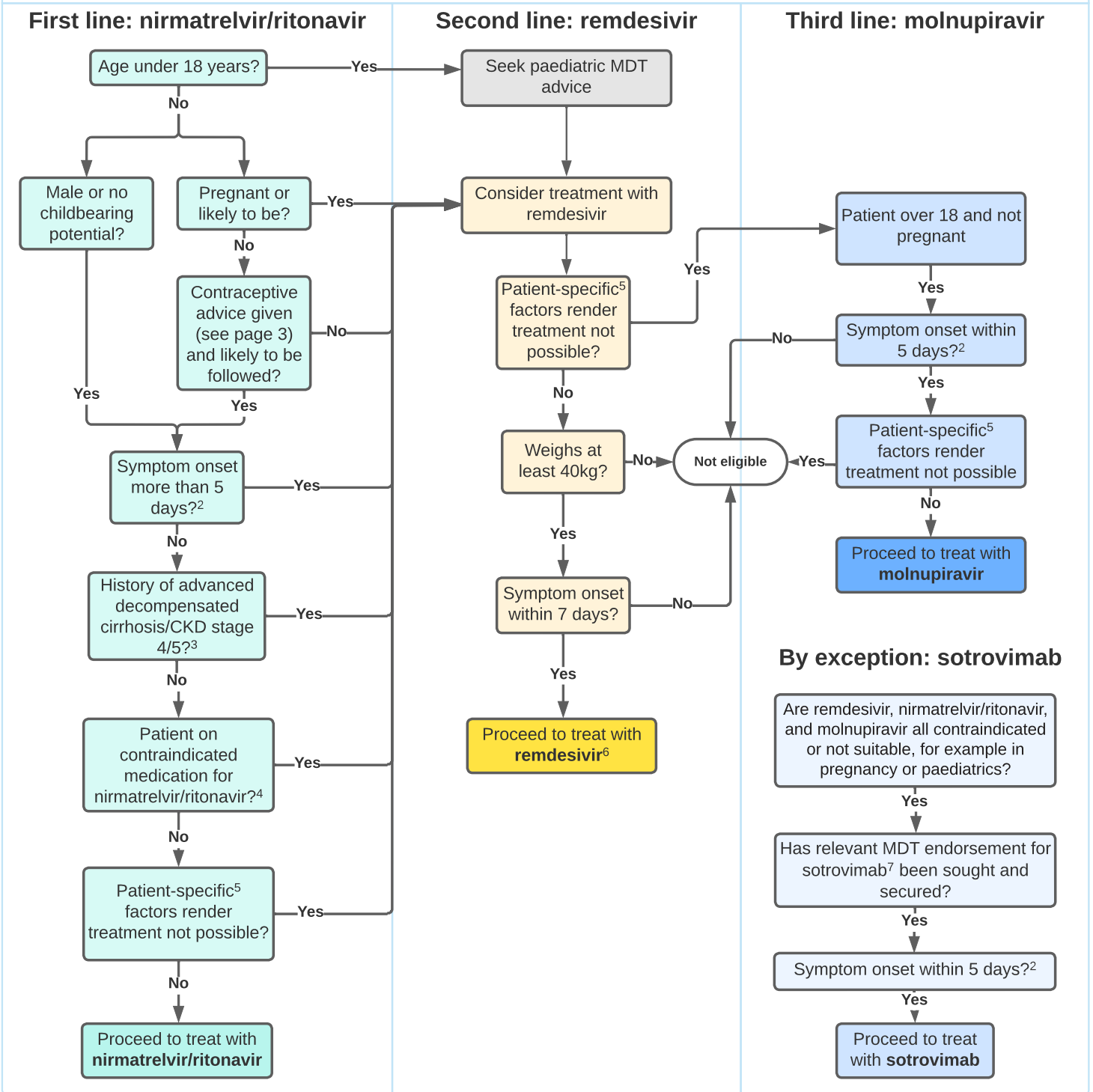
UK Interim Clinical Commissioning Policy

Therapies for symptomatic non-hospitalised adult and paediatric patients with COVID-19

Consider access to this clinical pathway under the following conditions:

- Onset of symptoms of COVID-19 within the last 5 days (for nirmatrelvir/ritonavir[1], molnupiravir and sotrovimab) or 7 days (for remdesivir), remains symptomatic and with no signs of clinical recovery
- SARS-CoV-2 infection is confirmed by either lateral flow test or PCR (registered via gov.uk or NHS 119)
- The patient is a member of a 'highest' risk group (as defined in the Department of Health and Social Care commissioned Independent Advisory Group report)
- The patient is not hospitalised for COVID-19 and is not requiring new supplemental oxygen specifically for the management of COVID-19 symptoms

Treatment options under the policy for eligible patients are now: First-line: nirmatrelvir/ritonavir(Paxlovid), administered orally. Second-line: remdesivir, administered intravenously over three sequential days. Third-line: molnupiravir, administered orally



[1] May also be known as paxlovid
[2] Treatment commencement may be extended up to a maximum of 7 days from symptom onset if clinically indicated (this would be off-label)
[3] Nirmatrelvir/ritonavir may be considered in patients with stage 3 CKD. Dose modification is required. See the Summary of Product Characteristics and the section on dosing in the policy for more information.
[4] See Specialist Pharmacy Service (SPS) guidance for nirmatrelvir/ritonavir and University of Liverpool COVID-19 Drug Interactions checker
[5] Patient-specific factors could include needle phobia and inability to receive intravenous treatment (for remdesivir) or swallowing difficulties with oral tablets (nirmatrelvir/ritonavir)
[6] Please see remdesivir specific exclusion criteria in the clinical commissioning policy
[7] Please see sotrovimab specific exclusion criteria in the clinical commissioning policy

Clinical Guide: Therapy characteristics when deciding on treatment choice

Use this guide to assist in decision making on which therapeutic option to use:

- Two products have similar relative risk reduction of reducing hospitalisation: nirmatrelvir/ritonavir and remdesivir
- Molnupiravir has a substantially lower level of efficacy - reserve when the others cannot be used
- Medicines availability will be monitored nationally and regionally, so unless otherwise directed do not consider supply issues in your decision making

Nirmatrelvir/ritonavir (Paxlovid)	Remdesivir (Veklury)	Molnupiravir (Lagevrio)
Antiviral (dual therapy)	Antiviral (monotherapy)	Antiviral (monotherapy)
Administered **orally**: 3 tablets twice a day for 5 days	Administered **intravenously**: one infusion every 24 hours for 3 days	Administered **orally**: 4 capsules twice a day for 5 days
Adults only (aged 18 years and over)	Adults and paediatric patients (weighing at least 40 kg)	Adults only (aged 18 years and over)
Evidence based on treatment within **5** days of symptom onset	Evidence based on treatment within **7** days of symptom onset	**Not recommended in pregnancy**
Not recommended in pregnancy	May be used in **pregnancy** where benefits of treatment outweigh risks	Breast-feeding should be discontinued during treatment and for 4 days after last dose
Breast-feeding should be discontinued during treatment and for 7 days after last dose	No specific advice on discontinuation of breast-feeding during treatment	May be used in severe liver and kidney disease (no dose adjustment recommended)
Contraindicated in severe liver and kidney disease	Not recommended in individuals with ALT ≥5 times the upper limit of normal or eGFR <30ml/min	No significant drug-drug interactions
Multiple significant drug-drug interactions (see SPS guidance)	No significant drug-drug interactions	30% Relative Risk Reduction of hospitalisation
88% Relative Risk Reduction of hospitalisation	87% Relative Risk Reduction of hospitalisation	

Sotrovimab (Xevudy)	
Neutralising monoclonal antibody	May be used in **pregnancy** although there is no safety data available
Administered **intravenously**: single infusion	No specific advice on discontinuation of breast-feeding during treatment
Adults and adolescents (aged 12 years and over and weighing at least 40kg)	No dose adjustment recommended in liver or renal impairment*
Evidence based on treatment within **5** days of symptom onset	No significant drug-drug interactions

For the key publications of trial results and licence click here

- Nirmatrelvir/ritonavir NEJM Feb 2022
- Nirmatrelvir/ritonavir SmPC
- Remdesivir NEJM Dec 2021
- Remdesivir SmPC
- Sotrovimab NEJM Nov 2021
- Sotrovimab SmPC
- Molnupiravir NEJM Dec 2021
- Molnupiravir SmPC

*there are limited/no data on the use of sotrovimab in patients with a creatinine clearance of <30ml/min/1.73m^2 and those with severe elevations ALT (5 - <10 x upper limit of normal)

Clinical Guide: Speciality advice for 'highest-risk' cohorts

Speciality-specific advice on the management of patients within each of the highest-risk cohorts (particularly around the use of nirmatrelvir/ritonavir) may be found in the table below. Contact your local specialist team for further guidance on issues not covered by this advice.

Cohort	Advice/guidance
Liver disease	Nirmatrelvir/ritonavir should not be administered to patients with advanced decompensated cirrhosis. Such patients can be identified by questioning or review of medical records. Patients should be asked if they have ever been admitted to hospital with liver disease and if they are currently receiving regular ascitic drainage. A positive response is a contraindication to nirmatrelvir/ritonavir. If blood tests are available a bilirubin >50 at any time is a contraindication to nirmatrelvir/ritonavir, if the jaundice is due to liver disease. Patients receiving rifaximin (only used in very advanced liver disease) should not receive nirmatrelvir/ritonavir.
Solid organ transplant (non-renal)	Nirmatrelvir/ritonavir is currently contraindicated in both Solid Organ and Islet Transplant recipients due to significant harmful drug interactions especially anti-rejection medication. These patients should be triaged to receive sotrovimab.
Renal disease (including renal transplant)	Currently nirmatrelvir/ritonavir is not indicated in the majority of at-risk individuals with renal disease, due to lack of dosing information or drug interactions. These include patients with CKD stage 4 and 5, including those on dialysis, and in transplant patients due to interactions with immunosuppressive therapy. Nirmatrelvir/ritonavir requires dose modification in people with CKD stage 3 (see product information). When nMAbs are not indicated or available, clinicians can discuss alternative treatment options such as remdesivir with renal provider clinicians. Remdesivir may be used in patients with an eGFR of ≥30ml/min/1.73m^2 and in some patients on haemodialysis (discuss with renal clinicians for further guidance).
Solid cancer (including metastases); Haematological disease (including non-malignant conditions)	Specialist cancer and haematology teams are encouraged to establish a central provider email account to receive queries from clinicians treating patients with COVID-19 with antivirals and/or nMABs. For patients who are receiving SACT or complex supportive care for malignancy or stem cell transplantation, please ask whether the patient has already been contacted or reviewed by their specialist haematology/oncology/bone marrow transplant team. If the patient has not already been in contact with their specialist, please establish the location of the provider and consider referral to the respective specialist team via the central provider email where available. Please ask the patient to have details of their current medication available for any following consultation.
Rare neurological conditions	There are no specific needs for specialist neurology services to prescribe nirmatrelvir/ritonavir, though care should be taken with those who have difficulty swallowing or have supported feeding, and for those with behavioural or psychiatric concerns. If a patient is identified as eligible for nirmatrelvir/ritonavir due to neurology risk factors then ask about swallowing difficulties. Disease-specific advice is as follows: **Multiple Sclerosis (MS)** • In addition to the medicines listed in the SPS guidance, avoid concurrent use of nirmatrelvir/ritonavir with the following: siponimod, cladribine and modafinil • For those patients taking oral or intravenous methylprednisolone discuss the steroid dose with the MS neurology team as nirmatrelvir/ritonavir may increase corticosteroid levels. **Myasthenia Gravis** • This includes muscle specific kinase (MUSK) myasthenia and the Lambert-Eaton Myasthenic Syndrome (LEMS). There are anecdotal reports of myasthenia gravis worsening in association with nirmatrelvir/ritonavir • There are no known specific drug interactions. Myasthenia can be aggravated by COVID-19 and COVID-19 vaccination and requires close monitoring given the risk of bulbar and respiratory failure. **Motor Neurone Disease (MND)** • Discuss patients on quinine with an MND physician • Levels of riluzole treatment may be increased by nirmatrelvir/ritonavir and should be temporarily suspended following discussion with an MND physician. **Huntington's Disease** • In addition to the medicines listed in the SPS guidance, avoid concurrent use of nirmatrelvir/ritonavir with the following: primidone, tetrabenazine and trihexyphenidyl
Immunology	Considering commonly prescribed medications in immunology, there are no issues with concomitant immunoglobulin replacement therapy and nirmatrelvir/ritonavir and nMABs. Patients should be informed by specialist clinicians and clinical/patient networks to maintain a list of all medications including those prescribed in hospital. Patients may be taking prophylactic antimicrobials - please refer to the list of contraindicated medications in the SPS guidance for further reference.
Obstetrics and gynaecology	It is recommended that CMDU staff liaise with their Maternity COVID Champion, or dedicated clinician when assessing a pregnant patient with COVID. Please ensure that a full drug history and past medical history is taken as other specialists may also need to be involved, for example renal or transplant teams. 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 nirmatrelvir/ritonavir.
Paediatrics	For paediatric/adolescent patients, paediatric multidisciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from treatment.

Clinical Guide: Speciality advice for 'highest-risk' cohorts

Speciality-specific advice on the management of patients within each of the highest-risk cohorts (particularly around the use of nirmatrelvir/ritonavir) may be found in the table below. Contact your local specialist team for further guidance on issues not covered by this advice.

Cohort	Advice/guidance
IMID	**Factors to be considered in IMID patients**: • Consistent with existing guidance on management of COVID-19 in patients with IMID, patients should temporarily suspend their conventional DMARD(s), biologic and/or JAK inhibitor until the course of antiviral treatment has been completed and symptoms of COVID-19 are improving (this will usually be between 1-3 weeks). For most patients this will not require specific contact with the specialty team. • Do not stop or decrease corticosteroids • Swallowing difficulties may preclude the use of oral antivirals e.g. in patients with dysphagia due to myositis, oesophageal dysmotility due to scleroderma/systemic sclerosis because of the size of the tablets (approximately 2cm long) • Do not delay antiviral treatment pending specialist advice The following links on speciality websites may be useful: • The British Society for Rheumatology website • COVID-19 guidance | British Society for Rheumatology • COVID-19 Guidance & Advice - The British Society of Gastroenterology (bsg.org.uk) • British Thoracic Society website: https://www.brit-thoracic.org.uk/covid-19/ • British Association of Dermatologists Advice for Dermatology HCPs during COVID-19 pandemic: https://www.bad.org.uk/healthcare-professionals/covid-19
HIV/AIDS	• It is recommended that each CMDU has details of their local HIV specialist service (both specialist HIV pharmacist and HIV physician) to discuss individuals where advice is needed. Speciality arrangements for referral to HIV specialist advice may be regional in some areas. • The majority of individuals living with HIV and referred to CMDUs for nirmatrelvir/ritonavir treatment should be managed in accordance with the guidance without the need for referral to the specialist centre. There are no antiretroviral treatment (ART) regimens that are a contraindication to nirmatrelvir/ritonavir treatment. No dose adjustment of any ART agent including ritonavir or cobicistat is needed. Interactions with other generalist co-medications prescribed should be assessed according to guidance including by reference to the Liverpool Covid drug interaction website. • Some individuals living with HIV do not disclose their HIV status to their GPs. It is therefore good practice to enquire of individuals during triage if they have any other medical conditions or take any other medications not managed directly by their GP. • CD4 counts are no longer routinely monitored in those with virological suppression and previous counts above 350 cells/mm3. These individuals will generally be assessed as not meeting the immunosuppression criteria although some patients may still meet the criteria that take account of other demographic factors and co-morbidities. We suggest using an age threshold of 55 years or older as an appropriate indicator for treatment in these circumstances as this was the inclusion criteria used in clinical studies.

Down's syndrome[1]	• The following issues should be given due consideration when assessing a patient for treatment with a suitable antiviral or nMAB:
	  • The individual is likely to have impaired ability to understand the information given and they may be more likely to have hearing and communication difficulties
	  • There is significant potential for co-existence of significant health conditions
	  • There is a need for a corroborated and detailed collateral medical and drug history from an informant
	  • Mental capacity assessment is an essential part of the assessment/triage process in these individuals
	  • Other people cannot consent for an individual's treatment unless they are legally permitted to do so
	  • In patients iudged not to have capacity, a process of best interests decision-making should be pursued.
	• A person with Down's syndrome may be more likely to be taking medications that are contra-indicated or which may lead to interactions with nirmatrelvir/ritonavir e.g.:
	  • For heart conditions and high blood pressure
	  • Antipsychotics, antidepressants, anxiolytics
	  • Anticonvulsants (anti-epileptics)
	  • Statins
	• Nirmatrelvir/ritonavir tablets are relatively large (8-9mm diameter) and should not be crushed. Patients with swallowing difficulties will need support to ensure these are taken safely.
	• Contact the hospital learning disability liaison nurse (if available) or the local specialist learning disability service for clinical advice around psychotropic medications and the implication of contraindications and potential interactions

[1]This advice may also apply to individuals with other chromosomal abnormalities affecting immune competence.