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Clinical guidelines for management of patients with COVID-19

COVID-19 CLINICAL GUIDANCE

Scope of Guidance

- This information has been created to provide guidance for clinicians in NHS Borders but clinical acumen should be used when interpreting the information for use with individual patients.

- The guidance is intended for patients who have confirmed or suspected (i.e. not yet tested, awaiting swab results or swab negative but clinically demonstrating signs) COVID-19 infection.

- This guidance provides
    - parameters to consider when assessing a patient with COVID symptoms to determine if admission is appropriate
    - treatment protocols for management of patients admitted with different Covid-19 variants
    - treatment protocols for patients who become COVID-19 positive in hospital
    - escalation criteria for more severely ill patients
    - guidance on the processes to ensure safe discharge to the community

Hospital admission guidance for adults with confirmed or suspected COVID-19

NHS Borders

Clinical features triggering MEDICAL REVIEW or ADMISSION

History

- Breathless at rest or on minimal exertion e.g. walking to the bathroom, walking up the stairs, recovery time >2 mins post-exertion
- Worsening clinical condition >5 days after symptom onset if risk factors (boxes 1-3)
- Fever >37.8 for >72h
- Delirium in older adults (aged >65 years)
- Does not have support network at home
- Unable to isolate from an extremely vulnerable individual at home (box 1)

Examination

- Unable to speak in full sentences, use of accessory muscles of breathing
- Dry mucous membranes, clinically 'dry'
- Heart rate >110 /min OR Respiratory rate>20 /min

Observations & Investigations

- SaO2 < 94% on room air
- >3% fall in sats on 1 minute sit-to-stand test or 40 step test (see appendix 1)
- AKI confirmed
- Widespread chest X-ray infiltrates
- Abnormal ECG / Bloods—troponin/d dimer U&E/CRP
- Clinical frailty score (see Appendix 2)
- Consider ISARIC score

If a patient is suitable for **ED discharge**

- Advise patient to isolate at home for 10 days from their first positive PCR/lateral flow test
- If risk factors present consider referring to the COVID virtual ward for monitoring - see flow chart
- Advise patient to contact their GP or phone 111/999 if they deteriorate

PATIENT RISK GROUPS

Box 1.HIGH-RISK ('clinically extremely vulnerable') includes:

- Solid organ transplant recipients
- Chemotherapy or immunotherapy for cancer
- Radical radiotherapy for lung cancer
- Blood or bone marrow cancer at any stage of treatment
- Bone marrow or stem cell transplant within the last 6 month
- Severe lung conditions e.g. cystic fibrosis, severe asthma, severe COPD
- Diseases that increase the risk of infection e.g. sickle cell disease
- HIV: CD4 <50 or opportunistic infection in the last 6 months (BHIVA advice)
- Immunosuppression therapies in the last 3 months e.g. high-dose corticosteroids (>40mg prednisolone per day for >1 week) OR lower-dose corticosteroids (>20mg prednisolone per day for >14 days)
- Pregnancy with significant heart disease

Box 2. MODERATE-RISK ('clinically vulnerable') includes:

- 65 years of age or older
- Very obese (BMI ≥ 40)
- Diabetes (Type 1 or 2)
- Chronic respiratory conditions e.g. asthma, COPD
- Chronic heart disease e.g. heart failure
- Chronic kidney disease stages 3, 4 or 5 (eGFR < 60mls/min)
- Chronic liver disease
- HIV: CD4 <200, detectable viral load or not on ART (BHIVA advice)
- Neurological conditions e.g. Parkinson's disease, cerebral palsy, multiple sclerosis, motor neurone disease
- Drugs that suppress the immune system (see also Box 1)
- Pregnancy

Box 3. OTHER RISKS include:

- 55 years of age with comorbidity
- Obese (BMI ≥ 30)
- BAME ethnic background

COVID-19: Assessment Flow Chart

Mild
O_2 saturation ≥ 95%*
NEWS2 = 0-2
* Or O_2 saturation > 86% if baseline sats 88%

Is the patient at higher risk from Covid-19?
- Aged 65 0r over
- Comorbidities
- Not fully vaccinated
- Pregnant
- Other factors e.g. learning disabilities, deprivation etc.

No

Sign post to NHS Inform guidance AND/OR consider referral to national remote health monitoring service

Yes

Is active clinical contact required?

No

Consider referral to national remote health monitoring service

Yes

Moderate
O_2 saturation 93-94%*
NEWS2 = 3-4
* Or O_2 saturation 84- 86% if baseline sats 88%

Check oxygen saturation after exertion test
(1 minute sit to stand or 40 step test)

Oxygen saturation fall of 3% or more from baseline?

No

Refer to COVID virtual ward

Yes

Severe
O_2 saturation ≤92%*
NEWS2 ≥5
* Or O_2 saturation ≤84% if baseline sats 88%

Admit to BGH for monitoring

Severe symptoms
Breathlessness • At rest • Minimal exertion
Severe fatigue
New confusion
Chills/rigors
Non-severe symptoms
Fever without chills/rigors
Cough
Sputum
Dizziness
Headache
Nausea and vomiting
Diarrhoea
Sore throat
Nasal congestion

Non-hospitalised patients

Consider whether patients are eligible for treatment with neutralising monoclonal antibodies or antivirals. See latest clinical guidelines as treatment options are subject to change.

Does the patient meet criteria for referral to the PANORAMIC study?
- COVID-19 symptom onset in the last 5 days
- AND positive PCR or lateral flow test
- AND aged 50+ OR aged 18-49 with an underlying condition that increases the risk of severe COVID-19 (see table)

COVID-19: Quick guide to assessment

SYMPTOMS AND SIGNS

- Fever (may be absent on admission)
- Cough, breathlessness, wheeze
- Loss of taste or smell
- Fatigue, myalgia, headache, sore throat
- "Silent hypoxia" – respiratory compromise (SaO2 < 94%) without breathlessness especially in elderly
- GI symptoms e.g. anorexia, nausea, vomiting, diarrhoea may be present
- May present in hospitalised patients as a hospital-acquired pneumonia

POTENTIAL COMPLICATIONS

- Acute Respiratory Distress Syndrome and Respiratory Failure
- Highest risk of respiratory failure at around 10 days from symptom onset
- Sepsis +/- Septic Shock
- Disseminated Intravascular Coagulation
- Pulmonary Embolism
- Arrhythmias/Heart Failure/Myocarditis
- Stroke
- Delirium

INVESTIGATIONS

- **SARS-CoV-2 Spike Antibody**
- **SARS-CoV-2 genotyping. Send second swab with clinical details "Urgent – treatment is variant dependent" where variant will influence treatment options with nMABs/antivirals**
- FBC, U&Es, LFT, CRP, Lactate
- Coagulation screen including D-dimer
- ABG if low oxygen saturation
- Blood cultures and other microbiological specimens – as required
- ECG

CRP is usually high and may be helpful to track disease progress
Lymphocyte and eosinophil counts are usually low
Markers of disease severity and poor prognosis include DIC, platelets < 100, D-dimer > 1000 ng/mL, raised troponin

IMAGING

CXR – Patchy ground glass opacities (peripheral and basal). Unilateral changes can be seen. Masses, cavitation, lymphadenopathy and pleural effusions are uncommon. If a CXR is normal but severe hypoxia consider other causes.

Chest CT – Ground glass opacities, consolidation, reticular pattern are typical manifestations of COVID-19. Cardinal hallmark is bilateral ground glass opacities without consolidation in posterior and peripheral lungs. Atypical CT manifestations include airway changes, pleural changes, fibrosis and nodules.

CTPA – Pulmonary emboli have been seen in COVID-19 and CTPA should strongly be considered if D-Dimer >2000, ECG changes, persistent tachycardia, hypotension or clinical suspicion of PE.

Ensure Treatment Escalation Plan or End of Life Care plan is documented

COVID-19: Quick guide to management

NHS Borders

ONGOING WARD CARE

- Admit patients to an appropriate COVID cohort area
- Observations – Respiratory Rate, Oxygen Saturations, Temperature, BP and HR at least 4 hourly
- Pay early attention to nutritional requirements
- Prone positioning (Appendix 3 and 4)
- Blood tests should be repeated only when clinically required
- Consider total patient care (physical, emotional and social needs)
- Ensure a multidisciplinary assessment on COVID-19 cohort wards
- Keep family or next of kin up to date with patient's condition
- Start discharge planning early

MEDICATIONS

- VTE thromboprophylaxis – all patients
- Corticosteroids
- Antivirals
- IL-6 Inhibitors
- Neutralisng Monoclonal Antibodies
- Treatment options vary depending on SARS-CoV-2 genotype, anti-spike protein serology and clinical features. See detailed eligibility criteria and dosing regimes for each drug.
- Consider eligibility for RECOVERY or other clinical trials

ONCOLOGY

- Stop prescribed systemic anti-cancer therapy (SACT) and inform
- Oncology Bleep 3041 or Out of Hours Oncology Reg at WGH
- Haematology bleep 6246 or Out of Hours Haematology SpR

RESPIRATORY SUPPORT

- Maintain oxygen saturation 92 - 96% (88-92% in known COPD with CO_2 retention)
- Titrate oxygen (both up and down) to maintain SaO2 in target range
- Nasal cannulae 1-5 litres/min **OR**
- Ventimask 2-15 litres/min (24-60%) **OR**
- Non-rebreathe mask 15 litres/min (90%) **OR**
- CPAP **OR** IPPV (See guidance)

ESCALATION TO INTENSIVE CARE

Patients who are for escalation of care and have any of the following parameters should be discussed with ICU:

- RR>30
- SBP <90mmHg
- Oxygen requirement >40% to maintain SaO2 ≥ 94% (as patients can deteriorate very quickly)
- Reduced level of consciousness

FLUID MANAGEMENT

- Accurate fluid balance
- Avoid vigorous fluid resuscitation (may exacerbate ARDS) but do not let patients get dehydrated
- Cover insensible losses (high Temp and RR) - max 2 litres/day
- Ensure intravenous fluid management plan is reviewed daily

DIABETIC MANAGEMENT

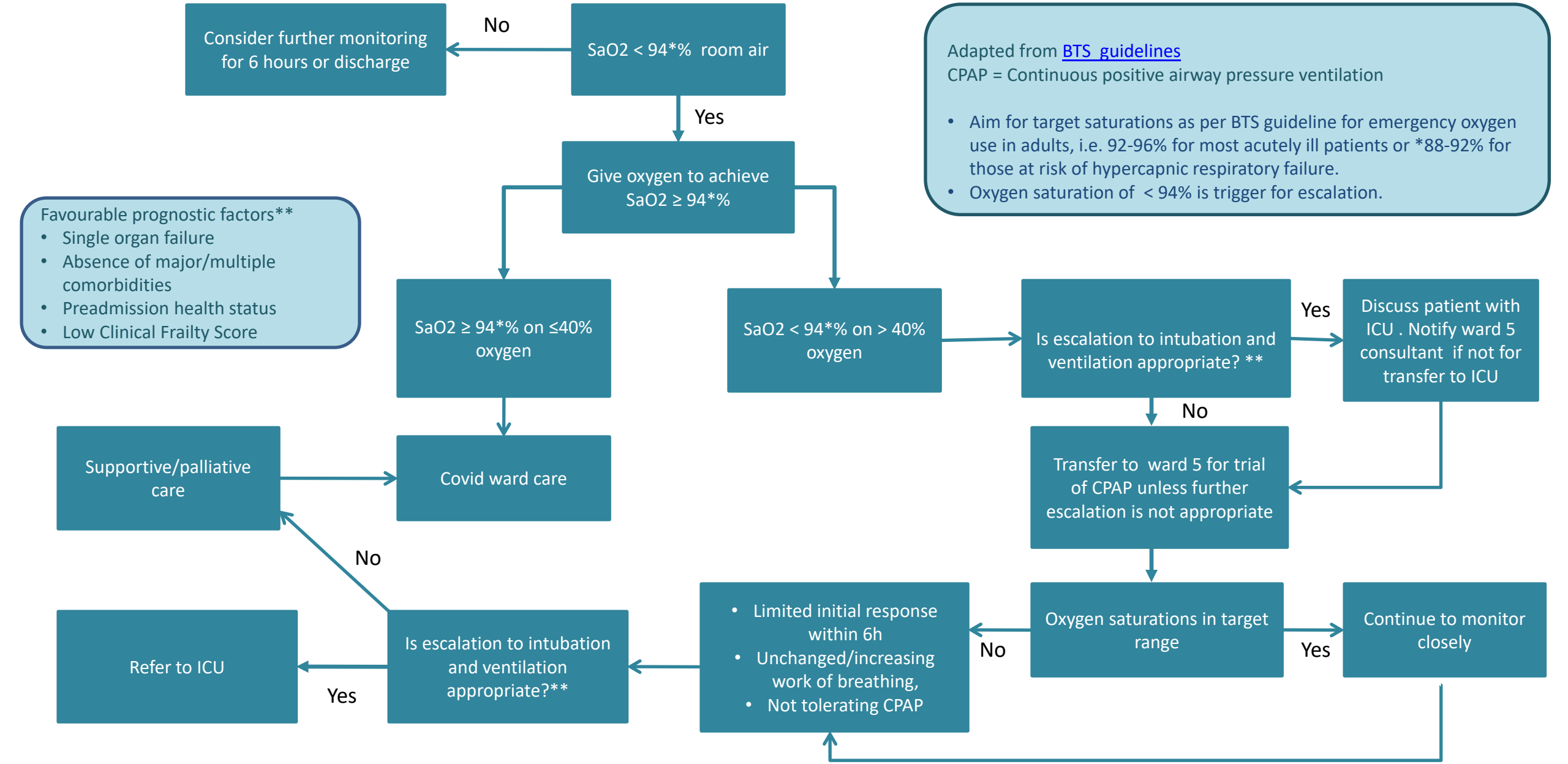
- Stop SGLT-2 inhibitors, GLP-1 analogues and metformin on admission. Stop gliclazide in DKA/HHS.
- Check glucose in all patients and ketones in all patients with diabetes or those with admission glucose > 12 mmol/l
- Follow national guidance on insulin dosing regimes, management of steroid induced hyperglycaemia and reintroduction of metformin

PALLIATION AND END OF LIFE CARE

- Non-ventilated patients with severe COVID-19 disease may benefit from symptom control advice from the Palliative Care Team (bleep 6838 during working hours or via switchboard out of hours).
- Symptom control e.g. breathlessness, reassurance and emotional support (including staff support) are key in the end of life phase. Early involvement of the palliative care team is advised.
- Prescribe anticipatory medication and ensure regular communication with family/significant others.
- See link to Scottish Palliative Care guidance for specific COVID end of life care guidance

Regularly review and update Treatment Escalation Plan

Ward 5 Respiratory Escalation Plan



COVID-19 treatment: Management of fluid balance

NHS Borders

WHO IS AT RISK OF AKI?

- Poor oral intake for > 48 hours
- Age > 65 years
- Delirium
- On non-invasive ventilation
- CKD 3b (eGFR < 45mls/min) or previous AKI
- Diabetes, liver disease or heart failure (on ACEI/ARB)
- On diuretics or given contrast

ASSESS FLUID STATUS ON ADMISSION

- Measure heart rate, lying & standing BP & **record weight** if possible
- Review U&E
- Start accurate fluid balance
- Many patients are admitted dry May need 2 – 3L in first 24 hours on top of replacement

FLUID BALANCE IN COVID-19 PATIENTS

- Can be difficult – if in doubt, request senior review
- Postural hypotension = significant dehydration
- Daily or alternate day weights are useful
- Record input as oral + IV fluids
- Record urine output – a catheter is not usually necessary
- Diarrhoea, vomit, NG aspirate, drain fluid should be Included in output calculations
- Estimate **INSENSIBLE LOSSES** - Fever, high respiratory rate and oxygen therapy results in ≥ 1-2L/day of insensible loss

DEHYDRATED

- 500ml fluid challenge & re-assess
- Stop: diuretics/SGLT2i/metformin & ACEI/ARBs
- Consider further fluid challenge
- Encourage oral fluids 2 - 3L/day

EUVOLAEMIC

- Maintain daily +500 to 1000mL fluid balance
- Stop:diuretics/SGLT2i/metformin/ACEI & ARBs
- Encourage oral fluids 2- 3L/day
- If unable to drink, prescribe IV Fluids

OVERLOADED

- Request Senior review
- Consider diuretics
- Investigate cause, consider echocardiogram
- Set appropriate negative fluid target
- Review *at least* daily

WHICH IV FLUID?

- Balanced solutions for **resuscitation.** Never use 5% dextrose for resuscitation.
- Alternate 1L 0.9% saline or plasmalyte with 5% dextrose + 40mmol KCl for **maintenance**
- Check U&E, Mg^{2+} daily for those on IV fluids
- If hypernatraemic, increase oral or NG water in the first instance

Corticosteroid treatment for adults hospitalised with COVID-19

NHS Borders

Dexamethasone or Hydrocortisone

ELIGIBILITY CRITERIA

- Confirmed COVID-19 based on PCR /lateral flow test or suspected Covid-19 based on clinical features and CXR changes **AND**
- Requiring supplemental oxygen to keep SaO2 ≥ 90% **OR**
- Requiring any form of assisted ventilation **OR**
- WHO features of severe or critical COVID-19

WHO CRITERIA OF COVID SEVERITY

SEVERE

- SaO2 < 90% on room air
- Respiratory rate > 30 breaths/minute
- Signs of respiratory distress

CRITICAL

- ARDS, sepsis, septic shock
- Requirement for invasive ventilation or vasopressors

EXCLUSION CRITERIA

- Mild to moderate symptoms
- Contraindication to corticosteroid use

Oral

- **Dexamethasone 6mg once a day for 10 days**
- Stop treatment if discharged from hospital within 10 days

Consider proton pump inhibitor if risk of gastric ulceration

Intravenous

- **Hydrocortisone 50mg IV three times a day for 10 days**
- IV to be used only if oral administration not viable
- Consider a longer low dose duration for patients with septic shock

- Monitor blood glucose four times a day initially
- Aim for target glucose of 6-10 mmol/L

Pregnancy

- Prednisolone 40mg orally or Hydrocortisone 80mg IV twice daily
- **Discuss with on call obstetrician**

IL-6 inhibitor therapy (Tocilizumab or Sarilumab) for adults hospitalised with COVID-19

Tocilizumab or Sarilumab

ELIGIBILITY CRITERIA

- Confirmed COVID-19 based on PCR /lateral flow test or suspected COVID-19 based on clinical features and CXR changes **AND**
- Receiving Dexamethasone **AND**
- CRP ≥ 75 mg/L **AND**
- Oxygen saturation < 92% on air **OR**
- Within 48 hours of commencement of respiratory support (CPAP, NIV HFNO, or invasive mechanical ventilation) irrespective of CRP

- Prescribe **Tocilizumab 8mg/kg (max dose 800 mg) IV single dose** (see chart below) **OR Sarilumab 400mg IV single dose**
- Dilute in 100 mls 0.9% saline and infuse over 1 hour
- Do not give concomitantly in the same line as other IV medications

EXCLUSION CRITERIA

- Known hypersensitivity to Tocilizumab or Sarilumab
- Co-existing infection that might be worsened
- Has already received an IL-6b inhibitor during this admission
- Baseline ALT or AST > 5 times upper limit of normal
- Baseline platelet count < 150 x 10^9/L
- Pre-existing condition or treatment resulting in ongoing immunosuppression

Avoid in pregnancy unless benefits outweigh the risks. Discuss with on call obstetrician

Weight (kg)	Tocilizumab dose
< 41	8mg/kg rounded to 20mg
41-45	360mg
46-55	400mg
56-65	480mg
66-80	600mg
81-90	680mg
≥ 91	800 mg

IL-6 inhibitors are immunosuppressants which can suppress C-Reactive Protein response for up to 3 months after administration.

Antiviral treatment (Remdesivir) for adults hospitalised with COVID-19

NHS Borders

Remdesivir

ELIGIBILITY CRITERIA

- Patients hospitaliised with COVID-19
- Patients with pneumonia requiring requiring low-flow oxygen (oxygen delivered by a simple face mask or nasal cannula at a flow rate usually up to 15 litres/minute)
- Adults and adolescents ≥ 12 years of age and ≥ 40 kg
- eGFR ≥ 30 ml/min*
- ALT < 5 times upper limit of normal at baseline
- Patients not receiving mechanical ventilation or ECMO
- If patients receiving Remdesivir require escalation of treatment continuation of the drug should be considered only after multidisciplinary discussion

- Prescribe **Remdesivir 200 mg IV loading dose on day one then 100mg IV daily for 4 days**
- Maximum treatment course of 5 days (this may be extended to a maximum of 10 days in significantly immunocompromised patients)

EXCLUSION CRITERIA

- Presents >10 days after symptom onset
- Avoid in pregnancy unless benefits outweigh risks
- Contraindication to Remdesivir

- Monitor for sign of hypersensitivity reactions such as nausea, chills, dizziness, rash, urticaria and anaphylaxis up to 1 hour post infusion.
- Monitor renal function and LFTs
- Stop Remdesivir if
  - 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 INR
  - eGFR < 30 mls/min
- Consider stopping treatment at 72 hours if clinical improvement and not requiring supplemental oxygen or patient deteriorates despite 48 hours of mechanical ventilation

*Patients with end stage renal disease on haemodialysis are exempt from the eGFR treatment threshold above. Discuss with BGH renal consultant or on call renal registrar at Edinburgh Royal Infirmary

Neutralising Monoclonal Antibody treatment for adults acutely hospitalised with COVID-19

Casirivumab and Imdevimab

ELIGIBILITY CRITERIA

- Confirmed COVID-19 based on PCR/lateral flow test or suspected COVID-19 based on clinical features and CXR changes
- **AND** Hospitalised for management of acute COVID-19 symptoms
- **AND** Negative for baseline anti-spike (anti-S) antibodies
- **AND** Genotyping confirms non-Omicron variant

- Prescribe off label **2.4 g casirivimab plus imdevimab combination** (1.2g casirivimab and 1.2g imdevimab) **IV single dose**
- Dilute in 250mls 0.9% saline and infuse over a minimum of 30 minutes via a giving set with 0.2 micron low protein filter

EXCLUSION CRITERIA

- < 40 kg
- < 12 years of age
- Omicron variant of SARS-CoV-2
- Has already received casirivumab & imdevimab during this admission
- Known sensitivity to casirivumab or imdevimab

- Monitor for sign of infusion related reactions such as nausea, chills, dizziness, rash, urticaria and anaphylaxis up to 1 hour post infusion.
- For minor reactions consider changing the infusion rate to one hour.
- For anaphylaxis stop the infusion and treat appropriately.

Send second COVID-19 swab with clinical details "Urgent-treatment is variant dependent"

There are no available nMABs for patients infected with the Omicron variant unless they are enrolled in the RECOVERY trial.

Clinical pathway: Therapies for patients hospitalised due to COVID-19

- This guide aims to support treatment decisions for commissioned COVID-19 therapies and outlines their position in the treatment pathway for patients hospitalised due to COVID-19
- Patients must be hospitalised specifically for management of COVID-19
- Consult the relevant Summary of Product Characteristics for advice on contraception and use in pregnancy
- Please refer to the NICE COVID-19 Rapid Guideline (NG 191) for other treatments

Consider the patient's oxygen requirement as a starting point for determining the most appropriate therapy/therapies

Low-flow supplemental oxygen

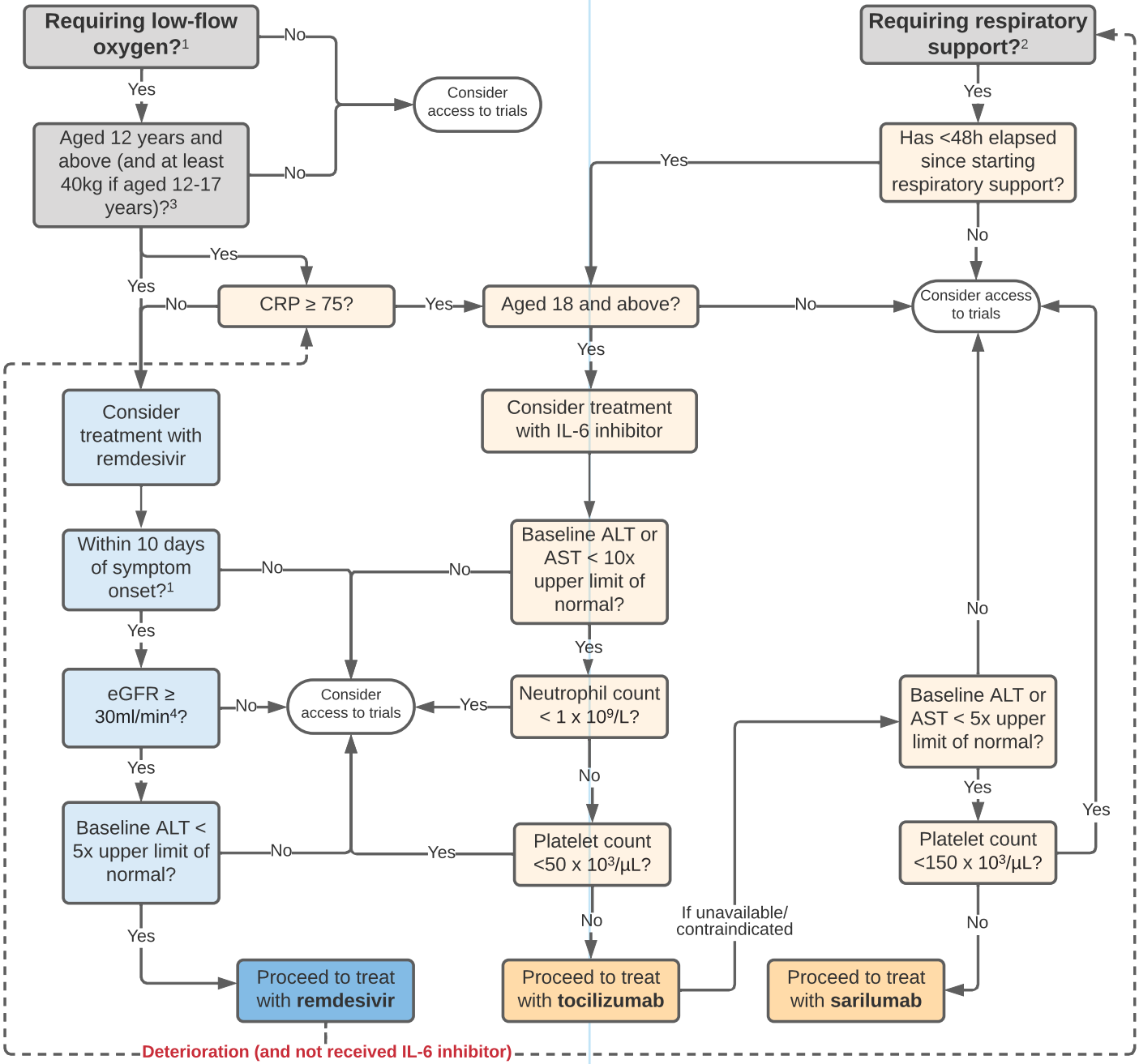
Respiratory support

CORTICOSTEROIDS

Consider dexamethasone (or hydrocortisone or prednisolone if treatment with dexamethasone is unavailable/not possible) in patients who require supplemental oxygen to maintain prescribed oxygen saturation levels

RECOVERY TRIAL

All **Hospitalised** patients can consider joining the RECOVERY trial. They should have: a **viral pneumonia syndrome**; confirmed **SARS-CoV-2 infection**; and no **medical history** that might put the patient at risk from entering a trial. All patients in the RECOVERY trial should be included in the pathway of care described here. They can enter the RECOVERY trial at any stage in the care pathway.



[1] For treatment with remdesivir, the criteria with regard to need for supplemental oxygen and the treatment window from symptom onset do not apply to significantly immunocompromised patients

[2] Defined as: high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation

[3] Clinicians are encouraged to seek paediatric MDT advice for patients aged 12-17 years to determine clinical capacity to benefit from treatment

[4] Patients with end-stage renal disease on haemodialysis are exempt from the specified eGFR threshold

Version 1. 24 February 2022. Not valid if printed

Anticoagulation for patients with suspected or confirmed COVID-19

Principles

- COVID is prothrombotic and can cause venous and arterial clots e.g. aorta, ventricle , mesenteric vessels. Many Covid deaths are due, in part, to thrombosis.
- Standard anticoagulation may be inadequate in ill patients because COVID increases factor 8 and reduces antithrombin 3 causing a hypercoaguable state and resistance to heparin
- ICU patients and the severely ill managed at ward level have a higher incidence of thrombosis and heparin resistance
- Only withhold prophylaxis if platelets are below 30 (discuss with haematology).
- Patients should be entered into clinical trials where possible e.g. REMAP-CAP trial.
- Diagnosis of VTE should be made using standard methods including Doppler and CTPA based on clinical suspicion and risk assessment.
- Routine screening for VTE is not advised.
- Do not use D-dimers to influence treatment decisions.
- LMWH or Unfractionated Heparin should be adjusted for weight and creatinine clearance (monitor platelet count).
- Do not use treatment dose heparin for primary prevention unless part of a clinical trial.
- Indications for thrombolysis for PE and peripheral systemic delivery of thrombolysis remain as per standard
- Review detailed NHS Borders anticoagulation guidelines

Anticoagulation for patients with suspected or confirmed COVID-19

The VTE risk assessment in the BGH medicine chart should be completed and the clinically appropriate dose of dalteparin should be prescribed . (If patient is frail/elderly/other concerns, creatinine clearance should be used in preference to eGFR.)

Patients on dalteparin prophylaxis do NOT require routine anti Xa levels, unless creatinine clearance <30ml/min. Anti Xa level is essential in renal impairment as accumulation can occur.
Check anti Xa level 2-4 hours after dalteparin dose after 4 days and repeat level every 4 days unless creatinine clearance improves to > 30ml/min or levels have been stable with no accumulation after 10 days. Anti Xa target level = 0.1-0.4.
Prophylactic dalteparin should be prescribed for 0800 for patients requiring anti Xa monitoring.

There is currently no evidence that enhanced thromboprophylaxis for critically ill COVID patients offers increased benefit in preventing thrombosis or reducing death

- In patients hospitalised with COVID-19 who require oxygen therapy, routine coagulation should be checked. Patients with suspected DIC should have measurement of prothrombin time, fibrinogen concentration, platelet count and D-dimer. If results are significantly abnormal please discuss with haematology.
- The majority of ICU patients can be maintained on standard dalteparin thromboprophylaxis. Enhanced dosing increases the risk of significant bleeding.
- Post-ICU patients who have been ventilated require up to 6 weeks (or longer if remaining inpatients) of prophylactic dose dalteparin. Duration of treatment is a senior clinical decision.
- Patients who are less unwell (ward level care rather than ICU or HDU) with additive risk factors should be considered on discharge for 7-14 days prophylaxis with once daily VTE prophylaxis at standard dose. If unable to self inject then apixaban 2.5mg twice daily for 7-14 days is an alternative (likely less effective, but better than nothing). Decision to continue treatment at discharge and duration of treatment is a senior clinical decision.
- Pregnant patients should go home with 10 days supply of once daily prophylactic dalteparin. Pregnant patients should not receive apixaban.

Treatment of COVID-19 related thrombosis

- Most patients with COVID induced thrombosis can be managed with dalteparin at standard dose BUT with anti Xa monitoring and dose adjustment.
- Do not assume treatment is therapeutic on the basis of correct dose for weight and renal function. This should be a guide to starting dose, but in hospital patients with COVID, higher doses may be needed until heparin resistance settles. This may take days to weeks.
- **Recommendation: Aim for anti Xa level of 0.5-1.0. Repeat levels every 3-4 days.**

Stable patients with thrombosis

- Check anti Xa level 2-4 hours after 3-4 doses. Target **anti Xa level of 0.5-1.0.**
- If anti Xa level is outwith target range, the dalteparin dose should be adjusted (if anti Xa level subtherapeutic , step up dose to next band, if anti Xa level above target range , step down a dose band) and repeat the anti Xa level after 4 further doses.
- In general underdosing in COVID will do more harm than increasing the dose as long as appropriate monitoring is done with anti Xa level

Patients admitted on oral anticoagulants

- Patients who are admitted on oral anticoagulation for the management of atrial fibrillation or PE/DVT/ Heart valves should continue on their oral anticoagulation.

Treatment of massive thrombosis

•Patients with massive thrombosis who are unstable should be treated with IV heparin initially and can be directly converted to dalteparin once stable unless they have major heparin resistance (needing huge doses of IV heparin to achieve therapeutic anti Xa levels) in which case please discuss with haematology before doing so.

•The APPT is not helpful for monitoring heparin pumps in presence of COVID and should NOT be checked (even if test negative but suspect COVID induced clots). Anti Xa levels should be monitored instead with a target of between 0.5-1.0. Please tell the lab the patient is on unfractionated heparin so that they can run the correct assay.

•Once patients are stable and heparin resistance has improved, with reducing requirement for IV heparin, they can be converted to dalteparin (started as soon as heparin pump is stopped with anti Xa monitoring **after the first dose** and again after the 3rd and 4th doses to ensure the anti Xa level is in the therapeutic range.

•Guidance for treatment dose dalteparin for patients with creatinine clearance < 30ml/min can be found at http://intranet/resource.asp?uid=39651

Ward discharge guidance for adults with confirmed or suspected COVID-19

Patient is suitable for Ward DISCHARGE

- No fever for 48h consecutively without medication to reduce fever
- Blood tests improving
- If NEWS Score stable (0-4):
  - SaO2 >/= 95% **– self manage**
  - SaO2 93-94% with HR <90 and RR <20 **– consider referral for remote monitoring on COVID virtual ward**
  - SaaO2 93-94% with RR 21-24 or HR 90-130 **– Refer to COVID virtual ward for ongoing monitoring if discharge being considered**
- Discharge may be considered in stable patients when sats <93% if baseline / expected baseline sats are below this range or NEWS 0-4 but stable > 48 hrs
- Any patient being considered for oxygen therapy on discharge must be discussed with the Respiratory Nurse Specialist

Consider remote monitoring if:

- ≥ 65 years of age
- ≥ 50 years of age with moderate to severe co-morbidity
- Lives alone
- SaO2 not back to baseline of 93-95%
- Immunosuppression
- Severe long term condition
- Very overweight
- Diabetes
- BAME

Ward discharge check list

Check:

- Patient contact details
- Patient given advice to isolate at home until recovered i.e. at least 10 days from their first positive SARS-CoV-2 PCR or lateral flow test

Patient given:

- Follow up information
- Patient information leaflets as appropriate
- Advice to contact their GP or NHS 24 if they deteriorate

Ensure discharge summary contains:

- Date patient's symptoms started
- SARS-CoV-2 PCR test status
- Whether patient desaturates on exertion
- RR, HR and oxygen saturation at rest
- **Details of treatment with corticosteroids, IL-6 inhibitors, antivirals or monoclonal antibodies**
- Trial participation and treatment randomisation
- **Recommended 3 months delay to COVID vaccinations if received Neutralising Monoclonal Antibodies**
- Oxygen plan
- Remote monitoring plan (if applicable)
- AHP & rehabilitation plans

For patients with moderate/severe pneumonia or requiring care in ICU/ward 5 and who are not frail elderly:

- Anticoagulation plan – patients with severe pneumonia requiring additional respiratory support should receive Dalteparin for 4-6 weeks
- CXR 6 weeks post discharge
- Follow up plan – 4-6 week Respiratory review for severe pneumonia
- Copy discharge letter to RespiratoryMedicine@borders.scot.nhs.uk for follow up arrangements

Management of patients admitted to hospital for a non-COVID reason but who test positive for COVID-19 during admission

Treatment of adults with hospital onset COVID-19 (nMABs and antivirals)

ELIGIBILITY CRITERIA

- Hospitalised for indications other than for the management of acute symptoms of COVID-19
- **AND** positive COVID-19 PCR/lateral flow test
- **AND** symptomatic with COVID-19 and showing no signs of clinical recovery
- **AND** member of a highest risk group (see Appendix 5 &6 for list of qualifying conditions)
- **OR** COVID-19 infection presents significant risk of destabilising pre-existing condition or illness or compromising recovery from surgery

EXCLUSION CRITERIA

- Requires hospital care for the management of acute COVID-19 illness
- New requirement for supplemental oxygen
- Children < 12 years of age
- Adolescents (aged 12-17) weighing < 40 kg
- Known sensitivity to any of the nMABs or Remdesivir

1st Line
PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid)

OR

2nd Line
Remdesivir

OR

3rd Line
Sotrovimab

Combination treatment with an nMAB and an antiviral is NOT routinely recommended.

Adolescents aged 12-17 years may be considered for treatment with Remdesivir or Sotrovimab only

Read in conjunction with UK Interim Clinical Commissioning Policy: Therapies for patients with symptomatic hospital-onset COVID-19

1st Line treatment for patients with hospital onset COVID-19: PF-07321332 (nirmatrelvir) plus ritonavir

PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid)

ELIGIBILITY CRITERIA

- Hospitalised for indications other than for the management of acute symptoms of COVID-19
- **AND** positive COVID-19 PCR/lateral flow test
- **AND** symptomatic with COVID-19 and showing no signs of clinical recovery
- **AND** member of a highest risk group (see Appendix 1 & 2 for list of qualifying conditions) **OR** COVID-19 infection presents significant risk of destabilising pre-existing condition or illness or compromising recovery from surgery
- **AND** treatment is commenced within 5 days of symptom onset
- **AND** no history of decompensated liver cirrhosis or stage 4-5 chronic kidney disease
- **AND** treatment is deemed safe by specialty team (see full clinical guidance)

EXCLUSION CRITERIA

- Age < 18 years
- Pregnancy
- The patient is not taking any of the medications listed in Appendix 7
- Requires hospital care for the management of acute COVID-19 illness
- New requirement for supplemental oxygen

- Prescribe **PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid)** 300 mg (2x 150 mg tablets) PF-07321332 (nirmatrlevir) with 100mg ritonavir taken together orally twice daily for 5 days

- **Serious risk of adverse reactions with other medicines (Appendix 7)**
- Caution in patients with pre-existing liver disease or liver enzyme abnormalities - causes raised liver transaminases, hepatitis and jaundice
- May decrease efficacy of combined hormonal contraceptives. Advise patients 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 treatment.

Read in conjunction with UK Interim Clinical Commissioning Policy: Therapies for patients with symptomatic hospital-onset COVID-19

1st Line treatment for patients with hospital onset COVID-19: PF-07321332 (nirmatrelvir) plus ritonavir

Drug interactions

PF-07321332 (nirmatrelvir) plus ritonavir is a CYP3A inhibitor. This can cause increased plasma concentrations of other drugs metabolised by CYP3A. If new medications are started that inhibit or induce CYP3A they may increase or decrease concentrations of PF-07321332 (nirmatrelvir).

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 PF-07321332 (nirmatrelvir) plus ritonavir
- Loss of therapeutic effect of PF-07321332 (nirmatrelvir) plus ritonavir and possible development of viral resistance

Liver function

Hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering PF-07321332 (nirmatrelvir) plus ritonavir to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

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 PF-07321332 (nirmatrelvir) plus ritonavir.

2nd Line treatment for patients with hospital onset COVID-19: Remdesivir

Remdesivir

ELIGIBILITY CRITERIA

- Hospitalised for indications other than for the management of acute symptoms of COVID-19
- **AND** positive COVID-19 PCR/lateral flow test
- **AND** symptomatic with COVID-19 and showing no signs of clinical recovery
- **AND** member of a highest risk group (see Appendix 5 & 6 for list of qualifying conditions) **OR** COVID-19 infection presents significant risk of destabilising pre-existing condition or illness or compromising recovery from surgery
- **AND** Treatment with PF-07321332 (nirmatrelvir) plus ritonavir is contraindicated or not possible
- **AND** treatment is commenced within 7 days of symptom onset

- Prescribe **Remdesivir** 200mg IV loading dose followed by 100mg IV days 2 and 3
- Dilute in 100 or 250mls 0.9% saline and infuse over a minimum of 30 minutes

- Not recommended in individuals with ALT ≥ 5 times the upper limit of normal or eGFR < 30 ml/min
- Monitor for sign of hypersensitivity reactions such as nausea, chills, dizziness, rash, urticaria and anaphylaxis up to 1 hour post infusion.
- For mild to moderate reactions consider slowing the infusion rate up to a maximum infusion time of 120 minutes.
- For anaphylaxis stop the infusion immediately and treat appropriately

EXCLUSION CRITERIA

- Age < 12 years
- Adolescents (aged 12-17) weighing < 40 kg
- Requires hospital care for the management of acute COVID-19 illness
- New requirement for supplemental oxygen
- Known sensitivity to Remdesivir

Use of remdesivir in children aged 12-17 years would be off-label

3rd Line treatment for patients with hospital onset COVID-19: Sotrovimab

Sotrovimab

ELIGIBILITY CRITERIA

- Hospitalised for indications other than for the management of acute symptoms of COVID-19
- **AND** positive COVID-19 PCR/lateral flow test
- **AND** symptomatic with COVID-19 and showing no signs of clinical recovery
- **AND** member of a highest risk group (see Appendix 5 & 6 for list of qualifying conditions) **OR** COVID-19 infection presents significant risk of destabilising pre-existing condition or illness or compromising recovery from surgery
- **AND** clinical judgment is that treatment with an nMAB is the preferred treatment option
- **AND** treatment with remdesivir and PF-07321332 (nirmatrelvir) plus ritonavir are both contraindicated or not possible
- **AND** treatment is commenced within 5 days of symptom onset

- Prescribe **Sotrovimab** 500mg IV
- Dilute in 100mls 0.9% saline and infuse over 30 minutes
- Do not give concomitantly with other IV drugs

- Monitor for sign of hypersensitivity reactions such as nausea, chills, dizziness, rash, urticaria and anaphylaxis up to 1 hour post infusion.
- For minor reactions consider changing the infusion rate to one hour.
- For anaphylaxis stop the infusion and treat appropriately

EXCLUSION CRITERIA

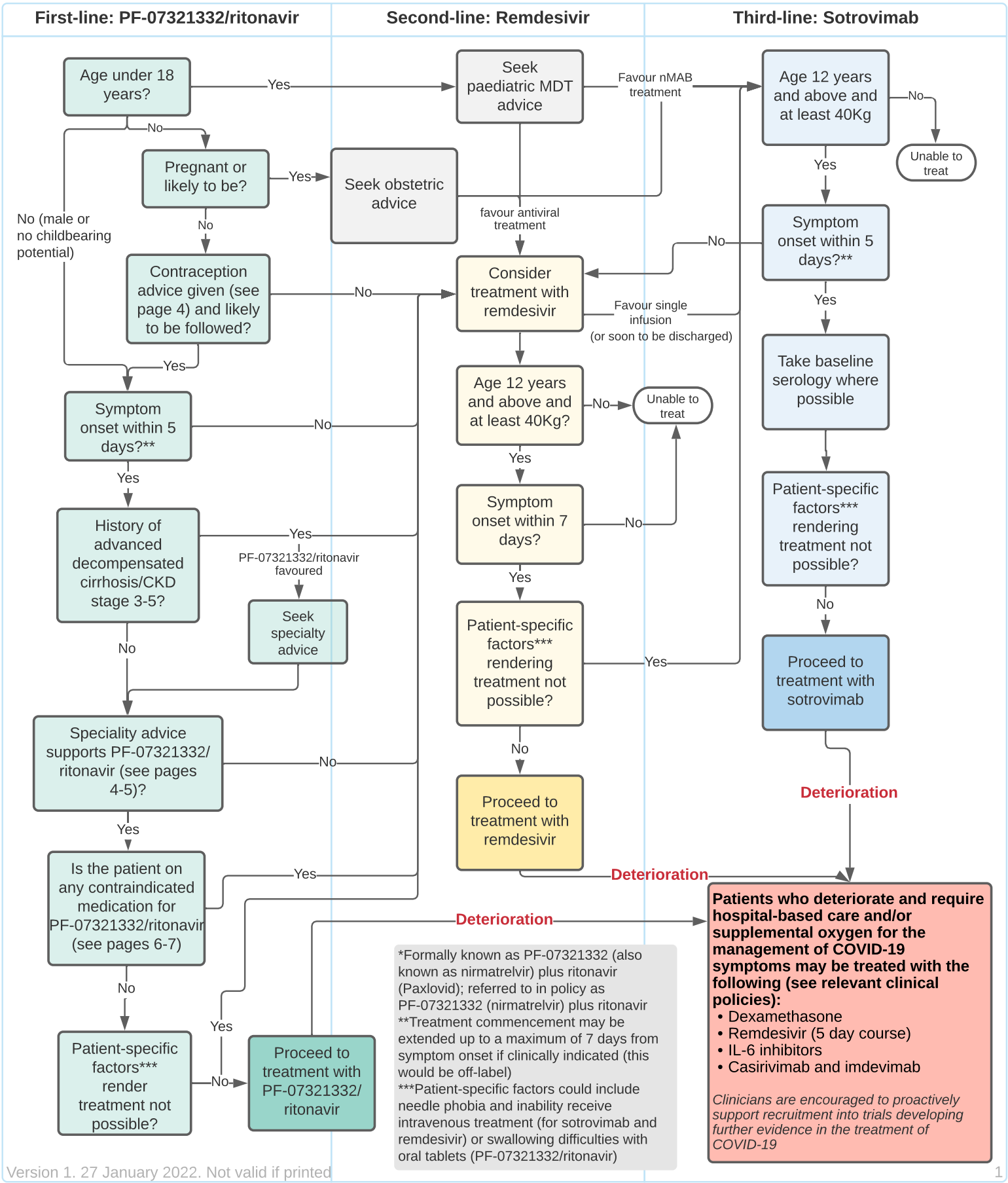
- Age < 12 years
- Adolescents (aged 12-17) weighing < 40 kg
- Requires hospital care for the management of acute COVID-19 illness
- New requirement for supplemental oxygen
- Known sensitivity to nMABs

Patients considered for treatment with sotrovimab should have samples taken for serology testing against SARS-CoV-2 prior to treatment. However, serology results are not a requirement for treatment.

UK Interim Clinical Commissioning Policy
Therapies for patients with symptomatic hospital-onset COVID-19

Consider access to this clinical pathway under the following conditions:

- Hospitalised for indications other than for the management of acute symptoms of COVID-19
- Onset of symptoms of COVID-19 within the last 5 days (for PF-07321332/ritonavir* and sotrovimab) or 7 days (for remdesivir), remains symptomatic and with no signs of clinical recovery
- SARS-CoV-2 infection is confirmed by either PCR or lateral flow test
- The patient is a member of a 'highest' risk group (see page 2) OR COVID-19 infection presents a material risk of destabilising a pre-existing condition or compromising recovery from a procedure (as determined by MDT assessment)
- The patient is not requiring new supplemental oxygen specifically for the management of COVID-19 symptoms



*Formally known as PF-07321332 (also known as nirmatrelvir) plus ritonavir (Paxlovid); referred to in policy as PF-07321332 (nirmatrelvir) plus ritonavir
**Treatment commencement may be extended up to a maximum of 7 days from symptom onset if clinically indicated (this would be off-label)
***Patient-specific factors could include needle phobia and inability receive intravenous treatment (for sotrovimab and remdesivir) or swallowing difficulties with oral tablets (PF-07321332/ritonavir)

Clinical Guide: The 'highest risk' cohort for access to treatment

The following cohorts were determined by an independent advisory group commissioned by the Department of Health and Social Care (DHSC). Patients in these cohorts are determined to be at highest risk of adverse outcomes from COVID-19 and are to be prioritised for treatment with nMABs and antivirals.

Cohort	Definition
Down's syndrome	All patients with Down's syndrome
Patients with a solid cancer	Active metastatic cancer and active solid cancers (at any stage) • All patients receiving chemotherapy within the last 3 months • Patients receiving group B or C chemotherapy 3-12 months prior (see Appendix 3) • Patients receiving radiotherapy within the last 6 months
Patients with haematological disease and stem cell transplant recipients	• Allogeneic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months or active graft vs 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 chimaeric antigen receptor (CAR)-T cell therapy in the last 24 months. or ◦ radiotherapy in the last 6 months • Individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months except patients with chronic phase chronic myeloid leukaemia (CML) in molecular response; or first or second line tyrosine kinase inhibitors (TKI) • All patients with myeloma (excluding MGUS) or chronic B-cell lymphoproliferative disorders (e.g.chronic lymphocytic leukaemia, follicular lymphoma) or myelodysplastic syndrome (MDS) who do not fit the criteria above. • All patients with sickle cell disease. • Individuals with non-malignant haematological disorder (e.g.aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic treatment (e.g.anti-CD20, anti-thymocyte globulin [ATG] andalemtzumab) within the last 12 months.
Patients with renal disease	• Renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who: ◦ Received B cell depleting therapy within the past 12 months (including alemtuzumab, rituximab [anti-CD20], anti-thymocyte globulin) ◦ Have an additional substantial risk factor which would in isolation make them eligible for nMABs or oral antivirals ◦ Not been vaccinated prior to transplantation • Non-transplant patients who have received a comparable level of immunosuppression • Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 ml/min/1.73m2) without immunosuppression
Patients with liver disease	Patients with cirrhosis Child's-Pugh class B and C (decompensated liver disease) • Patients with a liver transplant • Liver patients on immune suppressive therapy (including patients with and without liver cirrhosis) Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease)
Patients with immune-mediated inflammatory disorders	• IMID treated with rituximab or other B cell depleting therapy in the last 12 months • IMID with active/unstable OR stable disease on corticosteroids, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate • IMID patients with active/unstable disease including those on biological monotherapy and on combination biologicals with thiopurine or methotrexate
Immune deficiencies	• Primary immunodeficiency associated with impaired type I interferon signalling • Good's syndrome (thymoma plus B-cell deficiency) • X-linked agammaglobulinaemia (and other primaryagammaglobulinaemias) • Any patient with a secondary immunodeficiency receiving, or eligible for, immunoglobulin replacement therapy • Common variable immunodeficiency (CVID) • Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig) • Hyper-IgM syndromes • Severe Combined Immunodeficiency (SCID) • Autoimmune polyglandular syndromes /autoimmunepolyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome)
HIV/AIDS	• Patients with high levels of immune suppression, have uncontrolled/untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis • On treatment for HIV with CD4 <350 cells/mm3 and stable on HIV treatment or CD4>350 cells/mm3 and additional risk factors (e.g. age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, those with alcohol-dependence)
Solid organ transplant recipients	All recipients of solid organ transplants not otherwise specified above
Rare neurological conditions	Multiple sclerosis Motor neurone disease Myasthenia gravis Huntington's disease

Clinical Guide: Therapy characteristics when deciding on treatment choice

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

- Three products have similar relative risk reduction of reducing hospitalistion: PF-07321332/ritoniavir, remdesivir; and sotrovimab
- 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

PF-07321332/ritonavir (Paxlovid)	Remdesivir (Veklury)	Sotrovimab (Xevudy)
Antiviral (dual therapy)	Antiviral (monotherapy)	Neutralising monoclonal antibody
Administered **orally**: 3 tablets twice a day for 5 days	Administered **intravenously**: one infusion every 24 hours for 3 days	Administered **intravenously**: single infusion
Adults only (aged 18 years and over)	Adults and adolescents (aged 12 years and over and weighing at least 40kg)	Adults and adolescents (aged 12 years and over and weighing at least 40kg)
Evidence based on treatment within **5** days of symptom onset	Evidence based on treatment within **7** days of symptom onset	Evidence based on treatment within **5** days of symptom onset
Not recommended in pregnancy	May be used in **pregnancy** where benefits of treatment outweigh risks	May be used in **pregnancy** although there is no safety data available
Breast-feeding should be discontinued during treatment and for 7 days after last dose	No specific advice on discontinuation of breast-feeding during treatment	No specific advice on discontinuation of breast-feeding during treatment
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 dose adjustment recommended in liver or renal impairment*
Multiple significant drug-drug interactions (see page 4)	No significant drug-drug interactions	No significant drug-drug interactions
88% Relative Risk Reduction of Hospitalisation	87% Relative Risk Reduction of Hospitalisation	85% Relative Risk Reduction of Hospitalisation

Molnupiravir (Lageviro)

Antiviral (monotherapy)	Breast-feeding should be discontinued during treatment and for 4 days after last dose
Administered **orally**: 4 capsules twice a day for 5 days	May be used in severe liver and kidney disease (no dose adjustment recommended)
Adults only (aged 18 years and over)	No significant drug-drug interactions
Not recommended in pregnancy	
30% Relative Risk Reduction of Hospitalisation	

For the key publications of trial results and licence click here

PF-07321332/ritonavir publication due	PF-07321332/ritonavir SmPC
Remdesevir 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)

Version 1. 27 January 2022. Not valid if printed

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

Specialty-specific advice on the management of patients within each of the highest-risk cohorts (particularly around the use of PF-07321332/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	PF-07321332/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 PF-07321332/ritonavir. If blood tests are available a bilirubin >50 at any time is a contraindication to PF-07321332/ritonavir, if the jaundice is due to liver disease. Patients receiving rifaximin (only used in very advanced liver disease) should not receive PF-07321332/ritonavir.
Solid organ transplant (non-renal)	PF-07321332/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 PF-07321332/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. PF-07321332/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 PF-07321332/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 PF-07321332/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 pages 6-7, avoid concurrent use of PF-07321332/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 PF-07321332/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 PF-07321332/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 PF-07321332/ritonavir and should be temporarily suspended following discussion with an MND physician. **Huntington's Disease** • In addition to the medicines listed in pages 6-7, avoid concurrent use of PF-07321332/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 PF-07321332/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 on pages 6-7 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 PF-07321332/ritonavir.
Paediatrics	For paediatric/adolescent patients (aged 12-17 year inclusive), paediatric multidisciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from treatment.

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

Specialty-specific advice on the management of patients within each of the highest-risk cohorts (particularly around the use of PF-07321332/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. Specialty 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 PF-07321332/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 PF-07321332/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	• 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 PF-07321332/ritonavir e.g.:
	  • For heart conditions and high blood pressure
	  • Antipsychotic, antidepressants, anxiolytics A
	  • Anticonvulsants (anti-epileptics)
	  • Statins
	• PF-07321332/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

Clinical Guide: Medicines where PF-07321332/ritonavir is NOT an appropriate option

These tables show the medicines where there are contraindications with PF-07321332/ritonavir and cautions that are not easily managed. If a patient is currently prescribed any of these medicines, then PF-07321332/ritonavir is NOT a treatment option. Please refer to SPS Guidance here.

What the medicine is used for	Specific Medicines
Irregular heartbeats	Digoxin, Disopyramide, Amiodarone, Quinidine, Dronedarone, Flecainide, Propafenone
Treating and preventing blood clots	Apixaban, Dabigatran, Rivaroxaban, Warfarin, Clopidogrel, Ticagrelor
High blood pressure (hypertension)	Aliskiren, Lercanidipine
Lowering cholesterol	Rosuvastatin, Simvastatin, Lomitapide
Erection problems	Avanafil, Sildenafil, Tadalafil, Vardenafil
Inhalers Inhaled or oral medicines to relieve asthma and COPD	Salmeterol, Budesonide, Fluticasone Propionate, Theophylline
Cold-like symptoms caused by allergic rhinitis (nasal spray)	Budesonide, Fluticasone propionate
Underactive thyroid (hypothyroidism)	Levothyroxine
Prostate gland enlargement	Alfuzosin
Heart failure or angina	Ranolazine, Ivabradine, Eplerenone, Digoxin
Pain	Fentanyl, Midazolam, Pethidine, Piroxicam, Propoxyphene
Heroin dependence	Methadone
Bipolar disorder, schizophrenia, epilepsy, migraine or cluster headaches	Carbamazepine, Clozapine, Eletriptan, Lamotrigine, Lurasidone, Phenobarbital, Phenytoin, Quetiapine, Ergotamine, Dihydroergotamine, Valproic acid, Pimozide, Midazolam, Clonazepam
Nerve pain or trigeminal neuralgia	Carbamazepine
Gout	Colchicine
Pulmonary arterial hypertension (PAH)	Sildenafil, Bosentan, Riociguat, Tadalafil
Herbal medicines	St. John's Wort
Anxiety, problems sleeping, muscle spasms, fits, narcolepsy and ADHD	Flurazepam, Diazepam, Clonazepam, St John's Wort, Methylphenidate, Dexamphetamine

Clinical Guide: Medicines where PF-07321332/ritonavir is NOT an appropriate option

These tables show the medicines where there are contraindications with PF-07321332/ritonavir and cautions that are not easily managed. If a patient is currently prescribed any of these medicines, then PF-07321332/ritonavir is NOT a treatment option. Please refer to SPS Guidance here.

What the medicine is used for	Specific Medicines
Cancer	Abemaciclib, Acalabrutinib, Ceritinib, Encainide, Encorafenib, Enzalutamide, Everolimus, Apalutamide, Ibrutinib, Neratinib, Venetoclax, Vinblastine, Vincristine
Infections	Bedaquiline, Delamanid, Ketoconazole, Rifabutin, Rifampicin, Voriconazole, Fusidic acid / sodium fusidate
Transplant	Letermovir
Immunosuppressant medicines which can be used for a range of conditions	Ciclosporin, Sirolimus, Tacrolimus, Everolimus
Hepatitis C	Maviret (contains glecaprevir and pibrentasvir), Zepatier (contains elbasvir and grazoprevir), Exviera (contains dasabuvir), Viekierax (contains ombitasvir, paritaprevir and ritonavir)
Blood Disorder	Fostamatinib
Hormonal contraception	Check COVID-19 Drug Interaction Checker
Illegal substances	

A-Z: All medicines where PF-07321332/ritonavir is NOT an appropriate option

DO NOT USE | CONSIDER RISKS AND BENEFITS

Abemaciclib, Acalabrutinib, Alfuzosin, Aliskiren, Amiodarone, Apalutamaide, Apixaban, Avanafil, Bedaquiline, Bosentan, Budesonide, Carbamazepine, Ceritinib, Ciclosporin, Cisapride, Clonazepam, Clopidogrel, Clozapine, Colchicine, Contraception, hormonal, Dabigatran, Delamanid, Dexamphetamine, Diazepam, Digoxin, Dihydroergotamine, Disopyramide, Dronedarone, Elbasvir/grazoprevir (Zepatier), Eletriptan, Encorafenib, Enzalutamide, Eplerenone, Ergotamine, Everolimus, Exviera, Fentanyl, Flecainide, Flurazepam, Fluticasone, Fostamatinib, Fusidic acid, Glecaprevir/pibrentasvir (Maviret), Ibrutinib, Ivabradine, Ketoconazole, Lamotrigine, Lercanidipine, Letermovir, Levothyroxine, Lomitapide, Lurasidone, Methadone, Methylphenidate, Midazolam, Neratinib, Pethidine, Phenobarbital, Phenytoin, Pimozide, Piroxicam, Propafenone, Propoxyphene, Quetiapine, Quinidine, Ranolazine, Rifabutin, Rifampicin, Riociguat, Rivaroxaban, Rosuvastatin, Salmeterol, Sildenafil, Simvastatin, Sirolimus, Sodium fusidate, St. John's Wort, Tacrolimus, Tadalafil, Theophylline, Ticagrelor, Valproic acid, Vardenafil, Venetoclax, Viekirax, Vinblastine, Vincristine, Voriconazole, Warfarin

More detail of drug/drug interactions in found on the Liverpool COVID Drug Interaction Checker - Click Here

Appendix 1: Exertional Desaturation Tests

Sit to Stand Test (STST) to detect desaturation:

- A STST is performed using a standard height chair without armrests positioned against a wall
- The patient needs to be seated upright on the chair with knees and hips flexed at 90° feet placed flat on the floor and hip width apart
- Ask the patient to put hands on hips (or folded across their chest) or arms are kept stationary
- Record Heart Rate and O2 Saturation from pulse oximeter
- O2 saturation should be 94% or above to proceed
- The patient needs to stand straight upright and then sit down again and repeat this for 1 minute. Their bottom must contact the chair on each repetition
- Record the number of times they can do this in 1 minute. There must be a minimum of 5 cycles for the test to be diagnostic
- This test is self -paced and patients can stop, and rest should they need to
- Explain to patients "*The purpose of the test is to assess your exercise capacity and leg muscle strength. The movement required is to get up from this chair with the legs straight and sit back continuing the repetitions as fast as possible within one minute. I will give you the countdown 3-2-1-Go, as an indication to start and, I will tell you when there are 15 seconds remaining. If required, youcan take a break and resume the test as soon as possible*"
- Desaturation of 3% or more from baseline is considered significant and the patient should initially be monitored in a clinical environment rather than remotely.

40 Step Test to detect desaturation

If the patient is unable to perform a Sit to Stand Test the 40 Step Test can be undertaken.

- O2 saturation should be 94% or above
- The patient is asked to take 40 steps either in the corridor if infection control measures permit, or alternatively 40 steps on the spot
- This should be done at the patient's own pace
- Desaturation of 3% or more is considered significant and the patient should initially be monitored in a clinical environment rather than remotely.

Appendix 2 – Rockwood Clinical Frailty Scale

Clinical Frailty Scale*

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3 Managing Well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4 Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medica- tions). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. Terminally Ill - Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In moderate dementia, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In severe dementia, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

Appendix 3: Conscious patient proning

Principles

Indications

- Confirmed or suspected COVID-19 patients requiring FiO2 of 28% or more or basic respiratory support (CPAP/ NIV/ HFNO) to achieve target O2 saturations (> 92 to 96% or 88 to 92% if at risk of hypercapnic respiratory failure).
- Proning should only be considered for appropriate patients and undertaken by trained staff with appropriate PPE

Aims

- Improve oxygenation & reduce Fi02 demand
- Reduce work of breathing
- Recruit collapsed alveoli in dorsal regions of the lungs

Absolute contraindications

- Immediate need for intubation
- Respiratory distress, use of accessory muscles , RR>35, PCO2>6.5 kPa
- Decreased consciousness level or agitation
- Recent abdominal surgery, intestinal ischaemia or raised intra-abdominal pressure
- Cardiovascular instability, recent pacemaker/ICD insertion or recent thromboembolic event

Relative contraindications

- Pregnancy (2nd and 3rd trimesters)
- Morbid obesity
- Facial injuries
- Inability to adopt a prone position independently
- Full stomach – including patients with NG bolus feed
- Pressure areas

Appendix 4: Conscious patient proning

Patient information sheet For "Conscious Proning"

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These instructions are for patients who have been advised to undertake "Conscious Proning"

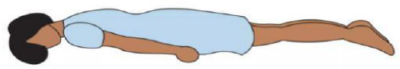
Please try to not spend a lot of time lying flat on your back. Lying on your stomach and in different positions will help your body to get air into all areas of your lungs.

It is recommended to change your position every 30 minutes to 2 hours rotating as below. Please note sitting up is better than lying on your back:

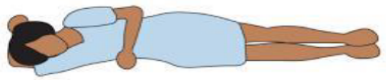
1. 30 minutes – 2 hours: lying fully prone on your stomach (bed flat)
2. 30 minutes – 2 hours: lying on your right side (bed flat)
3. 30 minutes – 2 hours: sitting up (30-60 degrees) by adjusting head of the bed
4. 30 minutes – 2 hours: lying on your left side (bed flat)
5. Then back to position 1 and continue to repeat the cycle.

In pictures:

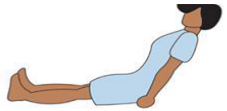
1. 30 minutes – 2 hours: lying fully prone (bed flat)



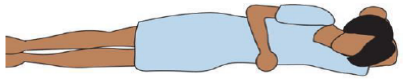
2. 30 minutes – 2 hours: lying on your right side (bed flat)



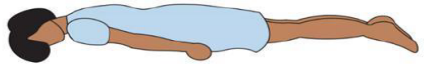
3. 30 minutes – 2 hours: sitting up (30-60 degrees) by adjusting head of the bed



4. 30 minutes – 2 hours: lying on your left side (bed flat)



5. Then back to Position 1. Lying fully prone (bed flat)



Adapted from Self Positioning Guide. Elmhurst Hospital. SB, https://www.embeds.co.uk/wp-content/uploads/2020/04/Self-Proning-Positioning-leaflet.pdf

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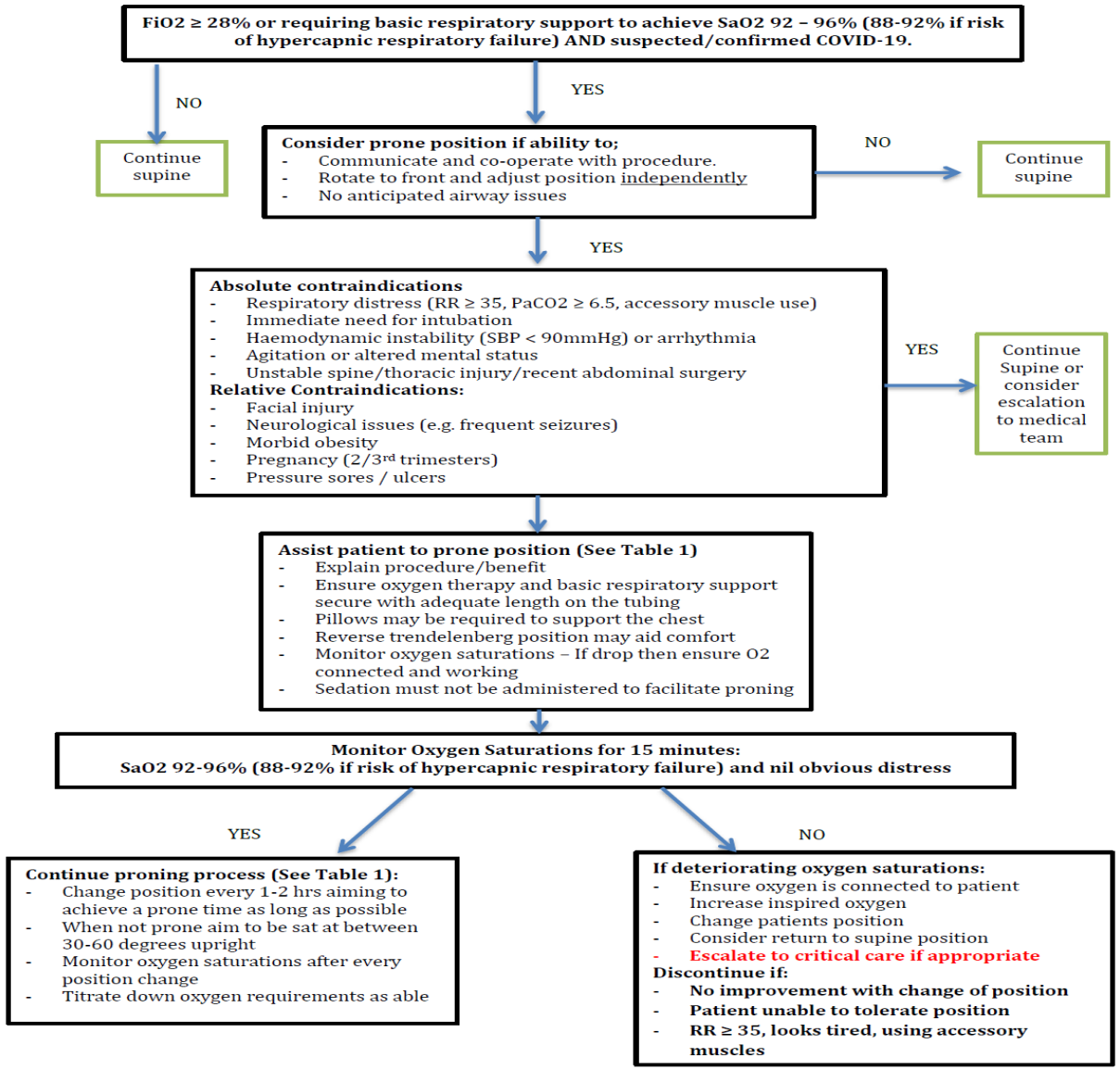
Figure 1 – Flow diagram decision tool for Conscious Proning process



Appendix 5: Patient cohorts considered at highest risk from COVID-19 and to be prioritised for treatment with nMABs and antivirals

Cohort	Description
Down's syndrome	All patients with Down's syndrome
Patients with a solid cancer	• Active metastatic cancer and active solid cancers (at any stage) • All patients receiving chemotherapy within the last 3 months • Patients receiving group B or C chemotherapy 3-12 months prior (see Appendix 3) • Patients receiving radiotherapy within the last 6 months
Patients with haematological diseases and stem cell transplant recipients	• Allogeneic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months or active graft vs 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 o received chimaeric antigen receptor (CAR)-T cell therapy in the last 24 months, or o radiotherapy in the last 6 months • Individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months except patients with chronic phase chronic myeloid leukaemia (CML) in molecular response or first or second line tyrosine kinase inhibitors (TKI). • All patients with myeloma (excluding MGUS) or chronic B-cell lymphoproliferative disorders (e.g. chronic lymphocytic leukaemia, follicular lymphoma) or myelodysplastic syndrome (MDS) who do not fit the criteria above. • All patients with sickle cell disease. • Individuals with non-malignant haematological disorder (e.g. aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic treatment (e.g. anti-CD20, antithymocyte globulin [ATG] and alemtzumab) within the last 12 months.

Patients with renal disease	• Renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who:
	  • Received B cell depleting therapy within the past 12 months (including alemtuzumab, rituximab [anti-CD20], anti-thymocyte globulin)
	  • Have an additional substantial risk factor which would in isolation make them eligible for nMABs or oral antivirals
	  • Not been vaccinated prior to transplantation
	• Non-transplant patients who have received a comparable level of immunosuppression
	• Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 ml/min/1.73m2) without immunosuppression

Cohort	Description
Patients with liver disease	• Patients with cirrhosis Child's-Pugh class B and C (decompensated liver disease). • Patients with a liver transplant • Liver patients on immune suppressive therapy (including patients with and without liver cirrhosis) • Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease)
Patients with immune-mediated inflammatory disorders (IMID)	• IMID treated with rituximab or other B cell depleting therapy in the last 12 months • IMID with active/unstable disease on corticosteroids*, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID with stable disease on either corticosteroids*, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID patients with active/unstable disease including those on biological monotherapy and on combination biologicals with thiopurine or methotrexate
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/autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome) • Primary immunodeficiency associated with impaired type I interferon signalling • X-linked agammaglobulinaemia (and other primary agammaglobulinaemias) • Any patient with a secondary immunodeficiency 14 receiving, or eligible for, immunoglobulin replacement therapy
HIV/AIDS	• Patients with high levels of immune suppression, have uncontrolled/untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis • On treatment for HIV with CD4 350 cells/mm3 and additional risk factors (e.g. age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, those with alcohol-dependence)
Solid organ transplant recipients	• All recipients of solid organ transplants not otherwise specified above
Rare neurological conditions	• Multiple sclerosis • Motor neurone disease • Myasthenia gravis • Huntington's disease

Appendix 6: Group B and C chemotherapeutic agents

Group B 10-50% risk of grade 3/4 febrile neutropenia or lymphopenia

- Etoposide based regimens; CMF
- Irinotecan and Oxaliplatin based regimens
- Cabazitaxel
- Gemcitabine
- Chlorambucil
- Temozolomide
- Daratumumab#
- Rituximab
- Obinutuzumab
- Pentostatin
- Proteosome inhibitors
- IMIDs
- PI3Kinase inhibitors
- BTK inhibitors
- JAK inhibitors
- Venetoclax
- Trastuzumab-emtansine
- Anthracycline-based regimens
- Fluorouracil, epirubicin and cyclophosphamide (FEC)
- Methotrexate, vinblastine, adriamycin/doxorubicin, cisplatin (MVAC)
- Adriamycin/doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD)
- Cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP)
- Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (BEACOPP)
- Liposomal doxorubicin
- Taxane – 3-weekly
- Nab-paclitaxel
- Carboplatin-based regimens • Ifosphamide-based regimens
- Bendamustine 12
- Cladrabine
- Topotecan
- Cyclophosphamide/Fludarabine combinations
- Ifosphamide, carboplatin, etoposide (ICE)
- Gemcitabine, dexamethasone, cisplatin (GDP)
- Isatuximab
- Polatuzumab
- Acalabrutinib
- Dexamethasone, cytarabine, cisplatin (DHAP)
- Etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP)
- Cyclophosphamide, vincristine, doxorubicin, dexamethasone (CVAD)
- Dacarbazine-based regimens
- Lomustine
- Magalizumab
- Brentuximab vedotin
- Asparaginase-based regimens

Group C >50% risk of grade 3/4 febrile neutropenia or lymphopenia

- All acute myeloid leukaemia/acute lymphocytic regimens
- Bleomycin, etoposide and platinum
- Highly immunosuppressive chemotherapy (e.g. FluDAP, high dose Methotrexate & Cytarabine)
- Trifluradine/ Tipiracil
- KTE-X19
- Gilteritinib

Appendix 7: Drug-drug interactions involving PF-07321332 (nirmatrelvir) plus ritonavir.

Table 1: List of medicines indicating that PF-07321132 (nirmatrelvir) plus ritonavir is not an appropriate option to be prescribed together.

Specific medicines	Medicine used for	Use of PF-07321132 (nirmatrelvir) plus ritonavir
Abemaciclib	Cancer	Consider risks and benefits
Acalabrutinib	Cancer	Consider risks and benefits
Alfuzosin	Prostate gland enlargement	Do not use
Aliskiren	High blood pressure (hypertension)	Do not use*
Amiodarone	Irregular heartbeats	Do not use
Apalutamide	Cancer	Consider risks and benefits
Apixaban	Treating or preventing blood clots	Do not use
Avanafil	Erection problems	Do not use
Bedaquiline	Infections	Consider risks and benefits
Bosentan	Pulmonary arterial hypertension	Do not use
Budesonide (inhaled, nasal spray)	Relieving asthma or COPD, or cold- like symptoms caused by allergic rhinitis	Consider risks and benefits
Carbamazepine	Epilepsy, nerve pain or trigeminal neuralgia	Do not use
Ceritinib	Cancer	Consider risks and benefits
Ciclosporin	Immunosuppressant	Do not use
Cisapride	Gastrointestinal motility problems	Do not use
Clonazepam	Epilepsy or anxiety	Do not use
Clopidogrel	Treating or preventing blood clots	Do not use*
Clozapine	Schizophrenia	Do not use
Colchicine	Gout	Do not use
Contraception, hormonal	Contraception	Consider risks and benefits
Dabigatran	Treating or preventing blood clots	Consider risks and benefits
Delamanid	Infections	Consider risks and benefits
Dexamphetamine	Narcolepsy or attention deficit hyperactivity disorder (ADHD)	Consider risks and benefits
Diazepam	Anxiety, muscle spasms or fits	Do not use
Digoxin	Irregular heartbeats or heart failure	Consider risks and benefits
Dihydroergotamine	Cluster headaches	Do not use
Disopyramide	Irregular heartbeats	Do not use*
Dronedarone	Irregular heartbeats	Do not use
Eletriptan	Migraines	Consider risks and benefits
Encorafenib	Cancer	Consider risks and benefits
Enzalutamide	Cancer	Consider risks and benefits

Specific medicines	Medicine used for	Use of PF-07321132 (nirmatrelvir) plus ritonavir
Eplerenone	Heart failure	Do not use*
Ergotamine	Cluster headaches	Do not use
Everolimus	Cancer or immunosuppressant	Do not use
Exviera (contains dasabuvir)	Hepatitis C	Consider risks and benefits
Fentanyl	Pain	Consider risks and benefits
Flecainide	Irregular heartbeats	Do not use
Flurazepam	Anxiety or problems sleeping	Do not use
Fluticasone propionate (inhaled or nasal spray)	Relieving asthma or COPD Cold-like symptoms caused by allergic rhinitis	Consider risks and benefits
Fostamatinib	Blood disorder	Consider risks and benefits
Fusidic acid (oral)	Infections	Do not use
Ibrutinib	Cancer	Consider risks and benefits
Illegal drugs	Substance abuse	Check advice in University of Liverpool COVID-19 Drug Interaction checker
Ivabradine	Heart failure or angina	Do not use*
Ketoconazole	Infections	Consider risks and benefits
Lamotrigine	Epilepsy or bipolar disorder	Consider risks and benefits
Lercanidipine	High blood pressure (hypertension)	Do not use*
Letermovir	Transplant	Consider risks and benefits
Levothyroxine	Underactive thyroid (hypothyroidism)	Consider risks and benefits
Lomitapide	Lowering cholesterol	Do not use
Lurasidone	Schizophrenia	Do not use
Maviret (contains glecaprevir and pibrentasvir)	Hepatitis C	Do not use
Methadone	Heroin dependence	Consider risks and benefits
Methylphenidate	Narcolepsy or attention deficit hyperactivity disorder (ADHD)	Consider risks and benefits
Midazolam	Epilepsy	Do not use
Neratinib	Cancer	Do not use
Pethidine	Pain	Do not use
Phenobarbital	Epilepsy	Do not use
Phenytoin	Epilepsy	Do not use
Pimozide	Schizophrenia	Do not use
Piroxicam	Pain	Do not use
Propafenone	Irregular heartbeats	Do not use
Propoxyphene	Analgesics	Do not use

Specific medicines	Medicine used for	Use of PF-07321132 (nirmatrelvir) plus ritonavir
Quetiapine	Bipolar disorder, depression, schizophrenia	Do not use
Quinidine	Antiarrhythmic	Do not use
Ranolazine	Heart failure or angina	Do not use
Rifabutin	Infections	Consider risks and benefits
Rifampicin	Infections	Do not use
Riociguat	Pulmonary arterial hypertension	Consider risks and benefits
Rivaroxaban	Treating or preventing blood clots	Do not use
Rosuvastatin	Lowering cholesterol	Consider risks and benefits
Salmeterol (inhaled)	Relieving asthma or COPD	Do not use
Sildenafil	Erection problems or pulmonary arterial hypertension	Do not use
Simvastatin	Lowering cholesterol	Do not use
Sirolimus	Immunosuppressant	Do not use*
Sodium fusidate (oral)	Infections	Do not use
St. John's Wort (Hypericum perforatum)	Herbal medicine	Do not use
Tacrolimus	Immunosuppressant	Do not use
Tadalafil	Erection problems or pulmonary arterial hypertension	Do not use
Theophylline	Relieving asthma or COPD	Consider risks and benefits
Ticagrelor	Treating or preventing blood clots	Do not use*
Vardenafil	Erection problems	Do not use
Valproic acid	Bipolar disorder, epilepsy or migraine	Consider risks and benefits
Venetoclax	Cancer	Do not use
Viekirax (contains ombitasvir, paritaprevir and ritonavir)	Hepatitis C	Consider risks and benefits
Vinblastine	Cancer	Consider risks and benefits
Vincristine	Cancer	Consider risks and benefits
Voriconazole	Infections	Consider risks and benefits
Warfarin	Treating or preventing blood clots	Consider risks and benefits
Zepatier (contains elbasvir and grazoprevir)	Hepatitis C	Do not use*

The information in this appendix is based on SPS guidance and is correct at the time of publication. Please refer to the SPS guidance for the most up to date information.

Table 2: Medications interacting with PF-07321332 (nirmatrelvir) plus ritonavir

What the medicine is used for	Specific medicine	Use of PF-07321132 (nirmatrelvir) plus ritonavir
Underactive thyroid (hypothyroidism)	Levothyroxine	Consider risks and benefits
Lowering cholesterol	Lomitapide Rosuvastatin Simvastatin	Do not use Consider risks and benefit Do not use
Treating or preventing blood clots	Apixaban Clopidogrel Dabigatran Rivaroxaban Ticagrelor Warfarin	Do not use Do not use* Consider risks and benefits Do not use Do not use* Consider risks and benefits
Relieving asthma or COPD (inhaled or oral)	Budesonide Fluticasone propionate Salmeterol Theophylline	Consider risks and benefits Consider risks and benefits Do not use Consider risks and benefits
Bipolar disorder, schizophrenia, epilepsy, migraine or cluster headaches	Carbamazepine Clonazepam Clozapine Dihydroergotamine Eletriptan Ergotamine Lamotrigine Lurasidone Phenobarbital Phenytoin Pimozide Quetiapine Valproic acid Midazolam	Do not use Do not use Do not use Do not use Consider risks and benefits Do not use Consider risks and benefits Do not use Do not use Do not use Do not use Do not use Consider risks and benefits Do not use

Specific medicines	Medicine used for	Use of PF-07321132 (nirmatrelvir) plus ritonavir
Erection problems	Avanafil Sildenafil Tadalafil Vardenafil	Do not use Do not use Do not use Do not use
Contraception. hormonal	Elicit name of medication and check COVID-19 Drug Interaction checker.	Consider risks and benefits
Irregular heartbeats	Amiodarone Digoxin Disopyramide Dronedarone Flecainide Propafenone Quinidine	Do not use Consider risks and benefits Do not use* Do not use Do not use Do not use Do not use
High blood pressure (hypertension)	Aliskiren Lercanidipine	Do not use* Do not use*
Prostate gland enlargement	Alfuzosin	Do not use
Cold-like symptoms caused by allergic rhinitis (nasal spray)	Budesonide Fluticasone propionate	Consider risks and benefits Consider risks and benefits
Pain	Fentanyl Midazolam Pethidine Propoxyphene Piroxicam	Consider risks and benefits Do not use Do not use Do not use Do not use
Nerve pain or trigeminal neuralgia	Carbamazepine	Do not use

Specific medicines	Medicine used for	Use of PF-07321132 (nirmatrelvir) plus ritonavir
Heart failure or angina	Eplerenone Ivabradine Ranolazine Digoxin	Do not use* Do not use* Do not use Consider risks and benefits
Gout	Colchicine	Do not use
Heroin dependence	Methadone	Consider risks and benefits
Substance abuse	Various illicit drugs	Check COVID-19 Drug Interaction checker
Herbal medicines	St. John's Wort (Hypericum perforatum)	Do not use
Infections	Bedaquiline Delamanid Fusidic acid/ sodium fusidate (oral) Ketoconazole Rifabutin Rifampicin Voriconazole	Consider risks and benefits Consider risks and benefits Do not use Consider risks and benefits Consider risks and benefits Do not use Consider risks and benefits
Pulmonary arterial hypertension	Bosentan Riociguat Sildenafil (Revatrio) Tadalafil	Do not use* Consider risks and benefits Do not use Do not use
Anxiety, problems sleeping, muscle spasms, fits, attention deficit hyperactivity disorder (ADHD) or narcolepsy	Diazepam Flurazepam Clonazepam St John's Wort Dexamphetamine Methylphenidate	Do not use Do not use Do not use Do not use Consider risks and benefits Consider risks and benefits

Specific medicines	Medicine used for	Use of PF-07321132 (nirmatrelvir) plus ritonavir
Immunosuppressant medications which can be used in a range of conditions	Ciclosporin Everolimus Sirolimus Tacrolimus	Do not use* Do not use* Do not use* Do not use*
Transplant	Letermovir	Consider risks and benefits
Hepatitis C	Exviera (contains dasabuvir) Maviret (contains glecaprevir and pibrentasvir) Viekirax (contains ombitasvir, paritaprevir and ritonavir) Zepatier (contains elbasvir and grazoprevir)	Consider risks and benefits Do not use Consider risks and benefits Do not use*
Cancer	Abemaciclib Acalabrutinib Apalutamide Ceritinib Encorafenib Enzalutamid Everolimus Ibrutinib Neratinib Venetoclax Vinblastine Vincristine	Consider risks and benefits Consider risks and benefits Consider risks and benefits Consider risks and benefits Consider risks and benefits Consider risks and benefits Do not use Consider risks and benefits Do not use Do not use Consider risks and benefits Consider risks and benefits
Blood disorders	Fostamatinib	Consider risks and benefits

*Not listed in PF-07321132 (nirmatrelvir plus ritonavir SmPC but use NOT advised by *COVID-19 Drug Interaction checker*

Clinical Evidence - Corticosteroids

CORTICOSTEROIDS

The RECOVERY trial showed that in adult patients hospitalised with COVID-19 dexamethasone 6mg per day for up to 10 days reduced 28- day mortality in those receiving invasive mechanical ventilation by one third, and by one fifth in patients receiving oxygen without invasive mechanical ventilation. Since then the REMAP-CAP trial for hydrocortisone and a meta-analysis of corticosteroids confirmed those results. The World Health Organization (WHO) has recently issued new interim guidance recommending the use of systemic corticosteroids in severe and critical COVID-19 disease. In RECOVERY only the group receiving respiratory support benefitted from dexamethasone. Possible harm was identified in the group not requiring oxygen. Similarly, benefit was clearer in patients treated more than 7 days after symptom onset, when inflammatory lung damage is likely to have been more common. Additionally, the study did not demonstrate that initiation of dexamethasone early in the admission was time critical.

Clinical Evidence - Antivirals

REMDESIVIR

Remdesivir is an adenosine nucleotide pro-drug that is metabolised intracellularly to form the pharmacologically active substrate remdesivir triphosphate which inhibits SARS-CoV-2 RNA polymerase and disrupts viral replication.

Remdesivir has shown a reduction in duration of hospitalisation of patients with COVID19 disease in one trial but no mortality benefit. An evidence review conducted by the National Institute for Health and Care Excellence (NICE) on 5 June 2020 indicated some benefit with remdesivir compared with placebo for reducing supportive measures – including mechanical ventilation – and reducing time to recovery in patients with mild, moderate or severe COVID-19 disease who are on supplemental oxygen treatment. Following the 15 October 2020 preprint publication of results from the SOLIDARITY trial the WHO made a weak or conditional recommendation against the use of remdesivir in hospitalised patients with COVID-19.

Remdesivir administered IV over 3 days to non- hospitalised patients within 7 days of COVID-19 symptom onset, and with high risk factors for disease progression, resulted in a relative risk reduction of 87% in hospitalisation or death at day 28.

PF-07321332 (nirmatrelvir) plus ritonavir

Final results from the EPIC HR trial indicate that the dual oral antiviral PF-07321332 (nirmatrelvir) plus ritonavir resulted in a relative risk reduction of hospitalisation or death by 89% (within 3 day of symptom onset) and 88% (within 5 days of symptom onset) compared to placebo in non-hospitalised, high-risk adults with COVID-19.

Clinical Evidence – IL-6 Inhibitors

INTERLEUKIN-6 INHIBITORS

Tocilizumab and Sarilumab are recombinant human monoclonal antibodies that bind to interleukin-6 (IL-6) receptors and block pro-inflammatory cytokines. By targeting IL-6 receptors, Tocilizumab and Sarilumab may mitigate the cytokine-release syndrome and prevent progression of disease.

Tocilizumab is a recombinant humanised monoclonal antibody of the IgG1 class, which is directed against both the soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor. RECOVERY has reported that in hospitalised COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved both 28-day survival (a relative reduction in mortality of 14%) and other clinical outcomes. These benefits were seen regardless of the level of respiratory support and were additional to the benefits of systemic corticosteroids, such as dexamethasone. A finding of survival and time to recovery benefits for tocilizumab or sarilumab, over and above current standard of care (including corticosteroids), has been reported in the immune modulation therapy domain of the REMAP-CAP platform trial. Mortality was reported as 35.8% in the standard of care group, compared to 27.3% in the treatment group, an overall reduction in the relative risk of death of 24%. The treatment also reduced the time patients spent in the intensive care unit (ICU) by more than a week on average.

Clinical Evidence – Monoclonal Antibodies

NEUTRALISING MONOCLONAL ANTIBODIES

Neutralising MABs (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. The following nMABs have conditional marketing authorisation for use in the treatment of COVID-19 in the UK.

Casirivimab and imdevimab

Ronapreve® is a combination nMAB containing equal amounts of casirivimab and imdevimab and binds specifically to two different sites on the spike protein of the SARS-CoV-2 virus particle . The RECOVERY trial has demonstrated that the casirivimab and imdevimab combination reduced the relative risk of mortality by 20%, and the absolute risk of mortality by 6%, in hospitalised patients with COVID-19 who had not mounted an antibody response of their own to the virus (i.e. were seronegative) at the time of treatment. Casirivimab and imdevimab have significantly lower efficacy against the Omicron variant of COVID-19.

Sotrovimab

Sotrovimab is a nMAB which blocks viral entry into healthy cells and clears cells infected with SARS-CoV-2. Sotrovimab administered intravenously to non-hospitalised patients with mild-tomoderate disease and at least one risk factor for disease progression resulted in a relative risk reduction in hospitalisation or death by 85%.

Clinical Evidence

CONTINUOUS POSITIVE AIRWAY PRESSURE VENTILATION (CPAP)

Evidence from two randomised controlled trials (Perkins et al, 2021 and Grieco 2021) was included in the analysis. CPAP significantly reduces tracheal intubation or mortality at 30 days [adjusted odds ratio (OR) 0.67 (95% CI 0.48 - 0.94)] in people with COVID-19 and acute respiratory failure. Median time to intubation was longer [adjusted hazard ratio (HR) 0.67 (95% CI 0.52 - 0.86)] while admission to critical care [adjusted OR 0.69 (95% CI 0.49 - 0.96)] was significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19. No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay. CPAP was associated with a greater number of adverse events than conventional oxygen (seven in the CPAP arm, one in the conventional oxygen arm).

No difference was observed between high flow nasal oxygen (HFNO) and conventional oxygen for any outcome measured. Compared with HFNO, helmet non-invasive ventilation followed by HFNO significantly reduced intubation within 28 days from enrolment [risk ratio (RR) 0.58 (95% CI 0.36 - 0.95)], intubation within 28 days from enrolment after adjudication of intubation criteria by external experts [RR 0.55 (95% CI 0.33 - 0.9)] and increases the number of invasive ventilation free days at 28 days. No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

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