Position Statement: Management of COVID-19 in adults with investigational agents

Interim Support for clinicians in England

Document management

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Document control

Date	Version	Amendments
23 Mar 2020	1.0	New document
23 Mar 2020	1.1	Updated Gilead compassionate use scheme 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.

Contents

1. Aim

1.1. This position statement provides interim supporting information on the pharmacological management of adult patients with COVID-19 and will be superseded when specific guidance is published by NHS England, Department of Health and Social Care or Public Health England.

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.

2. Interim supporting information

2.1. There are no anti-viral medicines or vaccinations approved to treat or prevent human coronaviruses.[1] There is no randomised controlled trial evidence that any treatment beyond best supportive care delivers improved outcomes for patients with COVID-19 as of 31 March 2020. [2,3]

2.2. Several investigative agents have potential to be repurposed for the management of COVID-19[1,2]; the risk-benefit of these agents is summarised in Appendix 1.

2.3. Investigative agents should only be used in the context of a clinical trial using supplies allocated for clinical trial use[a].

2.4. As relevant trials open, hospitals managing COVID-19 cases are encouraged to engage with their R&D services to adopt trials of investigative agents and establish capacity to recruit into those trials – refer to Section 3.

- The RECOVERY trial (UK study) is endorsed by NHS England[b] and opened to recruitment at all Trusts on 20 March 2020
  - Standard of care [SoC] *versus* lopinavir/ritonavir + SoC *versus* hydroxychloroquine + SoC *versus* interferon beta-1a + SoC *versus* dexamethasone + SoC
- The REMAP-CAP trial (international critical care study, UK sites) is also recruiting. Two new domains specific for COVID-19 have been granted ethical approval:
  - Antiviral therapy: evaluating no antiviral therapy (and no placebo), and lopinavir/ritonavir
  - Immune modulation therapy: evaluating no immune-modulating therapy (and no placebo), interferon-beta-1a, and anakinra

2.5. For clinicians unable access investigative agents within the context of a clinical trial, remdesivir can be considered for patients who meet the Gilead compassionate access programme eligibility criteria – refer to Section 4. This scheme is due to be replaced by an expanded access programme in the near future[5].

2.6. Clinicians should be reassured that, irrespective of whether or not their patients meet compassionate access criteria, best supportive care remains the optimal approach to management outside of a clinical trial.

2.7. Recruitment into the ISARIC-CCP study is strongly encouraged for any patient, including those receiving experimental or unlicensed therapies. Co-recruitment into the ISARIC-CCP study does not preclude enrolment into a clinical trial of investigative medicinal products (CTIMP).

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[a] MHRA recommends chloroquine and hydroxychloroquine are only used for the treatment and prevention of COVID-19 within the context of a clinical trial[4]

[b] NHS England & NHS Improvement suggest Trusts consider enrolling patients into UK clinical trials, including the RECOVERY trial[3]

2.8. Patients may be admitted into hospitals receiving interventional treatment from primary care e.g. PRINCIPLE trial. Where identified, treatment should usually be continued if clinically appropriate as enrolment into subsequent interventional trials may not be precluded (Figure 1).

2.9. No recommendations can be made at the current time about the appropriate use of off-label immunomodulatory medicines for the treatment of coronavirus outside of a clinical trial e.g. anakinra, tocilizumab, sarilumab or ruxolitinib.

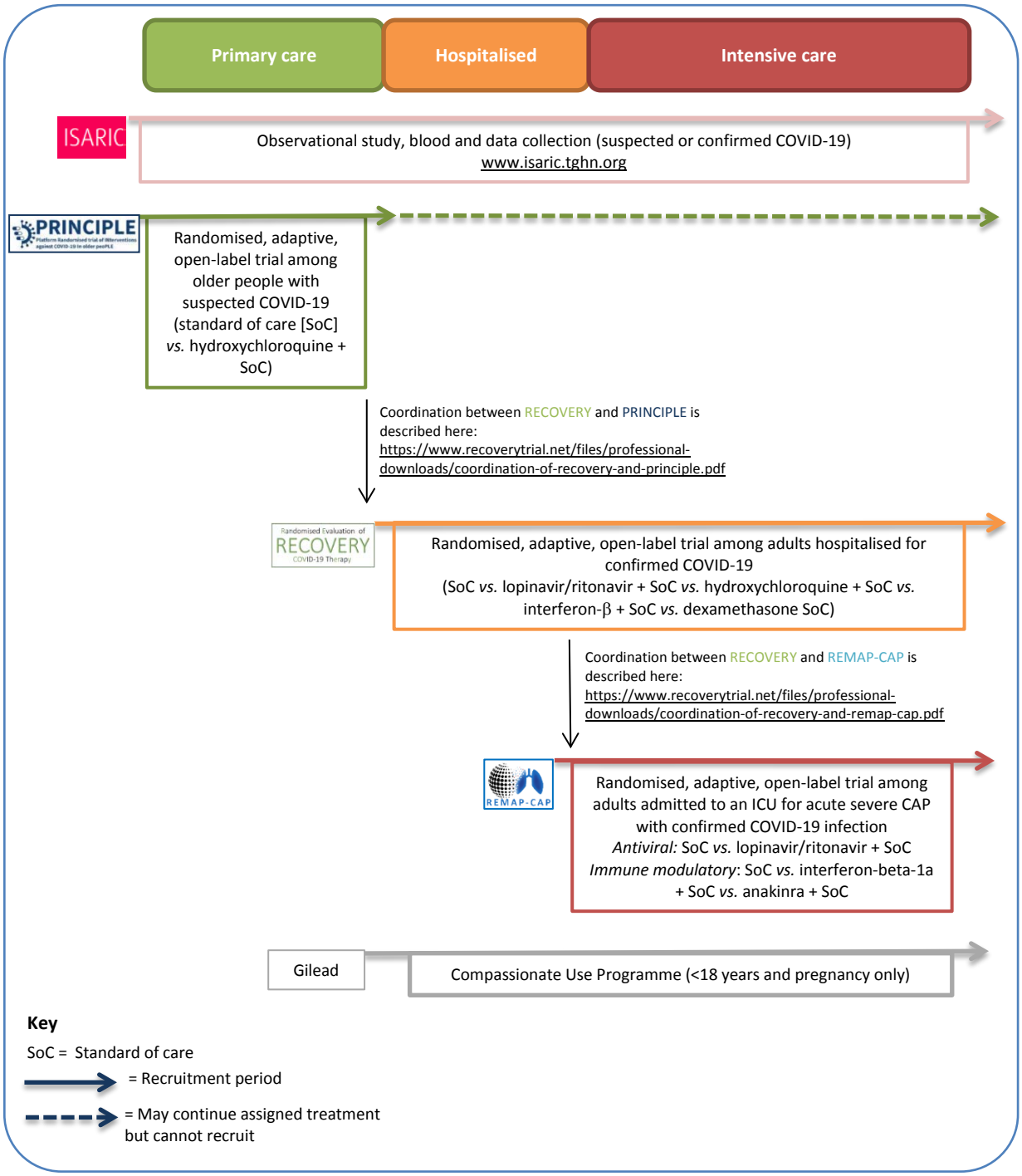

Figure 1: Active UK Clinical Studies as at 30 March 2020 (Figure will be updated as new studies are activated for UK patient recruitment). Participation for COVID-19 trials will be through adoption at local sites, information should be available at through local Research and Development Offices. There are a number of trials that are also undergoing contract amendments to include patient recruitment due to complications of COVID-19, including HLH and ARDS that your patients may be eligible for.

3. UK clinical studies

3.1. NIHR is working with the Department of Health and Social Care (DHSC) to coordinate the national research agenda[6].

3.2. Organisations should prioritise support for studies which have been nationally prioritised and pause any local studies that impede their ability to contribute to national research efforts[6].

3.3. A complete list of nationally prioritised research studies for COVID-19 is available on the NIHR website

3.4. The following interventional clinical trials and national observational studies are active in the UK for recruitment:

- ISARIC-CCP UK Case Record Forms (CRF) are available for the collection of standardised clinical data on suspected or confirmed cases of COVID-19
- PRINCIPLE trial (UK study open to Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) general practices) for patients with possible COVID-19 if ≥65 years or ≥50 years with pre-existing comorbidities
  - Standard of care [SoC] *versus* hydroxychloroquine + SoC
- RECOVERY trial (UK study open to all Trusts)
  - Standard of care [SoC] *versus* lopinavir/ritonavir + SoC *versus* hydroxychloroquine + SoC *versus* interferon beta-1a + SoC *versus* dexamethasone + SoC
- REMAP-CAP (international critical care study, UK sites); expanded to include two new domains specific for COVID-19 have been granted ethical approval:
  - Antiviral therapy: evaluating no antiviral therapy (and no placebo), and lopinavir/ritonavir
  - Immune modulation therapy: evaluating no immune-modulating therapy (and no placebo), interferon-beta-1a, and interleukin-1 receptor antagonist (anakinra)

3.5. The following interventional clinical trials and national observational studies are emerging or proposed in the UK:

- GS-5773 trial in patients with severe infection (multinational study, limited UK sites)
  - Part A (not mechanically ventilated): Remdesivir 5 days + SoC *versus* Remdesivir 10 days + SoC
  - Part B (mechanically ventilated and extension treatment group): Remdesivir 10 days + SoC
- GS-5774 trial in patients with moderate infection (multinational study, limited UK sites)
  - Part A: SoC *versus* Remdesivir 5 days + SoC *versus* Remdesivir 10 days + SoC
  - Part B (extension treatment group): Remdesivir 10 days + SoC
- Study to evaluate tocilizumab in patients with severe COVID-19 Pneumonia (tocilizumab *versus* placebo)
- DISCOVERY trial (WHO pan-European; SoC *versus* remdesivir + SoC *versus* lopinavir/ritonavir + SoC *versus* lopinavir/ritonavir + interferon beta-1a injection + SoC)
- ACTT trial (limited UK sites; remdesivir *versus* standard-of-care)
- Proposal to amend the REALIST trial (acute respiratory distress syndrome) to include patients with COVID-19 / HLH and use of anakinra or tocilizumab

4. Gilead compassionate use programme

Remdesivir infusion (formerly GS-5734; unlicensed medicine)						
Eligibility criteria*	**Exclusion criteria***	**Dose**	**Duration**	**Special precautions**	**Drug specific monitoring**	**Supply route***
Pregnant women or children less than 18 years of age with severe manifestations of the disease[5]	Nil pre-specified.	Adult and adolescent (≥ 40 kg) - 200 mg IV loading dose on Day 1 followed by 100 mg IV once-daily on Day 2 onwards. Infuse dose over 30 minutes[7] Dosing information may vary to the above and should be guided by ID/Virology and dosing protocol provided by Gilead.	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.[7]	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.[4] Daily monitoring of renal (creatinine and BUN) and liver (ALT, AST) functions should be performed[7]	Requests for remdesivir for individual patient use at https://rdvcu.gilead.com/. Any communication with Gilead should include UKICOVID-19@gilead.com[3]
Further information: https://www.who.int/ebola/drc-2018/summaries-of-evidence-experimental-therapeutics.pdf?ua=1 **As at 22 March 2020 Gilead is transitioning the provision of emergency access to remdesivir from individual compassionate use (CU) to expanded access programs (EAP). During this transition period Gilead is unable to accept new individual CU requests however anticipate the EAP will initiate in a similar timeframe that any new requests for CU would have been processed. Exceptions will be made only for pregnant women or children less than 18 years of age with confirmed COVID-19 and severe manifestations of disease.*						

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4. MHRA. Chloroquine and Hydroxychloroquine not licensed for coronavirus (COVID-19) treatment. https://www.gov.uk/government/news/chloroquine-and-hydroxychloroquine-not-licensed-for-coronavirus-covid-19-treatment.

5. Email communication with Gilead (Dr Shayon Shalehi). (2020).

6. National Institute for Health Research. NIHR's response to COVID-19. https://www.nihr.ac.uk/covid-19/.

7. World Health Organisation. WHO R&D Blueprint – Ad-hoc Expert Consultation on clinical trials for Ebola Therapeutics. Appendix 4. Summaries of evidence from selected experimental therapeutics. (2018).

6. Provenance: COVID-19 Therapeutics Advice & Support Group (CTAG)

The UK collaborative COVID-19 Therapeutics Advice & Support Group comprises of the following:

- Dr Jake Dunning (Consultant, Infectious Diseases; Royal Free London)
- Dr Sir Michael Jacobs (Consultant, Infectious Diseases; Royal Free London)
- Dr Michael Brown (Consultant, Infectious Diseases; UCL Hospitals)
- Prof Graham Cooke (Consultant, Infectious Diseases; Imperial)
- Dr Jonathan Edgeworth (Consultant, Microbiology; Guys & St Thomas')
- Prof Thomas Harrison (Consultant, Infectious Diseases; St Georges)
- Dr Laurence John (Consultant, Infectious Diseases; London North West)
- Prof Mahdad Noursadeghi (Consultant, Infectious Diseases; UCL Hospitals)
- Dr Sanjay Bhagani (Consultant, Infectious Diseases; Royal Free London)
- Dr Anna Goodman (Consultant, Infectious Diseases; Guys & St Thomas')
- Dr Matthias Schmid (Consultant, Infectious Diseases; Newcastle upon Tyne)
- Dr Anna Tunbridge (Consultant, Infectious Diseases; Sheffield)
- Dr Michael Beadsworth (Consultant, Infectious Diseases; Liverpool)
- Dr Meera Chand (Consultant, Microbiology; Public Health England)
- Dr David Price (Consultant, Infectious Diseases; Newcastle upon Tyne)
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- Ms Mehreen Kassam (Pharmacist, North Central London)

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: generic guidance is available elsewhere and is recommended for use until specific evidence emerges relating to COVID-19.

Methods

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

We reviewed the available data on treatment of betacoronaviruses and broadly hierarchised the evidence according to the following matrix:

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	

For relevant compounds, we then also considered the available safety data.

Therapies that are plausible and supported by reasonable body of *in vitro*, animal and/or clinical data are shown in the following tables. A large number of other compounds have been evaluated for *in vitro* inhibition of SARS-CoV-2 and/or other betacoronavirus replication, and some have demonstrated an inhibitory effect at serum concentrations that might be achieved in patients. However, without animal studies or well-documented experience of clinical use in comparable contexts, these are not currently recommended for clinical use in COVID-19 patients. Similarly, some drugs have theoretical potential for benefit in COVD-19 patients but no supporting data, and are not recommended for use. Drugs in these categories are not listed in the tables, with the exception of any that have been widely proposed as current treatment options for COVID-19.

Evidence summary

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

1) Benefit may exceed risk, potentially suitable for compassionate use (Table 1)
2) Inadequate data to recommended compassionate use currently, await further data (Table 2)

Table 1: Evidence base for specific therapies for SARS-CoV-2 infection: Benefit may exceed risk, potentially suitable for compassionate use

*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 Several non-UK S2c studies in progress and expected to report Apr 2020	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.	Inhibits SARS-CoV-2 replication in Vero cells with a low micromolar EC50 value.	Manufacturer reports two phase 1 human trials completed, results not published. Phase 2 trial in Ebola Virus Disease (EVD) survivors (NCT 02818582) fully recruited but not yet reported. Extensive therapeutic use in 2018-20 Ebola outbreak in DRC, but trials designed for efficacy and only limited interpretation of safety is possible: no significant adverse safety signal detected.	Limited supply available for compassionate use (March 2020) and use is restricted to specific patient groups; refer to compassionate use programme details at: https://rdcvu.gilead.com International clinical trials (manufacturer's website): https://www.gilead.com/purpose/advancing-global-health/covid-19/remdesivir-clinical-trials

Table 2. Evidence base for specific therapies for SARS-CoV-2 infection: Inadequate data to recommended compassionate use currently, await further data

*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.. One observational study in COVID-19 patients did not find reduced duration of viral RNA detection in those receiving lopinavir-ritonavir. 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. Lopinavir-ritonavir recipients spent less time in hospital (12 vs. 14 days) and less time in intensive care (6 vs. 11 days).	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 as an arm in the UK RECOVERY trial and REMAP-CAP trial (recruiting).

Chloroquine (CQ) / Hydroxychloroquine (HCQ)				
Studies performed*	**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.* HCQ given in a small (n=36), open-label, non-randomised trial in France, with and without azithromycin, with a reduction in viral load reported; however, no quantitative PCR results, 6 patients were excluded, no ITT analysis, and trial was underpowered. Abstract from China reported small (n=30) randomised trial of HCQ, with no difference observered in negative conversion rate of SARS-CoV-2 PCR at day 7 between HCQ group and standard care group.	Well established agent, defined safety profile as antimalarial drug; however, safety in acute viral illness is not established and studies, albeit with unrelated viruses, raise concerns (see data).	Various licensed indications, including malaria and rheumatoid arthritis. Included as an arm in the UK RECOVERY trial and PRINCIPLE trial (recruiting).

Interferon (systemic)				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; Miv Sa; Ma Sc; Mc	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.	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. Injection: included as an arm in REMAP-CAP trial (recruiting) Nebulised: included as an arm in the UK RECOVERY trial (recruiting).

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