



Department
of Health &
Social Care



The Scottish
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Llywodraeth Cymru
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Department of
Health

An Roinn Sláinte
Máinystrie O Poustie



Rapid Policy Statement

Interim Clinical Commissioning Policy: Antivirals or neutralising monoclonal antibodies for non-hospitalised patients with COVID-19 (Version 6)

Published on: 30 May 2022

Effective from: 13 June 2022

Commissioning position

The proposal is: antivirals or neutralising monoclonal antibodies (nMABs) are recommended to be available as a treatment option through routine commissioning for non-hospitalised adults with COVID-19 treated in accordance with the criteria set out in this document.

This policy applies to non-hospitalised patients with COVID-19 who are symptomatic and showing no evidence of clinical recovery and covers the following treatment options:

- First-line: nirmatrelvir plus ritonavir (antiviral) OR sotrovimab (nMAB), as clinically indicated
- Second-line: remdesivir (antiviral)
- Third-line: molnupiravir (antiviral)

Further information on selecting the most appropriate treatment can be found in the [Clinical Guide which accompanies this policy](#).

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

Where patients are ineligible for treatment under this policy, recruitment to the [PANORAMIC trial](#), which is building the evidence for novel oral antivirals in a broader cohort of at risk patients, should be supported.

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. Antiviral medications inhibit viral replication and prevent progression of infection.

Recent evidence suggests that antivirals and neutralising monoclonal antibodies (nMABs) significantly improve clinical outcomes in non-hospitalised patients with COVID-19 who are at high risk of progression to severe disease and/or death. The following products have conditional marketing authorisation for the treatment of non-hospitalised patients with COVID-19:

1) **Nirmatrelvir/ritonavir**

Evidence

[Final results](#) from the EPIC HR trial indicate that the dual oral antiviral nirmatrelvir/ritonavir resulted in a relative risk reduction of hospitalisation or death by 89% (within 3 days of symptom onset) and 88% (within 5 days of symptom onset) compared to placebo in non-hospitalised, high-risk adults with COVID-19 (Hammond et al, 2022).

Marketing authorisation

Nirmatrelvir/ritonavir administered orally has conditional marketing authorisation in Great Britain (England, Scotland and Wales) for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19. Access to nirmatrelvir/ritonavir in Northern Ireland for this indication is through a Regulation 174 approval or a licensing determination by the European Medicines Agency.

2) **Sotrovimab**

Evidence

Interim analysis of the COMET-ICE trial, which studied sotrovimab administered intravenously to non-hospitalised patients with mild-to-moderate disease and at least one risk factor for disease progression, showed a relative risk reduction in hospitalisation or death at day 29 by 85% in patients treated with sotrovimab compared with placebo (Gupta et al, 2021a). The final analysis of this study has shown a relative risk reduction in hospitalisation or death at day 29 by 79% in patients treated with sotrovimab compared with placebo (Gupta et al, 2021b).

Marketing authorisation

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 40kg) 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 via the European Medicines Agency conditional marketing authorisation.

3) **Remdesivir**

Evidence

A three-day intravenous course of remdesivir administered within 7 days of COVID-19 symptom onset to non-hospitalised patients with risk factors for disease progression, resulted in a relative risk reduction of 87% in hospitalisation or death at day 28 (Gottlieb et al, 2021).

Marketing authorisation

Remdesivir delivered intravenously has conditional marketing authorisation in the UK for the following indications:

- treatment of COVID-19 in adults, and adolescents (aged 12 to less than 18 years and weighing at least 40kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment), for a treatment duration of 5-10 days.

- treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 within 7 days of symptom onset, for a treatment duration of 3 days.

Use of remdesivir under this policy in children aged 12-17 years would be off-label.

4) Molnupiravir

Evidence

Final results from the Phase 3 MOVE-OUT trial show that the oral antiviral molnupiravir administered within 5 days of COVID-19 symptom onset to high-risk, non-hospitalised patients resulted in a relative risk reduction of 30% in the composite primary outcome of hospitalisation or death at day 29 (Bernal et al, 2021).

Marketing authorisation

Molnupiravir administered orally has conditional marketing authorisation in Great Britain (England, Scotland and Wales) for use in the treatment of mild to moderate COVID-19 in adults (aged 18 years and over) with a positive SARS-CoV-2 diagnostic test and who have at least one risk factor for developing severe illness. Access to molnupiravir in Northern Ireland for this indication is through a Regulation 174 approval or a licensing determination by the European Medicines Agency.

Eligibility criteria

Non-hospitalised patients are eligible for treatment with any one of the four medicines if:

- SARS-CoV-2 infection is confirmed by either:
 - Lateral flow test (registered via gov.uk or NHS 119) OR
 - Polymerase chain reaction (PCR) testing

AND

- [Symptomatic with COVID-19](#) and showing no signs of clinical recovery

AND

- The patient is a member of a 'highest' risk group (as defined in the Department of Health and Social Care commissioned [Independent Advisory Group Report](#))

Available treatment options for eligible patients are:

- First-line: nirmatrelvir/ritonavir (antiviral) OR sotrovimab (nMAB), as clinically indicated
- Second-line: remdesivir (antiviral)
- Third-line: molnupiravir (antiviral).

Further information on selecting the most appropriate treatment can be found in the accompanying [Clinical Guide associated with this policy](#).

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

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

Children aged 12-17 years may only be considered for treatment with sotrovimab or remdesivir. For paediatric/adolescent patients (aged 12-17 years inclusive), the eligibility criteria above must be met. Paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment. Additional criteria can be found in the Department of Health and Social Care commissioned [Independent Advisory Group Report](#).

Where patients are ineligible for treatment under this policy, recruitment to the [PANORAMIC trial](#), which is building the evidence for novel oral antivirals in a broader cohort of at risk patients, should be supported.

Exclusion criteria

Patients would not be eligible for treatment if any of the following apply:

- Requirement for hospitalisation for COVID-19
- New supplemental oxygen requirement specifically for the management of COVID-19 symptoms
- Known hypersensitivity reaction to the active substances or to any of the excipients of the medications below as listed in their respective Summary of Product Characteristics.

Nirmatrelvir/ritonavir

If the initial criteria above are met, patients may be considered for treatment with **nirmatrelvir/ritonavir** if:

- Clinical judgement deems that an antiviral is the preferred option

AND

- Treatment is commenced within 5 days of symptom onset¹

AND

- The patient does NOT have a history of advanced decompensated liver cirrhosis or stage 4-5 chronic kidney disease (CKD)²

AND

- Nirmatrelvir/ritonavir treatment has been deemed safe following guidance from the appropriate specialty team(s) – see the accompanying [Clinical Guide for treatment with antivirals and nMABs](#)

The following additional **exclusion criteria** apply if considering treatment with nirmatrelvir/ritonavir:

- Children aged less than 18 years
- Pregnancy
- The patient is taking any of the medications listed as 'do not use' in the [Specialist Pharmacy Service \(SPS\) guidance](#) for nirmaltrevir/ritonavir.

¹ Treatment commencement may be extended up to a maximum of 7 days from symptom onset if clinically indicated (treatment commencement beyond 5 days from symptom onset is off-label).

² Nirmatrelvir/ritonavir may be considered in non-hospitalised patients with stage 3 CKD, if providers can assure themselves that the required dose modification can be delivered safely. See the Summary of Product Characteristics and the section on dosing in the policy for more information.

Sotrovimab

If the initial criteria above are met, patients may be considered for treatment with **sotrovimab** if:

- Clinical judgement deems that an nMAB is the preferred option

AND

- Treatment is delivered within 5 days of symptom onset¹.

Patients who have received an nMAB within a post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP) trial (such as the PROTECT-V trial) who meet the eligibility criteria of this policy can still receive treatment with sotrovimab, if this is deemed the most appropriate treatment option.

The following additional **exclusion criteria** apply if considering treatment with sotrovimab:

- Children aged under 12 years
- Adolescents (aged 12-17) weighing less than 40kg.

Remdesivir

If the initial criteria above are met, patients may be considered for treatment with **remdesivir** if:

- Clinical judgement deems that an antiviral is the preferred option

AND

- Treatment with nirmatrelvir/ritonavir is contraindicated or not possible

AND

- Treatment is commenced within 7 days of symptom onset.

The following additional **exclusion criteria** apply if considering treatment with remdesivir:

- Children aged under 12 years
- Adolescents (aged 12-17) weighing less than 40kg
- Estimated glomerular filtration rate (eGFR) <30 mL/min (except in patients with end-stage renal disease on haemodialysis)
- Alanine transaminase (ALT) \geq 5 times the upper limit of normal.

Remdesivir should be discontinued in patients who develop **any** of the following:

- ALT \geq 5 times the upper limit of normal during treatment with remdesivir (remdesivir may be restarted when ALT is < 5 times the upper limit of normal)
- ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR).

An individual clinical decision should be made as to whether pre-treatment urea and electrolytes and liver function tests are required based upon whether recent bloods are available or the patient is considered at risk of undiagnosed liver or kidney disease.

If the patient experiences clinical deterioration such that hospitalisation and low-flow supplemental oxygen is required, the patient may be considered for treatment with a 5-day course of remdesivir as outlined in the UK Clinical Commissioning [Policy](#) for remdesivir in patients hospitalised due to COVID-19.

Molnupiravir

If the initial criteria above are met, patients should only be considered for treatment with **molnupiravir** if:

- Treatment with nirmatrelvir/ritonavir, remdesivir AND sotrovimab are contraindicated or not possible

AND

- Treatment is commenced within 5 days of symptom onset¹.

The following additional **exclusion criteria** applies if considering treatment with molnupiravir:

- Children aged less than 18 years
- Pregnancy.

Dose and administration

Nirmatrelvir/ritonavir

The recommended dose of nirmatrelvir/ritonavir is 300mg (two 150mg tablets) nirmatrelvir with 100mg (one 100mg tablet) ritonavir taken together orally twice daily for 5 days. In patients with moderate renal impairment (CKD stage 3), the dose of nirmatrelvir/ritonavir should be reduced to nirmatrelvir/ritonavir 150 mg/100 mg (1 tablet of each) twice daily for 5 days. The remaining tablet of nirmatrelvir should be disposed of in accordance with local requirements.

Nirmatrelvir/ritonavir should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of onset of symptoms¹. Clinicians should assure themselves that patients are able to swallow the oral tablets.

Refer to the [Specialist Pharmacy Services guidance](#) and [University of Liverpool COVID-19 Drug Interactions Checker](#) for further information.

A missed dose should be taken as soon as possible and within 8 hours of the scheduled time, and the normal dosing schedule should be resumed. If more than 8 hours has elapsed, the missed dose should not be taken and the treatment should resume according to the normal dosing schedule.

If a patient requires hospitalisation due to severe or critical COVID-19 after starting treatment with nirmatrelvir/ritonavir the patient should complete the full 5-day treatment course at the discretion of their healthcare provider.

Sotrovimab

The recommended dose of sotrovimab is 500mg to be administered as a single intravenous infusion³. Treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset¹.

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. 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.

³ No dose adjustment is recommended in patients with renal or hepatic impairment.

Sotrovimab should not be infused concomitantly in the same intravenous line with other medication.

Remdesivir

The recommended dose of remdesivir for this cohort is 200mg intravenously on day 1 followed by 100mg intravenously on days 2 and 3. Treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 7 days of symptom onset.

200mg of remdesivir (day 1 loading dose) and 100mg of remdesivir (days 2 and 3 maintenance doses) should be diluted in either a 250ml or 100ml pre-filled bag of 0.9% sodium chloride solution and infused over a minimum of 30 minutes.

Molnupiravir

The recommended dose of molnupiravir is 800mg (four 200mg capsules) taken orally every 12 hours for 5 days. Treatment must not be extended beyond 5 days. Molnupiravir should be commenced as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset¹. Clinicians should assure themselves that patients are able to swallow the oral capsules.

To reduce the possibility of emerging resistance, patients should be advised to complete the whole course of treatment even if their symptoms improve and/or they feel better. If a patient requires hospitalisation due to severe or critical COVID-19 after starting treatment with molnupiravir, the patient should complete the full 5-day treatment course at the discretion of his/her healthcare provider.

Cautions

Please refer to the Summary of Product Characteristics (SmPC) for [nirmatrelvir/ritonavir](#), [sotrovimab](#), remdesivir ([Great Britain](#) and [Northern Ireland](#)) and [molnupiravir](#) for special warnings and precautions for use.

Nirmatrelvir/ritonavir

Nirmatrelvir/ritonavir has a risk of serious adverse reactions due to interactions with other medicinal products (see the [SPS guidance](#) for a list of these products).

Initiation of nirmatrelvir/ritonavir, a CYP3A inhibitor, in patients receiving medicinal products metabolised by CYP3A or initiation of medicinal products metabolised by CYP3A in patients already receiving nirmatrelvir/ritonavir, may increase plasma concentrations of medicinal products metabolised by CYP3A. Initiation of medicinal products that inhibit or induce CYP3A may increase or decrease concentrations of nirmatrelvir/ritonavir, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening or fatal events from greater exposures of concomitant medicinal products
- Clinically significant adverse reactions from greater exposures of nirmatrelvir/ritonavir
- Loss of therapeutic effect of nirmatrelvir/ritonavir and possible development of viral resistance

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

Patients should be advised of the possible gastro-intestinal side-effects of treatment with nirmatrelvir/ritonavir (e.g. nausea, vomiting). If such side-effects are experienced, anti-emetics should be considered that are not contra-indicated. If nirmatrelvir/ritonavir treatment cannot be

tolerated, an alternative treatment can be considered within the options and criteria of this policy. Combination treatment should not be provided⁴.

Sotrovimab

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.

Remdesivir

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Patients should be monitored for hypersensitivity reactions during and following administration of remdesivir as clinically appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, administration of remdesivir should be discontinued immediately and appropriate treatment initiated.

Patients receiving remdesivir in an outpatient setting should be monitored according to local medical practice.

Molnupiravir

The most common adverse reactions ($\geq 1\%$ of subjects) reported during treatment and during 14 days after the last dose of molnupiravir were diarrhoea (3%), nausea (2%), dizziness (1%) and headache (1%) all of which were Grade 1 (mild) or Grade 2 (moderate).

COVID-19 vaccines

Sotrovimab is not intended to be used as a substitute for vaccination against COVID-19.

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

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

- [Liverpool COVID-19 Interactions \(covid19-druginteractions.org\)](https://www.liverpool.ac.uk/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 for the relevant products for further information on use in pregnancy and women of childbearing potential. All healthcare professionals are asked to ensure that any patients who receive a COVID antiviral while pregnant are reported to the UK COVID-19 antivirals in pregnancy registry on 0344 892 0909 (available 9:00am to 5:00pm, Monday to Friday, excluding bank holidays) so that they can be followed up. For more information, go to <https://www.medicinesinpregnancy.org/COVID-19-Antivirals-Pregnancy-Registry/>. Clinicians are

⁴ Unless as part of a formal clinical trial.

advised to refer to the SmPC nirmatrelvir/ritonavir and molnupiravir for more information on use during pregnancy or lactation.

Nirmatrelvir/ritonavir

There are no human data on the use of nirmatrelvir/ritonavir during pregnancy to inform the drug-associated risk of adverse developmental outcomes, women of childbearing potential should avoid becoming pregnant during treatment with nirmatrelvir/ritonavir. Nirmatrelvir/ritonavir is **not recommended** during pregnancy and in women of childbearing potential not using effective contraception.

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment and until after one complete menstrual cycle after stopping nirmatrelvir/ritonavir.

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.

Remdesivir

There are no or limited amount of data from the use of remdesivir in pregnant women. Remdesivir should be avoided in pregnancy unless clinicians believe the benefits of treatment outweigh the risks to the individual (please see SmPC for further information).

Molnupiravir

There are no data from the use of molnupiravir in pregnant women. Studies in animals have shown reproductive toxicity. Molnupiravir is **not recommended** during pregnancy. Individuals of childbearing potential should use effective contraception for the duration of treatment and for 4 days after the last dose of molnupiravir.

Co-administration

Please see the [SPS guidance](#) for potential interactions involving nirmatrelvir/ritonavir.

There is no interaction expected between sotrovimab, remdesivir or molnupiravir and other commissioned treatments for COVID-19. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (<https://www.covid19-druginteractions.org/checker>).

Please refer to other published UK clinical commissioning policies setting out available COVID-19 treatments [here](#).

Safety reporting

It is vital that any suspected adverse reactions (including congenital malformations and/or neurodevelopmental problems following treatment during pregnancy) are reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: <https://coronavirus-yellowcard.mhra.gov.uk/>.

Governance

Data collection requirement

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 research around the use of nMABs and antivirals (see 'Research' section below).

Effective from

This policy will be in effect from the 13 June 2022.

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 nMABs and/or antivirals for COVID-19 would supersede this policy when completed.

This policy will be reviewed, if required, as further data emerge on the population prevalence of the omicron variant and any impact it may have on the efficacy of COVID-19 therapies.

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 and antiviral use, such as generation of new mutations and/or variants.

Treating clinicians are asked to ensure that all PCR tests undertaken as part of routine clinical care should do this through the hospital laboratory where these samples should be retained for sequencing. Please note that during times of high prevalence, labs will prioritise sending samples from clinical priority groups only. To aid with this, clinicians should ensure PCR samples from clinical priority groups are clearly labelled as such. 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

References

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5. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of the Neutralizing SARS-CoV-2 Antibody Sotrovimab in Preventing Progression of COVID-19: A Randomized Clinical Trial. Preprint available at: <https://www.medrxiv.org/content/10.1101/2021.11.03.21265533v1>