1. Aim

1.1. This position statement for hospital clinicians provides interim supporting information on the appropriate use of investigational anti-viral agents in the management of adult patients with COVID-19. This interim position statement will be superseded when specific guidance is published by NHS England, Department of Health and Social Care, Public Health England or the National Institute for Health and Care Excellence.

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 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 03 April 2020. [2,3]

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

2.3. Investigative anti-viral agents should be used in the context of a clinical trial[a,c] using supplies allocated for clinical trial use.

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 anti-viral agents and establish capacity to recruit into those trials – refer to Section 3.

2.5. The following hospital-only trials are urgent public health research studies for COVID-19:

- RECOVERY (in hospital trial; UK study open to all Trusts) is endorsed by NHS England[b] and the Chief Medical Officer (CMO)[c]
- REMAP-CAP (critical care trial; international with UK sites) added immunomodulatory and anti-viral domains for COVID-19. It is endorsed by the CMO and is open to recruitment
- ACTT (in hospital severe infection trial; international with UK sites)
- GS-5773 (in hospital moderate infection trial; international with UK sites)
- GS-5774 (in hospital severe infection trial; international with UK sites)

2.6. For clinicians unable to access investigative agents within the context of a clinical trial, Gilead have a remdesivir Expanded Access Programme and organisations can contact Gilead to discuss participation in this programme. A Compassionate Access Programme is also available – refer to Section 4.

2.7. 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.

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

[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]

[c] Chief Medical Officers have specified PRINICPLE, RECOVERY and REMAP-CAP are key national trials and strongly discourage the use of off-licence treatments outside of a trial, where participation in a trial is possible[5]

3. UK clinical studies

3.1. The Chief Medical Officer for England recommends that any treatment given for coronavirus other than general supportive care, treatment for underlying conditions, and antibiotics for secondary bacterial complications, should currently be as part of a trial, where that is possible[5]

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

3.3. 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].

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

- Anti-viral interventional studies and observational studies are summarised in Table 1.
- Emerging or proposed anti-viral interventional studies are summarised in Table 2.

Table 1: Anti-viral interventional clinical trials and observational studies in the UK – recruiting

Status	Trial	Cohort	Interventions
Nationally prioritised by NIHR and recruiting	ISARIC-CCP (International observational study)	Suspected or confirmed COVID-19.	NA Case Record Forms (CRF) are available for the collection of standardised clinical data on suspected or confirmed cases of COVID-19
	PRINCIPLE (UK study)	Primary care; higher risk individuals with suspected or confirmed COVID-19	– SoC – Hydroxychloroquine + SoC
	RECOVERY (UK study, open to all Trusts)	Hospital inpatients; adults with confirmed COVID-19	– SoC – Lopinavir/ritonavir + SoC – Hydroxychloroquine + SoC – Dexamethasone + SoC
	REMAP-CAP (International study with UK sites)	Critical care; adults with suspected or confirmed COVID-19	Anti-viral domains for COVID-19: – SoC – Lopinavir/ritonavir + SoC
	ACTT (International study with limited UK sites)	Hospital inpatients; adults with severe disease	– Placebo + SoC – Remdesivir + SoC
	GS-5773 (International study with UK sites)	Hospital inpatients; adult or adolescents weighing ≥40 kg with severe disease	Part A (not mechanically ventilated): – Remdesivir 5 days + SoC – Remdesivir 10 days + SoC Part B (mechanically ventilated and extension treatment group): – Remdesivir 10 days + SoC
	GS-5774 (International study with UK sites)	Hospital inpatients; adult or adolescents weighing ≥40 kg with moderate disease	Part A: – SoC – Remdesivir 5 days + SoC – Remdesivir 10 days + SoC Part B (extension treatment group): – Remdesivir 10 days + SoC

Table 2: Anti-viral interventional clinical trials in the UK – emerging or proposed in the UK

Status	Trial	Cohort	Interventions
Emerging or proposed in the UK	DisCoVeRy trial (add-on trial to the pan-European WHO Global SOLIDARITY Trial)	Hospital inpatients	• SoC • Remdesivir + SoC • Lopinavir/ritonavir + SoC • Lopinavir/ritonavir + interferon beta-1a injection + SoC • Hydroxychloroquine + SoC
	SG016 (Phase II study, UK study with limited sites[7])	Hospital inpatients	• Placebo + SoC • Inhaled interferon (SNG001) + SoC
	COPCOV (UK study)	Preventative treatment for healthcare workers	• Placebo • Chloroquine/hydroxychloroquine

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)