Royal College of Physicians

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
CMA	Conditional Marketing Authorisation
CMO	Chief Medical Officer
CUP	Compassionate Use Programme
DHSC	Department of Health and Social Care
EAMS	Early Access to Medicines Scheme
EMA	European Medicines Agency
MHRA	Medicines Healthcare Products Regulatory Agency
NIHR	National Institute for Health Research
R&D	Research and Development
SARS-Cov-2	Severe acute respiratory syndrome coronavirus 2
SoC	Standard of Care

Key messages

- Remdesivir is the only antiviral medicine approved for use in the treatment of COVID-19, receiving a conditional marketing authorisation on 3rd July 2020
- DHSC and the devolved nations have produced an interim clinical commissioning policy and MHRA has issued an updated alert for the UK on use of remdesivir
- Hospitals managing COVID-19 cases should make every effort to enrol COVID-19 patients in national priority clinical trials
- Advice on the appropriate use of dexamethasone for COVID-19 is available at https://www.ctag-support.org.uk/immunomodulators
- 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. This position statement will be updated in response to relevant developments and superseded when specific national guidance is published by UK health technology assessment bodies (e.g. National Institute for Health and Care Excellence, All Wales Medicines Strategy Group or Scottish Medicines Consortium).

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. Treatment: Supporting information

2.1. Remdesivir is the only antiviral medicine approved for use in the treatment of COVID-19. It received a conditional marketing authorisation on 3rd July 2020.

2.2. Several 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 should make every effort to enrol COVID-19 patients in national priority clinical trials[1,2] – refer to Section 4.

2.4. The following nationally prioritised trials for investigative antiviral medicines for hospitalised patients with COVID-19 are open to recruitment (both allow concurrent use of remdesivir):

- RECOVERY (in hospital trial; UK study open to all Trusts)
- REMAP-CAP (critical care trial; international with UK sites) COVID-19 antiviral and immunomodulatory domains
- ACCORD-2 (UK Phase II clinical trials program) antiviral and immunomodulatory subprotocols

2.5. Preliminary results from one randomised controlled trial suggest remdesivir reduces time to recovery in hospitalised patients with confirmed SARS-CoV-2 infection and radiographic infiltrates or hypoxia (full results in Appendix 1).[3]

2.5.1. EMA has now granted a "Conditional Marketing Authorisation" for remdesivir for the treatment of COVID-19 in adults and adolescents ≥ 12 years and ≥ 40kg with pneumonia requiring supplemental oxygen.[a] This superceded the 'Early Access to Medicines Scheme' which lapsed on 3rd July 2020[4,5].

- This designation means remdesivir has a positive risk/benefit profile and targets a high unmet clinical need on the basis of less comprehensive data than normally required.
- Supporting information for the CMA is available on the EMA website[6]

2.6. DHSC and the other devolved administrations have produced an interim clinical commissioning policy for remdesivir which can be accessed from the DHSC website[7,8].

2.6.1. Guidance has been issued on use of remdesivir under the CMA – refer to Section 5[8]

- Hospitals managing COVID-19 patients are encouraged to submit data through the (CRF)
- CTAG are of the opinion that patients should ideally have laboratory confirmed SARS-CoV-2 infection.[b] In the absence of a confirmed virological 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.
- CTAG are of the opinion that remdesivir is unlikely to improve clinical outcome in people who appear clinically to be in the recovery phase of the illness, or those who have required mechanical ventilation or ECMO for a number of days and do not have ongoing evidence of high viral burden or ongoing viral replication, nor have advanced immunosuppression that may put them at risk of reactivation.

[a] Licensed indication: Remdesivir [Veklury] is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (see section 5.1).

[b] Benefit associated with remdesivir has been demonstrated in trials which required a recently positive PCR result for enrolment.

2.6.2. Patients with severe COVID-19 who are not eligible for remdesivir under the CMA (i.e. children <12 years old or adolescents aged 12-17 years and weighing <40 kg) can apply to the Compassionate Use Programme (CUP) – refer to Section 6.
   - CTAG encourages enrolment into ISARIC-CCP case report forms (Tier 0; no consent required) for patients accessing the CUP as data for young children will not be available from interventional clinical trials.

2.6.3. CTAG are of the opinion that trials offering host directed therapy (particularly immunomodulation) seek to ensure access to administration of licensed remdesivir (under the CMA) where appropriate for participants within the trial.

2.7. Patients diagnosed with COVID-19 in the community may be admitted into hospitals receiving an investigative antiviral from primary care e.g. PRINCIPLE trial. Where identified, treatment should usually be continued if clinically appropriate as enrolment into subsequent interventional trials may still be permitted (Figure 1)

2.8. 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.

2.9. 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/

2.10. Recruitment to trials of immunomodulation therapy should not preclude concurrent therapy with active antiviral therapy or dexamethasone
   - Supporting information for the use of immunomodulators for COVID-19 associated hyperinflammation and patients requiring oxygen therapy, non-invasive or invasive ventilation or ECMO (including dexamethasone, anakinra, tocilizumab, sarilumab and ruxolitinib) is available at https://www.ctag-support.org.uk/immunomodulators

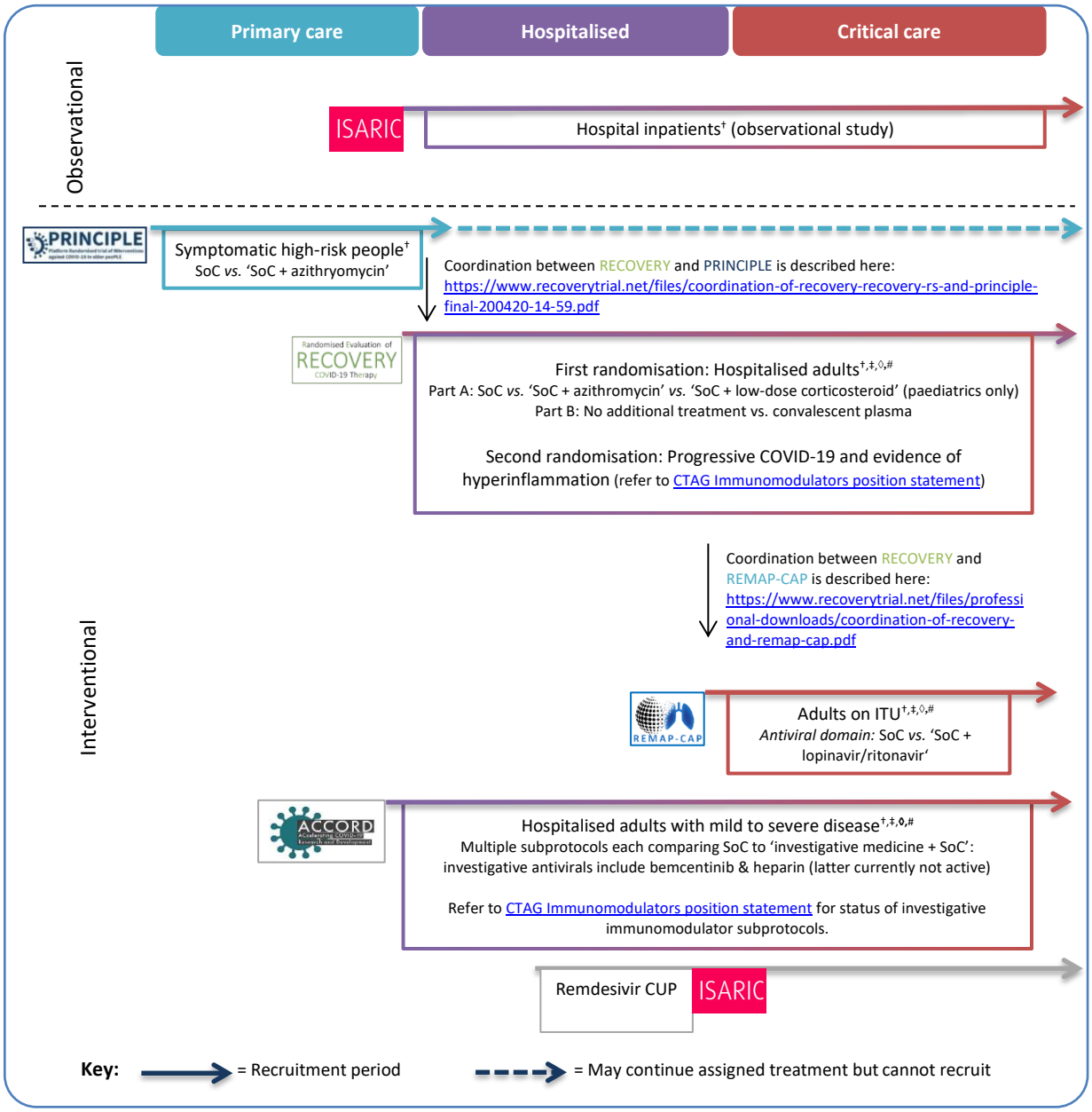

Figure 1: **Antiviral components for recruiting UK clinical studies as at 10 July 2020 (excludes trials of antiviral prophylaxis).** SoC; standard of care. CUP; compassionate use programme. † Nationally prioritised research study for COVID-19 https://www.nihr.ac.uk/covid-studies/. ‡ These studies also include domains which are outside the scope of this document (e.g. immunomodulators, anticoagulation). ◊ These studies allow the use of remdesivir, both before enrolment and during the study (except REMAP-CAP if >36hrs of treatment has been received). Studies without this annotation have not confirmed whether the use of remdesivir before or during the study is permitted. # Concurrent use of dexathasone permitted (except with interferon arm of REMAP-CAP).

3. Prophylaxis: Supporting information

3.1. Refer to information in 2.1 to 2.3

3.2. The following prioritised trials for investigative antiviral medicines for the prevention of COVID-19 are open to recruitment:

- COPCOV (healthcare workers or hospitalised patients or relatives exposed or potentially exposed or other high risk groups; international with UK sites)

4. UK clinical studies investigating antiviral medicines

4.1. NIHR is working with the Department of Health and Social Care (DHSC) to coordinate the national research agenda[9].

4.2. Organisations should prioritise support for Urgent Public Health COVID-19 studies which have been nationally prioritised[9]. Non-prioritised research should continue, subject to it not having a negative impact on the system's ability to recruit participants and provide the resources needed to support priority clinical studies[2].

4.3. A complete list of nationally prioritised research studies for COVID-19 is available on the NIHR website https://www.nihr.ac.uk/covid-studies/

4.4. Antiviral interventional studies and observational studies of relevance to COVID-19 treatment are summarised below:

- Table 1: Active studies
- Table 2: Proposed studies (not all nationally prioritised)
- Table 3: Closed to recruitment

4.5. For trials investigating immunomodulatory medicines, please refer to https://www.ctag-support.org.uk/immunomodulators

Table 1: Recruiting in the UK - Antiviral interventional clinical trials and observational studies

Status	Trial		Cohort	Interventions
Recruiting	Interventional	PRINCIPLE[†] (UK study; ISRCTN86534580)	Primary care; higher risk individuals (≥65 years or ≥50 years with specified illness) with suspected or confirmed COVID-19	– SoC – Azithromycin + SoC
		RECOVERY[†,‡,◊,#] (UK study, open to all Trusts; ISRCTN16912075)	First randomisation (Part A & B simultaneously): Hospital inpatients; adults and paediatrics (any age) with suspected or confirmed COVID-19 Second randomisation: Progressive COVID-19 (SpO2 <92% on room air or requiring oxygen) and CRP ≥75 mg/L **Patients receiving dexamethasone, or remdesivir (either by CMA or by CUP) are eligible for RECOVERY[10,11].**	First randomisation – Part A[§]: – SoC – Azithromycin + SoC – Low-dose corticosteroids + SoC (paediatrics only) First randomisation – Part B: – No additional treatment – Convalecent plasma Second randomisation[§] in addition to the first randomisation (refer to CTAG Immunomodulators position statement): – No additional treatment – Tocilizumab
		REMAP-CAP[†,‡,◊,#] (International study with UK sites; NCT02735707)	Critical care; adults (≥18 years) with suspected or confirmed COVID-19. **Patients receiving dexamethasone, or remdesivir (either by CMA or by CUP) are eligible for REMAP-CAP[12,13].**	Antiviral domains for COVID-19: – SoC – Lopinavir/ritonavir + SoC Note: three other COVID-19 domains are available; prolonged macrolide therapy, alternative corticosteroid strategies, immune modulation therapy (refer to CTAG Immunomodulators position statement).
		COPCOV[†] (UK study; NCT04303507)	– Preventative treatment for healthcare workers (≥16 years)	• Placebo • Hydroxychloroquine **MHRA have approved a request to recommence recruitment (link)**
		ACCORD-2[‡,◊,#] (UK Phase II clinical trials program)	Potentially different for each sub-protocol **Patients receiving dexamethasone or remdesivir (either by CMA or by CUP) are eligible for ACCORD-2[14,15].**	Multiple subprotocols including: • Bemcentinib + SoC vs. SoC • Heparin + SoC vs. SoC **(inactive)** • Refer to CTAG Immunomodulators position statement for status of investigative immunomodulator subprotocols.

Status	Trial		Cohort	Interventions
	Observational	ISARIC-CCP† (International study; ISRCTN66726260)	– Hospital inpatients; confirmed COVID-19.	• N/A – study has multiple objectives (see protocol); including describing clinical features and response to treatments. Case Record Forms (CRF) are available.

† Nationally prioritised research study for COVID-19 https://www.nihr.ac.uk/covid-studies/ ‡ These studies also include domains which are outside the scope of this document (e.g. immunomodulators). § Not all paediatric age groups are eligible for all treatment arms, refer to trial protocol for arm specific eligibility criteria. ◊ Concurrent use of is permitted. # Concurrent use of dexathasone permitted (except with interferon arm of REMAP-CAP).

Table 2: Proposed in the UK - Antiviral interventional clinical trials

Status	Trial		Cohort	Interventions
Proposed	Interventional	CROWN CORONATION (International study with UK sites; NCT04333732)	Preventative treatment for healthcare workers	• Low-dose chloroquine • Mid-dose chloroquine • High-dose chloroquine • Placebo

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Table 3: Closed to recruitment in the UK - Antiviral interventional clinical trials

Status	Trial	Cohort	Interventions
Closed to recruitment	ACTT Stage1† (International study with limited UK sites; NCT04280705)	Hospital inpatients (≥18 years); adults with confirmed COVID-19 (severe disease)	(result) – Placebo + SoC – Remdesivir + SoC
	GS-5774† (International study with UK sites; NCT04292730)	Hospital inpatients; adult or adolescents (≥12 years) weighing ≥40 kg with confirmed COVID-19 (moderate disease)	Part A: – SoC – Remdesivir 5 days + SoC – Remdesivir 10 days + SoC Part B (extension treatment group): Remdesivir 10 days + SoC
	GS-5773† (International study with UK sites; NCT04292899)	Hospital inpatients; adult or adolescents (≥12 years) weighing ≥40 kg with confirmed COVID-19 (severe disease)	Part A (result; not mechanically ventilated): – Remdesivir 5 days + SoC – Remdesivir 10 days + SoC Part B (mechanically ventilated and extension treatment groups): Remdesivir 10 days + SoC
	SNG016† (Phase II study, UK study with limited sites[16]; 2020-001023-14) *This study is listed as SARS-CoV-2 infection on the NIHR website*	Hospital inpatients; adults (≥18 years) with confirmed COVID-19[17]	• Placebo + SoC • Inhaled interferon (SNG001) + SoC
	RECOVERY†	Hospital inpatients; adults	First randomisation – Part A:

	(UK study, open to all Trusts; ISRCTN16912075)	and paediatrics (any age) with suspected or confirmed COVID-19	• Hydroxychloroquine + SoC (result) • Lopinavir-ritonavir + SoC (result) • Low-dose dexamethasone (result)

† Nationally prioritised research study for COVID-19 https://www.nihr.ac.uk/covid-studies/

5. NHS implementation of Conditional Marketing Authorisation for remdesivir

Remdesivir 100 mg concentrate for solution for infusion / Remdesivir 100 mg powder for concentrate for solution for infusion (Veklury®; conditional marketing authorisation)						
Indication[7,8,18]	**Dose**[8,18]	**Duration**[8,18]	**Exclusion criteria**[7,8,18]	**Stopping criteria**[7,8,18]	**Drug specific monitoring**[8,18]	**Supply**
As per SPC • Treatment of patients hospitalised with COVID-19 • Adults and adolescents (≥12 years with body weight ≥40 kg) • Pneumonia requiring supplemental oxygen • Use of remdesivir is confined to healthcare facilities in which patients can be monitored closely	• Day 1 – single loading dose of remdesivir 200 mg given by intravenous infusion • Day 2 onwards – 100 mg given once daily by intravenous infusion Infuse dose over 30 -120 minutes; see the SPC for the relevant product for full details, and Medusa for local variations: https://injmed.wales.nhs.uk/IVGuideDisplay.asp	The total duration of treatment should be at least 5 days and not more than 10 days	• Remdesivir should not be used in patients with eGFR < 30ml/min • Remdesivir should not be initiated in patients with ALT ≥ 5 times the upper limit of normal (ULN) at baseline	Remdesivir should be discontinued in patients who develop: • ALT ≥ 5 times the ULN during treatment. It may be restarted when the ALT is < 5 times the ULN • Or ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase or INR	Limited information available, generally well tolerated. Reversible Grade 1 or 2 ALT or AST elevation observed. Daily monitoring of renal (creatinine and BUN) and liver (ALT, AST) functions should be performed.	Refer to the Interim Clinical Commisioning Policy In times of limited supply, additional criteria must be met in order to allocate remdesivir to those with the greatest capacity to benefit (refer to commissioning policy)

6. Gilead compassionate use programme for remdesivir

Remdesivir infusion (formerly GS-5734)						
Eligibility criteria[19]	**Exclusion criteria**[19]	**Dose**[4]	**Duration**[19]	**Special precautions**[4]	**Drug specific monitoring**[4]	**Supply route**[19]
• Children <12years of age • Adolescents aged 12-17 years and weighing <40 kg • Hospitalization • Confirmed COVID-19 • Severe manifestation of disease	○ Evidence of Multi-organ failure ○ Pressor requirement to maintain blood pressure ○ ALT levels > 5 X ULN ○ Creatinine Clearance <30 mL/min or dialysis or Continuous Veno-Venous Hemofiltration ○ Concomitant administration of other investigational medicines for COVID-19 is not permitted while receiving remdesivir.	Infuse dose over 30 -120 minutes; see the EAMS treatment protocol for the relevant product for full details. See Medusa for full details https://injmed.wales.nhs.uk/IVGuideDisplay.asp Dosing information may vary to the above and should be guided by ID/Virology and dosing protocol provided by Gilead. Support for the management of paediatrics is not within scope. For paediatric dosing, please contact Gilead directly.	10 days but may continue for an additional 4 days at 100 mg IV once-daily if COVID-19 remains detectable at day 10 of treatment.	No information for dose adjustment in liver and renal impairment (likely would be excluded from the programme)	Limited information available, generally well tolerated. Reversible Grade 1 or 2 ALT or AST elevation observed. Daily monitoring of renal (creatinine and BUN) and liver (ALT, AST) functions should be performed	Requests for remdesivir for individual patient use at https://rdvcu.gilead.com/. Any communication with Gilead should include UKICOVID-19@gilead.com

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8. 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

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.

We broadly hierarchised the evidence according to the following matrix and considered the available safety data.

Virus tested	Evidence of benefit	
SARS-CoV-2	Human controlled intervention trial	Greatest evidence ↕ Least evidence
SARS-CoV	Human observational study	
MERS-CoV	Nonhuman primate experimental	
Other betacoronavirus	Small animal experimental	
	In vitro	
	Theoretical	

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 4: Benefit may exceed risk
- Table 5: Inadequate data to recommend use

Table 4: Evidence base for specific therapies for SARS-CoV-2 infection: Benefit exceeds risk

*S=SARS, M=MERS, S2=SARS-CoV-2; iv=in vitro, a=animal, c=clinical.

Remdesivir				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; Miv; S2iv Sa; Ma; S2c	Nucleotide prodrug with activity against a number of unrelated RNA viruses. Potent inhibition of SARS-CoV, MERS-CoV and bat coronaviruses with pandemic potential in human airway epithelial cells *in vitro*, with sub-micromolar EC50 values. In a mouse model of SARS-CoV, prophylactic and early therapeutic administration significantly reduces lung viral load and improves clinical signs of disease and respiratory function; later treatment, initiated at peak viral replication, reduces lung viral loads but does not alter clinical outcome. In a nonhuman primate model of MERS-CoV infection, prophylactic or early treatment improves clinical respiratory function and radiological signs, and reduces lung viral load and histopathological changes. Direct comparison with combination lopinavir/ritonavir and interferon-beta *in vitro* and in mouse models of MERS-CoV infection demonstrated greater virological, clinical and histopathological benefit with remdesivir.	**NICE have published rapid evidence summary for remdesivir: https://www.nice.org.uk/advice/es27/chapter/Key-messages** 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[20]. 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. A preliminary report of a double-blind, randomized, controlled trial among adults hospitalized with COVID-19 with evidence of lower respiratory tract involvement compared remdesivir to placebo[3]. Preliminary results from the 1059 patients with data available showed shorter time to recovery with remdesivir (median 11 days (95% CI 9-12) in remdesivir arm, *vs.* 15 days (13-19) in placebo arm (rate ratio for recovery 1.32; 95% CI 1.12-1.55; P<0.001). Mortality was numerically lower in the remdesivir group than in the placebo group, but the difference was not significant. Kaplan Meier 14-day mortality estimates were 7.1% with remdesivir *vs.* 11.9% with placebo (hazard ratio for death 0.70; 95% CI 0.47-1.04). Final report awaited. An open-label randomized, controlled trial of 397 hospitalized patients with SARS-CoV-2 pneumonia compared 10-day *vs.* 5-day courses of remdesivir.[21] 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).	No significant adverse safety signals detected in the COVID-19 RCTs[20].	Refer to the Interim Clinical Commissioning Policy and the compassionate use programme criteria at: https://rdvcu.gilead.com

Table 5. Evidence base for specific therapies for SARS-CoV-2 infection: Inadequate data to recommend use

*S=SARS, M=MERS, S2=SARS-CoV-2; iv=in vitro, a=animal, c=clinical.

Lopinavir/ritonavir				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; Miv Ma Sc; S2c	Protease inhibitor developed for HIV, a completely unrelated virus. In vitro data for both MERS and SARS-CoV are variable but suggest low potency inhibition at clinically achievable concentrations. No animal studies of SARS-CoV. In a nonhuman primate model of MERS, early treatment improved clinical, radiological and pathological features and reduced viral loads. In two retrospective, matched cohort studies of SARS, early but not rescue LPV/r treatment was associated with improved clinical outcomes, but interpretation is difficult because of multiple other uncontrolled interventions (ribavirin, corticosteroids) in these patients. Compassionate use in the S. Korea MERS outbreak was not informative about efficacy; no preliminary results available from ongoing MERS clinical trial in KSA. Combination LPV/r and ribavirin appeared beneficial in a small study of post-exposure prophylaxis against MERS in healthcare workers. Direct comparison between remdesivir, lopinavir/ritonavir, and interferon-beta *in vitro* and in mouse models of MERS-CoV infection demonstrated greater virological, clinical and histopathological benefit with remdesivir.	Unpublished data indicate that lopinavir is inhibitory at uM concentrations for SARS-CoV-2 in Vero cell culture. An exploratory RCT assessing lopinavir/ritonavir or arbidol 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 LPV/r 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.[22] 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).[23(p19)] An open-label multicentre RCT in Hong Kong comparing treatment with subcutaneous IFNβ-1b, ribavirin & lopinavir/ritonavir, to lopinavir/ritonavir alone (n=41), in hospitalized patients with mild-moderate COVID-19 is described in the Interferon (systemic) table.[24] The RECOVERY randomised controlled trial issued a press release announcing closure of recruitment to the trial's lopinavir-ritonavir arm (n=1,596 *vs.* 3,376 randomised to usual care) following a data monitoring review. There was no significant difference in the primary endpoint of 28-day mortality (22.1% lopinavir-ritonavir vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91-1.18]; p=0.58). However, the investigators note that they were unable to study a large number of patients on invasive mechanical ventilation because of difficulty administering the drug to patients on ventilators. Therefore, conclusions could not be made regarding effectiveness among mechanically ventilated patients. Full results are awaited.	Well established agent with well understood toxicity profile. Gastrointestinal side effects are very common. Note multiple, significant drug-drug interactions.	Licensed for the treatment of HIV-1 infection. Included in REMAP-CAP trial

Chloroquine (CQ) / Hydroxychloroquine (HCQ)				
Studies perfor-med*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; S2iv; S2c	Inhibitory *in vitro* for SARS-CoV but the selective index is low. In one murine model of SARS intraperitoneal chloroquine was ineffective in inhibiting lung virus titers. For multiple other viruses, potent *in vitro* activity has not translated into benefit in animal or clinical studies. In some cases, CQ has been shown to enhance viral replication in animal models, probably because of its immunomodulatory effects. In both a nonhuman primate model and clinical trial in chickungunya infection (which is unrelated to SARS-CoV-2), CQ treatment resulted in worse outcomes, despite promising antiviral activity *in vitro*.	Effective inhibition of SARS-CoV-2 replication *in vitro*.[25] An abstract from China reported a small (n=30) randomised trial of HCQ, with no difference observed in negative conversion rate of SARS-CoV-2 PCR at day 7 between HCQ and SoC.[26] A small trial from China (n=22) compared CQ with lopinavir-ritonavir[27] and reported earlier improvement in chest CT appearances and earlier discharge (100% vs 50% at day 14) in the CQ group. It is not clear if the study was randomised, and it was not powered to detect clinical outcomes. Two randomised trials from China have compared HQ with SoC in hospitalised patients with mild-moderate COVID-19. The first (n=150, open-label[28]) reported no difference between arms in viral negative conversion 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%) reported in the HCQ arm. There were low rates of progression to severe disease and no mortality in the trial cohort. The second, released as a preprint (n=62, blinding unclear[29]), reported faster time to clinical recovery with HCQ, defined by normalisation of body temperature (1 day quicker) and faster time to chest CT improvement (80.6% vs 54.8% at day 6). Eventual clinical outcomes are not reported. It is stated that other antiviral treatments are used in the SoC arm, but these are not specified. Two large observational studies from the USA report associations between treatment with HCQ and intubation or mortality. The first study (1446 consecutive patients, 58.9% of whom received HCQ)[30] found no association between HCQ and a composite endpoint of intubation or death. The second study (1438 patients treated with either HCQ, azithromycin, both or neither, with an aggregate 70% of patients receiving a HCQ-containing regimen)[31] also found no association between HCQ and mortality. The RECOVERY randomised controlled trial, a multi-arm multi-centre open-label study which recruited hospitalised COVID-19 patients in the UK, issued a press release announcing closure of recruitment to the trial's HCQ arm following a data monitoring review. This identified no significant difference between the HCQ arm (1542 patients) and the SoC arm (3132 patients) in the trial's primary endpoint of mortality at 28 days: 25.7% mortality in the HCQ group versus 23.5% in the SoC group, HR 1.11 (95% CI 0.98-1.26). Secondary outcome data were not reported but the investigators state that no beneficial effects were observed for length of stay or other outcomes. Publication of the full results is awaited.	Well established agent, defined safety profile as antimalarial drug; however, safety in acute viral illness is not established and studies raise concerns. A publication reports findings from a randomised trial of CQ in Brazil, which stopped recruitment to its higher dose arm (600mg BD for 10 days) early, due to a safety signal for QTc prolongation and fatality.[32] The EMA issued a public health statement on 23/04/2020 cautioning clinicians to closely monitor QTc intervals in patients receiving HCQ/CQ, particularly at higher doses or when taken in combination with azithromycin.[33] After the initial publication of the now-retracted study in the Lancet which reported concerns about mortality with HCQ, the UK RECOVERY trial released a statement advising it would continue recruiting to its HCQ arm after an urgent review of unblinded data did not identify any safety concerns precluding this. The trial subsequently closed recruitment to this arm after no mortality benefit was identified with HCQ.	Various licensed indications, including malaria and rheumatoid arthritis. Included in COP-OV trial (prophylaxis)

Interferon (systemic)				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; Miv Sa; Ma Sc; Mc S2iv; S2c	Type I (α, β), type II (γ), and type III (λ) IFNs all show activity against SARS-CoV in extensive *in vitro* studies. Type I (α, β) IFNs have shown activity in limited animal and observational clinical studies. Dose-related reductions in lung viral titers were found in In mice dosed intraperitoneally with IFN- B/D beginning 4 h after SARS-CoV exposure. One small observational study of IFN-aflacon-1 combined with corticosteroids reported improved clinical outcomes in SARS. *In vitro*, MERS-CoV appears to be more sensitive to type I IFNs than SARS-CoV, especially IFN-β. Some animal evidence of benefit of early treatment with IFN-β1b in nonhuman primate model of severe disease. Observational studies of IFN-α combined with ribavirin have yielded inconclusive results; the largest study found no evidence for reduced mortality or for an antiviral effect. There are no preliminary results available from ongoing MERS clinical trial of systemic IFN- β-1b combined with lopinavir-ritonavir in the Kingdom of Saudi Arabia.	Unpublished in vitro data indicate that SARS-CoV is more susceptible to IFN- β-1a and -1b than to IFN- α. A preprint reports in vitro data indicating that SARS-CoV2 is more susceptible than SARS-CoV to pre-treatment with IFNα-, when cultured in Vero cells.[34] 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 intervention group had significantly shorter times to positive-to-negative viral conversion of NP swabs (using RT-PCR)s: 7 days versus 12 days, HR 4.37. Significant findings are also reported for secondary outcomes including shorter time to clinical recovery in the intervention group (4 days versus 8 days) and shorter length of hospital stay (9 days versus 14.5 days). The trial was not blinded and observer bias may confound subjective clinical endpoints. The majority of patients had mild disease and no mortality was observed, so it is not clear if findings can be generalized to patients with severe disease. There is heterogeneity in the intervention arm, as IFNβ treatment was only used in patients randomized to the 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. Further trials comparing IFNβ with standard of care or placebo would be required to confirm this finding. A preprint reports an open-label RCT carried out in a single centre in Iran, comparing SoC plus subcutaneous IFNβ-1a (three times per week for 2 weeks, n=42), to SoC alone (n=39).[35] 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 assessed on a 6 category ordinal scale. 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 are excluded from the intervention arm because of mortality within the 1st week of treatment.	Well established agent with defined but complex safety profile. Clinicians experienced in managing side effects should be consulted e.g. those who have treated hepatitis C virus (HCV) infection and multiple sclerosis.	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. IFN-β injection: included as an arm in the immune modulation domain of REMAP-CAP trial (recruiting)

Interferon (nebulised)				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; Miv S2iv; S2c	Please see "Interferon (systemic)" for a summary of *in vitro* and animal model data regarding IFN, SARS-CoV and MERS. To date, there have been no animal studies reported investigating inhaled interferon in models of SARS or MERS. To date, there have been no clinical trials reported of inhaled interferon therapies in SARS or MERS.	Please see "Interferon (systemic)" for a summary of *in vitro* data regarding IFN and SARS-CoV-2. To date, there have been no animal studies of inhaled interferon in models of SARS-CoV-2. An retrospective study in China assessed patients classified as having moderate (n=22) or severe (n=21) COVID-19, who were treated with nebulized IFNα-2b alongside other interventions including unspecified oral antivirals & ribavirin.[36] Patients classified as having mild disease (n=12) had not received IFN. The moderate group were combined with patients with mild disease for analysis, in comparison to the severe group. Outcomes were similar in the 2 groups with resolution of clinical manifestations by 2 weeks in 85.7% of patients in the severe group, and 91.2% patients in the mild/moderate group). No conclusions can be drawn as the study was not randomized and analysis was not stratified by use of interferon. A preprint reports a retrospective study in China (n=77) which assessed hospitalized patients treated with nebulized IFN-α2b versus those treated with the oral antiviral umifenovir (arbidol), versus those treated with both in combination.[37(p19)] The authors report significantly shorter times to viral clearance on throat swabs, and lower circulating inflammatory markers (IL-6 and CRP), in the groups who received nebulized IFNα-2b. However, no clinical outcomes are reported, and findings may be confounded as the study was not randomized or blinded. Furthermore, the patients in the group who did not receive IFN treatment were significantly older than the IFN-treated groups (median age 64.5 versus 40.4 or 41.3) and had higher rates of comorbidities (54% versus 15.2% or 14.3%).	No reported safety data in the context of human coronaviruses. A phase II human trials 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.[38]	One clinical formulation made by Synairgen, SNG001, a nebulised formulation of IFNβ-1a. It is not currently available in the UK for compassionate use but this may be subject to change (https://www.synairgen.com/) . Phase II clinical trial of SNG001 in COVID-19 sponsored by Synairgen, SNG016 has completed recruitment in the UK (EudraCT number - 2020-001023-14, https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001023-14/GB)

Azithromycin				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Mc, S2c	Macrolide antibiotic. Reported to have *in vitro* activity against the unrelated RNA virus Zika virus (ZIKV) in cultured glial cells & astrocytes. Reported to have *in vitro* activity against the unrelated virus rhinovirus in cultures of bronchial epithelial cells. Reported to have *in vitro* activity against influenza virus by blocking viral internalisation, and was effective in a mouse model of influenza. Reported to have *in vitro* activity against the unrelated RNA virus Ebola virus (EBOV), but was not effective in small animal models of EBOV infection. Mechanisms of antiviral activity have not been identified. To date, there have been no reported *in vitro* studies testing the effect of azithromycin against SARS-CoV or MERS-CoV. To date, there have been no reported animal models testing the effect of azithromycin on SARS or MERS. An observational cohort study of 349 critically ill MERS patients in Saudi Arabia, of whom 136 (39%) received macrolide therapy, showed no association of macrolide therapy with 90-day mortality or time to viral clearance (using RT-PCR).	To date, there have been no reported in vitro studies or animal models testing the effect of azithromycin on SARS-CoV2. Azithromycin was given in two small, open-label SARS-CoV-2 studies in France.[39,40] In the first non-randomised study, 20 patients receiving HCQ (6 of whom received azithromycin) were compared to 16 controls with a reduction in viral load reported; however, there were no quantitative PCR results, 6 patients were excluded, no ITT analysis, and trial was underpowered. In the second observational cohort study, all patients received HCQ and azithromycin (n=80), reporting a reduction in viral load and clinical improvement in most patients. However, there was no control group, unclear eligibility criteria, and it was underpowered for clinical outcomes.	Well established agent with well understood toxicity profile including gastrointestinal upset (common) and QT prolongation (uncommon).	Various licensed indications as an antimicrobial. Included as an arm in the UK RECOVERY trial. Prolonged macrolide therapy is also an existing arm in REMAP-CAP trial, but with immunomodulatory rather than antiviral intent.

Convalescent Plasma				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; Miv Sa; Ma Sc; Mc S2c	*In vitro* evidence demonstrates neutralisation of SARS-COV2 and MERS-CoV by specific antibodies. Animal models of SARS and MERS suggest neutralising antibodies or convalescent plasma may be efficacious for prophylaxis and/or treatment. Retrospective observational clinical studies in SARS report improvements in mortality, or time to clinical improvement, in patients treated with convalescent plasma in comparison to groups who did not receive the treatment. These studies were small, non-randomised and at risk of bias. No RCTs of convalescent plasma for treatment of SARS or MERS have been performed. A clinical trial (NCT02190799) assessing feasibility and safety of convalescent plasma treatment in MERS was initiated, but did not recruit any patients and was withdrawn. Several RCTs have been performed assessing hyperimmune plasma or immunoglobulin for treatment of severe influenza. While one small trial comparing hyperimmune IVIG with standard IVIG reported a mortality benefit in patients with pandemic H1N1 influenza, others have not replicated this benefit. A pooled meta-analysis assessed effectiveness of convalescent plasma or hyperimmune immunoglobulin in treatment of SARS or severe influenza (Mair-Jenkins et al, 2015). The authors report a pooled odds ratio of 0.25 (95% CI 0.14-0.45) for mortality, although they note that the included studies were mainly of low quality and at high risk of bias.	Four case series of between 5-25 patients with severe or life-threatening COVID-19 described outcomes following convalescent plasma administration[41–44]. Where reported, viral loads decreased, SARS-CoV-2–specific ELISA and neutralizing antibody titers increased or remained high, and clinical improvement occurred among most patients. No specific adverse events were reported. However, inference is limited by the lack of control groups and the administration of concurrent therapies, including unspecified antivirals, steroids and supportive care. A preprint compared outcomes among 39 patients with severe to life-threatening COVID-19 who received convalescent plasma to a cohort of propensity score- matched controls (matching based on age, sex, comorbidities, severity, insurance, co-administered therapies)[45]. In a covariate-adjusted Cox model, convalescent plasma transfusion improved survival for non-intubated patients (hazard ratio 0.19; 95% CI 0.05-0.72; p=0.015), but not for intubated patients (1.24; 0.33-4.67; p=0.752). However, this was an observational study with the potential for residual confounding; inferences are therefore limited. 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[46]. 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.	Transfusion-related adverse events well-recognised. 2/52 patients who received convalescent plasma in the RCT from China[46] experienced transfusion-associated adverse events; both improved with supportive care.	Included as an arm in the UK RECOVERY trial.

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