Department of Health & Social Care

The Scottish Government
Riaghaltas na h-Alba

Llywodraeth Cymru
Welsh Government

Department of Health
An Roinn Sláinte
Männystrie O Poustie

NHS

Rapid Policy Statement

Interim Clinical Commissioning Policy: Neutralising monoclonal antibodies in the treatment of COVID-19 in hospitalised patients

Publication date: 16 December 2021

Effective from: 20 December 2021

Commissioning position

The proposal is: Neutralising monoclonal antibodies are recommended to be available as a treatment option for COVID-19 through routine commissioning for hospitalised adults and children (aged 12 years and above) in accordance with the criteria set out in this document.

Background

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 (or Regulation 174 emergency use authorisation in Northern Ireland) for use in the treatment of COVID-19 in the UK:

- **Casirivimab and imdevimab (Ronapreve®)**: an nMAB combination that binds specifically to two different sites on the spike protein of the SARS-CoV-2 virus particle
- **Sotrovimab (Xevudy®)**: an nMAB that both blocks viral entry into healthy cells and clears cells infected with SARS-CoV-2

Evidence suggests that nMABs significantly improve clinical outcomes in unvaccinated[1] non-hospitalised patients with COVID-19 who are at high risk of progression to severe disease and/or death. This evidence formed the basis for the conditional marketing authorisations for these products in the treatment of COVID-19 (see Marketing Authorisation section below). Key findings are as follows:

[1] This evidence has only been collected in unvaccinated populations – further research on vaccinated populations is needed.

- Sotrovimab administered intravenously to non-hospitalised patients with mild-to-moderate disease and at least one risk factor for disease progression resulted in a relative risk reduction in hospitalisation or death by 85% (Gupta et al, 2021).
- Casirivimab and imdevimab administered intravenously reduced the composite outcome of hospitalisation or death by 70% (1.0% in the treatment arm vs 3.2% in the placebo arm) and reduced median time to resolution of COVID-19 symptoms by 4 days in non-hospitalised patients with mild-to-moderate disease (Weinrich et al, 2021).

In June 2021 the RECOVERY trial announced findings that casirivimab and imdevimab reduced the relative risk of mortality by 20% (24% in the treatment group vs 30% in those who received standard care alone) in hospitalised patients with COVID-19 who had not mounted an antibody response of their own to the virus (were seronegative[2]) at the time of treatment. A national expert group was convened and considered available evidence, including risk of hospital admission and mortality from COVID-19 in both community and hospitalised patients as per QCOVID3®[3].

Emerging evidence indicates that the casirivimab and imdevimab combination has significantly decreased efficacy against the Omicron variant of concern (Hoffmann et al, 2021). As the prevalence of this variant increases in the UK, use of casirivimab and imdevimab will be reduced and ultimately withdrawn, to be replaced by the introduction of other nMABs (e.g. sotrovimab).

This rapid policy statement outlines the eligibility criteria for the use of nMABs in the treatment of hospitalised patients with COVID-19 in the following settings:

1) **Patients hospitalised for acute COVID-19 illness** (PCR-positive and antibody seronegative): to be treated at the **off-label dose of 2.4g of casirivimab and imdevimab** [subject to specific requirements relating to local hospital Omicron variant prevalence and/or individual patient genotyping results]
2) **Patients with hospital-onset COVID-19** (please see eligibility criteria below): to be treated with 1.2g casirivimab and imdevimab (if genotyping is available and confirms infection with a non-Omicron SARS-CoV-2 variant of concern) or otherwise with sotrovimab

Providers may continue to use the casirivimab and imdevimab combination in the treatment of patients in Group 1 up to the point at which the Omicron variant accounts for more than 50% of the local hospital prevalence. After this threshold has been reached, where genotyping results are available and confirm infection with a non-Omicron variant, the casirivimab and imdevimab combination can continue to be used. Where genotyping is not available or genotyping confirms infection with the Omicron variant, nMABs can only be offered as part of a formal trial.

[2] Refers to patients who were negative for serum antibodies against SARS-CoV-2
[3] QCOVID3 is a population-based cohort study performed to derive and validate a risk prediction algorithm to estimate hospital admission and mortality outcomes from COVID-19 in adults in England. Additional work was undertaken by the QCOVID team on risk of death in hospitalised patients.

Eligibility criteria

Patients must meet all of the eligibility criteria and none of the exclusion criteria under one of the following pathways[4] [5]:

1) Patients hospitalised with acute COVID-19

Hospitalised patients are eligible to be considered for treatment with **casirivimab and imdevimab** if:

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) test or where a multidisciplinary team (MDT) has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis

  AND

- Hospitalised specifically for the management of acute symptoms of COVID-19[6]

  AND

- Negative for baseline serum anti-spike (anti-S) antibodies against SARS-CoV-2[7] (see section on 'Serum antibody status' below)

  AND EITHER

  - Local hospital prevalence of the Omicron variant is <50%

  OR

  - Genotype sequencing indicates the patient is infected with a non-Omicron variant.

2) Patients with hospital-onset[8] COVID-19

Patients are eligible to be considered for treatment with casirivimab and imdevimab (if genotyping is available and confirms infection with a non-Omicron variant) or otherwise with sotrovimab if:

- Hospitalised for indications other than for the management of acute symptoms of COVID-19[9];

  AND

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) test within the last 5 days

  AND

- A member of a 'highest' risk group (as defined in Appendix 1)

[4] For paediatric/adolescent patients (aged 12-17 years inclusive), paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment.
[5] Clinical judgement should be applied in making treatment decisions, and may be guided by validated decision support tools such as the ISARIC-4C Mortality and Deterioration Scores
[6] Eligible patients will be acutely ill and admitted specifically to manage symptoms of COVID-19 infection or if COVID-19 infection has been contracted during the hospital stay, symptoms are such that they would have otherwise prompted a hospital admission, independent of the other reasons for the patient's current admission.
[7] The RECOVERY trial population tested patients specifically for anti-S antibodies.
[8] The infection is likely to have been acquired in hospital.
[9] This includes patients admitted to community and mental health hospitals. Where possible patients should be transferred to a suitable facility for treatment with an nMAB.

or

COVID-19 infection presents a material risk of destabilising a pre-existing condition or illness or compromising recovery from surgery or other hospital procedure (as determined by multidisciplinary team [MDT] assessment).

AND

- A baseline serum antibody test (anti-S) against SARS-CoV-2 has been taken **prior** to treatment administration (see 'Data collection requirement' section)[10]

Patients in Group 2 may be eligible for a 2.4g dose of casirivimab and imdevimab if they continue to deteriorate such that their acute COVID-19 illness requires hospital-based care, providing they fulfil the eligibility criteria for Group 1 above. The serostatus result taken prior to initial treatment with an nMAB will inform eligibility for additional treatment[11].

Exclusion criteria

The following patients are not eligible for treatment:

- Children weighing less than 40kg
- Children aged under 12 years
- Known hypersensitivity reaction to the active substances or to any of the excipients of casirivimab and imdevimab or sotrovimab listed in the Summary of Product Characteristics (SmPC).

Serum antibody status

Patients may be tested for anti-S1 or anti-S2 antibodies using any validated quantitative or qualitative anti-S assay that measures either IgG or total antibody levels. Serostatus should be established in line with the pre-determined thresholds relevant to the assay being used by the testing laboratory. Quantitative assays with pre-specified thresholds for seropositivity should return clear binary (i.e. either 'negative' or 'positive') results based on these thresholds. For quantitative assays without a formal threshold for serostatus, clinical decision-making should guide treatment decisions.

In immunocompromised groups, very low 'positive' levels of anti-S antibody on a quantitative assay (within the bottom 10% of the assay's positive range) should be interpreted in the context of clinical decision-making and laboratory advice, and a decision to treat may still be made by the MDT on a case-by-case basis. Providers will be required to report anti-S antibody levels in treated patients, and the corresponding reference range of the local assay, for central monitoring.

In immunodeficient patients on replacement immunoglobulin (intravenous or subcutaneous), the positive detection of anti-S antibodies should be regarded as a 'positive result of unknown significance'. Patients on replacement immunoglobulin testing positive only for anti-S (and negative for anti-N) antibodies should therefore be considered to be seronegative for SARS-CoV-2, and MDT assessment should judge their eligibility for nMAB treatment. Should evidence for passive transmission of anti-N antibodies through replacement immunoglobulin

[10] Patients in Group 2 do NOT need to be seronegative for anti-S antibodies against SARS-CoV-2 to be eligible for initial treatment as specified in this policy.
[11] As those previously treated with an nMAB will be seropositive for anti-S antibodies against SARS-CoV-2, repeat serology need not be performed upon clinical deterioration. Patients who are seronegative on baseline testing will be eligible for treatment.

emerge in the future, the detection of anti-N antibodies should also be regarded as a 'positive of unknown significance'.

If there are concerns or questions around laboratory sensitivity or cut-offs these should be discussed in the first instance with local laboratory leads who will have access to comparative and performance data from the External Quality Assessment (EQA) scheme participation.

Dose

1) Patients hospitalised with COVID-19

   The recommended dose of casirivimab and imdevimab is 2.4g[12] (1.2g each of casirivimab and imdevimab) to be administered as a combined single intravenous infusion[13]. Patients may only receive one 2.4g dose of casirivimab and imdevimab during a course of infection.

   Please note that the use of casirivimab and imdevimab in patients hospitalised with COVID-19 at the 2.4g dose is off-label.

2) Patients with hospital-onset COVID-19

   The recommended dose of casirivimab and imdevimab is 1.2g (600mg each of casirivimab and imdevimab) to be administered as a combined single intravenous infusion[14].

   The recommended dose of sotrovimab is 500mg to be administered as a single intravenous infusion[15].

Administration

Casirivimab and imdevimab

Infusion solutions should be made up according to the following table:

Dose	Active substance	Diluent	Infusion time
2.4g	1.2g (10ml of 120mg/ml) of casirivimab and 1.2g (10ml of 120mg/ml) of imdevimab Total dose volume: 20ml	250mls of 0.9% sodium chloride	30 minutes (minimum)
1.2g	600mg (5ml of 120mg/ml) of casirivimab and 600mg (5ml of 120mg/ml) of imdevimab Total dose volume: 10ml	250mls of 0.9% sodium chloride	30 minutes (minimum)

[12] This dose for hospitalised patients was recommended by consensus of an expert group, based on available research and other pharmacokinetic data.
[13] No dose adjustment is recommended in patients with renal impairment. The pharmacokinetics of casirivimab and imdevimab have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is appropriate in patients with hepatic impairment.
[14] The 1.2g dose may also be delivered via the subcutaneous route; please refer to the SmPC for further information.
[15] No dose adjustment is recommended in patients with renal or hepatic impairment.

Casirivimab and imdevimab should not be infused concomitantly in the same intravenous line with other medication.

Preparation and administration of casirivimab and imdevimab should be initiated and monitored by a qualified healthcare provider using aseptic technique. Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be monitored post intravenous infusion according to local medical practice. Refer to the Specialist Pharmacy Services institutional readiness document for further information on the handling, reconstitution and administration of the product.

Hypersensitivity reactions, including anaphylaxis, have been reported with administration of casirivimab and imdevimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions (IRRs) have been observed with IV administration of casirivimab and imdevimab. IRRs observed in clinical studies were mostly mild to moderate in severity and were typically observed during or within 24 hours of infusion. The commonly reported signs and symptoms for these reactions included nausea, chills, dizziness (or syncope), rash, urticaria and flushing. However, IRRs may present as severe or life-threatening events and may include other signs and symptoms. If an IRR occurs, consider interrupting, slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Sotrovimab

8mls of sotrovimab (62.5mg/ml) should be added to a 100ml pre-filled infusion bag containing 0.9% sodium chloride and administered over 30 minutes. Sotrovimab should not be infused concomitantly in the same intravenous line with other medication.

Preparation and administration of sotrovimab should be initiated and monitored by a qualified healthcare provider using aseptic technique. Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be monitored post intravenous infusion according to local medical practice. Refer to the Specialist Pharmacy Services institutional readiness document for further information on the handling, reconstitution and administration of the product.

Hypersensitivity reactions, including serious and/or life-threatening reactions such as anaphylaxis, have been reported following infusion of sotrovimab. Hypersensitivity reactions typically occur within 24 hours of infusion. Signs and symptoms of these reactions may include nausea, chills, dizziness (or syncope), rash, urticaria and flushing. If signs and symptoms of severe hypersensitivity reactions occur, administration should be discontinued immediately and appropriate treatment and/or supportive care should be initiated.

If mild to moderate hypersensitivity reactions occur, slowing or stopping the infusion along with appropriate supportive care should be considered.

Cautions

Please refer to the Summary of Product Characteristics (SmPC) for casirivimab and imdevimab and sotrovimab for special warnings and precautions for use.

Casirivimab and imdevimab or sotrovimab are not intended to be used as a substitute for vaccination against COVID-19.

COVID-19 vaccines

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

Further information on the timing of COVID-19 vaccination following administration of casirivimab and imdevimab is available at the following sites:

- Liverpool COVID-19 Interactions (covid19-druginteractions.org)
- Interactions information for COVID-19 vaccines – SPS – Specialist Pharmacy Services

Pregnancy and women of childbearing potential

Clinicians should refer to the SmPCs of the relevant products for further information on use in pregnancy and women of childbearing potential.

Casirivimab and imdevimab

The RECOVERY trial included women who were pregnant or breastfeeding, and no serious adverse events were reported. The SmPC for casirivimab and imdevimab states that it should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the foetus considering all associated health factors.

Sotrovimab

There are no data from the use of sotrovimab in pregnant women. The SmPC for sotrovimab states that sotrovimab may be used during pregnancy where the expected benefit to the mother justifies the risk to the foetus.

Co-administration

There is no interaction expected between casirivimab and imdevimab or sotrovimab with the drugs listed below. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Corticosteroids

Administration of systemic dexamethasone or hydrocortisone is recommended in the management of patients with severe or critical COVID-19. Corticosteroids are not suggested in non-severe COVID-19 disease. Updated WHO guidance on the use of systemic corticosteroids in the management of COVID-19 can be found here. Casirivimab and imdevimab or sotrovimab should not be regarded as an alternative to corticosteroids.

Remdesivir

The Clinical Commissioning Policy for the use of remdesivir in hospitalised patients with COVID-19 can be found here.

IL-6 inhibitors

The Clinical Commissioning Policy for the use of IL-6 inhibitors (tocilizumab or sarilumab) in hospitalised patients with COVID-19 who require supplemental oxygen can be found here.

Safety reporting

Any suspected adverse reactions from treatment with casirivimab and imdevimab should be reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/.

Marketing authorisation

Casirivimab and imdevimab

Casirivimab and imdevimab delivered intravenously has conditional marketing authorisation in Great Britain (England, Scotland and Wales) for use in prophylaxis and treatment of acute COVID-19 infection. Access to casirivimab and imdevimab in Northern Ireland for the above indications is through a Regulation 174 approval or a licensing determination by the European Medicines Agency.

The use of casirivimab and imdevimab in patients at a dose of 2.4g is off-label, while its use at the 1.2g dose is within the conditional marketing authorisation.

Sotrovimab

Sotrovimab delivered intravenously has conditional marketing authorisation in Great Britain (England, Scotland and Wales) for the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40 kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 infection. Access to sotrovimab in Northern Ireland for the above indication is through a Regulation 174 approval or a licensing determination by the European Medicines Agency.

Governance

Off-label use of medication

Any provider organisation treating patients with these interventions will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the health board/hospital/trust's drugs and therapeutics committee, or equivalent.

Data collection requirement

All patients being considered for treatment with nMABs for COVID-19 during their hospital stay should have their baseline serum antibody (anti-S) status measured prior to treatment to enable further evidence generation around the differential impact of treatment based on serology status.

Provider organisations in England should register all patients using prior approval software (alternative arrangements in Scotland, Wales and Northern Ireland will be communicated) and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Clinicians are also required to ensure that any data collection requirements are met for the purpose of ongoing surveillance, audit and relevant evaluation, including of clinical effectiveness, around the use of nMABs (see 'Surveillance and service evaluation' section below).

Clinical outcome reporting

It is vital to be able to monitor the clinical progression of patients treated with nMABs. Hospitals managing COVID-19 patients are strongly encouraged to submit data through the ISARIC 4C Clinical Characterisation Protocol (CCP) case report forms (CRFs), as coordinated by the COVID-19 Clinical Information Network (CO-CIN) (https://isaric4c.net/protocols/). In addition, completion of the Blueteq forms (in England) will provide further essential data. Intermittent blood sampling (sparse sampling) may be required to collect serum concentration data. There will be a standard operating procedure circulated on sparse sampling to monitor serum concentration levels with nMAB treatment.

Effective from

This policy will be in effect from 20 December 2021.

Policy review date

This is an interim rapid clinical policy statement, which means that the full process of policy production has been abridged: public consultation has not been undertaken. This policy may need amendment and updating if, for instance, new trial data emerges, supply of the drug changes, or a new evidence review is required. A NICE Technology Appraisal or Scottish Medicines Consortium (SMC) Health Technology Assessment or All Wales Medicines Strategy Group (AWMSG) appraisal of casirivimab and imdevimab or sotrovimab for COVID-19 would supersede this policy when completed.

Surveillance and service evaluation

There is an urgent need to generate more evidence and greater understanding around the use of nMABs and antivirals in the treatment of patients with COVID-19. Both surveillance and service evaluation are necessary to gain knowledge around the following: factors of relevance in determining nMAB and antiviral treatment; the impact of nMAB and antiviral treatment in the community and hospital settings on the immune/virologic response and clinical recovery; and the public health sequelae of nMAB use, such as generation of new mutations.

Treating clinicians are asked to ensure that all PCR tests undertaken as an inpatient and/or in the community where any patient who is receiving ongoing PCR testing as part of secondary care (for example, through an outpatient clinic) should do this through the hospital laboratory where these samples should be retained for sequencing. Further serial sampling for specific patient groups may be requested as part of UKHSA genomic surveillance purposes, or country specific programmes.

Clinicians must ensure that any additional data collection requirements are met for the purpose of relevant surveillance, audit and evaluation around the use of nMABs and antivirals. It is expected that there will be ongoing monitoring (involving sample collection) of selected patients treated with nMABs and antivirals (led by UKHSA, for instance around the potential generation of new variants), as well as academic research to generate new knowledge around clinical effectiveness and other relevant aspects of public health.

Equality statement

Promoting equality and addressing health inequalities are at the heart of the four nations' values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010 or equivalent equality legislation) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

COVID-19	Refers to the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus
Neutralising monoclonal antibody	Synthetic antibodies that bind to a virus and inhibit its ability to infect host cells and replicate
Spike protein	The part of the SARS-CoV-2 virus that binds to the host cell, which then facilitates its entry into the cell
Anti-S antibody	Antibodies directed against the spike protein of the SARS-CoV-2 virus

References

1. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab [published online ahead of print, 2021 Oct 27]. N Engl J Med. 2021;10.1056/NEJMoa2107934. doi:10.1056/NEJMoa2107934
2. Hoffmann M, Kruger N, Schulz S, et al. The Omicron variant is highly resistant against antibody-mediated neutralisation – implications for control of the COVID-19 pandemic. Preprint available at: https://www.biorxiv.org/content/10.1101/2021.12.12.472286v1
3. O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. *N Engl J Med*. 2021;385(13):1184-1195. doi:10.1056/NEJMoa2109682
4. RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Preprint available at: https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1

5. Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19 [published online ahead of print, 2021 Sep 29]. *N Engl J Med*. 2021;NEJMoa2108163. doi:10.1056/NEJMoa2108163

Appendix 1: Patient cohorts considered at highest risk from COVID-19 and to be prioritised for treatment with nMABs

The following patient cohorts were determined by an independent advisory group commissioned by the Department of Health and Social Care (DHSC)[16].

Cohort	**Description**
Down's syndrome	All patients with Down's syndrome
Sickle cell disease	All patients with a diagnosis of sickle cell disease
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 • Patients receiving radiotherapy within the last 6 months

Patients with a haematologic malignancy	• Allogeneic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months or active graft vs host disease (GVHD) regardless of time from transplant
	• Autologous HSCT recipients in the last 12 months
	• Individuals with haematological malignancies who have
	  ○ received chimaeric antigen receptor (CAR)-T cell therapy in the last 24 months, or
	  ○ anti-CD20 monoclonal antibody therapy in the last 12 months

[16] For paediatric/adolescent patients (aged 12-17 years inclusive), paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment

	• Individuals with chronic B-cell lymphoproliferative disorders receiving systemic treatment or radiotherapy within the last 3 months • Individuals with chronic B-cell lymphoproliferative disorders with hypogammaglobulinaemia or reduced peripheral B cell counts • Individuals with acute leukaemias and clinically aggressive lymphomas who are receiving chemotherapy or within 3 months of completion at the time of vaccination • Individuals with haematological malignancies who have received anti-CD38 monoclonal antibody or B-cell maturation agent (BCMA) targeted therapy in the last 6 months • Individuals with chronic B-cell lymphoproliferative disorders not otherwise described above

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)	• 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
Primary 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)
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