Royal College of Physicians

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**Position Statement:**
**Use of antiviral medicines for COVID-19 in adults**

**Interim support for UK hospital clinicians**

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This document is subject to constant review. If you identify any information that needs to be updated please contact admin.ncl-mon@nhs.uk.

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# Contents

## Abbreviations

| Abbreviation | Meaning |
|---|---|
| CUP | Compassionate Use Programme |
| NIHR | National Institute for Health Research |
| SARS-Cov-2 | Severe acute respiratory syndrome coronavirus 2 |
| SoC | Standard of Care |

## Key messages

- Remdesivir (NHS stock) should only be offered to patients in line with the 'Eligibility criteria' as outlined in the UK interim Clinical Commissioning Policy for remdesvir. Patients receiving remdesivir should be reassessed and reviewed daily (see pragmatic 'Reassessment and review' criteria within the Commissioning Policy).
- Co-administration of dexmathasone or hydrocortisone is recommended for patients with critical or severe COVID-19, or those requiring supplemental oxygen to maintain target saturation – see CTAG treatment pathway
- Hospitals managing COVID-19 cases should make every effort to enrol COVID-19 patients in national priority clinical trials
- Suspected side effects to medicines used in coronavirus treatment should be reported via the Yellow Card COVID-19 reporting site: https://coronavirus-yellowcard.mhra.gov.uk/

# 1. Aim

1.1. To provide interim supporting information on the appropriate use of newly licensed and investigational antiviral medicines for the treatment and prevention of COVID-19 in adults, in the hospital setting.

1.2. Information contained within this position statement does not represent a 'recommendation'; however it is intended to provide support to healthcare professionals when considering available treatment options in patients with COVID-19.

# 2. Supporting information

**Remdesivir**

- Remdesivir (NHS stock) may only be offered to patients who meet **all** the following criteria[1,2]:
  - hospitalised with COVID-19[a]
  - adults, and adolescents ≥ 12 years of age and ≥ 40 kg
  - with pneumonia requiring supplemental oxygen
  - eGFR ≥ 30ml/min
  - ALT < 5 times the upper limit of normal at baseline

  Additional criteria & considerations[1,2]:
  - Decision to initiate is made by the admitting care consultant[b]
  - Do not initiate in patients who present to hospital > 10 days after symptom onset
  - Those with a low 4C Mortality Score[c] (0 to 3) are highly likely to recover without treatment with remdesivir
  - Do not initiate in patients who present to hospital and are unlikely to survive (determined by clinical judgment). The 4C Mortality Score[c] might be helpful in this assessment

  Reassessment and review[1,2]:
  - Daily reassessment is required. Consider stopping remdesivir if:
    - The patient clinically improves and no longer requires supplemental oxygen 72 hours after commencement of treatment
    - The patient continues to deteriorate despite 48 hours of sustained mechanical ventilation.
- Co-administration of corticosteroids is recommended for patients with critical or severe COVID-19, or those requiring supplemental oxygen to maintain target saturation – see CTAG treatment pathway.[3,4]
- A remdesivir Compassionate Use Programme (CUP) is available for children < 12 years or adolescents aged 12-17 years and weighing <40 kg with severe COVID-19; requests for remdesivir for individual patient use at https://rdvcu.gilead.com/.
- CTAG encourages enrolment into ISARIC-CCP CRF (Tier 0; no consent required). If there is limited research capacity, CTAG recommends prioritising enrolment into national priority interventional clinical trials ahead of enrolment into ISARIC-CCP CRF.

2.1. Remdesivir is licensed for the treatment of COVID-19 in adults and adolescents with pneumonia requiring supplemental oxygen

[a] Ensure only patients with SARS-CoV-2 infection infection are treated with remdesivir. In the absence of a confirmed diagnosis, a multidisciplinary team should have a high level of confidence that the clinical and radiological features suggest that COVID-19 is the most likely diagnosis.[1,2]

[b] The decision to treat with remdesivir is not an emergency and should be made judiciously after assessment and in a timely manner[2]

[c] The 4C Mortality Score (available at https://isaric4c.net/risk/) is a validated risk stratification score, which can help inform clinical decision making for patients admitted to hospital with COVID-19 (Knight et al, 2020). Other clinical risk scores are available

2.1.1. The results of the SOLIDARITY trial and the associated meta-analysis have not yet been subject to peer review. Results from SOLIDARITY found remdesivir did not reduce the risk of death in the population treated, or in any subgroup of entry characteristics. The totality of evidence however suggests that there may be a small treatment effect of remdesivir in hospitalised patients requiring oxygen, especially early in disease course. This benefit does not appear to extend to patients who are mechanically ventilated. This small effect size could be taken into account in individual patient decisions around initiation and discontinuation of treatment.

2.1.2. Use in pregnancy: Remdesivir should be avoided in pregnancy unless clinicians believe the benefits of treatment outweigh the risks to the individual (see advice in **Error! Reference s ource not found.**).[2] CTAG are of the opinion that a decision to use remdesivir should be taken by an MDT (including Obstetric and Infection specialists) due to the uncertain fetal risk profile with treatment.

2.2. Other antiviral medicines are being investigated for the management of COVID-19; the current evidence-base for these medicines is summarised in Appendix 1.

2.3. Hospitals managing COVID-19 cases, including those treated with remdesivir, should make every effort to enrol COVID-19 patients in national priority clinical trials.[5–7]

2.4. Information for the use of dexamethasone and hydrocortisone, or investigational immunomodulators for COVID-19 (e.g. tocilizumab, sarilumab, anakinra) is available at https://www.ctag-support.org.uk/immunomodulators

2.5. Patients may be diagnosed with COVID-19 whilst receiving investigative prophylactic treatment e.g. COPCOV trial. When such a patient would otherwise be eligible for enrolment into an interventional treatment trial, discontinuation of the prophylactic agent should be discussed with the local Principal Investigator responsible for their treatment.

2.6. Suspected side effects to medicines used in coronavirus treatment should be reported via the Yellow Card COVID-19 reporting site: https://coronavirus-yellowcard.mhra.gov.uk/

## Membership and provenance

The support contained within this document is provided by the COVID-19 Therapeutics Advice & Support Group (CTAG) antiviral subgroup.

The provenance for this subgroup is the Network of High Consequence Infectious Diseases (HCID). In March 2020, the collaborative expanded to include experts in Infectious Diseases from other Provider Trusts.

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# Document control

| Date | Version | Amendments |
|---|---|---|
| 23 Mar 2020 | 1.0 | New document |
| 23 Mar 2020 | 1.1 | Updated Gilead remdesivir Compassionate Use Programme eligibility criteria |
| 27 Mar 2020 | 1.2 | Added NHS England and NHS Improvement speciality guide for patient management. Added MHRA advice on chloroquine and hydroxychloroquine. Added hydroxychloroquine arm of RECOVERY study; added link to NIHR website. |
| 01 Apr 2020 | 2.0 | Updated evidence summaries in Appendix 1 (new trials for lopinavir/ritonavir and chloroquine). Merged 'Position statement' and 'Decision Support Tool' into a single document. Updated Section 3 with new trials. Updated Figure 1 with relationship between RECOVERY and PRINCIPLE/REMAP-CAP. |
| 07 Apr 2020 | 2.1 | Updated title to reflect updated scope (antiviral use in hospitals). Updated Section 2, 3 and Figure 1 with new trials and trial status. Included reference to CMO letter. Reformatting throughout. Added BIA and UKCPA-PIN logos (with permission). |
| 08 Apr 2020 | 2.2 | Updated membership & provenance. Corrected typo (2.5). |
| 18 Apr 2020 | 2.3 | Updated arms of RECOVERY study. Provided additional information for Gilead remdesivir Compassionate Use Programme. Updated references and web links. Updated evidence summaries in Appendix 1. Added azithromycin and inhaled interferon tables to Appendix 1. |
| 01 May 2020 | 2.4 | Addition of 'Key messages' and 'Abbreviations'. Emphasised importance of avoiding off-label use of investigational antivirals. Added reference to 'CTAG: Position Statement on the use of investigational immunomodulatory agents for COVID-19 in adults'. Format change to clinical trials tables. Change SNG016 and COPCOV from 'proposed' to 'active'. Added GenOMICC study. Updated evidence summaries in Appendix 1 (remdesivir; nebulised interferon; added EMA statement for chloroquine/hydroxychloroquine). |
| 22 May 2020 | 2.5 | Included reference to CMO letter and COVID-19 Yellow Card reporting. Updated evidence summaries in Appendix 1 (interferon). Updated support for patients diagnosed with COVID-19 whilst receiving investigative prophylactic treatment. Removed reference to GenOMICC as out of scope. Updated RECOVERY eligibility criteria to include paediatrics. Changed COPCOV from chloroquine to hydroxychloroquine. Changed CROWN CORONATION from hydroxychloroquine to chloroquine. Removed DisCoVeRy from Table 2. |
| 06 June 2020 | 3.0 | Included unlicensed remdesivir EAMS and NHS implementation plan for that scheme; updated Section 2 accordingly and added a new monograph (Section 5). Moved studies ACTT-1, 5773, 5774 and SNG016 into a new 'Closed to recruitment' table. Updated evidence summaries in Appendix 1 (remdesivir; chloroquine/hydroxychloroquine). |
| 12 June 2020 | 3.1 | Updated NHS implementation plan for EAMS. Updated evidence summaries in Appendix 1 (remdesivir; chloroquine/hydroxychloroquine). |
| 29 June 2020 | 3.2 | Made reference to RECOVERY dexamethasone results. Added CTAG advice on the use of remdesivir. Updated arms of PRICIPLE study. Updated evidence summaries in Appendix 1 (systemic interferon; convalescent plasma). |
| 03 July 2020 | 3.3 | Moved ACCORD-2 to 'Active studies' table. Added discontinued arms of RECOVERY to 'Closed to recruitment' table. Updated evidence summaries in Appendix 1 (lopinavir/ritonavir). |
| 07 July 2020 | 4 | Updated with information on conditional marketing authorisation for remdesivir; EAMS programme lapsed so references removed |
| 18 Aug 2020 | 4.1 | Reformatting throughout. Updated evidence summaries in Appendix 1 (chloroquine/hydroxychloroquine, azithromycin, interferon (nebulised), convalescent plasma). |
| 15 Oct 2020 | 5.0 | Updated to reflect supply restrictions to remdesivir. Removed summary of individual trials. Removed prophylaxis chapter as out of scope. Updated all evidence summaries in Appendix 1. |

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| | 6.0 | Simplified position statement (removed monographs x 2 and signposting to relevant trials). Updated all evidence summaries in Appendix 1. |

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# Appendix 1: Evidence base for investigational antiviral agents to treat COVID-19

## Disclaimer

Due to the urgency for interim guidance, only a limited number of agents have been assessed and a wholly systematic approach to assessing the evidence (such as GRADE) has not been performed. Some subjective judgments are solely the consensus opinion of the authors and consulted experts.

The focus here is on investigational antiviral treatments for managing hospitalised COVID-19 patients. Supportive care and treatment of co-infections and complications, such as ARDS, are not addressed.

## Methods

COVID-19 is caused by infection with the newly emerged betacoronavirus SARS-CoV-2.

We reviewed the available data on treatment of betacoronaviruses but restricted the search to investigational antiviral agents being used, or considered, within the context of UK clinical trials. This includes all investigational antiviral agents identified in the NIHR list of nationally prioritised studies.

## Evidence summary

Summaries are provided for investigational antiviral treatments being used, or considered, within the context of UK clinical trials.

The summaries are divided into two categories in the following tables based on current evidence:

- Table 1: Benefit may exceed risk
- Table 2: Inadequate data to recommend use

**Table 1: Evidence base for specific therapies for SARS-CoV-2 infection: Benefit exceeds risk**

RCT = randomised-controlled trial; CI = confidence interval; HCQ = hydroxychloroquine. OR = odds ratio; HR = hazard ratio.

| Therapy | Data: SARS-CoV-2 | Safety profile | UK feasibility |
|---|---|---|---|
| **Remdesivir** | The highest level of evidence is: 4 RCTs.<br>**NICE have published rapid evidence summary for remdesivir: https://www.nice.org.uk/advice/es27/chapter/Key-messages**<br>**BMJ have published a rapid evidence summary for remdesivir: https://www.bmj.com/content/370/bmj.m2924**<br>A double-blinded RCT in China compared remdesivir to placebo among 237 adults with severe COVID-19 (defined as radiologically-confirmed pneumonia and either SpO2 ≤94 % on air or PaO2/FiO2 ratio ≤300), ≤12 days from symptom onset to enrolment[8]. At 28 days, remdesivir was not associated with difference in time to clinical improvement (hazard ratio 1.23; 95% CI 0.87–1.75) or overall mortality (22 (14%) died in the remdesivir group vs 10 (13%) in the placebo group). In a post-hoc analysis, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration ≤10 days at enrolment (hazard ratio 1.52; 0.95–2.43). However, the trial was underpowered.<br>A double-blind, randomized, controlled trial among adults hospitalized with COVID-19 with evidence of lower respiratory tract involvement (radiographic infiltrates, peripheral oxygen saturation ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation) compared remdesivir to placebo.[9] A total of 903/1,062 (85%) participants had severe disease (SpO2 ≤ 94% on room air, respiratory rate ≥24/min, requiring oxygen, invasive or non-invasive ventilation) at enrolment. Participants receiving remdesivir had a median recovery time of 10 days (95% CI 9 to 11), *vs.* 15 days (95% CI 13 to 18) in the placebo arm (rate ratio for recovery 1.29; 95% CI 1.12 to 1.49; log rank p<0.001). The rate ratio for recovery was largest among patients with a baseline ordinal score of 5 (receiving low flow oxygen therapy; rate ratio for recovery 1.45; 95% CI 1.18 to 1.79). The benefit of remdesivir was also larger when given earlier in the illness. Patients who underwent randomization during the first 10 days of illness had a rate ratio for recovery of 1.37 (95% CI 1.14 to 1.64), compared to 1.20 (95% CI 0.94 to 1.52) >10 days after symptom onset. Mortality was numerically lower in the remdesivir group than in the placebo group, but the difference was not significant. Kaplan Meier 15- and 29-day mortality estimates were 6.7% with remdesivir *vs.* 11.9% with placebo and 11.4% with remdesivir *vs.* 15.2% with placebo, respectively (hazard ratio, 0.73; 95% CI 0.52 to 1.03).<br>An open-label RCT compared the efficacy of 5 *vs.* 10 days of remdesivir treatment *vs.* standard care on clinical status (7-point ordinal scale) on day 11 after treatment initiation among 596 patients admitted with moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation >94%) [10]. On day 11, patients in the 5-day remdesivir group had higher odds of better clinical status than those receiving standard care (odds ratio, 1.65; 95% CI, 1.09-2.48; P = .02), but clinical status was not significantly different between the 10-day remdesivir and standard care groups (P = .18). At day 28, 2 patients (1%) in the 5-day remdesivir group died, compared to 3 (2%) in the 10-day remdesivir group, and 4 (2%) in the standard care group.<br>An open-label RCT of 397 hospitalized patients with SARS-CoV-2 pneumonia compared 10-day *vs.* 5-day courses of remdesivir.[11] By day 14, clinical improvement occurred in 64% of patients in the 5-day group and in 54% in the 10-day group. After adjustment for baseline clinical status, there was no significant difference between 5-day and 10-day courses at day 14 (P=0.14).<br>Results from a 'living' meta-analysis for these summaries is available on the Cochrane website. | See SPC & BNF.<br>No significant adverse safety signals detected in the COVID-19 RCTs. | Refer to the Interim Clinical Commissioning Policy and the compassionate use programme criteria at: https://rdvcu.gilead.com |

**Table 2. Evidence base for specific therapies for SARS-CoV-2 infection: Inadequate data to recommend use**

RCT = randomised-controlled trial; CI = confidence interval; HCQ = hydroxychloroquine. OR = odds ratio; HR = hazard ratio.

| Therapy | Data: SARS-CoV-2 | Safety profile | UK feasibility |
|---|---|---|---|
| **Lopinavir/ ritonavir** | The highest level of evidence is: 4 RCTs.<br><br>An exploratory RCT assessing lopinavir/ritonavir or Arbidol® (umifenovir) to among 86 hospitalised adults with mild/moderate COVID-19 reported no differences between arms in time from positive-to-negative viral conversion using RT-PCR (mean 9.0 days (SD 5.0) in the lopinavir/ritonavir group, 9.1 (SD 4.4) in the arbidol group and 9.3 (SD 5.2) in the control group), though the trial was underpowered.[12]<br><br>An open-label RCT of hospitalised adults in China with severe COVID-19 (n=199) found no benefit in time to clinical improvement for lopinavir-ritonavir over standard care (hazard ratio 1.31; 95% CI 0.95 to 1.80). 28-day mortality was similar in the lopinavir–ritonavir group and the standard-care groups (19.2% *vs.* 25.0%; difference −5.8; 95% CI, −17.3 to 5.7). Lopinavir-ritonavir recipients spent less time in hospital (12 *vs.* 14 days) and less time in intensive care (6 *vs.* 11 days).[13(p19)]<br><br>The open-label RECOVERY RCT allocated 1616 patients to receive lopinavir–ritonavir, compared to 3424 patients to receive usual care.[14] A total of 374 (23%) patients allocated to lopinavir–ritonavir and 767 (22%) patients allocated to usual care died within 28 days (rate ratio 1.03, 95% CI 0.91–1.17; p=0.60). Results were consistent among pre-specified subgroups and for secondary endpoints of time until discharge alive from hospital (median 11 days [IQR 5 to >28] in both groups), proportion of patients discharged from hospital alive within 28 days (rate ratio 0.98, 95% CI 0.91–1.05; p=0.53) and proportion who met the composite endpoint of invasive mechanical ventilation or death (risk ratio 1.09, 95% CI 0.99–1.20; p=0.092).<br><br>The SOLIDARITY trial issued a press release accouncing closure of the lopinavir/ritonavir arm following review of interim results, and evidence from all trials presented at a WHO Summit. Lopinavir/ritonavir was noted to produce little or no reduction in the mortality of hospitalized COVID-19 patients when compared to standard care. Full results awaited.<br><br>Results from a 'living' meta-analysis for these summaries is available on the Cochrane website. | See SPC & BNF.<br><br>Well established agent with well understood toxicity profile. Gastrointestinal side effects are very common.<br><br>Note multiple, significant drug-drug interactions.<br><br>No additional significant adverse safety signals detected in the COVID-19 RCTs. | Licensed for the treatment of HIV-1 infection.<br><br>Included in REMAP-CAP trial |

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| **Azithromycin** | The highest level of evidence is: 2 RCTs.<br>A multi-centre open-label RCT in Brazil (COALITION 1) compared HCQ (n=221), to HCQ plus azithromycin (n=217), to standard care (n=227) among hospitalised patients with mild-moderate COVID-19 (maximum O2 requirement of 4L/min or FiO2 40%).[15] In the primary modified intention to treat (mITT) analysis, there were no between-group differences in the primary outcome of clinical status at day 15 (measured on a 7 point ordinal scale; hydroxychloroquine plus azithromycin *vs.* standard care odds ratio 0.99; 95% CI 0.57 to 1.73; P=1.00) or in secondary outcomes including requirement for mechanical ventilation. There was low mortality in the cohort (n=18) with no between-group differences. Higher rates of adverse events were reported in the arms containing HCQ (39.3% among HCQ plus azithromycin arm; 33.7% among HCQ arm; 22.6% among standard care arm), including QTc prolongation and deranged liver function.<br>A second multi-centre open-label RCT in Brazil (COALITION 2) compared azithromycin to standard of care (including HCQ therapy) among patients hospitalised patients with severe COVID-19 (oxygen >4 L/min flow, high-flow nasal cannula oxygen, non-invasive mechanical ventilation or invasive mechanical ventilation).[16] In the primary analysis among the mITT population (n=397), there was no difference in the primary endpoint of clinical status at day 15 after randomisation (assessed by a 6-point ordinal scale) between the azithromycin and control groups (OR 1.36 [95% CI 0.94–1.97], p=0.11).<br>Results from a 'living' meta-analysis for these summaries is available on the Cochrane website. | See SPC & BNF.<br>Well established agent with well understood toxicity profile including gastrointestinal upset (common) and QT prolongation (uncommon).<br>No additional significant adverse safety signals detected in the COVID-19 RCTs. | Various licensed indications as an antimicrobial.<br>Included as an arm in the UK RECOVERY trial.<br>Prolonged macrolide therapy is also an existing arm in REMAP-CAP trial, but with immunomodulatory rather than antiviral intent. |

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| **Convalescent plasma** | The highest level of evidence is: 4 RCTs.<br>An open-label, multicenter, randomized clinical trial in Wuhan, China compared convalescent plasma to standard care among 103 patients with severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or requiring mechanical ventilation) COVID-19[17]. At 28 days, there was no difference between the convalescent plasma and standard care arms in clinical improvement (51.9% vs 43.1%; hazard ratio 1.40; 95% CI 0.79-2.49; P = .26) or mortality (15.7% vs 24.0%; OR 0.65; 95% CI 0.29-1.46]; P = .30). Convalescent plasma treatment was associated with negative conversion of viral PCR at 72 hours in 87.2% of the convalescent plasma group vs 37.5% of the control group (OR 11.39; 95% CI 3.91-33.18; P < .001). However, the trial was underpowered for clinical outcomes and median time between the onset of symptoms and randomization was 30 days, suggesting late initation of therapy. Adverse events were reported for the intervention group only (see 'Safety profile'). Furthermore, a greater proportion of participants in the treatment group received co-interventions, compared to the control group, which may have been influenced by knowledge of allocation.<br>A preprint of an open-label randomized trial comparing convalescent plasma with standard of care in patients hospitalized for COVID-19 in the Netherlands reported that the trial was stopped early (n=86 enrolled) as 53 of 66 patients tested had anti-SARS-CoV-2 antibodies at baseline.[18] At the time of cessation, the adjusted odds ratio for overall mortality for patients treated with convalescent plasma was 0.95 (CI 0.20 – 4.67; p=0.95) and for improvement in the WHO COVID-19 disease severity score on day 15 was 1.30 (CI 0.52 - 3.32).<br>A preprint of an open-label randomized trial comparing convalescent plasma with standard of care in patients hospitalized for COVID-19 in Spain was stopped after recruitment of 81 patients due to a fall in recruitment following population-level pandemic suppression.[19] The original intended primary endpoint was the proportion of patients in categories 5-7 of the COVID-19 ordinal scale at day 15. At enrolment, 49.4% of particpnts had evidence of anti-SARS-CoV-2 IgG antibodies. At closure, 0/38 patients had progressed to mechanical ventilation or death among patients assigned to receive plasma, *vs.* 6/43 (14%) in control arm (p=0.57). Mortality risk was 0% vs 9.3% at day 15 for the plasma and control groups, respectively. However, the study was severely underpowered due to early closure.<br>A preprint of an open-label randomized trial in India compared convalescent plasma with standard of care among 464 hospitalized patients with moderate PCR-confirmed COVID-19 (PaO2/FiO2 ratio: 200-300mmHg; or respiratory rate > 24/min and SpO2 ≤ 93% on room air).[20] There was no difference in the composite primary outcome of progression to severe disease (PaO2/FiO2<100 mmHg; 44/235 (18.7%) in intervention arm *vs.* 41/229 (17.9%) in the control arm; OR 1.09; 95% CI 0.67 - 1.77]) or mortality (34/235 (13.6%) *vs.* 31/229 (14.6%); OR 1.06; 95% CI: -0.61 - 1.83) at 28 days post-enrolment. Neutralising antibody titres were measured in 418 trial participants; 348 (83.2%) had detectable neutralising antibodies at enrolment.<br>Results from a 'living' meta-analysis for these summaries is available on the Cochrane website. | Transfusion-related adverse events well-recognised.<br>2/52 patients who received convalescent plasma in the RCT from China[17] experienced transfusion-associated adverse events; both improved with supportive care. No other additional significant adverse safety signals detected in the COVID-19 RCTs. | Included as an arm in the UK RECOVERY trial. |

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| **Hydroxychloroquine (HCQ) / Chloroquine (CQ)** | The highest level of evidence is: 11 RCTs. The highest quality four trial are summarised here, in addition to the SOLIDARITY press release.<br><br>The RECOVERY trial, a multi-arm multi-centre open-label RCT of hospitalised COVID-19 patients in the UK, has published results of its HCQ arm.[21] The authors report no significant difference between the HCQ arm (1561 patients) and the SoC arm (3155 patients) in the primary endpoint of all-cause mortality at 28 days: 27% mortality in the HCQ group versus 25% in the SoC group, RR 1.09 (95% CI 0.97-1.23). This finding is consistent in multiple pre-specified subgroup analyses including age and days since symptom onset. For secondary outcomes, HCQ was associated with a lower probability of discharge alive at 28 days (RR 0.90, 95% CI 0.83-0.98) and higher rate of progression to a composite outcome of death or invasive mechanical ventilation: 30.7% versus 26.9% (RR 1.14, 95% CI 1.03-1.27).<br><br>The COALITION 1 trial, a multi-centre open-label RCT in Brazil, compared HCQ, to HCQ plus azithromycin, to SoC.[15] Please see the azithromycin table above for a summary of this trial.<br><br>A double-blind RCT compared HCQ (n=212) to placebo (n=211) for treatment of non-hospitalised adults with either laboratory-confirmed COVID-19 or highly suspected COVID-19 following a high risk exposure, commenced within 4 days of symptom onset.[22] There was no difference in the primary endpoint of change in symptom severity at 14 days (measured on a 10 point visual analogue scale): between-group difference of −0.27 points (95% CI −0.61-0.07). The study was underpowered to detect differences in hospitalisation or mortality, but notes that the incidence of these events did not differ between groups (HCQ – 5 events, placebo – 10 events, p=0.29).<br><br>An open-label multi-centre RCT from China (n=150) compared HCQ with SoC in hospitalised patients with mild-moderate COVID-19.[23] The authors reported no difference between arms in SARS-CoV-2 negative conversion in respiratory tract specimens by 28 days: 85.4% (95% CI 73.8-93.8%) vs 81.3% (71.2-89.6%). There were higher rates of adverse events (30% versus 9%) in the HCQ arm. Clinical outcomes are not reported.<br><br>The SOLIDARITY RCT issued a press release accouncing closure of the HCQ arm following review of interim results, and evidence from all trials presented at a WHO Summit. HCQ was noted to produce little or no reduction in the mortality of hospitalized COVID-19 patients when compared with SoC. Publication of the full results is awaited.<br><br>Results from a 'living' meta-analysis for these summaries is available on the Cochrane website. | See SPC & BNF.<br><br>Well established agent, defined safety profile as antimalarial drug; however, safety in acute viral illness is not established and concerns about the risk of QTc prolongation were raised following early observational trials.<br><br>The COALITION 1 trial reported more frequent adverse events in participants in HCQ-containing arms.[15] These included QTc prolongation in 30 of 438 patients who received HCQ (in comparison to 1 of 227 who did not), and elevated liver transaminases in 43 of 438 (in comparison to 8 of 227).<br><br>The RECOVERY trial[21] reports that the excess risk of death seen in its HCQ group was not due to mortality due to COVID-19 (24.0% vs 23.5% in the SoC group), but notes a small excess risk of death from cardiac causes (mean±SE excess, 0.4±0.2 percentage points) and non–SARS-CoV-2 infection (mean excess, 0.4±0.2 percentage points). There were no differences in the overall frequency of arrythmia in the participants for whom this data was available in the HCQ arm (735 patients) or the SoC arm (1421 patients). One serious adverse event attributed to HCQ was reported (torsades de pointes).<br><br>Two RCTs have reported higher rates of adverse effects (primarily gastrointestinal) in participants receiving HCQ.[22,23] | Various licensed indications, including malaria and rheumatoid arthritis.<br><br>Included in COP-COV trial (prophylaxis) |

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| **Interferon (systemic)** | The highest level of evidence is: 3 RCTs.<br><br>An open-label multicentre RCT in Hong Kong compared treatment with subcutaneous IFNβ-1b, ribavirin & lopinavir/ritonavir (n=86) to lopinavir/ritonavir alone (n=41), in hospitalized patients with mild-moderate COVID-19.[24] Patients in the group who received IFN had significantly shorter times to positive-to-negative viral conversion of NP swabs: 7 days versus 12 days, HR 4.37 (95% CI 1·86-10·24). Significant findings are also reported for secondary outcomes including time to clinical recovery in the IFN group (4 days versus 8 days) and shorter length of hospital stay (9 days versus 14.5 days). The majority of patients had mild disease and no mortality was observed. There is heterogeneity in the intervention arm, as IFNβ treatment was only used in patients randomized to this group if they were within 1 week of symptom onset. A subgroup analysis indicated that the apparent benefits in the intervention group were only seen in the group of patients treated with IFNβ within the first week of symptoms.<br><br>A single-centre open-label RCT from Iran compared subcutaneous IFNβ-1a (three times per week for 2 weeks, n=42) plus SoC, to SoC alone (n=39), in patients with severe COVID-19.[25] SoC comprised HCQ and lopinavir/ritonavir for all patients, and antibiotics and corticosteroids in some patients. There was no difference between groups in the primary outcome of time to clinical improvement. The authors report a significant difference in 28 day mortality as secondary outcome (19% in the IFNβ-1a group vs 43.6% in the SoC group), however there is a high risk of bias due to missing outcome data as multiple patients were excluded from the intervention arm because of mortality within the 1st week of treatment.<br><br>A second open-label RCT, from the same single centre in Iran, compared subcutaneous IFNβ-1b given every 2nd day for 2 weeks (n=33) plus SoC, to SoC alone (n=33), in patients with severe COVID-19.[26] SoC again comprised HCQ and lopinavir/ritonavir. The authors report a significant difference in the primary outcome of time to clinical improvement: 9 days (IQR 6–10) versus 11 (9–15) days (p=0.002). Differences in secondary outcomes including discharge at day 14 are also reported: 78.79% in the IFN group versus 54.55% in the control group (OR 3.09; 95% CI: 1.05–9.11). No significant difference is reported for mortality at 28 days.<br><br>Results from a 'living' meta-analysis for these summaries is available on the Cochrane website. | See SPC & BNF.<br><br>Well established agent with defined but complex safety profile. Clinicians experienced in managing side effects should be consulted where there are concerns e.g. those who have treated hepatitis C virus (HCV) infection and multiple sclerosis.<br><br>Known IFN-related adverse effects including flu-like symptoms and neuropsychiatric effects have been reported in IFN arms of trials, but no increased numbers of serious adverse events.[25(p19)] | Several different interferons are available for systemic administration, for different licensed indications. There are insufficient data to strongly recommend a particular preparation, although IFN-β appears more promising based on available data.<br><br>IFN-β injection: included as an arm in the immune modulation domain of REMAP-CAP trial (recruiting) |

| Therapy | Data: SARS-CoV-2 | Safety profile | UK feasibility |
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| **Interferon (nebulised)** | The highest level of evidence is: 1 RCTs (data press-released but not yet published).<br><br>The SNG016 trial is a phase II double-blind multi-centre RCT of SNG001 (a nebulized formulation of IFNβ-1a) versus placebo in hospitalized patients with COVID-19, run by Synairgen. The trial issued results as a press release in July 2020 and further interim analyses in September 2020. The more detailed interim analysis reports that patients who received the drug (n=48) had significantly greater odds of clinical improvement by day 15/16 of illness as assessed on an 8 point ordinal scale, in comparison to the placebo group (n=50): OR 2.32 (95% CI 1.07-5.04). There were no significant differences between the groups in the time to development of severe disease or death (HR 0.50, 95% CI 0.18-1.38), or in the odds of severe disease or death (OR 0.28, 95% CI 0.07-1.08), when analysed in the intention to treat population. A significant difference is reported in the per-protocol population (n=86) for the odds of severe disease or death (OR 0.15, 95% CI 0.04-0.93). The event rates in each group were not reported and overall mortality in the trial was low (3/98 patients, all in the placebo group). Formal publication of the full results is required for full interpretation. The company subsequently announced they were extending the SNG-16 trial to a second phase recruiting patients in the community. | Nebulised IFN formulations not yet licensed in the UK. Please see IFN (systemic) table for medicines information for injectable IFNs.<br><br>A phase II human trial of SNG001 (nebulized IFN β-1a), in individuals with a background of viral-induced asthma who had new cold-like symptoms, reported that it was well tolerated with no safety signals flagged.[27] | Clinical formulation made by Synairgen, SNG001, a nebulised formulation of IFNβ-1a. Synairgen has announced a SNG001 Managed Access Program jointly with Clinigen, for hospitalised COVID-19 patients in Europe.<br><br>Recruitment to the second community-based phase of the SNG016 trial, run by Synairgen and the University of Southampton, is ongoing. |