PROTOCOL TITLE: European Clinical Research Alliance on Infectious Diseases –

PRIMary care adaptive platform trial for pandemics and Epidemics

EudraCTIS number: 2022-501707-27

A double-blind, randomised, comparative trial to investigate the effect of Investigational Medicinal Products and usual care in non-hospitalised patients with COVID-19 or COVID-like-illness

ECRAID-Prime: Participant Information Sheet

We would like to invite you to take part in a clinical trial. You have received this invitation because you are experiencing symptoms of a respiratory infection, COVID-19 or COVID-like-complaints, and/or have contacted your GP/primary care provider about such symptoms. Please take time to read the following information carefully before deciding if you wish to take part. Your participation is entirely voluntary.

1. Who is organising (sponsoring) and funding this trial?

This trial is being sponsored by the University Medical Center Utrecht (UMCU), the Netherlands; UMCU is referred to as "Sponsor". This trial is operationally managed by Ecraid (European Clinical Research Alliance on Infectious Diseases) in the Netherlands. Ecraid works to identify, prevent, and treat infectious diseases in Europe, through this ECRAID-Prime trial and other related studies.
You can find the contact details of the Sponsor and other relevant persons in **Appendix A.**
ECRAID-Prime is a collaboration between the UMCU, the University of Oxford (United Kingdom), the University of Antwerp (Belgium), ECRIN (European Clinical Research Infrastructure Network, France) and Ecraid. Funding has been provided by the European Union (No: 101046109).
The medical product that you might receive in this trial is produced and supplied by SaNOtize.

2. Who will be recruited to the trial?

This trial will enrol patients with a respiratory infection in about seven countries across Europe. We anticipate enrolling approximately 1000 patients in the trial so that we can test several different medical products. You are being invited to take part because you have visited or contacted your GP with symptoms suggestive of a respiratory infection, COVID-19 or COVID-like-complaints.

3. What is the purpose of the ECRAID-Prime trial?

Most people with a respiratory infection (this can be COVID-19 or COVID-like-illness) do not become seriously ill. Some people, however, do go on to have more serious symptoms and may even need to be admitted to hospital.
The ECRAID-Prime trial is an intervention trial that is investigating how well medical products to treat respiratory infections work and the safety of these products in non-hospitalised adult patients across Europe.
In this trial we want to investigate whether medical products:

- Help you to recover faster
- Reduce the severity of your symptoms
- Reduce complications that require treatment in hospital
- Prevent spread to your family members/house mates

4. What does the ECRAID-Prime trial involve?

If you decide to participate, a combined throat/nose swab will be taken so that we can find out what is causing your respiratory infection. Respiratory infections can be caused by various organisms (germs) such as SARS-CoV-2 (the virus that causes COVID-19), influenza virus, respiratory syncytial virus, rhinovirus, other coronaviruses, or a bacterium. This swab will be analysed at a later date. You will not receive the swab results.

You will be randomised (allocated purely by chance) to receive one of the medical products in addition to usual care, or to receive usual care without a trial medical product. The medical products you might be allocated to are described below. If you are randomised to receive one of the medical products, neither you nor the investigator will know which one it is. You are requested to take the medical product according to the instructions (for instructions see document “Instructions for use medical product”).

To find out how well the medical product works and how safe it is, we will collect health information and body material (a throat/nose swab) from you. We will also ask you to answer questions at the end of each day for 28 days about how you are feeling, the symptoms you are experiencing, your recovery, any side effects, and whether members in your household are experiencing respiratory symptoms. Additionally, we ask you to take a combined throat/nose self-swab on 4, 7 and 14 days after you join the trial (for instructions see document “Instructions combined throat/nose self-swab”).

5. Medical products

NONS

NONS (Nitric Oxide Nasal Spray) is a nasal spray containing Nitric Oxide, a naturally occuring chemical which is also produced in your body and is involved in various processes. Nitric Oxide may inactivate viruses in the nasal cavity and prevent viruses from entering the nasal mucosa cells. It could thereby reduce the amount of virus and reduce spreading of the virus into the lungs. NONS is approved as prophylactic medical device in several countries. In this trial we will test whether it can treat symptoms of a respiratory tract infection.

Saline

Regular use of saline (0.9% NaCl) nasal spray may wash out viruses from the nasal cavity, thereby reducing viral load and spreading of the virus into the lungs. Saline is a worldwide approved medical device.

If you are randomised to one of the medical products, you will be asked to use the nasal spray 6 times a day for 7 days.

6. How long will participation in the trial take?

Your participation will take 6 months. We will ask you to tell us about how you are feeling each day for 28 days via a daily diary. After 3 and 6 months you will receive an online questionnaire or a telephone call to ask about any long-term effects from your respiratory infection. Testing various medical products will take several years.

7. What is the difference with usual care?

Participation in the trial will not affect the care you receive and will not replace any usual care. Your GP will decide what care is best for you; your GP might prescribe medication and/or provide you with self-care advice. If you decide not to participate in the trial, your care will not be affected in any way.

8. What medications are not allowed to be used during the trial?

You are not allowed to use the following medications for 7 days before participating in the trial and for 7 days after starting the trial:

- NO donors/derivatives: isosorbide dinitrate, isosorbide mononitrate, nitroglycerine/glyceryl trinitrate, nitroprusside, nicorandil
- Phosphodiesterase inhibitors: avanafil, sildenafil, tadalafil, vardenafil
- Guanylate cyclase activators: riociguat, linaclotide.

Please discuss with your GP whether your medication use would mean that you should not take part in this trial.

9. What will happen if you take part?

Informed Consent

You will be given time to consider whether or not to take part in this trial. You will be able to speak to (by telephone if they are not with you) friends or family members if you wish to discuss taking part. If you would like to take part, you will be asked to sign a consent form. Your GP or a qualified delegate will go through the consent form with you. The original signed consent form will be safely stored at the trial site and you will receive a copy.

Initial Screening

After you have signed the consent form, your GP or a qualified delegate will complete a short questionnaire including some details about you (age, sex, and chronic diseases and ethnicity; ethnicity is part of the data collected as we need to differentiate the susceptibility and severity of respiratory infections between ethnic groups) and symptoms you have been experiencing. For women of child-bearing potential, a urine pregnancy test will be done to exclude a pregnancy before taking any trial medical product. Based on this screening information, your GP or qualified delegate will decide whether you can participate in the trial. We will also record your name, email address, home address and telephone number so that the coordinating team can contact you.

Inclusion

Upon inclusion in the trial, the following will be done:

- We will collect information from you about smoking, vaccinations, if you have had COVID-19, your usual care provided by your GP or delegate, weight and height and temperature. Oxygen saturation, respiratory rate and heart rate will also be measured if the visit is face-to-face.
- A combined throat/nose swab will be taken.
- You will be randomised to receive one of the medical products in addition to usual care, or usual care without a trial medical product (see section 4).

Follow-Up

The GP or delegate will give you a paper diary or provide you with a link to an online diary, whichever you prefer. They will explain how to complete the diary. You will be asked to complete the diary at the end of each day for 28 days. The diary will include questions about your symptoms, other medication, swabs taken, recovery, visits to the GP or hospital and whether people you are living with develop respiratory symptoms. It should take about ten minutes to complete the diary every day.

If you completed the paper diary, you return it to the coordinating team in the addressed envelope provided. If you complete your diary online it will automatically be included in the online database. If the diary is not

complete, we will call you after day 28 to ask some remaining questions about your illness. This call will take about ten minutes.

You will also receive a phone call by the site/coordinating team on approximately day 14. During this call, you will be asked about the diary and specific health issues related to the trial you might experience. This call will take about five to ten minutes.

We will keep in regular contact with you during the follow up period. If you have chosen to complete the diary online, we will send you an email with a link to your web-based daily symptom diary every day for 28 days. We may also send you text reminders to take your swab sample, and to complete the daily diary on the first day of your participation in the trial and on Day 4, Day 7, Day 14, Day 28, at Month 3 and Month 6. However, you will have the opportunity to opt out of this if you wish.

You may also participate in an interview about your experience of your consultation and participation in this trial. This is an optional interview and you will only participate if you give consent for this.

Swab collection and collection of unused medical product

You are being asked to take a combined throat/nose self-swab at day 4, 7 and 14 after you join the trial. You will receive materials for this, and an instruction booklet on how to take and store the swabs. You will also receive pre-paid postage materials so that you can post your samples to the research team. On day 14, you will also need to post your remaining trial medication. Instructions for packaging and posting the samples and medication can also be found in the swab instruction booklet.

Contact after 3 and 6 months

After 3 and 6 months we will contact you by telephone or you will receive an online questionnaire, with questions related to any long-term effects of your respiratory infection, impact of specific symptoms and GP and hospital visits. **Appendix B** contains a schedule of all follow-up procedures.

If at any point during the trial you decide to no longer take part, please let your GP practice or coordinating team know. No further follow up questionnaires will be send or calls will be made. You do not have to explain why you want to stop. A decision to withdraw will not affect the usual care you receive in any way, now, or in the future.

10. What agreements do we make?

We want the trial to go well, so if you do take part, we ask you:

- To take the medical product according to the instructions for use (in the participant pack).
- Please NOT to take part in any other trial with a medical product while you are part of this trial.
- To fill in the diary at the end of each day for 28 days.
- To keep the participant card of the trial with you at all times, in your wallet, for example. It states that you are taking part in this trial, and who should be contacted in an emergency. Please, show this card each time you visit another doctor.
- *For women of child bearing potential:*

- To use highly effective contraception for 30 days before and after starting the trial: sterilisation, long-acting reversible contraceptive methods (intrauterine devices and implants), combined hormonal methods (oral, transdermal, or intravaginal), or the progestogen only pill or injection; or
- To be abstinent for 30 days before and after starting the trial where this is in line with your preferred and usual lifestyle.

- To contact your GP practice, or the coordinating team as outlined in **Appendix A**, if:
  - You are admitted to a hospital, or get treatment in a hospital for your respiratory infection
  - You suddenly have problems with your health
  - You no longer want to take part in the trial
  - You became pregnant
  - Your telephone number, address or email address changes

11. *What side effects, adverse effects, or discomforts could you experience?*

The medical products may cause side effects. Side effects are problems you can experience after use of the product. You may experience the following side effects:

- Nasal burning or irritation (may affect up to 2 in 100 people (2%))
- Skin rash on your face and hands, if you accidentally spray on your face or hands (may affect less than 1 in 100 people (<1%))
- Headache (may affect less than 1 in 10000 people (<0.01%))
- Nosebleeds (may affect less than 1 in 10000 people (<0.01%))

In prior medical studies, these side effects were mild and resolved quickly. You should discontinue treatment in case of headache, nose bleed, or persistent burning sensation immediately after use of the medical product. If nasal burning persists more than 10 minutes, or the other symptoms are severe or persistent, contact your GP practice or the coordinating team as outlined in **Appendix A**.

The medical products we are investigating can have side effects that we do not know about at the moment. Notify your GP practice or the coordinating team as outlined in **Appendix A** if you experience or are concerned about unexpected symptoms.

12. *Will you get the results of the trial?*

We will not personally contact you about the results of the trial. Results of this trial will be published in scientific academic journals that can be accessed, as well as in the European database: https://euclinicaltrials.eu when the summaries become available. Findings will also be made available within one year after the trial ends on the Ecraid website: www.ecraid.eu. The information included in any trial publication cannot identify any trial participant.

13. *How will we use information about you?*

We will need to use information from you during the course of your respiratory infection and from your medical records supplied by your GP for this trial This information will include your:

- name, age, gender
- email address, home address, telephone number
- number of hospitalizations and GP consultations
- current and previous health status
  - o symptoms of your respiratory infection
  - o assessments conducted as part of standard of care

- medical information that we collect during the trial
    - o the types of treatments you received as part of usual care.

People will use this information to do the research or to check whether the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Some of your information will be sent to countries outside the UK. They must follow our rules about keeping your information safe. Once we have finished the trial, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the trial.

14. What will be done with your data and swabs?

If you agree to participate, you also give your consent to collect, use and store the data captured during inclusion and provided during the trial, as well as the combined throat/nose swabs. This is needed to answer the research questions of this trial and to be able to publish the results. In reports and publications about the trial, nobody will be able to see that you participated, because all data will be fully anonymised.

To protect your privacy, we give a code to your data and swabs, a "participant ID". This process is called "pseudonymisation". When we process your trial data and swabs we always use that code instead of your name. The code in itself contains no specific information about you by which you may be identifiable. We keep the key to that code in a safe place at your GP's practice, or at the trial centre. Only your GP or trial centre will have access to the key of that code. Only your pseudonymised trial data and swab material will be shared with partners in the ECRAID-Prime collaboration.

Where and for how long are your pseudonymised data stored?

Your pseudonymised trial data will be stored for 25 years in a centralised secure database in the Netherlands.

Where do we store/process your swabs?

Your swabs will initially be stored at a local laboratory and, at a later stage, transported to the Laboratory of Medical Microbiology of the University of Antwerp for analysis. Your swabs will be stored for 25 years in the "Biobank Antwerp" (BB190007) which is managed in accordance with the Royal Decree on Biobanks (Belgium). Your swabs will be registered with your participant ID in a fully secure laboratory management system. Your pseudonymised trial data will be linked to your swabs' analysis results, in accordance with General Data Protection Regulation (GDPR) rules.

Who can see your personal information?

Any identifying information such as your name, telephone number, email address and home address will only be accessed by your GP and by the local coordinating team. The provider of the system to securely store your personal information is called YourResearch (YR) and is based in the Netherlands. Your personal data entered in YR will never be exported or linked to any other database system used to store your pseudonymised trial data. At the end of the trial the data held in YR will be deleted. The system administrators will not have access to any of your personal information.

Some designated people will be able to see your data, including the data which is not pseudonymised. This is necessary to check whether the investigators are carrying out the trial properly and reliably, and to be able to run the trial and collect follow-up information. Persons who can have access to your data for review are: 1) A so-called monitor checking data on behalf of UMCU or Ecraid; 2) Auditors or (inter)national supervisory authorities; 3) Members of the coordinating team in order to be able to run the trial and collect follow-up information; 4) Members of a committee monitoring data and safety of the trial. These people will keep your personal information confidential.

What happens to your data and swabs if you consent for other research?

Your data and swabs may also be important for other related scientific research following this trial. It is very important to learn more about how various respiratory viruses affect people, change, as well as affect the population. As such, the Sponsor would also like to store your anonyimised trial data and pseudomised swab material for 25 years for other research. In the consent form you can indicate whether you agree to this or not. If you agree, you can always decide later to withdraw your consent for future use at any time. If you do not agree, you can still take part in this trial. If you do agree to have your trial data and swab material stored for other research, your trial data and swab material can be used by the Sponsor to answer related research questions in ongoing observational studies, or future studies. When the Sponsor shares your data with other research institutions for other related scientific research, pseudonymised swab material and anonymised trial data will be shared. Such studies outside the Sponsor need to be approved by an independent ethics committee. The Sponsor will take appropriate measures to ensure that they will protect your trial data and swab materials in the same way that they are protected under the privacy rules of the UK.

Will we send your data to countries outside the European Economic Area?

The European Economic Area (EEA) includes all EU countries, Iceland, Liechtenstein, and Norway. Ecraid includes researchers in Australia, and the UK, which are outside of the EEA. We might send your pseudonymised trial data and swab materials to partners in the ECRAID-Prime collaboration located inside and outside the UK. Other parties such as the medical product manufacturer (SaNOtize) which is located outside the UK will only receive anonymized trial data.

15. What are your choices about how your information is used?

You can stop being part of the trial at any time, without giving a reason, but we will keep information about you that we already have. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you. Your pseudonymised data and swab collected up to that point will still be used by the investigators for the ECRAID-Prime trial. They may also be used for other ongoing and possible other studies if you agree to this. Upon withdrawal, you will be asked whether you are okay with the continued use of your swab collected or if you wish for your swab to be destroyed.

If you wish to withdraw from the trial, please contact the trial team immediately using the details in **Appendix A**. You do not have to explain why you want to stop. However, we appreciate hearing why you no longer wish to take part as this helps us to improve our research processes. A decision to withdraw will not affect the standard of care you receive in any way, now, or in the future.

16. What are the possible disadvantages of taking part?

Taking part in the trial can have disadvantages:

- You may experience side effects of the medical product, as described in section 11
- There may be a brief period of discomfort from (self-)taking the combined throat/nose swabs
- Taking part in the trial will take up some of your time
- You are expected to comply with the requirements of the trial

17. What are the possible benefits of taking part?

You might benefit from the effects of any medical product you could be given. However, you might not

receive a medical product as part of the trial, and we do not yet confidently know how well any of the trial products work. Nevertheless, even though taking part may not benefit you personally, your participation will help researchers and doctors learn about the safety and any benefits from the medical products we are testing. Thereby, the treatment of other patients with respiratory infections might be improved. If you participate, it does not necessarily mean that your respiratory infection will recover any faster.

18. When does your participation in the trial end?

1. After follow-up at month 6, or
2. The trial team decides to stop your participation, or
3. You want to stop participating in the trial yourself (see below), or
4. One of the following authorities decides that the trial should stop:
    - European Commission
    - The Medical Ethics Review Committee that reviews the conduct of the trial
    - The UK government.

19. Will you be contacted again for other studies?

You may also be contacted to take part in an interview about your experiences with the consultation and participation in the ECRAID-Prime trial. You are likely to be contacted about 2-4 weeks after your consultation. The interview can be done at a time convenient to you either over the telephone, online, such as Teams teleconferencing, or in person if possible. Consent will be obtained verbally, or in writing, at the start of the interview. Interviews will be audio recorded on an encrypted device and sent securely to an independent transcription company (Bristol Transcription Services), who has signed a confidentiality agreement with the University of Oxford. If you are contacted, your local trial team will provide you with a separate Information Sheet with the specific details of that trial and what it would involve for you.

20. Expenses and Payments

You will not have to pay anything for the medical product you might receive as part of the trial. However, you will not receive any payment for taking part. You will be re-imbursed for any travel you do that the trial requires. Please contact the local coordinating team for more information about this. Upon completing the trial you will receive a gift card.

21. Who has reviewed the trial?

This trial has been reviewed and was approved by the Independent Ethics Committee in your country. The Ethics Committee ensures the protection of your safety, rights, wellbeing, and dignity.

22. Are you insured during the trial?

Insurance has been taken out for everyone who takes part in this trial. The insurance pays for damage caused by the trial. You can find more information about the insurance in **Appendix C**. It also says who you can report damage to.

23. What if there are any problems?

If you have general questions or complaints about this programme of work or to exercise your rights as a research participant, please contact the complaints officer at UMC Utrecht. **Appendix A** includes their contact details.

NHS England can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. NHS England is unable to provide information about this trial. If you wish to get in touch with the NHS England team please contact them at england.contactus@nhs.net. If you are making a complaint please state: '**For the attention of the complaints team**' in the subject line.

24. Do you have any questions?

You can ask questions about the trial to your GP and to the coordinating team.
Appendix A includes the coordinating team contact details.

Appendices to this information

A. Contact details
B. Trial schedule
C. Information about the insurance
D. Informed Consent Form

Appendix A: Contact details

Sponsor:

University Medical Center Utrecht

Coordinating Investigator: Alike van der Velden, PhD

Phone: +31 (0)6 3111 8081

E-mail: a.w.vandervelden@umcutrecht.nl

Coordinating team in [United Kingdom]:

Name: ECRAID-Prime Trial Team, University of Oxford

Phone number: 08001380880

Email: ecraid-prime@phc.ox.ac.uk

For complaints:

Should you have any complaints, please, report them to your GP practice or the coordinating team. If you are dissatisfied how this trial is being carried out and want to submit a complaint, contact the complaint mediators at the University Medical Center Utrecht:

By phone via: +31 (0)88 755 62 08

Online via: https://www.umcutrecht.nl/en/submitting-a-complaint

Information regarding your rights can be found at: https://www.umcutrecht.nl/nl/regels-en-rechten

Data Protection Officer of the University Medical Center Utrecht:

Email: privacy@umcutrecht.nl

Appendix B: Tests or procedures you will undergo

	Day 0	Day 1-28																										Month 3	Month 6
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28		
Consent	x																														
Questions at screening	x																														
Weight and height	x																														
Clinical assessments[1]	x																														
If needed: pregnancy test	x																														
Taking a nose/throat (self-)swab	x				x			x							x																
Medical product use	(x)[2]	x	x	x	x	x	x	(x)[2]																							
Fill in daily diary (paper or online)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Telephone call															x														X[4]		
Long-term consequences (call or online)																														x	x
Returning/collection swabs and unused medical products																x[3]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

[1] Clinical assessments include body temperature, oxygen saturation, respiratory rate and heart rate.
[2] Medical product use is 7 days, which can start on Day 0 or Day 1.
[3] After day 14 the swabs and unused medical products will be collected by a member of the research team/courier company.
[4] Only if daily diary is not complete.

Appendix C: information about the insurance

The Sponsor (University Medical Center Utrecht, the Netherlands) of the ECRAID-Prime trial has taken out insurance for everyone who takes part in the trial. The insurance pays for damage in case you have suffered because you participated in the trial. This concerns damage in case you suffer during the trial. You must report damage to the insurer within 12 months.

Have you suffered damage as a result of the trial? Please, report this to this insurer:

The insurer of the trial is:	
Name:	MCI Life Sciences & Healthcare Consortium 4985 Lloyd's
Address:	Medical & Commercial International Limited, 1st Floor, 145 Leadenhall Street, London, EC3V 4QT
Telephone:	+44 (0) 7718563782
Policy number:	MCIROW23003
Contact person:	Dan Starmer

The claims representative of the trial is:

Name: Andrew Missen

Address: 1st Floor, 3160 Park Square, Birmingham, B37 7YN

Email: Andrew.missen@uk.sedgwick.com

Telephone number: +44 (0) 7803211700