewer to 8 more)	⨁⨁⨁◯ Moderate	CRITICAL
Progression to non-invasive ventilation												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	818/3815 (21.4%)	904/3962 (22.8%)	OR 0.92 (0.83 to 1.03)	**14 fewer per 1,000** (from 31 fewer to 5 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Progression to Invasive ventilation												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	259/3815 (6.8%)	228/3962 (5.8%)	OR 1.19 (0.99 to 1.43)	**10 more per 1,000** (from 1 fewer to 23 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mechanical ventilation OR death												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	1344/5342 (25.2%)	1343/5469 (24.6%)	RR 1.02 (0.96 to 1.09)	**5 more per 1,000** (from 10 fewer to 22 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Small sample size

b. CI shows both beneficial and detrimental effects

c. Wide CI

d. CI shows appreciable harm

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												

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)		
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
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.
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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												

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	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

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

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 1.29** (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

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. the HEP-COVID Investigators (2021) "Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalised Patients With COVID-19 The HEP-COVID Randomized Clinical Trial" JAMA Intern Med. doi:10.1001/jamainternmed.2021.6203
2. The REMAP-CAP, ACTIV-4a, and ATTACC Investigators (2021) "Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19" DOI: 10.1056/NEJMoa2103417
3. Anna Cristina Bertoldi Lemos, Douglas Alexandre do Espírito Santo, Maísa Cabetti Salvetti, Renato Noffs Gilio, Lucas Barbosa Agra, Antonio Pazin-Filho, Carlos Henrique Miranda (2020) "Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID)" Thrombosis Research 196 (2020) 359–366
4. The ATTACC, ACTIV-4a, and REMAP-CAP Investigators (2021) "Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19" DOI: 10.1056/NEJMoa2105911
5. The ACTION Coalition COVID-19 Brazil IV Investigators (2021) "Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial" Lancet 2021; 397: 2253–63

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anticoagulation therapy	standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Major bleed												
5	randomised trials	not serious	not serious	not serious	not serious	none	74/2159 (3.4%)	31/2047 (1.5%)	OR 2.39 (1.56 to 3.66)	**20 more per 1,000** (from 8 more to 38 more)	⨁⨁⨁⨁ High	CRITICAL
Mortality												
5	randomised trials	not serious	not serious	not serious	serious[a]	none	346/2164 (16.0%)	343/2048 (16.7%)	RR 1.01 (0.88 to 1.14)	**2 more per 1,000** (from 20 fewer to 23 more)	⨁⨁⨁◯ Moderate	CRITICAL
Hospital Discharge												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	1420/1705 (83.3%)	1326/1612 (82.3%)	OR 1.00 (0.82 to 1.21)	**0 fewer per 1,000** (from 31 fewer to 26 more)	⨁⨁⨁◯ Moderate	CRITICAL
Major thrombotic event or death												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anticoagulation therapy	standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	not serious	not serious	not serious	serious[b]	none	390/2151 (18.1%)	430/2034 (21.1%)	OR 0.86 (0.73 to 1.01)	**24 fewer per 1,000** (from 48 fewer to 2 more)	⨁⨁⨁◯ Moderate	CRITICAL

Major thrombotic event

5	randomised trials	not serious	not serious	not serious	not serious	none	86/2160 (4.0%)	148/2043 (7.2%)	RR 0.58 (0.45 to 0.74)	**30 fewer per 1,000** (from 40 fewer to 19 fewer)	⨁⨁⨁⨁ High	CRITICAL

Organ support-free days

2	randomised trials	not serious	not serious	not serious	serious[a]	none	-/0	-/0	1.03 (0.89 to 1.20)	**-- per 1,000** (from -- to --)	⨁⨁⨁◯ Moderate	IMPORTANT

Mortality- ICU only

2	randomised trials	not serious	not serious	not serious	serious[a]	none	200/544 (36.8%)	203/574 (35.4%)	OR 0.92 (0.38 to 2.24)	**19 fewer per 1,000** (from 182 fewer to 197 more)	⨁⨁⨁◯ Moderate	CRITICAL

Mortality- non-ICU

2	randomised trials	not serious	not serious	not serious	serious[a]	none	121/1491 (8.1%)	109/1350 (8.1%)	OR 1.11 (0.64 to 1.93)	**8 more per 1,000** (from 28 fewer to 64 more)	⨁⨁⨁◯ Moderate	CRITICAL

Major thrombosis- ICU

2	randomised trials	not serious	not serious	not serious	not serious	none	36/540 (6.7%)	60/569 (10.5%)	OR 0.60 (0.39 to 0.93)	**39 fewer per 1,000** (from 61 fewer to 7 fewer)	⨁⨁⨁⨁ High	CRITICAL

Major Thrombosis- non-ICU

2	randomised trials	not serious	not serious	not serious	not serious	none	36/1491 (2.4%)	52/1350 (3.9%)	OR 0.64 (0.41 to 0.99)	**14 fewer per 1,000** (from 22 fewer to 0 fewer)	⨁⨁⨁⨁ High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anticoagulation therapy	standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Major bleeding- ICU												
3	randomised trials	not serious	not serious	not serious	serious[a,c]	none	24/584 (4.1%)	13/610 (2.1%)	OR 1.95 (0.75 to 5.09)	**19 more per 1,000** (from 5 fewer to 78 more)	⨁⨁◯ Moderate	CRITICAL
Major bleeding- non-ICU												
3	randomised trials	not serious	not serious	not serious	not serious	none	50/1575 (3.2%)	18/1437 (1.3%)	OR 2.63 (1.51 to 4.56)	**20 more per 1,000** (from 6 more to 42 more)	⨁⨁⨁ High	CRITICAL

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. CI shows both beneficial and detrimental effects

b. CI crosses 1, therefore cannot rule out detrimental effect

c. Wide CI's

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.

PICO Quetion 11a – Is continuous positive airway pressure (CPAP) therapy, in comparison to usual care (defined as the absence of these interventions or invasive mechanical ventilation), beneficial in the treatment for COVID-19?

Setting: Hospitalised patients

Bibliography:

The Recovery- RS collaborators (2021) "An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19" medRxiv 2021.08.02.21261379; doi: https://doi.org/10.1101/2021.08.02.21261379

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Tracheal intubation or death												
1	randomised trials	not serious	not serious	not serious	not serious	none	137/377 (36.3%)	158/356 (44.4%)	OR 0.72 (0.53 to 0.96)	**79 fewer per 1,000** (from 147 fewer to 10 fewer)	⊕⊕⊕⊕ High	CRITICAL
Intubation within 30days												
1	randomised trials	not serious	not serious	not serious	not serious	none	126/377 (33.4%)	147/356 (41.3%)	OR 0.71 (0.53 to 0.96)	**80 fewer per 1,000** (from 141 fewer to 10 fewer)	⊕⊕⊕⊕ High	CRITICAL
Tracheal intubation rate												
1	randomised trials	not serious	not serious	not serious	not serious	none	126/377 (33.4%)	147/356 (41.3%)	OR 0.71 (0.53 to 0.96)	**80 fewer per 1,000** (from 141 fewer to 10 fewer)	⊕⊕⊕⊕ High	CRITICAL
Admission to critical care												
1	randomised trials	not serious	not serious	not serious	not serious	none	205/379 (54.1%)	219/356 (61.5%)	OR 0.74 (0.55 to 0.99)	**73 fewer per 1,000** (from 147 fewer to 2 fewer)	⊕⊕⊕⊕ High	CRITICAL
Median time to tracheal intubation												
1	randomised trials	not serious	not serious	not serious	not serious	none	-/0	-/0	HR 0.74 (0.58 to 0.94)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕⊕⊕⊕ High	CRITICAL
Mean length of stay in critical care												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	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	377	356	-	MD **0.1 lower** (2.22 lower to 2.02 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Mean duration of invasive mechanical ventilation												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	-/0	-/0	HR 0.76 (0.56 to 1.03)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Mean length of hospital stay												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	377	356	-	MD **0.9 lower** (3.48 lower to 1.68 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Mortality												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	63/378 (16.7%)	69/359 (19.2%)	OR 0.84 (0.58 to 1.23)	**26 fewer per 1,000** (from 71 fewer to 34 more)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse Events												
1	randomised trials	not serious	not serious	not serious	not serious	none	130/380 (34.2%)	65/475 (13.7%)	OR 3.28 (2.34 to 4.59)	**205 more per 1,000** (from 134 more to 284 more)	⨁⨁⨁⨁ High	CRITICAL
Serious adverse events												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	7/380 (1.8%)	1/475 (0.2%)	OR 8.90 (1.09 to 72.62)	**16 more per 1,000** (from 0 fewer to 131 more)	⨁⨁⨁◯ Moderate	CRITICAL
Median time to death												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	-/0	-/0	HR 0.86 (0.61 to 1.21)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard Ratio; **MD:** mean difference; **OR:** odds ratio

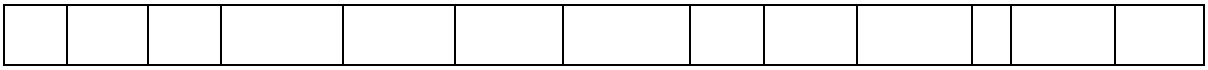
Explanations

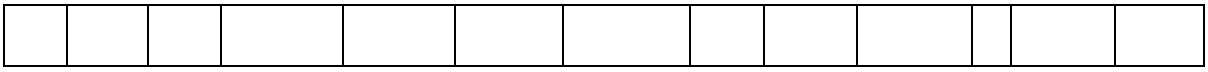
a. CI shows both beneficial and detrimental effects

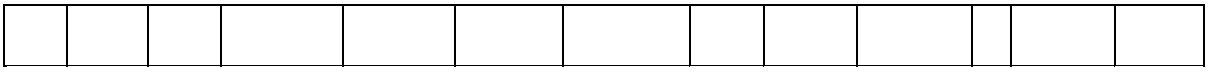
b. Wide CI's and few events

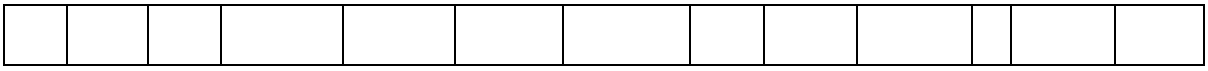
PICO Question 11b – Is high-flow nasal oxygen (HFNO) therapy, in comparison to usual care (defined as the absence of these interventions or invasive mechanical ventilation), beneficial in the treatment for COVID-19?
Setting: Hospitalised patients
Bibliography:

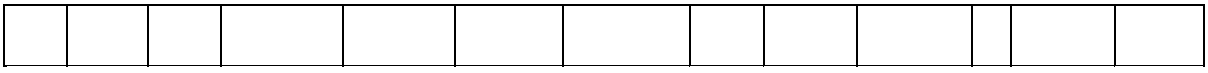
1. The Recovery- RS collaborators (2021) "An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19" medRxiv 2021.08.02.21261379; doi: https://doi.org/10.1101/2021.08.02.21261379
2. Teng X, Shen Y, Han M, Yang G, Zha L and Shi J (2020) "The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia". Eur J Clin Invest. 2021;51:e13435. https://doi.org/10.1111/eci.13435
3. Gustavo A. Ospina-Tascón, Luis Eduardo Calderón-Tapia, Alberto F. García et al. Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapyon Invasive Mechanical Ventilation and Clinical Recovery in PatientsWith Severe COVID-19. JAMA. 2021;326(21):2161-2171. doi: 10.1001/jama.2021.20714

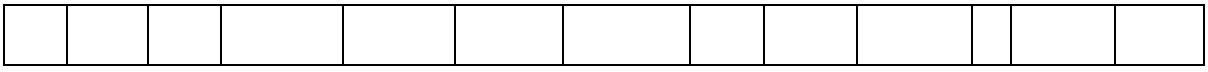


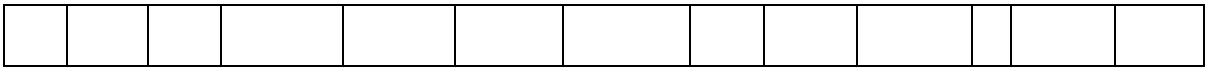












Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HFNO	standard of care	Relative (95% CI)	Absolute (95% CI)		
Tracheal intubation or death												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	184/414 (44.4%)	166/368 (45.1%)	**OR 0.97** (0.73 to 1.29)	**8 fewer per 1,000** (from 76 fewer to 63 more)	⨁⨁⨁◯ Moderate	CRITICAL
Tracheal intubation rate												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	169/414 (40.8%)	154/368 (41.8%)	**OR 0.96** (0.72 to 1.27)	**10 fewer per 1,000** (from 77 fewer to 59 more)	⨁⨁⨁◯ Moderate	CRITICAL
Admission to critical care												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	253/416 (60.8%)	214/368 (58.2%)	**OR 1.12** (0.84 to 1.49)	**27 more per 1,000** (from 43 fewer to 93 more)	⨁⨁⨁◯ Moderate	CRITICAL
Median time to tracheal intubation												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	0/0	0/0	**HR 0.96** (0.77 to 1.20)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Mean length of stay in critical care												

2	randomised trials	not serious	not serious	not serious	serious[a]	none	426	378	-	MD **0.68 lower** (1.39 lower to 0.02 higher)	⨁⨁⨁◯ Moderate	IMPORTANT

Median duration of invasive mechanical ventilation

1	randomised trials	not serious	not serious	not serious	serious[a]	none	0/0	0/0	**HR 0.93** (0.72 to 1.20)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

Mean length of hospital stay

2	randomised trials	not serious	not serious	not serious	serious[a]	none	426	378	-	MD **0.85 lower** (2.42 lower to 0.71 higher)	⨁⨁⨁◯ Moderate	IMPORTANT

Median time to death

1	randomised trials	not serious	not serious	not serious	serious[a]	none	0/0	0/0	**HR 0.94** (0.68 to 1.30)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

Adverse Events

1	randomised trials	not serious	not serious	not serious	not serious	none	86/417 (20.6%)	65/475 (13.7%)	**OR 1.64** (1.15 to 2.33)	**70 more per 1,000** (from 17 more to 133 more)	⨁⨁⨁⨁ High	CRITICAL

Serious adverse events

1	randomised trials	not serious	not serious	not serious	serious[a]	none	0/417 (0.0%)	1/475 (0.2%)	**OR 0.38** (0.02 to 9.32)	**1 fewer per 1,000** (from 2 fewer to 17 more)	⨁⨁⨁◯ Moderate	CRITICAL

Intubation within 30days

2	randomised trials	not serious	not serious	not serious	serious[a]	none	204/513 (39.8%)	204/468 (43.6%)	**OR 0.86** (0.66 to 1.10)	**37 fewer per 1,000** (from 98 fewer to 24 more)	⨁⨁⨁◯ Moderate	CRITICAL

Mortality

2	randomised trials	not serious	not serious	not serious	serious[a]	none	86/514 (16.7%)	90/470 (19.1%)	**RR 0.87** (0.66 to 1.13)	**25 fewer per 1,000** (from 65 fewer to 25 more)	⨁⨁⨁◯ Moderate	CRITICAL

Improvement in ordinal scale

1	randomised trials	not serious	not serious	not serious	serious[a]	none	77/99 (77.8%)	71/100 (71.0%)	**OR 1.43** (0.75 to 2.71)	**68 more per 1,000** (from 63 fewer to 159 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard Ratio; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. CI shows both beneficial and detrimental effects

PICO Question 12: Should convalescent plasma compared to standard care (defined as control, placebo or normal background therapy) be used for COVID-19

Setting: hospital

Bibliography:

1. RECOVERY Collaborative Group (2021) "Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial" Lancet 2021; 397: 2049–59 https://doi.org/10.1016/S0140-6736(21)00897-7

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3. Bennett-Guerrero, E. *et al.* Severe Acute Respiratory Syndrome Coronavirus 2 Convalescent Plasma Versus Standard Plasma in Coronavirus Disease 2019 Infected Hospitalised Patients in New York: A Double-Blind Randomized Trial∗. *Crit. Care Med.* 1015–1025 (2021) doi:10.1097/CCM.0000000000005066.

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5. Ling Li, Wei Zhang, Yu Hu, Xunliang Tong, Shangen Zheng, Juntao Yang,. ...Zhong Liu (2020) "Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19 A Randomized Clinical Trial" JAMA. 2020;324(5):460-470. doi:10.1001/jama.2020.10044

6. Manaf AlQahtani, Abdulkarim Abdulrahman, Abdulrahman Almadani, Salman Yousif Alali, Alaa Mahmood Al Zamrooni, Amal Hamza Hejab, Ronán M. Conroy, Pearl Wasif, Sameer Otoom, Stephen L. Atkin, Manal Abduljalil (2020) "Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19disease" Scientific Reports (2021) 11:9927 https://doi.org/10.1038/s41598-021-89444-5

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Convalescent plasma	standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Mortality												
17	randomised trials	serious [a]	not serious	serious[b]	serious[c]	none	1704/7673 (22.2%)	1643/7154 (23.0%)	OR 0.97 (0.89 to 1.04)	**5 fewer per 1,000** (from 20 fewer to 7 more)	⨁◯◯◯ Very low	CRITICAL
Adverse Events												
9	randomised trials	serious [a]	not serious	serious[b]	serious[c,d]	none	1857/6545 (28.4%)	1733/6275 (27.6%)	OR 1.03 (0.95 to 1.11)	**6 more per 1,000** (from 10 fewer to 21 more)	⨁◯◯◯ Very low	CRITICAL
Serious Adverse Events												
6	randomised trials	serious [a]	not serious	not serious	serious[c]	none	342/1139 (30.0%)	162/594 (27.3%)	OR 1.17 (0.93 to 1.46)	**32 more per 1,000** (from 14 fewer to 81 more)	⨁⨁◯◯ Low	CRITICAL
Proportion discharged												
6	randomised trials	serious [a]	not serious	not serious	serious[c]	none	4119/6289 (65.5%)	3989/6092 (65.5%)	OR 1.01 (0.93 to 1.08)	**2 more per 1,000** (from 17 fewer to 17 more)	⨁⨁◯◯ Low	CRITICAL
Progression to non-invasive ventilation												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Convalescent plasma	standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	888/3951 (22.5%)	889/3825 (23.2%)	OR 0.95 (0.86 to 1.06)	**9 fewer per 1,000** (from 26 fewer to 11 more)	⨁◯◯◯ Very low	IMPORTANT

Progression to invasive ventilation

7	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	301/4444 (6.8%)	300/4077 (7.4%)	RR 0.91 (0.78 to 1.06)	**7 fewer per 1,000** (from 16 fewer to 4 more)	⨁◯◯◯ Very low	CRITICAL

Negative conversion

2	randomised trials	serious[a]	serious[e]	not serious	not serious	none	158/220 (71.8%)	108/209 (51.7%)	OR 2.32 (1.57 to 3.45)	**196 more per 1,000** (from 110 more to 270 more)	⨁⨁◯◯ Low	IMPORTANT

Improvement in ordinal scale

4	randomised trials	serious[a]	not serious	not serious	serious[c]	none	80/184 (43.5%)	58/139 (41.7%)	OR 1.44 (0.90 to 2.31)	**90 more per 1,000** (from 25 fewer to 206 more)	⨁⨁◯◯ Low	IMPORTANT

Length of hospital stay

5	randomised trials	serious[a]	not serious	not serious	serious[c]	none	-/0	-/0	HR 1.05 (0.87 to 1.26)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁◯◯ Low	IMPORTANT

Progression to severe disease

3	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	35/352 (9.9%)	47/336 (14.0%)	RR 0.69 (0.46 to 1.04)	**43 fewer per 1,000** (from 76 fewer to 6 more)	⨁◯◯◯ Very low	IMPORTANT

ICU admission

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Convalescent plasma	standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious[b]	serious[c]	none	2/80 (2.5%)	6/80 (7.5%)	RR 0.33 (0.07 to 1.60)	**50 fewer per 1,000** (from 70 fewer to 45 more)	⨁◯◯◯ Very low	CRITICAL

Progression to severe disease or death

1	randomised trials	not serious	not serious	not serious	serious[c]	none	44/235 (18.7%)	41/229 (17.9%)	RR 1.05 (0.71 to 1.54)	**9 more per 1,000** (from 52 fewer to 97 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard Ratio; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Includes trials which were terminated early

b. Includes a study of mild disease

c. CI shows both beneficial and detrimental effects

d. Includes studies with significantly wide CI's for specific outcome

e. Heterogeneity between studies

PICO Question 13: Should other monoclonal antibodies compared to standard care (defined as control, placebo or normal background therapy) be used for COVID-19

Setting: hospital

Bibliography:

1. RECOVERY Collaborative Group. (2021) "Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial." medRxiv preprint doi: https://doi.org/10.1101/2021.06.15.21258542

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	other monoclonal antibodies	standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	953/5002 (19.1%)	1031/5097 (20.2%)	RR 0.94 (0.87 to 1.02)	**12 fewer per 1,000** (from 26 fewer to 4 more)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events (organ dysfunction or serious infection)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	49/163 (30.1%)	37/151 (24.5%)	OR 1.32 (0.80 to 2.18)	**55 more per 1,000** (from 39 fewer to 169 more)	⨁⨁⨁◯ Moderate	CRITICAL
Death, SAE or AE grade 3/4												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	38/163 (23.3%)	30/151 (19.9%)	OR 1.23 (0.71 to 2.10)	**35 more per 1,000** (from 49 fewer to 144 more)	⨁⨁⨁◯ Moderate	CRITICAL
Time to improvement												
1	randomised trials	not serious	not serious	not serious	serious[a]	none			Rate ratio 1.06 (0.77 to 1.46)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁◯ Moderate	CRITICAL
Proportion discharged												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	3518/5002 (70.3%)	3549/5097 (69.6%)	RR 1.01 (0.98 to 1.04)	**7 more per 1,000** (from 14 fewer to 28 more)	⨁⨁⨁◯ Moderate	CRITICAL
Progression to ventilation												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	other monoclonal antibodies	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	751/3312 (22.7%)	793/3325 (23.8%)	RR 0.95 (0.87 to 1.04)	**12 fewer per 1,000** (from 31 fewer to 10 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Progression to NIV												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	726/3312 (21.9%)	765/3325 (23.0%)	RR 0.95 (0.87 to 1.04)	**12 fewer per 1,000** (from 30 fewer to 9 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Progression to IMV												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	181/3312 (5.5%)	211/3325 (6.3%)	RR 0.86 (0.71 to 1.04)	**9 fewer per 1,000** (from 18 fewer to 3 more)	⨁⨁⨁◯ Moderate	CRITICAL
Progression to death or IMV												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	1089/4556 (23.9%)	1151/4642 (24.8%)	RR 0.96 (0.90 to 1.04)	**10 fewer per 1,000** (from 25 fewer to 10 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mortality (seronegative patients only)												
1	randomised trials	not serious	not serious	not serious	not serious	none	396/1633 (24.2%)	451/1520 (29.7%)	RR 0.82 (0.73 to 0.92)	**53 fewer per 1,000** (from 80 fewer to 24 fewer)	⨁⨁⨁⨁ High	CRITICAL
Proportion discharged from hospital at 28days (seronegative patients only)												
1	randomised trials	not serious	not serious	not serious	not serious	none	1059/1633	888/1520	Rate ratio 1.19 (1.08 to 1.31)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁⨁ High	CRITICAL
Progression to IMV (seronegative patients only)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	189/1599	200/1484	Rate ratio 0.88 (0.73 to 1.06)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁◯ Moderate	CRITICAL
Progression to death or IMV (seronegative patients only)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	other monoclonal antibodies	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	not serious	none	487/1599	542/1484	Rate ratio 0.83 (0.75 to 0.92)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁⨁ High	CRITICAL
Progression to NIV (seronegative patients only)												
1	randomised trials	not serious	not serious	not serious	not serious	none	341/1267	360/1143	Rate ratio 0.85 (0.75 to 0.96)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁⨁ High	IMPORTANT

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. CI shows both beneficial and detrimental effects

PICO Question 14: IL-1 receptor antagonists compared to standard care (defined as control, placebo or normal background therapy) for COVID-19

Setting: hospital

Bibliography:

1. Derde, L. P. G. (2021). “Effectiveness of Tocilizumab, Sarilumab, and Anakinra for critically ill patients with COVID-19 The REMAP-CAP COVID-19 Immune Modulation Therapy Domain Randomised Clinical Trial.” MedRxiv, 2021.06.18.21259133. Retrieved from http://medrxiv.org/content/early/2021/06/22/2021.06.18.21259133.abstract

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-1 receptor antagonists	standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Adverse events												
3	randomised trials	not serious	not serious	not serious	serious[a]	none	486/689 (70.5%)	299/467 (64.0%)	OR 1.05 (0.81 to 1.38)	**11 more per 1,000** (from 50 fewer to 70 more)	⨁⨁⨁◯ Moderate	CRITICAL
Serious adverse events												
3	randomised trials	not serious	not serious	not serious	serious[a]	none	128/689 (18.6%)	108/467 (23.1%)	OR 0.79 (0.59 to 1.06)	**39 fewer per 1,000** (from 81 fewer to 11 more)	⨁⨁⨁◯ Moderate	CRITICAL
Time to hospital discharge												
2	randomised trials	not serious	not serious	not serious	not serious	none			HR 1.14 (1.00 to 1.31)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁⨁ High	IMPORTANT
Clinical change on OS												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-1 receptor antagonists	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			HR 1.18 (0.87 to 1.60)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Progression to intubation, ECMO or death												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	122/228 (53.5%)	147/276 (53.3%)	OR 1.01 (0.71 to 1.44)	**2 more per 1,000** (from 85 fewer to 89 more)	⨁⨁⨁◯ Moderate	CRITICAL
Proportion discharged												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	34/59 (57.6%)	34/55 (61.8%)	OR 0.84 (0.40 to 1.78)	**42 fewer per 1,000** (from 225 fewer to 124 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mechanical ventilation or death												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	20/59 (33.9%)	19/55 (34.5%)	OR 0.97 (0.45 to 2.11)	**7 fewer per 1,000** (from 154 fewer to 181 more)	⨁⨁⨁◯ Moderate	CRITICAL
Progression to severe disease or death												
1	randomised trials	not serious	not serious	not serious	not serious	none	-/0	-/0	HR 0.62 (0.45 to 0.85)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁⨁⨁⨁ High	CRITICAL
Duration of ICU stay												
1	randomised trials	not serious	not serious	not serious	serious[b]	none			HR 2.33 (1.11 to 4.89)	**2 fewer per 1,000** (from 5 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
Mortality												
4	randomised trials	not serious	not serious	not serious	serious[a]	none	183/1052 (17.4%)	192/872 (22.0%)	OR 0.97 (0.76 to 1.24)	**5 fewer per 1,000** (from 44 fewer to 39 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard Ratio; **OR:** odds ratio

Explanations

a. CI shows both beneficial and detrimental effects

b. wide CI

PICO Question 15 – Should JAK inhibitors compared to standard care (defined as control, placebo or normal background therapy) be used for COVID-19
Setting: hospital
Bibliography:
1. The STOP-COVID Trial Investigators (2021) "Tofacitinib in Patients Hospitalised with Covid-19 Pneumonia" N Engl J Med 2021;385:406-15. DOI: 10.1056/NEJMoa2101643
2. The COV-BARRIER Study Group (2021) "Efficacy and safety of baricitinib for the treatment ofhospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo controlled phase 3 trial" Lancet Respir Med September 1, 2021 https://doi.org/10.1016/S2213-2600(21)00331-3
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4. the ACTT-2 Study Group Members (2021) "Baricitinib plus Remdesivir for Hospitalised Adults with Covid-19" N Engl J Med 2021;384:795-807. DOI: 10.1056/NEJMoa2031994

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Adverse events												
4	randomised trials	serious [a]	not serious	not serious	serious[b]	none	594/1427 (41.6%)	619/1433 (43.2%)	OR 0.94 (0.81 to 1.09)	**15 fewer per 1,000** (from 51 fewer to 21 more)	⨁⨁◯◯ Low	CRITICAL
Mortality												
4	randomised trials	serious [a]	not serious	not serious	not serious	none	90/1443 (6.2%)	148/1445 (10.2%)	OR 0.58 (0.44 to 0.76)	**40 fewer per 1,000** (from 55 fewer to 23 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Length of hospital stay												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	-/0	-/0	HR 1.18 (0.94 to 1.48)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
Progression to respiratory failure or death												
1	randomised trials	not serious	not serious	not serious	not serious	none	26/144 (18.1%)	42/145 (29.0%)	RR 0.62 (0.40 to 0.96)	**110 fewer per 1,000** (from 174 fewer to 12 fewer)	⨁⨁⨁⨁ High	CRITICAL
Time to 2+ point WHO scale improvement												
1	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	-/0	-/0	HR 1.67 (0.84 to 3.33)	**2 fewer per 1,000** (from 3 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	standard care (defined as control, placebo or normal background therapy)	Relative (95% CI)	Absolute (95% CI)		
Progression to NIV or HFNO												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	-/0	-/0	Rate ratio 0.82 (0.60 to 1.12)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁◯ Moderate	IMPORTANT
Progression to MV or death												
1	randomised trials	not serious	not serious	not serious	not serious	none	-/0	-/0	Rate ratio 0.69 (0.50 to 0.95)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁⨁ High	CRITICAL
Progression to MV or NIV or death												
1	randomised trials	not serious	not serious	not serious	not serious	none	-/0	-/0	Rate ratio 0.77 (0.60 to 0.99)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁⨁ High	CRITICAL
Median duration of mechanical ventilation												
0	randomised trials	not serious	not serious	not serious		none	-/0	-/0	not pooled	see comment	-	CRITICAL
Time to viral clearance												
1	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	-/0	-/0	HR 0.78 (0.27 to 2.26)	**1 fewer per 1,000** (from 2 fewer to 0 fewer)	⨁⨁◯◯ Low	IMPORTANT
Serious adverse events												
4	randomised trials	serious[a]	not serious	not serious	not serious	none	212/1427 (14.9%)	265/1433 (18.5%)	OR 0.77 (0.63 to 0.94)	**36 fewer per 1,000** (from 60 fewer to 9 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard Ratio; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Included trial(s) with hierarchical testing

b. CI shows both beneficial and detrimental effects

c. Small study (n=41)

PubMed search strings

Concept 1: COVID	("COVID-19"[MeSH] OR nCoV[all] OR 2019nCoV[all] OR COVID[all] OR COVID19[all] OR "SARS-Cov-2"[MeSH] 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[EDAT]:2030[EDAT])
AND	
Concept 2: RCT	("Clinical Trial"[pt] OR placebo[tiab] OR "drug therapy"[sh] OR random*[tiab] OR RCT[tiab] OR trial[tiab] OR groups[tiab] OR "phase 1"[tiab] OR "phase 2"[tiab] OR "phase 3"[tiab] OR "phase 4"[tiab] OR "phase I"[tiab] OR "phase II"[tiab] OR "phase III"[tiab] OR "phase IV"[tiab] OR "clinical study"[tiab] OR "controlled study"[tiab] OR "controlled design"[tiab] OR multicenter[tiab] OR multicentre[tiab] OR "multi center"[tiab] OR "multi centre"[tiab] OR "open label"[tiab] OR "parallel group*"[tiab] OR "double blind*"[tiab] OR "single blind"[tiab] OR compare[ti] OR compared[ti] OR comparison[ti]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])
AND	
Concept 3: Anti-IL-1 therapy	("Interleukin 1 Receptor Antagonist Protein"[Mesh] OR “interleukin 1 receptor antagonist”[tiab] OR “IL 1 receptor antagonist”[tiab] OR “IL1 receptor antagonist”[tiab] OR “IL1 Febrile Inhibit*”[tiab] OR “IL 1 febrile inhibit*”[tiab] OR “interleukin 1 febrile inhibit*”[tiab] OR IL1Ra[tiab] OR “IL-1Ra”[tiab] OR “interleukin 1ra”[tiab] OR “IL1 Inhibit*”[tiab] OR “IL 1 Inhibit*”[tiab] OR “interleukin 1 Inhibit*”[tiab] OR antril[tiab] OR amtril[tiab] OR kineret[tiab] OR anakinra[tiab] OR “interleukin 1 receptor block*”[tiab] OR “IL 1 receptor block*”[tiab] OR “IL1 receptor block*”[tiab] OR “interleukin 1 antagonist”[tiab] OR “IL 1 antagonist”[tiab] OR “IL1 antagonist”[tiab])
Concept 4: Anti-IL-6 therapy	((("Interleukin-6"[Mesh] OR "IL-6"[tiab] OR IL6[tiab] OR "interleukin 6"[tiab] OR "BSF-2"[tiab] OR "Hybridoma Growth Factor"[tiab] OR "Plasmacytoma Growth Factor"[tiab] OR "Hepatocyte Stimulating Factor"[tiab] OR "MGI-2"[tiab] OR "Myeloid Differentiation-Inducing Protein"[tiab] OR "Myeloid Differentiation Inducing Protein"[tiab] OR "B Cell Differentiation Factor"[tiab] OR "Interferon beta 2"[tiab] OR "IFN-beta 2"[tiab] OR "IFN b 2"[tiab] OR "B Cell Stimulatory Factor 2"[tiab] OR "Receptors, Interleukin-6"[Mesh] OR "antigen cd126"[tiab] OR "cd126 antigen"[tiab] OR "IL6R"[tiab] OR "IL 6R"[tiab]) AND ("Antibodies, Monoclonal"[Mesh:NoExp] OR "Antibodies, Monoclonal, Humanized"[Mesh:NoExp] OR "Antibodies, Monoclonal, Murine-Derived"[Mesh:NoExp] OR antibod*[tiab] OR antagon*[tiab] OR inhibit*[tiab] OR block*[tiab])) OR "anti-interleukin-6"[tiab] OR "anti-IL-6"[tiab] OR "anti-IL6"[tiab] OR "tocilizumab" [Supplementary Concept] OR Tocilizumab[tiab] OR atlizumab[tiab] OR Actemra[tiab] OR Roactemra[tiab] OR luzinex[tiab] OR "sarilumab" [Supplementary Concept] OR sarilumab[tiab] OR kevzara[tiab] OR "regn 88"[tiab] OR regn88[tiab] OR "sar 153191"[tiab] OR sar153191[tiab] OR "siltuximab" [Supplementary Concept] OR Siltuximab[tiab] OR CLLB8[tiab] OR Sylvant[tiab] OR "CNTO-328"[tiab] OR CNTO328[tiab])
Concept 5: Other monoclonal antibodies (COVID-19 concept incorporated – no need to add Concept 1)	((((("COVID-19"[MeSH] OR nCoV[all] OR 2019nCoV[all] OR COVID[all] OR COVID19[all] OR "SARS-Cov-2"[MeSH] 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 ("Antibodies, Monoclonal"[Mesh:NoExp] OR "Antibodies, Monoclonal, Humanized"[Mesh:NoExp] OR "Antibodies, Monoclonal, Murine-Derived"[Mesh:NoExp] OR "monoclonal antibod*"[tiab] OR "humanized antibod*"[tiab] OR "humanised antibod*"[tiab])) OR "anti-HCoV-19"[tiab] OR "anti-nCoV-2019"[tiab] OR "anti-SARS-CoV-2"[tiab] OR "anti-SARS-CoV2"[tiab] OR "anti-SARS2"[tiab] OR "anti-severe acute respiratory syndrome coronavirus 2"[tiab] OR "COVID-19 virus antibod*"[tiab] OR "HCoV-19 antibod*"[tiab] OR "nCoV-2019 antibod*"[tiab] OR "SARS-CoV-2 antibod*"[tiab] OR "SARS2 antibod*"[tiab] OR "SARS2 virus antibod*"[tiab] OR "severe acute respiratory syndrome coronavirus 2 antibod*"[tiab] OR "bamlanivimab" [Supplementary Concept] OR Bamlanivimab[tiab] OR "LY-3819253"[tiab] OR "LY-COV555"[tiab] OR "LY COV

	555"[tiab] OR LYCOV555[tiab] OR LY3819253[tiab] OR "cilgavimab" [Supplementary Concept] OR Cilgavimab[tiab] OR "azd 1061"[tiab] OR "azd1061"[tiab] OR "cilgavimab and tixagevimab drug combination" [Supplementary Concept] OR AZD7442[tiab] OR "AZD 7442"[tiab] OR "bamlanivimab and etesevimab drug combination" [Supplementary Concept] OR "etesevimab" [Supplementary Concept] OR etesevimab[tiab] OR "LY CoV016"[tiab] OR "LY CoV 016"[tiab] OR "LYCoV016"[tiab] OR "JS016"[tiab] OR "JS 016"[tiab] OR "LY3832479"[tiab] OR "LY 3832479"[tiab] OR "cb 6"[tiab] OR "cb6"[tiab] OR "np 005"[tiab] OR "np005"[tiab] OR "sotrovimab" [Supplementary Concept] OR sotrovimab[tiab] OR "GSK-4182136"[tiab] OR GSK4182136[tiab] OR "VIR-7831"[tiab] OR "VIR7831"[tiab] OR "casirivimab" [Supplementary Concept] OR casirivimab[tiab] OR "REGN-10933"[tiab] OR "REGN10933"[tiab] OR "imdevimab" [Supplementary Concept] OR "imdevimab"[tiab] OR "REGN-10987"[tiab] OR "REGN10987"[tiab] OR "casirivimab and imdevimab drug combination" [Supplementary Concept] OR "REGN-COV"[tiab] OR "REGN-COV2"[tiab] OR "REGEN-COV"[tiab] OR "REGEN-COV2"[tiab] OR "regdanvimab" [Supplementary Concept] OR "regdanvimab"[tiab] OR "CT P59"[tiab] OR "CTP 59"[tiab] OR "CTP59"[tiab] OR "tixagevimab" [Supplementary Concept] OR "tixagevimab"[tiab] OR "azd 8895"[tiab] OR "azd8895"[tiab]) AND 2019/12[EDAT]:2030[EDAT])
Concept 6: 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 7: Colchicine	("Colchicine"[Mesh] OR colchicin*[tiab] OR colchin*[tiab] OR colchichin*[tiab] OR colchily[tiab] OR colchimedio[tiab] OR colchiquim[tiab] OR colchisol[tiab] OR colchysat[tiab] OR colcin*[tiab] OR colcrys[tiab] OR colctab[tiab] OR colgout[tiab] OR colrefuz[tiab] OR gloperba[tiab] OR goutichin*[tiab] OR goutnil[tiab] OR kolkicin*[tiab] OR kolkisin*[tiab] OR mitigare[tiab] OR “mpc 004”[tiab] OR mpc004[tiab] OR “nsc 757”[tiab] OR nsc757[tiab] OR tolchicin*[tiab])
Concept 8: JAK inhibitors	("Janus Kinase Inhibitors"[Mesh] OR "Janus Kinases/antagonists and inhibitors"[Mesh] OR "jak inhibit*"[tiab] OR "janus kinase inhibit*"[tiab] OR "janus tyrosine kinase inhibit*"[tiab] OR "jak 1 inhibit*"[tiab] OR "jak1 inhibit*"[tiab] OR "janus kinase 1 inhibit*"[tiab] OR "janus tyrosine kinase 1 inhibit*"[tiab] OR "jak 2 inhibit*"[tiab] OR "jak2 inhibit*"[tiab] OR "janus kinase 2 inhibit*"[tiab] OR "janus tyrosine kinase 2 inhibit*"[tiab] OR "janus kinase 1 2 inhibit*"[tiab] OR "janus tyrosine kinase 1 2 inhibit*"[tiab] OR "jak 3 inhibit*"[tiab] OR "jak3 inhibit*"[tiab] OR "janus kinase 3 inhibit*"[tiab] OR "janus tyrosine kinase 3 inhibit*"[tiab] OR jakinib*[tiab] OR "TYK2 inhibit*"[tiab] OR "TYK2 kinase inhibit*"[tiab] OR "tyrosine kinase 2 inhibit*"[tiab] OR "INCB018424" [Supplementary Concept] OR Ruxolitinib[tiab] OR "INCB-018424"[tiab] OR "INCB018424"[tiab] OR "INCB-18424"[tiab] OR "INCB18424"[tiab] OR INCA24[tiab] OR "INCA 24"[tiab] OR "inc 424"[tiab] OR inc424[tiab] OR "incb 424"[tiab] OR incb424[tiab] OR Jakafi[tiab] OR jakavi[tiab] OR deuruxolitinib[tiab] OR "baricitinib" [Supplementary Concept] OR Baricitinib[tiab] OR "INCB-28050"[tiab] OR "INCB28050"[tiab] OR "Olumiant"[tiab] OR "INCB028050"[tiab] OR "INCB-028050"[tiab] OR "LY3009104"[tiab] OR "LY-3009104"[tiab] OR Brepocitinib[tiab] OR "PF-06700841"[tiab] OR "PF06700841"[tiab] OR "delgocitinib" [Supplementary Concept] OR delgocitinib[tiab] OR "JTE-052"[tiab] OR JTE052[tiab] OR "leo 124249"[tiab] OR leo124249[tiab] OR Deucravacitinib[tiab] OR "bms 986165"[tiab] OR "bms 98616501"[tiab] OR bms986165[tiab] OR bms98616501[tiab] OR "tyk2-in-4"[tiab] OR "Fedratinib" [Supplementary Concept] OR fedratinib[tiab] OR TG101348[tiab] OR "TG 101348"[tiab] OR SAR302503[tiab] OR "SAR 302503"[tiab] OR Inrebic[tiab] OR Fosifidancitinib[tiab] OR "gusacitinib" [Supplementary Concept] OR "gusacitinib"[tiab]

	OR "asn 002"[tiab] OR asn002[tiab] OR "en 3351"[tiab] OR "en3351"[tiab] OR Ilginatinib[tiab] OR "ns 018"[tiab] OR ns018[tiab] OR "itacitinib" [Supplementary Concept] OR "itacitinib"[tiab] OR "incb 039110"[tiab] OR "incb 39110"[tiab] OR incb039110[tiab] OR incb39110[tiab] OR "Izencitinib"[tiab] OR "jnj 8398"[tiab] OR jnj8398[tiab] OR "td 1473"[tiab] OR td1473[tiab] OR "abrocitinib" [Supplementary Concept] OR abrocitinib[tiab] OR "pf 04965842"[tiab]OR "pf 4965842"[tiab] OR "pf04965842"[tiab] OR "pf4965842"[tiab] OR "GLPG0634" [Supplementary Concept] OR filgotinib[tiab] OR "g 146034"[tiab] OR "g146034"[tiab] OR "glpg 0634"[tiab] OR "glpg0634"[tiab] OR "gs 6034"[tiab] OR "gs6034"[tiab] OR "jyseleca"[tiab] OR "Lorpucitinib"[tiab] OR "N-(cyanomethyl)-4-(2-((4-(4-morpholinyl)phenyl)amino)-4-pyrimidinyl)benzamide" [Supplementary Concept] OR "cyt 387"[tiab] OR "cyt387"[tiab] OR "momelotinib"[tiab] OR "tofacitinib" [Supplementary Concept] OR Tofacitinib[tiab] OR "tasocitinib"[tiab] OR "Xeljanz"[tiab] OR "CP690 550"[tiab] OR "CP 690 550"[tiab] OR "CP690550"[tiab] OR "CP 690550"[tiab] OR Nezulcitinib[tiab] OR "TD 0903"[tiab] OR "R333" [Supplementary Concept] OR R333[tiab] OR "upadacitinib" [Supplementary Concept] OR upadacitinib[tiab] OR "ABT-494"[tiab] OR "ABT494"[tiab] OR Rinvoq[tiab])
Concept 9: Convalescent plasma	("COVID-19 serotherapy"[Supplementary Concept] OR serotherap*[tiab] OR “serum therap*”[tiab] OR “convalescent serum”[tiab] OR “convalescent sera”[tiab] OR “hyperimmune globulin therap*”[tiab] OR “convalescent plasma“[tiab] OR "Immunization, Passive"[Mesh] OR “passive immunization*”[tiab] OR “passive immunisation*”[tiab] OR “passive antibody transfer*”[tiab] OR “passive transfer of immunity”[tiab] OR “passive immunotherap*”[tiab] OR “adoptive transfer*”[tiab] OR “adoptive cell transfer*”[tiab] OR “adoptive immunotherap*”[tiab] OR “adoptive cellular immunotherap*”[tiab] “convalescence phase plasma” [tiab] OR “convalescent human plasma” [tiab] OR “convalescent immune plasma”[tiab] OR “convalescent patient plasma”[tiab] OR “convalescent phase plasma”[tiab] OR “plasma from convalescent*” [tiab] OR “passive immune therap*”[tiab] OR “passive immunity therap*”[tiab] OR “passive immunization therap*”[tiab] OR “passive immuno-therap*”[tiab] OR “passive immunoglobulin therap*”[tiab] OR “CP therap*”[tiab] OR “CP immunotherap*”[tiab] OR “CP transfusion”[tiab] OR CPT[tiab] OR “passive immunity transfer”[tiab] OR “passively acquired immunity”[tiab] OR “passive immunity”[tiab] OR “adoptive immunisation”[tiab] OR “adoptive immunization”[tiab] OR “plasma transfusion*”[tiab] OR “plamsa infusion*”[tiab] OR “serum transfusion*”[tiab] OR “serum infusion*”[tiab] OR “CP transfusion*”[tiab] OR CPT[tiab])
Concept 10: Anti-coagulation	"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 11: Ventilation	"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 “hyperbaric oxygenation”[tiab] OR PEEP[tiab] OR “positive end expiratory pressure breathing”[tiab] OR HFNC[tiab] OR “high flow nasal cannula”[tiab] OR "Oxygen Inhalation Therapy"[Mesh] OR “oxygen inhalation”[tiab] OR “HF oxygen*”[tiab] OR HFNCT[tiab] OR “high flow nasal prong”[tiab] OR “high flow nasal therap*”[tiab] OR “high flow oxygen*”[tiab] OR “highflow nasal cannula”[tiab] OR “highflow nasal prong”[tiab] OR “highflow nasal therap*”[tiab] OR “highflow oxygen*”[tiab] OR “HFHHNC ventilation”[tiab] OR HHFNC[tiab] OR “high flow high humidity nasal cannula”[tiab] OR “high flow humidified nasal cannula”[tiab] OR “humidified high flow cannula”[tiab] OR “humidified high flow nasal cannula”[tiab] OR “highflow high humidity nasal cannula”[tiab] OR “highflow humidified nasal cannula”[tiab] OR “humidified highflow cannula”[tiab] OR “humidified highflow nasal cannula”[tiab] OR THRIVE[tiab] OR “transnasal humidified rapid insufflation ventilatory exchange”[tiab] OR “trans-nasal humidified rapid insufflation ventilatory exchange”[tiab] OR “trans-nasal rapid insufflation ventilatory exchange”[tiab] OR “transnasal rapid insufflation ventilatory exchange”[tiab]

EMBASE search strings

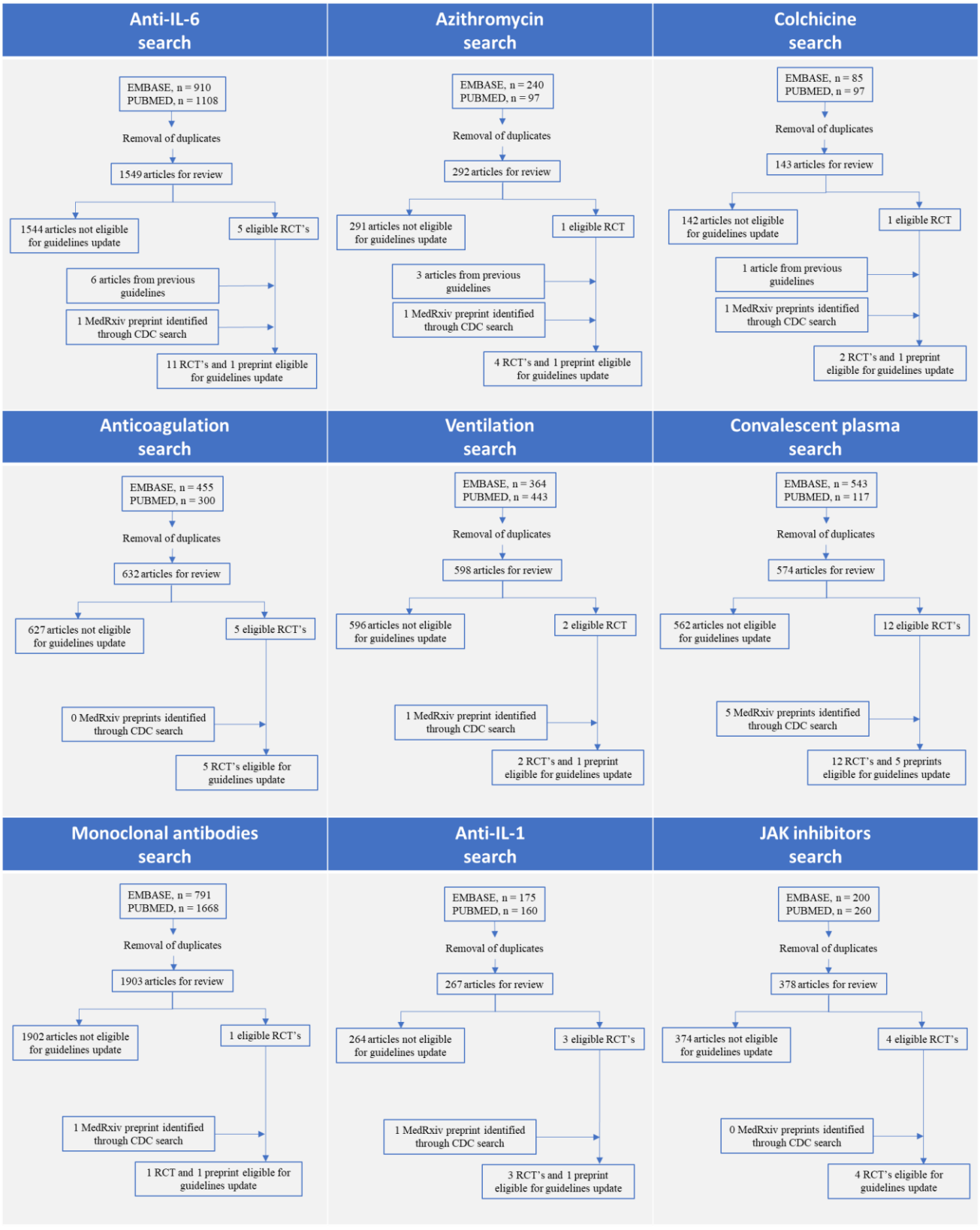
Concept 1: COVID	(('coronavirus disease 2019'/exp OR ncov:ti,ab,kw,ff OR 2019ncov:ti,ab,kw,ff OR covid:ti,ab,kw,ff OR covid19:ti,ab,kw,ff OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'severe acute respiratory syndrome coronavirus 2':ti,ab,kw,ff OR 'sars cov 2':ti,ab,kw,ff OR sars2:ti,ab,kw,ff 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 [2019-2022]/py)
AND	
Concept 2: RCT	(('clinical trial'/exp OR placebo:ti,ab,kw OR random*:ti,ab,kw OR trial:ti,ab,kw OR groups:ti,ab,kw OR 'phase 1':ti,ab,kw OR 'phase 2':ti,ab,kw OR 'phase 3':ti,ab,kw OR 'phase 4':ti,ab,kw OR 'phase I':ti,ab,kw OR 'phase II':ti,ab,kw OR 'phase III':ti,ab,kw OR 'phase IV':ti,ab,kw OR 'clinical study':ti,ab,kw OR 'controlled study':ti,ab,kw OR 'controlled design':ti,ab,kw OR multicenter:ti,ab,kw OR multicentre:ti,ab,kw OR 'multi center':ti,ab,kw OR 'multi centre':ti,ab,kw OR 'open label':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'double blind*':ti,ab,kw OR 'single blind*':ti,ab,kw OR compare:ti OR compared:ti OR comparison:ti) NOT 'conference abstract':it)
AND	
Concept 3: Anti-IL-1 therapy	('anakinra'/exp OR anakinra:ti,ab,kw OR kineret:ti,ab,kw OR ‘ interleukin 1 receptor antagonist’:ti,ab,kw OR ‘IL 1 receptor antagonist’:ti,ab,kw OR ‘IL1 receptor antagonist’:ti,ab,kw OR ‘interleukin 1 receptor block*’:ti,ab,kw OR ‘IL 1 receptor block*’:ti,ab,kw OR ‘IL1 receptor block*’:ti,ab,kw OR 'interleukin 1 receptor blocking agent'/exp OR amtril:ti,ab,kw OR antril:ti,ab,kw OR ‘il 1ra’:ti,ab,kw OR ‘il1ra’:ti,ab,kw OR ‘interleukin 1 antagonist’:ti,ab,kw OR ‘IL 1 antagonist’:ti,ab,kw OR ‘IL1 antagonist’:ti,ab,kw OR ‘interleukin 1ra’:ti,ab,kw OR ‘IL1 Febrile Inhibit*’:ti,ab,kw OR ‘IL 1

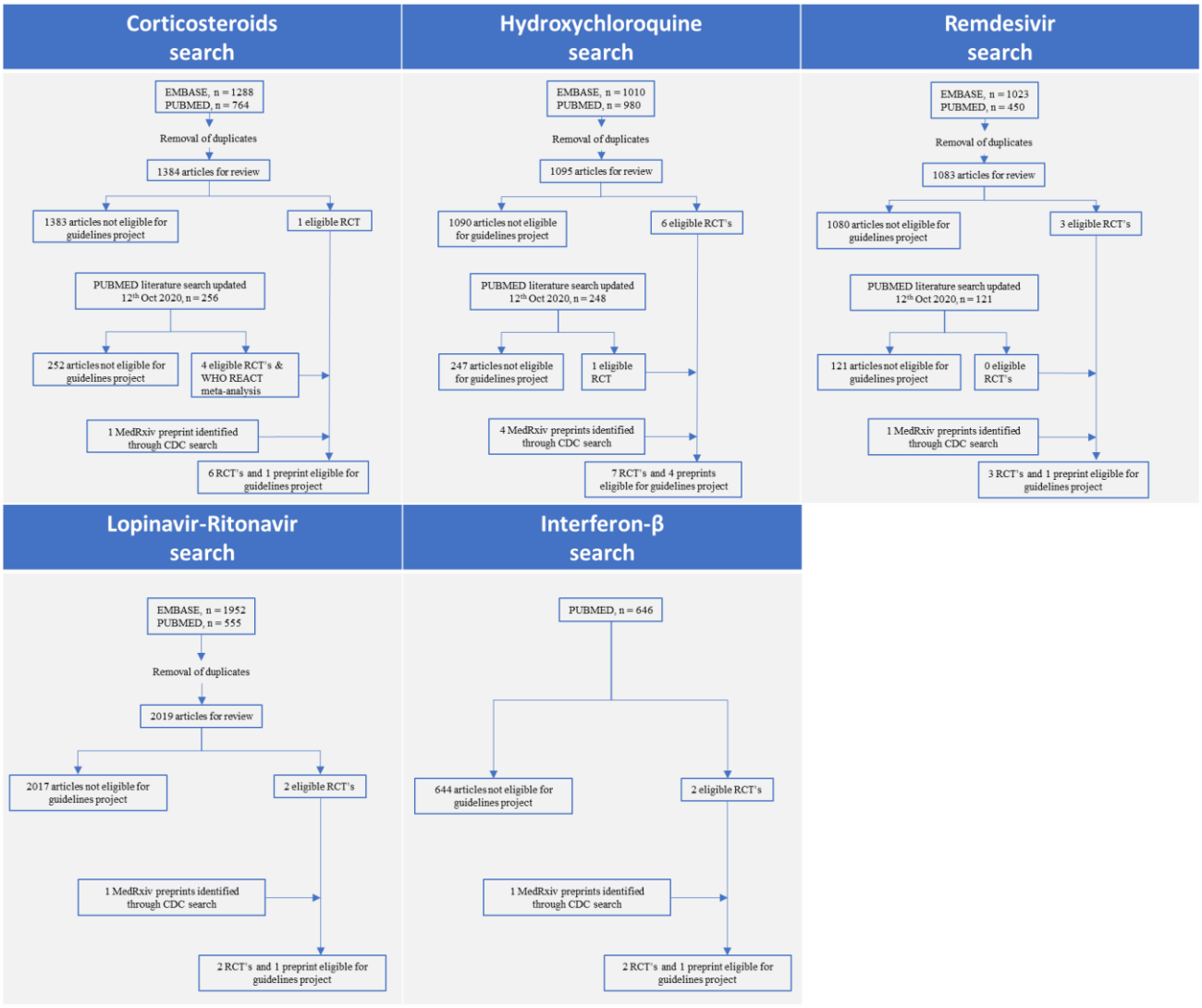
	febrile inhibit*’:ti,ab,kw OR ‘interleukin 1 febrile inhibit*’:ti,ab,kw OR ‘interleukin 1ra’:ti,ab,kw OR ‘IL1 Inhibit*’:ti,ab,kw OR ‘IL 1 Inhibit*’:ti,ab,kw OR ‘interleukin 1 Inhibit*’:ti,ab,kw)
Concept 4: Anti-IL-6 therapy	((('interleukin 6'/exp OR 'IL-6':ti,ab,kw OR IL6:ti,ab,kw OR 'interleukin 6':ti,ab,kw OR 'BSF-2':ti,ab,kw OR 'Hybridoma Growth Factor':ti,ab,kw OR 'Plasmacytoma Growth Factor':ti,ab,kw OR 'Hepatocyte Stimulating Factor':ti,ab,kw OR 'MGI-2':ti,ab,kw OR 'Myeloid Differentiation-Inducing Protein':ti,ab,kw OR 'Myeloid Differentiation Inducing Protein':ti,ab,kw OR 'B Cell Differentiation Factor':ti,ab,kw OR 'Interferon beta 2':ti,ab,kw OR 'IFN-beta 2':ti,ab,kw OR 'IFN b 2':ti,ab,kw OR 'B Cell Stimulatory Factor 2':ti,ab,kw OR 'interleukin 6 receptor'/exp OR 'antigen cd126':ti,ab,kw OR 'cd126 antigen':ti,ab,kw OR 'IL6R':ti,ab,kw OR 'IL 6R':ti,ab,kw) AND ('monoclonal antibody'/de OR 'human monoclonal antibody'/exp OR antibod*:ti,ab,kw OR antagon*:ti,ab,kw OR inhibit*:ti,ab,kw OR block*:ti,ab,kw)) OR 'interleukin 6 antibody'/exp OR 'anti-interleukin-6':ti,ab,kw OR 'anti-IL-6':ti,ab,kw OR 'anti-IL6':ti,ab,kw OR 'tocilizumab'/exp OR Tocilizumab:ti,ab,kw OR atlizumab:ti,ab,kw OR Actemra:ti,ab,kw OR Roactemra:ti,ab,kw OR luzinex:ti,ab,kw OR 'sarilumab'/exp OR sarilumab:ti,ab,kw OR kevzara:ti,ab,kw OR 'regn 88':ti,ab,kw OR regn88:ti,ab,kw OR 'sar 153191':ti,ab,kw OR sar153191:ti,ab,kw OR 'siltuximab'/exp OR Siltuximab:ti,ab,kw OR CLLB8:ti,ab,kw OR Sylvant:ti,ab,kw OR 'CNTO 328':ti,ab,kw OR CNTO328:ti,ab,kw)
Concept 5: Other monoclonal antibodies	((((('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 ('monoclonal antibody'/de OR 'human monoclonal antibody'/exp OR 'monoclonal antibod*':ti,ab,kw OR 'humanized antibod*':ti,ab,kw OR 'humanised antibod*':ti,ab,kw)) OR 'SARS-CoV-2 antibody'/exp OR 'anti-HCoV-19':ti,ab,kw OR 'anti-nCoV-2019':ti,ab,kw OR 'anti-SARS-CoV-2':ti,ab,kw OR 'anti-SARS-CoV2':ti,ab,kw OR 'anti-SARS2':ti,ab,kw OR 'anti-severe acute respiratory syndrome coronavirus 2':ti,ab,kw OR 'COVID-19 virus antibod*':ti,ab,kw OR 'HCoV-19 antibod*':ti,ab,kw OR 'nCoV-2019 antibod*':ti,ab,kw OR 'SARS-CoV-2 antibod*':ti,ab,kw OR 'SARS2 antibod*':ti,ab,kw OR 'SARS2 virus antibod*':ti,ab,kw OR 'severe acute respiratory syndrome coronavirus 2 antibod*':ti,ab,kw OR Bamlanivimab:ti,ab,kw OR 'LY-3819253':ti,ab,kw OR 'LY COV555':ti,ab,kw OR 'LY COV 555':ti,ab,kw OR LYCOV555:ti,ab,kw OR LY3819253:ti,ab,kw OR Cilgavimab:ti,ab,kw OR 'azd 1061':ti,ab,kw OR azd1061:ti,ab,kw OR etesevimab:ti,ab,kw OR 'LY CoV016':ti,ab,kw OR 'LY CoV 016':ti,ab,kw OR 'LYCoV016':ti,ab,kw OR 'JS016':ti,ab,kw OR 'JS 016':ti,ab,kw OR 'LY3832479':ti,ab,kw OR 'LY 3832479':ti,ab,kw OR 'cb 6':ti,ab,kw OR 'cb6':ti,ab,kw OR 'np 005':ti,ab,kw OR 'np005':ti,ab,kw OR sotrovimab:ti,ab,kw OR 'GSK 4182136':ti,ab,kw OR GSK4182136:ti,ab,kw OR 'VIR 7831':ti,ab,kw OR 'VIR7831':ti,ab,kw OR casirivimab:ti,ab,kw OR 'REGN-10933':ti,ab,kw OR 'REGN10933':ti,ab,kw OR 'imdevimab':ti,ab,kw OR 'REGN 10987':ti,ab,kw OR 'REGN10987':ti,ab,kw OR 'REGN-COV':ti,ab,kw OR 'REGN-COV2':ti,ab,kw OR 'REGEN-COV':ti,ab,kw OR 'REGEN-COV2':ti,ab,kw OR 'regdanvimab':ti,ab,kw OR 'CT P59':ti,ab,kw OR 'CTP 59':ti,ab,kw OR 'CTP59':ti,ab,kw OR 'tixagevimab':ti,ab,kw OR 'azd 8895':ti,ab,kw OR 'azd8895':ti,ab,kw) AND [2019-2022]/py)
Concept 6: 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 7: Colchicine	('colchicine'/exp OR colchicin*:ti,ab,kw OR colchin*:ti,ab,kw OR colchichin*:ti,ab,kw OR colchily:ti,ab,kw OR colchimedio:ti,ab,kw OR colchiquim:ti,ab,kw OR colchisol:ti,ab,kw OR colchysat:ti,ab,kw OR colcin*:ti,ab,kw OR colcrys:ti,ab,kw OR colctab:ti,ab,kw OR colgout:ti,ab,kw OR colrefuz:ti,ab,kw OR gloperba:ti,ab,kw OR goutichin*:ti,ab,kw OR goutnil:ti,ab,kw OR kolkicin*:ti,ab,kw OR kolkisin*:ti,ab,kw OR mitigare:ti,ab,kw OR 'mpc 004':ti,ab,kw OR mpc004:ti,ab,kw OR 'nsc 757':ti,ab,kw OR nsc757:ti,ab,kw OR tolchicin*:ti,ab,kw)
Concept 8: JAK inhibitors	('Janus kinase inhibitor'/exp OR 'jak inhibit*':ti,ab,kw OR 'janus kinase inhibit*':ti,ab,kw OR 'janus tyrosine kinase inhibit*':ti,ab,kw OR 'jak 1 inhibit*':ti,ab,kw OR 'jak1 inhibit*':ti,ab,kw OR 'janus kinase 1 inhibit*':ti,ab,kw OR 'janus tyrosine kinase 1 inhibit*':ti,ab,kw OR 'jak 2 inhibit*':ti,ab,kw OR 'jak2 inhibit*':ti,ab,kw OR 'janus kinase 2 inhibit*':ti,ab,kw OR 'janus tyrosine kinase 2 inhibit*':ti,ab,kw OR 'jak 1 2 inhibit*':ti,ab,kw OR 'jak1 2 inhibit*':ti,ab,kw OR 'janus kinase 1 2 inhibit*':ti,ab,kw OR 'janus tyrosine kinase 1 2 inhibit*':ti,ab,kw OR 'jak 3 inhibit*':ti,ab,kw OR 'jak3 inhibit*':ti,ab,kw OR 'janus kinase 3 inhibit*':ti,ab,kw OR 'janus tyrosine kinase 3 inhibit*':ti,ab,kw OR jakinib*:ti,ab,kw OR 'TYK2 inhibit*':ti,ab,kw OR 'TYK2 kinase inhibit*':ti,ab,kw OR 'tyrosine kinase 2 inhibit*':ti,ab,kw OR Ruxolitinib:ti,ab,kw OR 'INCB-018424':ti,ab,kw OR 'INCB018424':ti,ab,kw OR 'INCB-18424':ti,ab,kw OR 'INCB18424':ti,ab,kw OR INCA24:ti,ab,kw OR 'INCA 24':ti,ab,kw OR 'inc 424':ti,ab,kw OR inc424:ti,ab,kw OR 'incb 424':ti,ab,kw OR incb424:ti,ab,kw OR Jakafi:ti,ab,kw OR jakavi:ti,ab,kw OR deuruxolitinib:ti,ab,kw OR Baricitinib:ti,ab,kw OR 'INCB-28050':ti,ab,kw OR 'INCB28050':ti,ab,kw OR 'Olumiant':ti,ab,kw OR 'INCB028050':ti,ab,kw OR 'INCB-028050':ti,ab,kw OR 'LY3009104':ti,ab,kw OR 'LY-3009104':ti,ab,kw OR Brepocitinib:ti,ab,kw OR 'PF-06700841':ti,ab,kw OR 'PF06700841':ti,ab,kw OR Delgocitinib:ti,ab,kw OR 'JTE 052':ti,ab,kw OR 'JTE052':ti,ab,kw OR 'leo 124249':ti,ab,kw OR leo124249:ti,ab,kw OR Deucravacitinib:ti,ab,kw OR 'bms 986165':ti,ab,kw OR 'bms 98616501':ti,ab,kw OR bms986165:ti,ab,kw OR bms98616501:ti,ab,kw OR 'tyk2-in-4':ti,ab,kw OR fedratinib:ti,ab,kw OR TG101348:ti,ab,kw OR 'TG 101348':ti,ab,kw OR SAR302503:ti,ab,kw OR 'SAR 302503':ti,ab,kw OR Inrebic:ti,ab,kw OR fosifidancitinib:ti,ab,kw OR 'gusacitinib':ti,ab,kw OR 'asn 002':ti,ab,kw OR asn002:ti,ab,kw OR 'en 3351':ti,ab,kw OR 'en3351':ti,ab,kw OR Ilginatinib:ti,ab,kw OR 'ns 018':ti,ab,kw OR ns018:ti,ab,kw OR 'itacitinib':ti,ab,kw OR 'incb 039110':ti,ab,kw OR 'incb 39110':ti,ab,kw OR incb039110:ti,ab,kw OR incb39110:ti,ab,kw OR 'Izencitinib':ti,ab,kw OR 'jnj 8398':ti,ab,kw OR jnj8398:ti,ab,kw OR 'td 1473':ti,ab,kw OR td1473:ti,ab,kw OR abrocitinib:ti,ab,kw OR 'pf 04965842':ti,ab,kw OR 'pf 4965842':ti,ab,kw OR 'pf04965842':ti,ab,kw OR 'pf4965842':ti,ab,kw OR 'filgotinib':ti,ab,kw OR 'g 146034':ti,ab,kw OR 'g146034':ti,ab,kw OR 'glpg 0634':ti,ab,kw OR 'glpg0634':ti,ab,kw OR 'gs 6034':ti,ab,kw OR 'gs6034':ti,ab,kw OR 'jyseleca':ti,ab,kw OR 'lorpucitinib':ti,ab,kw OR 'cyt 387':ti,ab,kw OR 'cyt387':ti,ab,kw OR 'momelotinib':ti,ab,kw OR Tofacitinib:ti,ab,kw OR 'tasocitinib':ti,ab,kw OR 'Xeljanz':ti,ab,kw OR 'CP690 550':ti,ab,kw OR 'CP 690 550':ti,ab,kw OR 'CP690550':ti,ab,kw OR 'CP 690550':ti,ab,kw OR Nezulcitinib:ti,ab,kw OR 'TD 0903':ti,ab,kw OR R333:ti,ab,kw OR upadacitinib:ti,ab,kw OR 'ABT494':ti,ab,kw OR 'ABT-494':ti,ab,kw OR Rinvoq:ti,ab,kw)
Concept 9: Convalescent plasma	('convalescent plasma'/exp OR 'convalescent plasma':ti,ab,kw OR 'convalescence phase plasma':ti,ab,kw OR 'convalescent human plasma':ti,ab,kw OR 'convalescent immune plasma':ti,ab,kw OR 'convalescent patient plasma':ti,ab,kw OR 'convalescent phase plasma':ti,ab,kw OR 'plasma from convalescent*':ti,ab,kw OR 'passive immunotherapy'/exp OR 'passive immunotherap*':ti,ab,kw OR 'passive immune therap*':ti,ab,kw OR 'passive immunity therap*':ti,ab,kw OR 'passive immunization therap*':ti,ab,kw OR 'passive immuno-therap*':ti,ab,kw OR 'passive immunoglobulin therap*':ti,ab,kw OR 'CP therap*':ti,ab,kw OR 'CP immunotherap*':ti,ab,kw OR 'CP transfusion':ti,ab,kw OR CPT:ti,ab,kw OR 'passive immunization'/exp OR 'passive immunization*':ti,ab,kw OR 'passive immunisation*':ti,ab,kw OR 'passive antibody transfer':ti,ab,kw OR 'passive immunity transfer':ti,ab,kw OR 'passively acquired immunity':ti,ab,kw OR 'passive immunity':ti,ab,kw OR 'adoptive immunotherapy'/exp OR 'adoptive immunotherap*':ti,ab,kw OR 'adoptive immunisation':ti,ab,kw OR 'adoptive immunization':ti,ab,kw OR 'adoptive transfer':ti,ab,kw OR 'serotherapy'/exp OR serotherap*:ti,ab,kw OR 'serum therap*':ti,ab,kw OR 'convalescent serum':ti,ab,kw OR 'convalescent sera':ti,ab,kw OR 'hyperimmune globulin therap*':ti,ab,kw OR 'passive transfer of immunity':ti,ab,kw OR 'adoptive cell transfer*':ti,ab,kw OR 'adoptive cellular immunotherap*':ti,ab,kw OR 'plasma transfusion'/exp OR 'plasma transfusion*':ti,ab,kw OR 'plamsa infusion*':ti,ab,kw OR 'serum transfusion*':ti,ab,kw OR 'serum infusion*':ti,ab,kw OR 'CP transfusion*':ti,ab,kw OR CPT:ti,ab,kw)
Concept 10: Anti-coagulation	'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
Concept 11: Ventilation	'positive end expiratory pressure'/exp OR 'positive end expiratory pressure’:ti,ab,kw OR ‘constant positive pressure breathing’:ti,ab,kw OR ‘continuous positive airway pressure’:ti,ab,kw OR ‘continuous positive pressure breathing’:ti,ab,kw OR CPAP:ti,ab,kw OR nCPAP:ti,ab,kw OR cppb:ti,ab,kw OR cppv:ti,ab,kw OR ‘hyperbaric respiration’:ti,ab,kw OR ‘hyperbaric ventilation’:ti,ab,kw OR ‘hyperbaric oxygen*’:ti,ab,kw OR PEEP:ti,ab,kw OR ‘positive end expiratory pressure breathing’:ti,ab,kw OR 'airway pressure release ventilation'/exp OR ‘airway pressure release ventilation’:ti,ab,kw OR APRV:ti,ab,kw OR 'high flow nasal cannula therapy'/exp OR ‘high flow nasal cannula’:ti,ab,kw OR HFNC:ti,ab,kw OR ‘HF oxygen therap*’:ti,ab,kw OR HFNCT:ti,ab,kw OR ‘high flow nasal prong’:ti,ab,kw OR ‘high flow nasal therap*’:ti,ab,kw OR ‘high flow oxygen*’:ti,ab,kw OR OR ‘highflow nasal cannula’:ti,ab,kw OR ‘highflow nasal prong’:ti,ab,kw OR ‘highflow nasal therap*’:ti,ab,kw OR ‘highflow oxygen*’:ti,ab,kw OR ‘ HFHHNC ventilation’:ti,ab,kw OR HHFNC:ti,ab,kw OR ‘high flow high humidity nasal cannula’:ti,ab,kw OR ‘high flow humidified nasal cannula’:ti,ab,kw OR ‘humidified high flow cannula’:ti,ab,kw OR ‘humidified high flow nasal cannula’:ti,ab,kw OR ‘highflow high humidity nasal cannula’:ti,ab,kw OR ‘highflow humidified nasal cannula’:ti,ab,kw OR ‘humidified highflow cannula’:ti,ab,kw OR ‘humidified highflow nasal cannula’:ti,ab,kw OR THRIVE:ti,ab,kw OR ‘transnasal humidified rapid insufflation ventilatory exchange’:ti,ab,kw OR ‘trans-nasal humidified rapid insufflation ventilatory exchange’:ti,ab,kw OR ‘trans-nasal rapid insufflation ventilatory exchange’:ti,ab,kw OR ‘transnasal rapid insufflation ventilatory exchange’:ti,ab,kw
At the end of the search strategy add: NOT ‘conference abstract’:it	

Flow charts – Outcomes from the systematic review Evidence to decision frameworks




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 2020, 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
Hydroxychloroquine 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
PUBMED literature search updated 12th Oct 2020, n = 248
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
Remdesivir 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 2020, 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
Lopinavir-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
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

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 variability ○ No known undesirable outcomes	There is no uncertainty or variability about how clinicians and patients value mortality.

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	There are no implementation concerns as this therapy is widely used.

	○ Varies ○ 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

Problem Is the problem a priority?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes. There is a need for additional anti-inflammatory/immunomodulatory treatments for hospitalised patients with COVID-19. Evidence suggests the involvement of Interleukin-6 in the pathogenesis of severe COVID-19. This has led to the use of anti-IL-6 therapies in clinical practice. There is therefore a need to know whether these treatments improve clinical outcomes such as mortality or requirement for mechanical ventilation.
Desirable Effects How substantial are the desirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Although no significant mortality decrease was found using the prespecified level of statistical significance a trend towards mortality reduction could be seen in the meta-analysis with many of the studies seen to be favouring the intervention. The largest trial contributing to the meta-analysis showed a statistically significant reduction in mortality. This was confirmed when mortality was combined with mechanical ventilation and/or ECMO. In these composite endpoints a significant reduction in progression towards mechanical ventilation, ECMO or death was seen. Significant but smaller positive effects were seen in time to hospital discharge, time to ICU discharge and time to improvement on an ordinal scale in the meta-analysis.

Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large ○ Moderate • Small ○ Trivial ○ Varies ○ Don't know	We can conclude with moderate certainty that no increase in adverse or serious adverse events was noted. Clinical experience suggests that IL-6 receptor antagonist treatment can be associated with a significant increase in bacterial infections, although this was not seen in the randomised trials.	There is however serious imprecision as the confidence intervals both show beneficial and detrimental effects.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ○ Low ○ Moderate • High ○ No included studies	With the addition of 4 further trials since the previous guideline, the panel rate the certainty of evidence as high as no major risk of bias, inconsistency, indirectness or imprecision could be identified in the majority of studies. Overall, we would score the certainty of evidence as high.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	All variables were deemed to be important or critical. Patient input confirmed that mortality or requirement for mechanical ventilation were key outcomes.

• No important uncertainty or variability	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention • Favors the intervention ○ Varies ○ Don't know	There's a non-significant increase in adverse events with no effect on serious adverse events but with a significant effect on important and critical outcome measures such as: the combined outcomes of progression towards mechanical ventilation, ECMO or death; the combined outcome of mechanical ventilation or death and mechanical ventilation. A trend towards mortality reduction was seen and a small but significant effect was seen on other variables such as time to hospital discharge, time to ICU discharge and time to improvement on an ordinal scale.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings • Varies ○ Don't know	IL6-receptor antagonists are expensive, however they are relatively straightforward to administer in a hospital environment. The cost savings have not been fully quantified but reducing mortality and requirement for ICU admission is likely to offset some of the costs of therapy.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE

○ Very low ○ Low ○ Moderate ○ High ● No included studies	No studies tackled the cost-effectiveness of IL6-receptor antagonists.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	The positive effect on mechanical ventilation, ECMO, death, as well as time to hospital or ICU discharge and clinical improvement need to be weighed against the cost of the treatment. All these factors will vary significantly based on country and hospital setting. Further economic analysis is warranted. No studies included evaluated this aspect.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE
○ Reduced ● Probably reduced ○ Probably no impact	This is an expensive therapy that may not be available in all countries or regions of the world. There is therefore a risk that recommending this therapy will decrease health equity unless measures are taken to ensure broad access.

○ Probably increased ○ Increased ○ Varies ○ Don't know	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	The treatment has been used for other disease and is likely to be acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	IL6-receptor antagonists are easy to administer and therefore feasible to implement in practice.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

The panel recommends offering IL-6 receptor antagonist monoclonal antibody therapy to hospitalised patients with COVID-19 requiring oxygen or ventilatory support who have received systematic corticosteroids (Strong recommendation, high 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)

Justification

The panel found a large volume of evidence supporting beneficial effects of IL-6 receptor antagonist monoclonal antibodies in COVID-19. The benefits are have the potential to significantly impact upon mortality and requirement for critical care in hospitalised patients. The adverse events were few and no increase in serious adverse events was observed. Therefore the balance of risk and benefit clearly favours the intervention. The benefit of IL-6 receptor antagonists is only seen in patients who have also received corticosteroids and therefore this treatment should be administered alongside or in addition to corticosteroids.

Subgroup considerations

No further specific subgroup considerations.

Implementation considerations

Further research on cost-effectiveness is warranted as well as studies to establish the relative benefit of IL-6 therapy compared to other emerging anti-inflammatory treatments.

Monitoring and evaluation

Tocilizumab was most often prescribed as a 8 mg/kg dose IV over 1 hour (with a maximum of 800mg). This dose could be repeated after 12-24 hours depending on the evolution of the patient. In some studies, a lower dose was used due to cost and supply considerations (6mg/kg with a maximum dose of 480mg or a flat dose of 400mg). Sarilumab was used in studies in both 400mg and 200mg intravenously or subcutaneously.

Research priorities

Due to the cost of the treatment, further cost-effectiveness trials are warranted.

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	Hydroxychloroquine is widely available for appropriate use but is not recommended for COVID-19 due to safety reasons.

	○ Varies ○ 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

Problem Is the problem a priority?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes. There is a need for additional anti-inflammatory/immunomodulatory treatments for hospitalised patients with COVID-19. Evidence suggests that azithromycin has anti-inflammatory effects which has led some to use it for treatment of SARS-CoV-2. There is therefore a need to know whether these treatments improve clinical outcomes such as mortality or requirement for mechanical ventilation.
Desirable Effects How substantial are the desirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No significant improvements were seen in any outcomes after the administration of azithromycin.
Undesirable Effects How substantial are the undesirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**

○ Large • Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	There was no significant increase in adverse events noted in the included trials.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ○ Low • Moderate ○ High ○ No included studies	The previous guidelines noted low certainty of evidence however with the addition of RECOVERY and ATOMIC2 (additional 8000 patients) the certainty has improved in all outcomes.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	All variables were deemed to be important or critical as assessed by the panel and patient.

• No important uncertainty or variability	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison • Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Azithromycin is generally safe to use, however as no beneficial evidence for its use in COVID-19 has yet been found when no underlying infection is present, it is not recommended for use so as to avoid unnecessary side efects.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Large costs • Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Azithromycin is readily available and relatively inexpensive

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE

○ Very low ○ Low • Moderate ○ High ○ No included studies	Azithromycin is used for other conditions and is widely available

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison • Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Azithromycin is inexpensive but with no clinical benefit, there is no cost saving through its use.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE
○ Reduced ○ Probably reduced • Probably no impact	Health equity would be increased only for those treated with an additional underlying bacterial infection and not for those whose primary condition is SARS-CoV-2.

○ Probably increased ○ Increased ○ Varies ○ Don't know	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no • Probably yes ○ Yes ○ Varies ○ Don't know	yes, the treatment is widely used.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	yes, the treatment is widely used and available.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

●	○	○	○	○

CONCLUSIONS

Recommendation

The panel suggest the recommendations issued from the original guidelines remain in place - treatment should only be given to those who have underlying bacterial infection.

Justification

Original guideline justification remains; 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. The panel suggest the recommendations issued from the original guidelines remain in place - treatment should only be given to those who have underlying bacterial infection.

Subgroup considerations

No subgroup analysis has been performed.

Implementation considerations

It is not recommended that this intervention is implemented as a standard of care treatment for COVID-19

Monitoring and evaluation

Research priorities

It is not believed that any further studies of azithromycin for the treatment of COVID-19 are required or will change the recommendations.

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 randomised, 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

Problem Is the problem a priority?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes. There is a need for additional anti-inflammatory/immunomodulatory treatments for hospitalised patients with COVID-19. Colchicine has been shown to have anti-inflammatory effects in various models and is used for anti-inflammatory effects in gout. There is therefore a need to know whether these treatments improve clinical outcomes such as mortality or requirement for mechanical ventilation.
Desirable Effects How substantial are the desirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Despite one additional trial being added to the analysis since the original guidelines, the only significance treatment response was seen in "deterioration" (defined as 2 points on an ordinal scale) where in the colchicine arm, fewer patients showed deterioration (OR 0.11 (95% CI: 0.01 to 0.96)). This was based on small trials which were found to be of low methodological quality. Other important outcome measures were not significant. The majority of data informing this question were from the large RECOVERY trial which found no benefit of Colchicine compared to standard care.
Undesirable Effects How substantial are the undesirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**

○ Large • Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	The most prominent side-effects are diarrhoea which is a well known side effect of colchcine. Colchicine has an OR of 3.70 (95% CI: 1.68 to 8.16) indicating a substantially higher risk of diarrhoea.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ○ Low • Moderate ○ High ○ No included studies	Overall we deemed the certainty of the evidence moderate which has improved substantially since the original guidelines.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability • No important uncertainty or variability	All endpoints evaluated are rated as important or critical.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
• Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The absence of a significant effect on the majority of outcomes with only a significant effect on deteriorationg (2 points on an ordinal scale) but with a significant increase in diarrhoea, results in favoring the comparison group.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Large costs ○ Moderate costs • 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

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE

○ Very low ○ Low ○ Moderate • High ○ No included studies	Colchicine price is widely known to be cheap but the effects in clinical practice do not support its use.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
• Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Due to the lack of significant clinical effect but with relevant adverse effects (which also need treatment), this analysis probably favors the comparison although no formal economic analysis has been performed.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE
○ Reduced ○ Probably reduced • Probably no impact	No clinical significant effect in most outcome variables with increased adverse effects.

○ Probably increased ○ Increased ○ Varies ○ Don't know	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	Yes, widely used drug without issues around acceptability.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	yes

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
●	○	○	○	○

CONCLUSIONS

Recommendation

The panel recommend NOT to offer colchicine to hospitalised patient with COVID-19 infection (strong recommendation, moderate quality of evidence)

Justification

Colchicine had only an effect on deterioration (based on a 2 point difference on an ordinal scale) which was deemed an important outcome but failed to show an effect on all other important and critical outcomes. The largest randomised study convincingly showed not clinical benefits of treatment. Moreover a significant effect on increased adverse effects was noted (diarrhoea).

Subgroup considerations

Subgroup analyses did not identify a group of patients with a significant benefit from Colchicine.

Implementation considerations

Straightforward to implement if colchicine was shown to have a more pronounced beneficial effect.

Monitoring and evaluation

Dosage of colchicine differed across all three trials. Deftereos et al. used a 1.5-mg loading dose followed by 0.5 mg after 60 min and maintenance doses of 0.5 mg twice daily for three weeks, whereas Lopes et al. preferred a 0.5mg thrice daily for 5 days followed by 0.5mg twice daily for 5 days. Finally Horby et al. gave 1mg followed by 0.5mg 12 hours later and then 0.5mg twice daily for 10 days in total.

Research priorities

The panel suggests further trials of colchicine are not warranted in this patient population and recommends studying alternative anti-inflammatory and immunomodulatory agents.

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	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.

	○ Varies ○ 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 clearly show 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 randomised 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	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.

	○ Varies ○ 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 randomised 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	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.

	○ 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 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

Problem Is the problem a priority?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Clinicians and patients regard this question as a priority. Pulmonary embolism and other thrombotic complications have been reported frequently in patients with COVID-19 in hospital. There is wide variation in anticoagulation practice globally.
Desirable Effects How substantial are the desirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	We identified no trials of anticoagulation vs no anticoagulation but conducted analysis of high vs low dose anticoagulation. Although no reduction in mortality rate was seen in the trials, there were significant desirable effects noted in the reduction of major thrombotic events.
Undesirable Effects How substantial are the undesirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**

○ Large • Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	A significant rise in major bleeds was identified across all five studies

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ○ Low • Moderate ○ High ○ No included studies	The overall evidence is rated as moderate and high quality using the GRADE framework. Since the update of the guideline the confidence in the evidence has risen due to the availability of robust randomised controlled trials.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	Outcomes such as mortality are clearly recognised as important by patients and clinicians.

• No important uncertainty or variability	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the comparison • Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The panel feels that the reduction of thrombotic events with high dose anticoagulation is balanced by the increased risk of major bleeding with therapeutic anticoagulation dosing. Patients at highest risk, such as those with suspected PE, would be anticoagulated as standard and would not be included in trials.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Large costs ○ Moderate costs ○ Negligible costs and savings • 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.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE

○ Very low ○ Low • Moderate ○ High ○ No included studies	Although not formally established in COVID-19, studies on the cost effectiveness of prophylactic anticoagulation have been conducted in other contexts and it has been shown to be a cost-effective measure.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison • Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Although no specific data are available in COVID-19, it is highly likely that anticoagulation is cost-effective. It is also highly likely that performing future trials would not be regarded as ethical if comparing anticoagulation with no anticoagulation. The cost effectiveness of therapeutic dose vs prophylactic dose anticoagulation has not been established.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE
○ Reduced ○ Probably reduced • Probably no impact	None

○ Probably increased ○ Increased ○ Varies ○ Don't know	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	Anticoagulation is widely used in hospitalised patients and is both available and acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	Yes, the intervention of prophylactic anticoagulation is widely used in hospitalised patients worldwide. The patient representative confirmed that this was acceptable to patients.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**

○	○	○	○	●

CONCLUSIONS

Recommendation

The panel recommends offering a form of anticoagulation to hospitalised patients with COVID-19 (Strong recommendation, Moderate quality of evidence)

Justification

Although the amount of evidence is limited, 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.

As per the original guideline, 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 where clinicians may select one or the other depending on the individual risks of the individual for thrombotic complications vs bleeding complications.

Subgroup considerations

No subgroup analyses were completed.

Implementation considerations

As this is widely used and inexpensive, implementation should be straightforward

Monitoring and evaluation

Research priorities

Since therapeutic anticoagulation appears to be beneficial in some patient groups but not in others, we recommend studies to determine whether biomarkers of other clinical markers can identify patients likely to experience a mortality benefit from therapeutic anticoagulation.

PICO 11a: CPAP strategies

Problem Is the problem a priority?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes. Avoiding invasive mechanical ventilation is highly desirable and there is evidence in other contexts that this can be achieved through the use of non-invasive ventilation. CPAP is widely used and therefore evidence is required to support its use and understand the risks and benefits.
Desirable Effects How substantial are the desirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Substantial significant reductions in the need for admission to critical care, tracheal intubation and need for further mechanical ventilation were seen in patients treated with CPAP therapy in the RECOVERY-RS randomised trial. Reductions in length of hospital stay were also seen but no clinically meaningful reductions on mortality were noted.
Undesirable Effects How substantial are the undesirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**

○ Large • Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	The most commonly reported adverse event was hemodynamic instability in 43 patients (11.3%) followed by cutaneous pressure sores (8.8%) and oronasal dryness (6.4%). Four of seven SAE's were classified as probably or possibly linked to CPAP which involved one case of surgical emphysema and pneumomediastinum, two cases of pneumothorax and pneumomediastinum and one case of vomiting requiring emergency tracheal intubation.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ○ Low • Moderate ○ High ○ No included studies	The RECOVERY_RS trial is a well conducted randomised controlled trial providing high quality of evidence for the majority of pre-specified endpoints. There is only one randomised controlled trial, however, which suggests repeating more trials would further improve the certainty of evidence.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	The outcomes were all rated important or critical by the task force including the patient representative.

• No important uncertainty or variability	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison • Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Statistically significant improvements have been found in critical outcomes following the use of CPAP. The risks associated with the treatment are minimal and therefore are likely to be outweighed by the benefits.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies • 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 HFNO and non-invasive CPAP have not been clearly established, any comment on relative costs is speculative

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE

○ Very low ○ Low ○ Moderate ○ High • No included studies	We did not identify any formal studies of resource use or cost-effectiveness.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison • Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	We did not identify any formal studies of resource use or cost-effectiveness. It is likely that the reduction in ICU and mechanical ventilation requirements would be make CPAP cost-effective.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE
○ Reduced ○ Probably reduced ○ Probably no impact	ICU beds are highly limited in most countries worldwide and ICU capacity was strained in many countries particularly during the pandemic leading to rationing of resources. The use of 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.

• Probably increased ○ Increased ○ Varies ○ Don't know	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no • Probably yes ○ Yes ○ Varies ○ Don't know	Non-invasive CPAP is 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?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	The therapy is already available in hospital and therefore should cause no issues in implementing. The main feasibility issue is around the appropriate environment, trained nursing resources and personal protective equipment to deliver the interventions.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention

○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest non-invasive CPAP delivered through either a helmet or a face-mask for patients with COVID-19 and hypoxaemic acute respiratory failure (conditional recommendation, high quality of evidence)

Notes accompanying this recommendation: HFNO 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

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 a significant reduction in mechanical ventilation requirement and ICU admission while acknowledging the studies did not identify a significant effect on mortality. The balance of risks and benefits favour the intervention.

Subgroup considerations

No subgroup considerations analysed

Implementation considerations

Monitoring and evaluation

Patients should be cared for in an environment with staff experienced in delivering HFNO 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

Further trials to the identify the optimal method and duration of non-invasive respiratory support are required.

PICO 11b: HFNO strategies

Problem Is the problem a priority?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Avoiding invasive mechanical ventilation is highly desirable and there is evidence in other contexts that this can be achieved through the use of high flow oxygen.
Desirable Effects How substantial are the desirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No clinically meaningful results were observed for any outcomes following the use of HFNO. The power of the study excludes a large effect but cannot exclude smaller effects. Any effects are likely to be of limited clinical relevance.
Undesirable Effects How substantial are the undesirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**

○ Large ○ Moderate • Small ○ Trivial ○ Varies ○ Don't know	Adverse events were reported from only one study (RECOVERY-RS). No serious AE's were recorded in the intervention arm and the main three adverse events recorded were haemodynamic instability in 36 patients (8.6%), oronasal dryness (6%) and claustrophobia (3.8%).

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ○ Low ○ Moderate • High ○ No included studies	Despite only three randomised controlled trials of HFNO being identified, the certainty of evidence is high due to well controlled/designed studies with good number of patients.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	No important uncertainty, all outcomes were decided as important or critical from all the taskforce members.

• No important uncertainty or variability	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison • Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	No overall differences were seen in any of the critical outcomes. Due to the trend towards reduced length of hospital stay and serious adverse events, HFNO may be better tolerated for those who cannot tolerate CPAP. Evidence in other diseases suggest that HFNO can be beneficial, therefore on balance the panel feels that there may be a benefit in patients who are unable to tolerate or are unsuitable for CPAP.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies • 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 HFNO has not been clearly established, any comment on relative costs is speculative.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE

○ Very low ○ Low • Moderate ○ High ○ No included studies	Delivery of care for patient requiring high flow nasal oxygen treatment is expensive but likely less expensive than the alternative of invasive mechanical ventilation.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the comparison • Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Hard to quantify cost effectiveness due to the lack of clear evidence of clinical benefit of HFNO over conventional oxygen therapy.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE
○ Reduced ○ Probably reduced ○ Probably no impact	The treatment is relatively easy to administer and is therefore likely to be acceptable.

• Probably increased ○ Increased ○ Varies ○ Don't know	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no • Probably yes ○ Yes ○ Varies ○ Don't know	The treatment is relatively easy to administer.

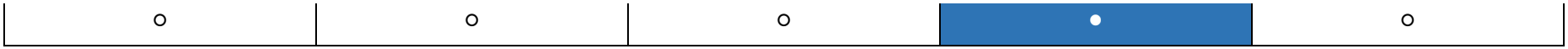
Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	The therapy is already available in hospital and therefore should cause no issues in implementing. The main feasibility issue is around the appropriate environment, trained nursing resources and personal protective equipment to deliver the interventions.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention



CONCLUSIONS

Recommendation

Consider high flow nasal oxygen therapy in patients without an immediate need for invasive mechanical intubation and who are unsuitable for continuous positive airway pressure due to intolerance or adverse effects (conditional recommendation, moderate quality of evidence)

Justification

No benefits for the use of HFNO were identified in the prespecified outcomes however the therapy may benefit those who cannot tolerate CPAP and help reduce the burden of endotracheal intubation based on clinical experience.

Subgroup considerations

No subgroups were prespecified

Implementation considerations

HFNO is considered as an aerosol generating procedure 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 HFNO with continuous monitoring of the patients' condition. In patients not responding to HFNO it is important that this is recognised promptly, and invasive ventilation is not delayed

Research priorities

None

PICO Question 12 – Convalescent plasma strategies

Problem Is the problem a priority?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Convalescent plasma was widely used worldwide as a treatment for COVID-19 and observational studies have reported large benefits. Therefore, robust evidence on the risks and benefits are required in order to inform clinical practice.
Desirable Effects How substantial are the desirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	The only benefit to be noted from our meta-analysis of outcomes with convalescent plasma was conversion of the RT-PCR for SARS-CoV-2 virus to negative (OR2.32, CI1.57-3.45) however this outcome was deemed important with none of the critical outcomes showing any treatment response. In particular there is convincing evidence that convalescent plasma does not provide a mortality benefit or prevent deterioration.
Undesirable Effects How substantial are the undesirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**

○ Large • Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	The majority of outcomes showed no treatment effect however there was an increase in the number of SAE's.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ○ Low ○ Moderate • High ○ No included studies	Although the quality of included trials and the sample sizes were variable, when the body of evidence as a whole are considered there is clear evidence that plasma therapy does not improve clinical outcomes and a high degree of certainty that if further trials were performed they would reach similar conclusions.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	All outcomes were deemed important or critical by all members of the panel.

• No important uncertainty or variability	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
• Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	No desirable effects were seen from the use of this treatment.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Large costs • Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Collection of plasma, storage and administration are not without their resource requirements. Therefore while it is feasible to do this, robust evidence of benefit would be required to justify the resource requirements.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE

○ Very low ○ Low • Moderate ○ High ○ No included studies	Requires availability of eligible donors and staff to process and extract the plasma ready for use.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison • Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	There are no benefits to this treatment and therefore no reason to spend time and money to provide availability of the treatment

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE
○ Reduced ○ Probably reduced • Probably no impact	Not relevant when there is no evidence to justify administration of the treatment.

○ Probably increased ○ Increased ○ Varies ○ Don't know	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE
○ No • Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	In the absence of evidence of benefit, use of the therapy is not acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no • Probably yes ○ Yes ○ Varies ○ Don't know	It has been done globally during the pandemic and is therefore clearly feasible.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

●	○	○	○	○

CONCLUSIONS

Recommendation

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

Justification

With no clinically meaningful benefits from the treatment and an increase in SAE's, the panel make a strong recommendation against the use of convalescent plasma in COVID-`19 patients (strong recommendation, low quality of evidence). The benefit-risk ratio does not qualify the use of this treatment

Subgroup considerations

We identified not subgroups in which evidence was demonstrated

Implementation considerations

Monitoring and evaluation

Research priorities

The panel do not think there is any need for further randomised controlled trials in convalescent plasma

PICO Question 13 – monoclonal antibodies strategies

Problem Is the problem a priority?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	Further treatments to reduce mortality and poor outcomes in severe COVID-19 are urgently needed.
Desirable Effects How substantial are the desirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ Trivial ○ Small • Moderate ○ Large ○ Varies ○ Don't know	An 18% reduction in mortality of patients with seronegative COVID-19 was shown and trends were seen in the reduction of progression to IMV or MV following the use of monoclonal antibodies in this subpopulation. No meaningful treatment responses were seen in any other outcomes. Seropositive patients did not response to treatment with no significant benefits across multiple outcomes.
Undesirable Effects How substantial are the undesirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**

○ Large ○ Moderate ○ Small • Trivial ○ Varies ○ Don't know	No clinically meaningful undesirable effects were seen.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ○ Low • Moderate ○ High ○ No included studies	There is a moderate certainty to the evidence provided as there are only two trials using monoclonal antibodies in hospitalised patients and both beneficial and detrimental effects are seen in the majority of outcomes. Only the seronegative subpopulation in RECOVERY showed a clear clinical benefit. Mortality and proportion discharged were the only two outcomes which were comparable between both trials.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	All variables were deemed to be important or critical.

• No important uncertainty or variability	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison • Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Although the effects are small, they trend towards beneficial and are clinically meaningful in the most critical outcomes such as mortality.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
• Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Experience from clinicians across Europe is that the therapy is difficult to acquire, and availability and cost are therefore barriers to use. To administer only to seronegative patients requires rapid testing for anti-SARS-CoV-2 spike antibodies which adds to the feasibility/resource considerations.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE

○ Very low ○ Low ○ Moderate ○ High • No included studies	The cost of newly designed medication has not been studied in these trials but has been determined by clinician experience from across Europe

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison • Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Not fully established but in view of the mortality benefit and need to administer only to a high-risk subgroup without spike antibodies, this may be cost-effective.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE
○ Reduced ○ Probably reduced ○ Probably no impact	Given the feasibility issues and cost it is unlikely this can be delivered in all healthcare systems, likely contributing to health inequalities.

• Probably increased ○ Increased ○ Varies ○ Don't know	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies • Don't know	The treatments have never been used before as they are designed to specifically target the spike protein of SARS-CoV-2

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no • Probably yes ○ Yes ○ Varies ○ Don't know	Similar infusions are easy to administer and readily available therefore it is not expected this infusion would be any different. Obtaining an antibody test rapidly in hospitalised patients requires setting up a testing system. The frequency of seronegative patients in an era of widespread vaccination is unknown. Note that the available evidence was for a single combination of antibodies- casirivimab and imdevimab

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention

○	○	○	●	○

CONCLUSIONS

Recommendation

The panel suggests to offer a combination of casirivimab and imdevimab to patients hospitalised with COVID-19 who have no detectable SARS-CoV-2 antibodies (seronegative). (conditional recommendation, moderate quality of evidence)

The panel recommends NOT to offer monoclonal antibodies to patients hospitalised with COVID-19 who have detectable SARS-CoV-2 antibodies (seropositive) or where SARS-CoV-2 antibody status is unknown. (strong recommendation, moderate quality of evidence)

Justification

This therapy provides clinical benefits in seronegative patients when administered.

Subgroup considerations

Other than the beneficial effect of treatment in the seronegative population, the RECOVERY trial found no effect modification in other subgroups.

Implementation considerations

Availability of seronegative testing, drug availability and cost all need to be considered.

Monitoring and evaluation

Research priorities

Most trials were conducted in the pre-vaccine era and with previous variants. In view of the mutations in the spike protein evident in the omicron variant data are required on the benefit of antibody treatments against new variants and in individuals who have received prior vaccination.

PICO Question 14 – IL-1 receptor antagonist monoclonal antibody

Problem Is the problem a priority?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes. There is a need for additional anti-inflammatory/immunomodulatory treatments for hospitalised patients with COVID-19. Evidence suggests the involvement of Interleukin-6 in the pathogenesis of severe COVID-19. This has led to the use of anti-IL-6 therapies in clinical practice. There is therefore a need to know whether these treatments improve clinical outcomes such as mortality or requirement for mechanical ventilation.
Desirable Effects How substantial are the desirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	A reduction in time to hospital discharge and progression to severe disease or death (as a composite endpoint) were the only beneficial treatment responses noted from the use of IL-1 receptor antagonists, however when looking at the outcomes as separate endpoints (i.e. mortality alone rather than as part of a composite) there was not the same evident benefit. One study which used a biomarker to select patients showed highly significant benefits. Independent validation of these data are required.
Undesirable Effects How substantial are the undesirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**

○ Large ○ Moderate ○ Small • Trivial ○ Varies ○ Don't know	There were no notable undesirable effects. As with all immunosuppressive treatments there is a risk of opportunistic infection.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ○ Low • Moderate ○ High ○ No included studies	The four available trials provided a moderate certainty of evidence

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	The panel members agreed all the outcomes were important or critical

• No important uncertainty or variability	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison • Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The panel agree more data is required for definitive evidence of benefit of this treatment. It was noted that the results for anti-IL1 therapy cannot be considered in isolation. Systematic corticosteroids, IL-6 receptor monoclonal antibodies and most recently JAK inhibitors have evidence in their favour in this indication. Therefore while there are some benefits associated with anti-IL1, they would not be selected in preference to these other treatments that have a larger or stronger body of evidence.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings • Varies ○ Don't know	These drugs are relatively expensive

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE

○ Very low ○ Low ○ Moderate • High ○ No included studies	No studies tackled the cost-effectiveness of IL-1 receptor antagonists.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies • No included studies	We identified no studies of the cost effectiveness of the treatment. The clinical effectiveness is not yet fully established.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE
○ Reduced ○ Probably reduced • Probably no impact	No such assessment was made. As there are few risks with possible benefits, but the treatment may not be universally available there is currently no impact on equity.

○ Probably increased ○ Increased ○ Varies ○ Don't know	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Anakinra is widely used for other conditions and therefore should be acceptable

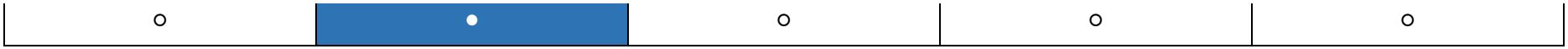
Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A Anakinra is widely used for other conditions and therefore should be acceptable although costs may need to be considered for some countries/healthcare systems,

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention



CONCLUSIONS

Recommendation

The panel suggests NOT to offer IL-1 receptor antagonist monoclonal antibodies for hospitalised patients with COVID-19 (conditional recommendation, moderate quality of evidence)

Justification

Not enough evidence to recommend the use of the therapy however it has been recognised that there could be beneficial effects seen if more trial data becomes available. When there are more established therapies available, anakinra should not be used. The conditional recommendation allows for the use of the therapy when there are no other therapies available and acknowledges there are likely to be some patients who will benefit from anakinra.

Subgroup considerations

Kyriazopoulou et al used a biomarker (urokinaseplasminogen receptor) to identify patients eligible for anakinra treatment, the results from this study were slightly more beneficial and therefore more work on this subgroup analysis may be beneficial.

Implementation considerations

Monitoring and evaluation

Research priorities

Further randomised controlled trials in anti-IL-1 receptor therapy is required, including validation of whether a biomarker guided approach provides benefit over an empirical approach.

PICO Question 15 – JAK inhibitors strategies

Problem Is the problem a priority?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes. There is a need for additional anti-inflammatory/immunomodulatory treatments for hospitalised patients with COVID-19. Evidence suggests the involvement of the JAK pathway in the pathogenesis of severe COVID-19. Mortality in severe patients remains high despite the availability of corticosteroids and therefore new therapies are required.
Desirable Effects How substantial are the desirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Desirable effects seen in decreased mortality and progression to more severe disease requiring non-invasive ventilation, high flow nasal oxygen and mechanical ventilation. A reduced number of serious adverse events was also noted in those treated with JAK inhibitors compared with those in the standard care arm. The magnitude of mortality benefit seen in the pooled data in the meta-analysis was the largest effect seen for any intervention to date.
Undesirable Effects How substantial are the undesirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**

○ Large ○ Moderate ○ Small • Trivial ○ Varies ○ Don't know	No significant undesirable events were seen in association with treatment of JAK inhibitors in the clinical trials included in the meta-analysis.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ○ Low • Moderate ○ High ○ No included studies	Despite low certainty evidence being shown in the adverse events and improvement in 2+ point ordinal scale, there were high certainty evidence showing the intervention is beneficial in reducing the progression of disease severity and critical outcomes. It was noted that the primary outcome for the trials included were negative but that pooled data from secondary endpoints provided much of the benefit observed in the meta-analysis. This impacts upon the level of certainty.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important	No important uncertainty, all outcomes were decided as important or critical from all the taskforce members.

uncertainty or variability • No important uncertainty or variability	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison • Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Due to high certainty evidence showing reduction in mortality rate and progression to more severe disease state, and no detrimental effect from the intervention on health status, it is likely JAK inhibitors have a favourable effect over and above that of standard care treatment alone.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Large costs • Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	This is not known as it has not been formally assessed however the therapy is expensive. It is possible that if found to be beneficial in real-life the treatment would be associated with cost savings.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ○ Low ○ Moderate ○ High • No included studies	This is highly uncertain. The treatment has a cost, but this may or may not be offset by the beneficial clinical effects

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention • Varies ○ No included studies	Availability and expense of the therapy makes this a variable judgement without a formal cost-effectiveness analysis.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	As with any new therapy that is expensive it has the potential to increase health inequalities if the treatment is not accessible globally.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Availability and expense does not make this therapy feasible in all healthcare systems

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
● No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	not accessible in every country

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Justification

JAK inhibitors appear to reduce mortality and improve other outcomes. While the RECOVERY trial showed the efficacy and safety of baricitinib was not affected by co-administration with tocilizumab, combination therapy has economic and clinical considerations and so may not be appropriate for all patients. Those at highest risk of deterioration such as those requiring non-invasive ventilation may be the optimal patient population and indeed this subgroup had the highest efficacy of baricitinib treatment.

Subgroup considerations

No relevant subgroup effects were observed.

Implementation considerations

Monitoring and evaluation

A full blood count, liver function tests, and kidney function tests should be obtained in all patients before JAK inhibitors are used and during treatment as clinically indicated. Screening for viral hepatitis and tuberculosis should be considered. Considering its immunosuppressive effects, all patients receiving JAK inhibitors should be monitored for secondary infections. The safety of JAK inhibitors in pregnancy is unknown.

Research priorities

Baricitinib is included in the RECOVERY trial and so further large scale data on this treatment are expected shortly.