Treatments for Highest Risk Non-Hospitalised Patients (adults and children) with COVID-19

Neutralising monoclonal antibodies (nMABs) are synthetic monoclonal antibodies that bind to the spike protein of SARS-CoV-2, preventing subsequent entry of the virus into the host cell and its replication. This effectively 'neutralises' the virus particle. Antiviral medications inhibit viral replication and prevent progression of infection.

The following products are licensed for use in patients with COVID-19 who do not require supplemental oxygen but are at high risk of progression to severe COVID19 (please refer to the current Summary of Product Characteristics (SmPCs) for further details of the individual marketing authorisations):

- **Antivirals**
  - Nirmatrelvir/ritonavir (Paxlovid®)
  - Remdesivir
  - Molnupiravir
- **nMABs**
  - Sotrovimab (Xevudy®)

The Scottish Medicines Consortium (SMC) collaborated with National Institute for Health and Care Excellence (NICE) on the Multiple Technology Appraisal (MTA) 878, which includes positive treatment recommendations for the following licensed COVID-19 treatments relevant to this guideline; nirmatrelvir plus ritonavir (Paxlovid®) and sotrovimab (Xevudy®). The recommendations are also applicable to NHS Scotland.

Final MTA treatment recommendations for molnupiravir (Lagevrio®) and remdesivir (Veklury®) are unlikely to be available until later in 2023 as they are subject to appeal. In the meantime, NICE's COVID-19 rapid guideline covers the use of these medicines.

1. Allowed Prescribers

Antivirals (nirmatrelvir/ritonavir (Paxlovid®); OR remdesivir; OR molnupiravir) or an nMAB (sotrovimab) for the treatment of COVID-19:

- must only be initiated by a General Practitioner alone or in conjunction with the relevant specialist
  must be prescribed on the Adastra system within the Covid Assessment Centre and in the case of remdesivir and sotrovimab, also on an Infusion Therapy Recording Chart.

2. Eligibility criteria

Non-hospitalised patients with COVID-19 are eligible to be considered for **one** of the treatment options if **all** of the initial access criteria are met:

2.1 Initial access criteria:

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) testing OR lateral flow test

AND

- Symptomatic with COVID-19 and showing no signs of clinical recovery

AND

- Do not require supplemental oxygen for COVID-19.

AND

- Have increased risk for progression to severe COVID-19, as defined in the independent advisory group report commissioned by the Department of Health (as defined in **Appendix 1 or 2 depending on the patient's age**). Further advice may be required from the speciality who manages this condition(s) for the patient.

Children and adolescents

- Eligible children and adolescents may **only** be considered for treatment with remdesivir (weighing 40kg and above) or sotrovimab (for those aged 12 years and above AND weighing 40kg and above).
- A national paediatric multi-disciplinary team (MDT) assessment is required to determine clinical capacity to benefit from the treatment, so contact should be made with the Duty Paediatrician to discuss. Additional criteria for this patient group can be found in appendix 2.
- In addition for this patient group, should one of the intravenous treatment options be required discussion should include where this will be administered.

2.2 Exclusion criteria

Patients are **not** eligible for treatment if any of the following apply:

- Require hospital-level care for the management of acute COVID-19 illness.
- Known hypersensitivity reaction to the active substances or to any of the excipients of the products as listed in the respective Summary of Product Characteristics (SmPC)

2.3 Treatment choice

Eligible patients may be considered for treatment with **one** of the following:

First-line	Nirmatrelvir/ritonavir (Paxlovid®) (antiviral - oral)
Alternative treatment options	Sotrovimab (nMAB – intravenous infusion) Remdesivir (antiviral – intravenous infusion) Molnupiravir (antiviral - oral)

- Combination treatment with an antiviral and an nMAB is **NOT** routinely recommended

- Patients who have previously received treatment with an antiviral or nMAB, and who meet the eligibility criteria above, may receive treatment under this policy for a subsequent infective episode, if clinically appropriate.

If the initial criteria are met, patients are eligible to be considered for **one** of the following treatment options where all the additional access criteria and none of the additional exclusion criteria are met

Medicine choice	
Nirmatrelvir/ ritonavir (Paxlovid®) ***First line***	**Additional access criteria** • Treatment is commenced within 5 days of symptom onset
	Additional exclusion criteria • under 18 years of age • pregnancy • severe hepatic impairment • stage 4-5 chronic kidney disease (CKD) • patient is taking any medications contraindicated with nirmatrelvir/ritonavir (Paxlovid®) (see table 1 in SmPC and see section 2.4 below for further information) **Cautions** • refer to the SmPC for special warnings and precautions for use. • nirmatrelvir/ritonavir (Paxlovid®) has a risk of serious adverse reactions due to interactions with other medicinal products (see table 2 in SmPC and section 2.4 below on drug interactions for additional information). • Hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering nirmatrelvir/ritonavir (Paxlovid®) to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.
Alternative treatment options	
Sotrovimab	**Additional access criteria** • Treatment is delivered within 5 days of symptom onset **AND** • Nirmatrelvir/ritonavir (Paxlovid®) is contraindicated or unsuitable
	Additional exclusion criteria • under 12 years of age • aged 12-17 years weighing less than 40kg • refer to the SmPC for special warnings and precautions for use.
Remdesivir	**Additional access criteria** • Treatment is commenced within 7 days of symptom onset **AND** • Treatment with nirmatrelvir/ritonavir (Paxlovid®) is contraindicated or unsuitable *NICE COVID-19 rapid guideline: Managing COVID-19, (published 29 March 2023), advises when assessing the person, take into account their*

	likely response to any vaccinations already given, any comorbidities or risk factors, and whether their condition is deteriorating.
	Additional exclusion criteria • children and young people weighing less than 40kg • Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 (except in patients with end-stage renal disease on haemodialysis – discuss with Renal Team) • Baseline ALT ≥5 times the upper limit of normal • Co-administration of remdesivir and chloroquine phosphate or hydroxychloroquine sulphate is not recommended • refer to the SmPC for special warnings and precautions for use. Remdesivir should be discontinued in patients who develop **any** of the following: • ALT ≥ 5 times the upper limit of normal during treatment with remdesivir (remdesivir may be restarted when ALT is < 5 times the upper limit of normal) • ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR). An individual clinical decision should be made as to whether pre-treatment urea and electrolytes and liver function tests are required based upon whether recent bloods are available or the patient is considered at risk of undiagnosed liver or kidney disease. If the patient experiences clinical deterioration such that hospitalisation and low-flow supplemental oxygen is required, the patient may be considered for treatment with a 5-day course of remdesivir as per ADTC 357: remdesivir in patients hospitalised due to COVID-19.
Molnupiravir	**Additional access criteria** • Treatment is commenced within 5 days of symptom onset *NICE COVID-19 rapid guideline: Managing COVID-19 (published 29 March 2023), advises when assessing the person, take into account their likely response to any vaccinations already given, any comorbidities or risk factors, and whether their condition is deteriorating.*
	Additional exclusion criteria • under 18 years of age • pregnancy • refer to the SmPC for special warnings and precautions for use.

2.4 Drug Interactions

- There is no interaction expected between remdesivir, molnupiravir or sotrovimab and other current treatments for COVID-19.
- Further information on interactions can be found within the SmPCs of the relevant products or via the University of Liverpool COVID-19 Drug Interactions website.

Additional information for nirmatrelvir/ritonavir (Paxlovid®)

- Initiation of nirmatrelvir/ritonavir (Paxlovid®), a CYP3A inhibitor, in patients receiving medicinal products metabolised by CYP3A or initiation of medicinal products metabolised by CYP3A in patients already receiving nirmatrelvir/ritonavir, may increase plasma concentrations of medicinal products metabolised by CYP3A. Initiation of medicinal products that inhibit or induce CYP3A may increase or decrease concentrations of nirmatrelvir/ritonavir, respectively. These interactions may lead to:
  - Clinically significant adverse reactions, potentially leading to severe, life-threatening or fatal events from greater exposures of concomitant medicinal products.
  - Clinically significant adverse reactions from greater exposures of nirmatrelvir/ritonavir (Paxlovid®).
  - Loss of therapeutic effect of nirmatrelvir/ritonavir (Paxlovid®) and possible development of viral resistance.
- A number of useful resources can be accessed to provide further guidance on these interactions and their management:
  - SmPC for nirmatrelvir/ritonavir (Paxlovid®)
  - University of Liverpool COVID-19 Drug Interactions website and their Prescribing Resources, which includes a guide on assessing a patient for treatment with Paxlovid®.

2.5 COVID-19 vaccines

nMABs (e.g. sotrovimab) is not intended to be used as a substitute for vaccination against COVID-19.

Concomitant administration of an nMAB with COVID-19 vaccines has not been studied. Refer to local/national guidelines for vaccine administration and guidance on the risks associated with administration of a SARS-CoV-2 vaccine.

Further information on the timing of COVID-19 vaccination following administration of an nMAB is available at the following sites:

- Liverpool COVID-19 Interactions (covid19-druginteractions.org)
- COVID-19: the green book, chapter 14a. UK Health Security Agency

3. Pregnancy, breastfeeding, use in women of childbearing potential and effect on fertility

In **all** cases of pregnancy and breastfeeding, senior Obstetric advice should be sought to ensure that theoretical risks to the fetus (or baby in the case of breastfeeding) do not outweigh proven benefits to the mother. In some cases of breastfeeding, it may be more appropriate to seek advice from a pediatrician.

Clinicians should refer to the SmPCs of the relevant products for further information on their use in pregnancy, breast feeding, women of childbearing potential and effects on fertility.

In addition the current guidance from the Royal College of Obstetricians and Gynaecologists on Coronavirus (COVID-19), infection in pregnancy should be followed.

All healthcare professionals are asked to ensure that any patients who receive a COVID-19 antiviral while pregnant are reported to the UK COVID-19 antivirals in pregnancy registry on 0344 892 0909 so that they can be followed up. For more information, go to https://www.medicinesinpregnancy.org/COVID-19-Antivirals-Pregnancy-Registry.

Nirmatrelvir/ritonavir (Paxlovid®)

- There are no human data on its use during pregnancy to inform the drug-associated risk of adverse developmental outcomes, women of childbearing potential should avoid becoming pregnant during treatment with Paxlovid®.
- Paxlovid® is **not recommended** during pregnancy and in women of childbearing potential not using effective contraception. Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment and until after one complete menstrual cycle after stopping Paxlovid®.
- There are no human data on the use of Paxlovid® in breast-feeding. It is unknown whether nirmatrelvir is excreted in human or animal milk, and the effects of it on the breast-fed newborn/infant, or the effects on milk production. Limited published data reports that ritonavir is present in human milk. Breast-feeding should be discontinued during treatment with Paxlovid® and for 7 days after the last dose of Paxlovid®.

Sotrovimab

- There are no data from its use in pregnant women. The SmPC for sotrovimab states that sotrovimab may be used during pregnancy where the expected benefit to the mother justifies the risk to the foetus.
- There are no data on the excretion of sotrovimab in human milk. The potential treatment benefit or risk to the newborn or infants via breastfeeding is not known. Decisions on whether to breastfeed during treatment or to abstain from sotrovimab therapy should take into account the benefit of breast-feeding for the child and the benefit of therapy for the woman**.**

Remdesivir

- There are no or limited amount of data from the use of remdesivir in pregnant women. Remdesivir should be avoided in pregnancy unless clinicians believe the benefits of treatment outweigh the risks to the individual (see SmPC for further information).
- Women of child-bearing potential have to use effective contraception during treatment.
- It is unknown whether remdesivir is excreted in human milk or the effects on the breast-fed infant, or the effects on milk production. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from remdesivir therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Molnupiravir

- no data from its use in pregnant women. Studies in animals have shown reproductive toxicity. Molnupiravir is **not recommended** during pregnancy.
- All individuals of childbearing potential who are prescribed molnupiravir should be advised to use effective contraception for the duration of treatment and for four days after the last dose of molnupiravir.
- Unknown whether molnupiravir or any of the metabolites of molnupiravir are present in human milk, affect human milk production, or have effect on the breastfed infant. Based on the potential for adverse reactions on the infant from molnupiravir, breast-feeding is not recommended during treatment and for 4 days after the last dose of molnupiravir.

4. Dosing, administration, supplies, preparation and monitoring requirements

4.1 Nirmatrelvir/ritonavir (Paxlovid®)	
Dose	Recommended dose of nirmatrelvir/ritonavir (Paxlovid®) is; 300mg (two 150mg tablets) of nirmatrelvir with 100mg (one 100mg tablet) ritonavir taken together orally twice daily for 5 days. In patients with **moderate renal impairment (CKD stage 3),** the dose of nirmatrelvir/ritonavir (Paxlovid®) should be reduced to nirmatrelvir 150mg (one 150mg tablet) with 100mg (one 100mg tablet) ritonavir taken together orally twice daily for 5 days. **NB:** *need to ensure that the required dose modification can be delivered safely.*
Supplies & Storage	Paxlovid® will be supplied from the pharmacy department. Pre-labelled packs of Paxlovid® containing 30 tablets, packaged in cartons containing 5 daily-dose blister cards. Each daily-dose blister card contains four nirmatrelvir tablets and two ritonavir tablets will be supplied to the Covid Assessment Centre from the Pharmacy Department, UHC and can be re-ordered during normal working hours. Stock is also located at Arran War Memorial Hospital and Lady Margaret Hospital Millport. Separate over labelled packs for those requiring a dose reduction will also be available – care should be taken to supply the correct pack. Arrangements should be made to ensure the patient can access the treatment without having to attend the service in person (e.g. courier delivery or medicine collected on behalf of the patient, depending on options available within the treatment window). This may include delivery to patients already admitted or resident in another facility.
Administration	Paxlovid® should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of onset of symptoms. Clinicians should assure themselves that patients are able to swallow the oral tablets. Refer to the University of Liverpool COVID-19 Drug Interactions Checker for further information on administration to patients with swallowing problems. Note these recommendations may be *off-label, refer to the NHS Ayrshire & Arran Code of Practice for Medicines Governance Section 9 (b) "Off-label use of medicines" for further information.* Patients should be advised of the possible gastro-intestinal side-effects of treatment with Paxlovid® (e.g. nausea, vomiting). If such side-effects are experienced, anti-emetics should be considered that are not contra-indicated. If Paxlovid® treatment cannot be tolerated, an alternative treatment can be considered within the options and criteria of this policy. Combination treatment should not be provided. A missed dose should be taken as soon as possible and within 8 hours of the scheduled time, and the normal dosing schedule should be resumed. If more than 8 hours has elapsed, the missed dose should not be taken and the treatment should resume according to the normal dosing schedule. If a patient requires hospital-based care due to severe or critical COVID-19 after starting treatment with Paxlovid®, the patient should complete the full 5-day treatment course at the discretion of their consultant.

4.2 Sotrovimab	
Dose	The recommended dose of **sotrovimab** is 500mg to be administered as a **single** intravenous infusion No dose adjustment is recommended in elderly patients or those with renal or hepatic impairment.
Supplies & Storage	• Sotrovimab will be supplied from the pharmacy department. • Each infusion should be prepared using vials and consumables kits which will be supplied to the Covid Assessment Centre from the Pharmacy Department, UHC and can be re-ordered during normal working hours. Stock is also located at Arran War Memorial Hospital and Lady Margaret Hospital Millport. • Vials containing 500mg of sotrovimab must be stored in a refrigerator between 2-8°C
Preparation	• Consumables kits contain a preparation worksheet which should be completed and filed in the patient's notes. Preparation requires a two person check for each stage of the process. • For further information refer to the drug monograph within the Medusa Injectable Medicines Guide available on AthenA.
Administration	• The recommended dose should be administered as a single intravenous infusion and be given over 30 minutes via a 0.2 micron in-line filter using an infusion pump. • Resuscitation and anaphylaxis treatment facilities must be readily available. • Sotrovimab should only be administered during daytime hours. • For further information refer to the drug monograph within the Medusa Injectable Medicines Guide available on AthenA.
Monitoring	Hypersensitivity reactions, including serious and/or life-threatening reactions such as anaphylaxis, have been reported following infusion of sotrovimab. Hypersensitivity reactions typically occur within 24 hours of infusion. Signs and symptoms of these reactions may include nausea, chills, dizziness (or syncope), rash, urticaria and flushing. If signs and symptoms of severe hypersensitivity reactions occur, administration should be discontinued immediately and appropriate treatment and/or supportive care should be initiated. If mild to moderate hypersensitivity reactions occur, slowing or stopping the infusion along with appropriate supportive care should be considered. **Baseline observations** should be recorded using the NEWS (National Early Warning Score) chart (or a PEWS chart if being used in paediatric patients) and repeated every 15 minutes during the infusion and then every 30 minutes until 1 hour post infusion. Note that hypersensitivity reactions can occur during or within 24 hours of the infusion and patients should be advised accordingly to report any signs.

4.3 Remdesivir	
Dose	Recommended dose of remdesivir is 200mg intravenously on day 1 followed by 100mg intravenously on days 2 and 3. Treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 7 days of symptom onset.
Supplies & Storage	• Remdesivir 100mg powder for solution for infusion will be supplied from the pharmacy department. • Each infusion should be prepared using vials and consumables kits which will be supplied to the Covid Assessment Centre from the Pharmacy Department, UHC and can be re-ordered during normal working hours. Stock is also located at Arran War Memorial Hospital and Lady Margaret Hospital Millport. • Vials must be stored at room temperature.
Preparation	• Consumables kits contain a preparation worksheet which should be completed and filed in the patient's notes. Preparation requires a two person check for each stage of the process. • For further information please see the drug monograph within the Medusa Injectable Medicines Guide available on AthenA.
Administration	• The recommended dose should be administered as a single intravenous infusion. • Infusions should be given over 30 to 120 minutes using an infusion pump. After the infusion is complete, flush with at least 30ml of 0.9% sodium chloride. • Resuscitation and anaphylaxis treatment facilities must be readily available. • Remdesivir should only be administered during daytime hours. • For further information, please see the drug monograph within the Medusa Injectable Medicines Guide available on AthenA.
Monitoring	• Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. • Patients should be monitored for hypersensitivity reactions during and following administration of remdesivir as clinically appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, administration of remdesivir should be discontinued immediately and appropriate treatment initiated. **Baseline observations** should be recorded using the NEWS (National Early Warning Score) chart (or a PEWS chart if being used in paediatric patients) and repeated every 15 minutes during the infusion and then every 30 minutes until a minimum of 30 minutes post infusion (this may be extended based on clinical judgement). • Renal and liver function should be monitored carefully during treatment with remdesivir as clinically appropriate. • Remdesivir should be discontinued in patients who develop **any** of the following:

	○ ALT ≥ 5 times the upper limit of normal during treatment with remdesivir (remdesivir may be restarted when ALT is < 5 times the upper limit of normal) ○ ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR). • If the patient experiences clinical deterioration such that hospitalisation and low-flow supplemental oxygen is required, the patient may be considered for treatment with a 5-day course of remdesivir as per ADTC 357: remdesivir in patients hospitalised due to COVID-19.

4.4 Molnupiravir	
Dose	The recommended dose of molnupiravir is 800mg (four 200mg capsules) taken orally every 12 hours for 5 days. No dose adjustment is recommended in patients with renal or hepatic impairment.
Supplies & Storage	• Pre-labelled packs of molnupiravir (Lagevrio®) containing 40 hard capsules (entire treatment course) will be supplied to the Covid Assessment Centre from the Pharmacy Department, UHC and can be re-ordered during normal working hours. Stock is also located at Arran War Memorial Hospital and Lady Margaret Hospital Millport. • Pre-labelled packs must be stored at room temperature. • Arrangements should be made to ensure the patient can access the treatment without having to attend the service in person (e.g. courier delivery or medicine collected on behalf of the patient, depending on options available within the treatment window). This may include delivery to patients already admitted or resident in another facility.
Administration	Molnupiravir should be commenced as soon as possible after a diagnosis of COVID-19 is made and within 5 days of onset of symptoms. Clinicians should assure themselves that patients are able to swallow the oral capsules. • Molnupiravir capsules should be swallowed whole with a sufficient amount of fluid (e.g., a glass of water). The capsules should not be opened, crushed or chewed. • Patients should be strongly encouraged to complete the 5-day course. Treatment must not be extended beyond 5 days. • If the patient misses a dose of molnupiravir within 10 hours of the time it is usually taken, the patient should take as soon as possible and resume the normal dosing schedule. If a patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose. • If a patient requires hospitalisation due to severe or critical COVID-19 after starting treatment with molnupiravir, the patient should complete the full 5-day treatment course at the discretion of their healthcare provider.

5. Adverse effects

- Also refer to the monitoring within sections 4.2 and 4.3.
- Also refer to the cautions section (2.3 and 2.4) for nirmatrelvir/ritonavir (Paxlovid®) specifically for details of interactions which may lead to adverse effects.
- Also refer to the SmPCs of the relevant products for further information on adverse effects.

6. Safety reporting

Any suspected adverse reactions (including congenital malformations and/or neurodevelopmental problems following treatment during pregnancy) from any of the treatments should be reported directly to the MHRA via the dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/.
It should be noted that Paxlovid®, sotrovimab, remdesivir and molnupiravir are all black triangle medicines.

7. Communication

All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospital and primary care) should explicitly record the treatment that has been given, together with the dose and date of administration.

8. Bibliography

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Appendix 1: Defining the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs independent advisory group report, updated 05 April 2023 - **INDIVIDUALS 18 YEARS OR OLDER ONLY**

The following is an extract from the above report and should be used in conjunction with the full independent advisory group report. The footnotes referred to in the table contain a hyperlink to their detail in the full report. The following recommendations apply to **individuals 18 years or older only** – see separate table in appendix 2 for PCR-positive symptomatic cases aged older than 12 and younger than 18 years, greater than 40kg weight, and clinical concern.

Cohort	Description
Down's syndrome and other genetic disorders	All individuals with Down's syndrome or other chromosomal disorders known to affect immune competence
Solid cancer	• metastatic or locally advanced inoperable cancer • lung cancer (at any stage) • people receiving any chemotherapy (including antibody-drug conjugates), PI3K inhibitors or radiotherapy within 12 months • people who have had cancer resected within 3 months and who received no adjuvant chemotherapy or radiotherapy • people who have had cancer resected within 3 to 12 months and receiving no adjuvant chemotherapy or radiotherapy are expected to be at less risk (and thus less priority) but still at increased risk compared with the non-cancer populations

Haematological diseases and recipients of haematological stem cell transplant (HSCT)	• allogeneic HSCT recipients in the last 12 months or active graft versus host disease (GVHD) regardless of time from transplant (including HSCT for non-malignant diseases)
	• autologous HSCT recipients in the last 12 months (including HSCT for non-malignant diseases)
	• individuals with haematological malignancies who have received CAR-T cell therapy in the last 24 months, or until the lymphocyte count is within the normal range
	• individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months, or radiotherapy in the last 12 months.
	• all people who do not fit the criteria above, and are diagnosed with:
	  ○ myeloma (excluding monoclonal gammopathy of undetermined significance (MGUS))
	  ○ AL amyloidosis
	  ○ chronic B-cell lymphoproliferative disorders (chronic lymphocytic leukaemia, follicular lymphoma)
	  ○ myelodysplastic syndrome (MDS)
	  ○ chronic myelomonocytic leukaemia (CMML)
	  ○ myelofibrosis
	  ○ any mature T-cell malignancy
	• all people with sickle cell disease
	• people with thalassaemia or rare inherited anaemia with any of the following:
	  ○ severe cardiac iron overload (T2 * less than 10ms)
	  ○ severe to moderate iron overload (T2 * greater than or equal to 10ms) plus an additional co-morbidity of concern (for example, diabetes, chronic liver disease or severe hepatic iron load on MRI)
	• individuals with non-malignant haematological disorders (for example, aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic treatment (for example, anti-CD20, anti-thymocyte globulin (ATG) and alemtuzumab) within the last 12 months

Renal disease	• renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who have:
	  ○ received B cell depleting therapy within the past 12 months (including alemtuzumab, rituximab (anti-CD20), anti-thymocyte globulin)
	  ○ an additional substantial risk factor which would in isolation make them eligible for monoclonals or oral antivirals

	• non-transplant renal patients who have received a comparable level of immunosuppression. [footnote 3] • patients with chronic kidney disease (CKD) stage 4 or 5 (an eGFR less than 30ml per min per 1.73m^2) without immunosuppression.
Liver diseases	• people with cirrhosis Child-Pugh class A,B and C, whether receiving immune suppressive therapy or not. Those with decompensated liver disease (Child-Pugh B and C) are at greatest risk • people with a liver transplant • people with liver disease on immune suppressive therapy (including people with and without cirrhosis)
Solid organ transplant recipients	• Solid organ transplant recipients not in any of the above categories.
Immune-mediated inflammatory disorders [footnote 4]	• people who have received a B-cell depleting therapy (anti-CD20 drug for example rituximab, ocrelizumab, ofatumab, obinutuzumab) in the last 12 months • people who have been treated with cyclophosphamide (IV or oral) in the 6 months prior to positive PCR or relevant COVID test • people who are on corticosteroids (equivalent to greater than 10mg per day of prednisolone) for at least the 28 days prior to positive PCR • people who are on current treatment with mycophenolate mofetil, oral tacrolimus, azathioprine/mercaptopurine (for major organ involvement such as kidney, liver and/or interstitial lung disease), methotrexate (for interstitial lung disease or asthma [footnote 5] only) and/or ciclosporin. No minimum dose threshold is suggested [footnote 6] • people who exhibit at least one of: (a) uncontrolled or clinically active disease (that is required recent increase in dose or initiation of new immunosuppressive drug or IM steroid injection or course of oral steroids within the 3 months prior to positive PCR); and/or (b) other high risk comorbidities (for example, body mass index (BMI) greater than 30, diabetes mellitus, hypertension, major organ involvement such as significant kidney, liver or lung inflammation or significantly impaired renal, liver and/or lung function).
Respiratory [footnote 7]	• asthma in people on oral corticosteroids (defined above) [footnote 8]. Any asthma patient taking immunosuppressants for their asthma including but not exclusively methotrexate, ciclosporin • COPD on long term home non-invasive ventilation (NIV). Patients on long term oxygen therapy. People with moderate or severe disease who have required 4 or more courses of prednisolone 30mg for 5 days or greater in last 12 months • interstitial lung disease (ILD) - all patients with idiopathic pulmonary fibrosis • sub-types of ILD - for example, connective tissue disease related, sarcoidosis, hypersensitivity pneumonitis, NSIP (non specific interstitial pneumonia) who have received a B-cell depleting therapy in last 12 months, or IV or oral cyclophosphamide in the 6 months prior to testing positive for COVID-19. Any ILD patient on current treatment with corticosteroids, mycophenolate mofetil, azathioprine, tacrolimus, ciclosporin or methotrexate. No minimum dose criteria • any people with any type of ILD who may not be on treatment due to intolerance but has severe disease with an FVC predicted less than 60% • NIV - all patients requiring this type of support regardless of the underlying disorder (which might include COPD, obesity hypoventilation syndrome, scoliosis, bronchiectasis, genetic muscular diseases refer to neurology section) [footnote 9] • lung cancer patients, refer to 'Solid cancer' section above • lung transplant patients (refer to solid organ transplant section) • pulmonary hypertension (PH): groups 1 and 4 from PH classification[footnote 10]
Immune deficiencies	• common variable immunodeficiency (CVID) • undefined primary antibody deficiency on immunoglobulin (or eligible for Ig) • hyper-IgM syndromes • Good's syndrome (thymoma plus B-cell deficiency) • severe combined immunodeficiency (SCID)

	• autoimmune polyglandular syndromes or autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome) • primary immunodeficiency associated with impaired type 1 interferon signalling • x-linked agammaglobulinaemia (and other primary agammaglobulinaemias) • any person with secondary immunodeficiency receiving, or eligible for, immunoglobulin replacement therapy
HIV/AIDS	• people with high levels of immune suppression, have uncontrolled or untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis • people on treatment for HIV with CD4 less than 350 cells per mm^3 and stable on HIV treatment or CD4 greater than 350 cells per mm^3 and additional risk factors (for example, age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, alcoholic dependency) [footnote 11]

Neurological disorders	• Conditions associated with neuromuscular respiratory failure requiring chronic ventilatory support:
	  ○ motor neurone disease
	  ○ Duchenne muscular dystrophy
	• Conditions that require use of specific immunotherapies:[footnote 12]
	  ○ multiple sclerosis (MS)
	  ○ myasthenia gravis (MG)
	  ○ other immune mediated disorders
	• Dementia and neurodegenerative disorders when associated with severe frailty:[footnote 13]
	  • Alzheimer's disease, vascular disease, Lewy body disease, or frontotemporal atrophy
	  • Parkinson's Disease
	  • Huntington's disease
	  • progressive supranuclear palsy and multiple system atrophy

Appendix 2: Defining the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs independent advisory group report, updated 05 April 2023 - PCR-positive symptomatic cases aged older than 12 and younger than 18 years, greater than 40kg weight, and clinical concern

The following is an extract from the above report and should be used in conjunction with the full independent advisory group report. The footnotes referred to in the table contain a hyperlink to their detail in the full report.

The following is for **PCR-positive symptomatic cases aged older than 12 and younger than 18 years, greater than 40kg weight, and clinical concern.** See appendix 1 for those 18 years or older.

Non-hospitalised individuals in the older than 12 and younger than 18 years of age range considered at high risk from COVID-19 and to be prioritised for consideration of treatment with neutralising monoclonal antibodies when symptomatic and SARS-CoV-2 PCR positive. Concerned clinicians should refer for regional MDT case discussion through local established pathways, who will confirm eligibility and consider risk benefit and whether to proceed with offer of treatment.

Cohort	Description
Children and young people at substantial risk	Complex life-limiting neurodisability with recurrent respiratory infections or compromise
Children and young people at significant risk if 2 or more of these risk factors are present	**Primary immunodeficiency:** • common variable immunodeficiency (CVID) • primary antibody deficiency on immunoglobulin (or eligible for immunoglobulin replacement) • hyper-IgM syndromes • Good's syndrome (thymoma plus B-cell deficiency) • severe combined immunodeficiency (SCID) • autoimmune polyglandular syndromes or autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome) • primary immunodeficiency associated with impaired type I interferon signalling • x-linked agammaglobulinaemia (and other primary agammaglobulinaemias) **Secondary immunodeficiency:** • HIV CD4 count less than 200 cells per mm^3 • solid organ transplant • HSCT within 12 months, or with GVHD • CAR-T therapy in last 24 months • induction chemotherapy for acute lymphoblastic leukaemia (ALL), non-Hodgkin's lymphoma, chemotherapy for acute myeloid leukaemia (AML), relapsed and/or refractory leukaemia or lymphoma **Immunosuppressive treatment:** • chemotherapy within the last 3 months • cyclophosphamide within the last 3 months • corticosteroids greater than 2mg per kg per day for 28 days in last 4 weeks • B cell depleting treatment in the last 12 months **Other conditions:** • high BMI (greater than 95th centile) • severe respiratory disease (for example, cystic fibrosis or bronchiectasis with FEV1 less than 60%) • tracheostomy or long-term ventilation • severe asthma (paediatric intensive care unit (PICU) admission in 12 months) • neurodisability and/or neurodevelopmental disorders • severe cardiac disease • severe chronic kidney disease • severe liver disease • sickle cell disease or other severe haemoglobinopathy • trisomy 21 • complex or chromosomal genetic or metabolic conditions associated with significant comorbidity

	• multiple congenital anomalies associated with significant comorbidity
	• bronchopulmonary dysplasia - decisions should be made taking in to account degree of prematurity at birth and chronological age
	• infants less than 1 year with congenital heart disease (CHD):[footnote 14]
	  ○ cyanotic congenital heart disease
	  ○ haemodynamically significant acyanotic CHD and history of prematurity
	  ○ those due for corrective surgery, to avoid complications or delay due to SARS-CoV-2 infection