Study Title: 'Treating COVID-19 infection with inhaled corticosteroids'

COPD: STerOids In Covid

Chief Investigator	**Professor Mona Bafadhel**
Sponsor	**University of Oxford**

Study Invitation: We would like to invite you to take part in a research study to assess a possible treatment (a steroid inhaler) for COVID-19 infection. We want to find out if the treatment works when given early at the start of COVID-19 symptoms. This information sheet will let you know why we are doing the study, what it involves and how you can help if you are interested.

Why are we doing the study? The world is experiencing a pandemic of SARS-CoV-2 coronavirus, which causes COVID-19. COVID-19 has spread across the world, with more infections and deaths than previous coronavirus outbreaks (SARS and MERS). Although most people suffering with COVID-19 experience mild or moderate symptoms, it can cause serious illness in some people, and has led to huge pressures on the available healthcare resources.

In order to contain the spread of COVID-19, **early treatment of a person with COVID-19 symptoms** could be very important. This study aims to find a treatment that works to stop someone with COVID-19 get worse or require going to hospital. At the moment, many drug studies are being done in patients already admitted to hospital. So far no one drug has been proven to be effective.

Why have you been invited? As we are trying to find a possible treatment for early symptoms of COVID-19 infection, we are inviting members of the public to take part in our study if they develop early COVID-19 symptoms. We aim to recruit 478 participants into this study.

If within the last 7 days, you have had a new cough, or fever or a loss of smell or taste and symptoms consistent with the COVID-19 illness as described in the NHS public health information (https://www.nhs.uk/conditions/coronavirus-covid-19/check-if-you-have-coronavirus-symptoms/), we would like to invite you to take part. The vast majority of people with COVID-19 will develop a breathing problem (respiratory illness). We want to find out if giving a steroid inhaler to people with early COVID-19 symptoms will reduce the chance of becoming admitted to hospital. To know for sure, we will provide half the people in our study a steroid inhaler and the other half will be asked to follow the standard NHS advice about how to manage COVID-19. This allocation will be done at random.

Do you have to take part? The study is entirely voluntary. You can email, call or text us (details at the end of the information sheet) to let us know if you are interested. You will have the opportunity to discuss any part of the study at any time. If you decline or withdraw, this will not affect your care now or in the future in any way.

What medicine are we testing? Inhaled steroids are a type of medicine usually used to treat asthma and chronic obstructive pulmonary disease. They have been studied extensively and are safe to use, including during pregnancy. Furthermore, in this study the time we expect people to need to take the steroid inhaler is short and so unlikely to be associated with any concerning side effects during pregnancy or breast-feeding. Common side effects at the dose and duration used in our study include a cough immediately after using the inhaler, croaky (hoarse) voice and mouth (oral) thrush. If you develop any of these side effects, we expect them to go away and we can also treat them.

What happens if you are allocated to the steroid inhaler? We will ask you to take the inhaler for no more than 28 days. You will be shown how to take the inhaler and provided with an information leaflet reminding you of these instructions. If your symptoms of COVID-19 (such as, but not limited to, fever and or new, continuous cough, and or loss of smell or taste) get better before 28 days, you can stop taking the steroid inhaler and we will record the date when it was stopped.

What happened if you are not allocated to the steroid inhaler? Participants not allocated to the steroid inhaler group will be asked to complete the study visits and to follow NHS 111 guidance on how to manage COVID-19 (https://www.nhs.uk/conditions/coronavirus-covid-19/what-to-do-if-you-or-someone-you-live-with-has-coronavirus-symptoms/how-to-treat-coronavirus-symptoms-at-home/). This is updated regularly, but included in the current NHS guidance, is that if you have a high temperature, you should get plenty of rest, drink plenty of fluids and if you feel uncomfortable to take paracetamol or ibuprofen. To treat a cough, the NHS guidance suggests trying to avoid lying on your back, and to take a teaspoon of honey. If you are unsure of how to manage your COVID-19 symptoms, please go to the NHS 111 website as listed above, contact the study team (email, or telephone) or your local pharmacy or doctor.

Will I definitely be able to take part? We have very few criteria that would mean you can't take part, however we may need to exclude you if you are under the age of 18, if you need to be hospitalised when we first meet you or if you are already taking a similar inhaler already. It is also possible that we may not have the nurses to see you if we already have many participants enrolled at the same time, or if you contact us later in your illness (closer to 7 days since the start of your symptoms). We apologise if that happens.

Where will the study be undertaken during the COVID-19 pandemic? Due to the pandemic, this study has been designed to have flexible settings for any of the assessments. You do not have to be seen in the same setting as the previous visit and we will take into account your preferences. Visit 1 can occur in the GP surgery/COVID-19 hub (but only if you attend these for clinical purposes), the home or the doorstep. Visit 2 and 3 can occur in the home or the doorstep. Visit 4 can occur in the GP surgery (if you are registered at a participating surgery) or in the Respiratory Medicine Unit at the University of Oxford (within the John Radcliffe Hospital). The study nurses, whether at the GP surgery/COVID Hub or the home visit, will be wearing personal protective equipment, for their safety during the study. In the unlikely event that there becomes a shortage of personal protective equipment during any of the study visits, only a doorstep visit will be offered and you will be asked to take your own nose & throat swabs and nasosorption samples.

Below is a description of where visits can occur.

GP surgery or dedicated COVID-19 hubs: If you are recruited directly from the GP surgery or COVID-19 hub, because you have attended the surgery clinically, your treating doctor will let us know if you are interested in taking part in the study. Our study nurses, if they are in attendance at the GP surgery or Hub, will then discuss the study with you and do a pre-screening check with a few questions. If you fulfil the study criteria and provide consent to entering the STOIC study, the study nurses could complete study assessments for visit 1, or if this is not convenient for you another time can be arranged to have this visit at home or at your doorstep. If the study nurses are not in attendance at the GP surgery or Hub when you are attending, you can contact the study team to register your interest in taking part (details at the end of this information sheet). For subsequent visits 2 and 3, you can choose a home or doorstep visit as described below. For the final study visit 4, we will arrange to see you in your GP surgery (if it is one of the surgeries taking part in our study) or at our University research site located within the John Radcliffe Hospital.

Home Visit or Doorstep Visit: If you have developed symptoms and have contacted the study team via telephone, email or the website, and are suitable for the study and have provided consent (initially verbally via telephone), you will have the option of being seen at home (home visit) or the nurses will arrange a doorstep visit. For the home visit, a study nurse will come into your house at a set time to run through the study details and perform the study assessments described in this information sheet.

For the doorstep visit, this will be a 'drop-off' of a study pack. The study nurse will contact you by phone when they get to your doorstep. They will leave a study pack at your doorstep. They will then step away from you or return to the car if they are unable to protect your privacy and/or unable to comply with social distancing. You will then be asked to read through all the paperwork and sign the paper version of the consent form to confirm you are happy to take part. You will be

provided with two copies of the consent form to sign and you can keep one of them for your records, the other copy will be collected by the research team. The study nurse will guide you through the visit over the phone explaining what assessments you need to complete and then ask you to leave the study pack outside your door for them to collect when you are ready.

Telephone assessments: After visit 1, you will be telephoned on a daily basis to record your symptoms, details of the inhaler use (if you are in this group), your oxygen levels and your temperature. This daily phone call will be continued until your COVID-19 symptoms have resolved or for up to 28 days.

What will happen if you take part? If you get a new cough, fever, loss of taste or smell or symptoms (within the last 7 days) suggestive of COVID-19 infection, we would like you to contact the study team, either via telephone or email or via the website (details are listed at the end of this information sheet). If you are attending your GP surgery or the COVID Hub locally, your medical doctor will ask you if you are interested in taking part in our study and our nurses can come and speak to you if they are also at the same surgery or Hub. If they are not there at the same time, you can contact us within 7 days after the start of your first symptoms. We will go through the study details with you and we will ask you a series of questions to assess whether you can take part. If you decide you would like to participate, after obtaining verbal (via telephone) or written consent, you will be entered into the study and take part in the study visits and assessments. We will arrange the first study visit to occur as soon as possible. The visits are described below:

Visit 1: We will ask you to complete symptom questionnaires and ask information on your general health. We will obtain a swab to test for COVID-19 (taken from the throat and nose), a further swab from the nose to test for inflammation (nasosorption) and we may take a blood test (about 4 tablespoons of blood at any one time). The final assessment at this visit is measuring your oxygen levels (using a small device called a pulse oximeter, which we will loan to you) and temperature (we will loan you this device). If you are having a doorstep visit, you will be asked to complete the swabs, temperature and oxygen level assessment on yourself. After this is completed, you will be randomised (entered into) one of 2 groups; only one group will receive an inhaled steroid (steroid inhaler). The group you will be in will be chosen by chance (like flipping a coin). We are testing a steroid inhaler called Budesonide. All the information about how many times you need to take the inhaler and for how long is described in the inhaler information sheet which will be provided.

Visit 2 and 3: At day 7 and day 14 of your participation we would like to follow you up to see how you are progressing and to repeat the swabs to test for COVID-19 (nose and throat swab) and to assess inflammation (nasosorption).

Visit 4: At day 28 we would like to see you to take a blood test to test if you have antibodies (a test that tells us if you have had COVID-19). We will also ask you some questions about any side effects that you may have experienced and do the final check of your inhaler use. We will also collect equipment, inhalers and the questionnaire booklet from you if we have not already done this.

Daily telephone visits: After visit 1, from the second day of you being entered in the study, we will make daily telephone calls to you to ask you how you are, about the inhaler use and to ask you to measure your temperature and oxygen levels for our study records. We will also remind you to complete the daily questionnaires in the study diary. These will be continued until your COVID-19 symptoms resolve, you have been hospitalised due to COVID-19 or to a maximum of 28 days.

Study assessments table

	Visit 1 (day 0)	Visit 2 (day 7 +/-1)	Visit 3 (day 14 +/-2)	Visit 4 (day 28, -2 to +7)	Telephone call (daily, until COVID-19 resolves)
Where can these visits be done?	1. GP Surgery 2. COVID-19 Hub 3. Home 4. Doorstep	1. Home 2. Doorstep	1. Home 2. Doorstep	1. GP Surgery 2. University research site (within John Radcliffe Hospital)	n/a
What will be done at this visit?	• Consent (telephone or written) • COVID-19 throat and nose swab • Nasosorption nose swab • Blood test (will only done if at GP surgery or Hub) • Temperature check • Oxygen level check • Symptoms check • Questionnaires • Dispense steroid inhaler if in the inhaler group • Safety data collection	• COVID-19 throat and nose swab • Inhaler use check • Dispense more inhaler if required • Safety data collection	• COVID-19 throat and nose swab • Nasosorption nose swab • Inhaler use check • Dispense more inhaler if required • Safety data collection	• Blood test • Safety data collection • Final inhaler use check If not already performed, collection of: • Equipment • Questionnaires • Consent forms • Inhalers	• Temperature check • Oxygen level check • Symptoms check • Inhaler use check • Reminder to complete questionnaires • Safety data collection

Study assessment information

Measuring your oxygen levels: A probe to be placed on your finger for 10 seconds to record your oxygen levels.

Measuring your temperature: A thermometer placed in your mouth, or armpit, for a maximum of 1 minute to measure your temperature.

Questionnaires: The questionnaires are designed to measure your symptoms. The questionnaire will take a maximum of 15 minutes to complete.

Blood test: A maximum of 60mLs (4 tablespoons equivalent) of blood will be taken and collected into tubes marked with your trial number and stored at the Respiratory Medicine Unit Laboratory (part of the University of Oxford) for testing.

Nose and throat swabs: COVID-19 virus is measured by a throat and nose swab. This can be performed by the study nurse or by yourself. You will be provided an information sheet on how to perform this. These samples will be marked with your trial number and transported to the Respiratory Medicine Unit Laboratory (part of the University of Oxford) for testing.

Nasosorption samples: To measure inflammation, we will also use another swab called nasosorption. This soft silicone-based swab will absorb a layer of the nasal secretions, which we can use to measure inflammation.

Safety data collection: We will ask you some questions to check if you have experienced any side effects whilst taking your inhaler.

What are the possible risks and disadvantages of taking part? The blood samples may cause some mild discomfort but this is expected to resolve very quickly. The nose and throat swabs and nasosorption may cause some mild discomfort, but this is expected to resolve very quickly. On very rare occasions, you may be allergic to the steroid inhaler. If you have an allergic reaction, we ask that you seek medical attention straight away (by calling your GP or calling 999) and later letting the study team know if this happens. We will be unable to immediately let you know if the COVID swab is positive or not. Result testing of swabs are accurate only about half the time, because of the machines we use to test the swab and how the swab is taken. We believe that if you develop new symptoms of COVID-19 during a pandemic, then we must assume this is the COVID-19 infection with or without the result. It may take months for us to know the result of your swab test and participation in the study will not be dependent on finding out the result of COVID-19 testing. If you consent to us contacting you in the future, we will try to let you know any results in the future.

You may also be worried about the study nurses coming into your home. We believe that risk of virus transmission increases in close contact scenarios, defined as close contact for more than 2 hours (this automatically includes household members). If one member of the household has symptoms, it must be assumed that everyone in the household has been exposed to the virus and thus, the risk of virus transmission is to the study staff coming into the home. To reduce this risk, the study nurses will be in personal protective equipment, which will include gloves, masks and aprons and they will spend less than 2hours with you undertaking the assessments. With these processes in place, the risk of getting infected from a nurse visiting for a brief period is thus very low. If you are still concerned, we understand and we can use the doorstep visit option if preferred.

Are there side effects from taking the inhaled corticosteroids? Inhaled corticosteroids are a class of medication that have been widely prescribed over the last 40 years. There has never been a report of a life-threatening reaction to taking inhaled corticosteroids. However, all medicines have potential side effects. Below are possible mild side effects from taking inhaled corticosteroids:

- Mild cough when performing the inhalation manoeuvre
- Mouth and throat pain. This normally resolves when you stop taking the inhaler.
- Hoarse voice from the drug depositing on your throat. This normally resolves when you stop taking the drug
- Oral candidiasis, otherwise known as oral thrush. This is unlikely due to the short nature of the treatment and is preventable if you gargle with water after you have taken the inhaler. This also resolves with stopping the treatment.

Many of the inhaled steroid side effects that have been encountered occur in people who take the inhalers for a long time. Due to the design of this study, the duration of the inhaled steroids is much shorter and so we expect these side effects to not be long-lasting, if they occur.

What are the possible benefits of taking part? You will have close monitoring with an experienced clinical research team. We will be able to monitor your oxygen levels as you measure them when we call you. We will also be able to give you advice about these results if they are abnormal, including seeking early medical attention if this is needed. The information we get from this study may be used to treat patients with COVID-19 infection across the world.

Will I receive any payment to take part? We will not be able to provide any payment for your study participation. We will provide the equipment to measure your oxygen levels and temperature, as a free loan to you for the length of the study.

Will my information be kept confidential? All the information you provide (study data) will be kept confidential and in line with the General Data Protection Regulation (GDPR) and Data Protection Act 2018. If you decide to take part, you will be allocated a unique study number and only specified research personnel will have access to the code to identify your details. Responsible members of the University of Oxford or the UK Regulatory Agency (the Medicines and Healthcare products Regulatory Agency - MHRA) may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. The results of the study may be published in the medical literature but you would never be identifiable from this. If there is new information about the study, we will keep you informed throughout and you will always have an opportunity to ask questions throughout the research study. At the end of the study, we will publish the results on the study website. You are free to read the results if you wish.

What will happen to my data? We will be using information from you and your medical records in order to undertake this study. Research is a task that we perform in the public interest. The University of Oxford, as sponsor, is the data controller. This means that we, as University of Oxford researchers, are responsible for looking after your information and using it properly. We will use the minimum personally-identifiable information possible. We will store the de-identified research data and any research documents with personal information, such as consent forms, securely on behalf of the University of Oxford in an appropriate archiving facility for 10 years after the end of the study as part of the research record. If you have consented to us using your samples for future research, a copy of your consent form will be kept for as long as your sample is kept (a maximum of 10 years after the end of this study).

If you agreed (by initialling the box on the consent form), the study team will use your NHS number name and address to contact you about the study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. A copy of your consent form or other personal details will be archived at the Respiratory Medicine Unit (University of Oxford). Your rights to access, change, or move your personal information may be limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data can be found at http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/

What happens to any samples I provide? With your permission, blood, nose & throat and nasosorption samples that you provide will be used for analysis to measure inflammation and also stored to be used in future research studies. All samples taken at each visit will be collected into barcoded blood tubes. These tubes will be transported to the John Radcliffe Hospital, Oxford without your personal details, and analysed and frozen for future research indefinitely in the

Respiratory Medicine Laboratory, part of the University of Oxford at the John Radcliffe Hospital, Oxford. The samples may be used by commercial companies or sent abroad and will remain de-identified, without any personal identifiable details now or in the future. If you would like us to use your samples for this study only, your samples will be analysed and may be stored for up 1 year only after the completion of the study and will then be destroyed.

What happens if you want to stop taking part in the study? You are free to stop taking part in the study at any time without giving a reason. This will not affect the medical care you receive now or in the future. If you would like to withdraw from the study, we will use the samples and data collected up to your withdrawal. Please contact the research team to inform us of your choice.

What happens if I feel worse during the study? COVID-19 can be a serious illness. Unfortunately, some participants will deteriorate during this study. If your blood oxygen saturations go below 92% on your home monitoring, we advise you to speak to your GP or call 111 or to call 999 and attend your local Emergency Department. If you have very severe difficulty breathing, please call 999 immediately. If you attend hospital, please inform your treating doctors and/or nurses that you have been part of this study and take along your allocated inhaler (and any other medicines that you are taking) with you to hospital. Please also take along the study card that we have given you. If they advise you to get more testing (outside of the study), you should follow their advice. As at the point of your hospital admission, it may not be clear whether you do or do not have COVID-19, so you should continue taking your medication unless your treating doctors ask you to stop taking it or it has been confirmed that your hospitalisation is related to COVID-19. We will attempt to contact you via phone daily even if you are hospitalised to ask how you are, record the reason for your admission and whether you are still taking the study medication. We understand that it may not always be possible for us to contact you or you may not wish to speak with us when you are at a hospital. If possible, we would ask you to ask a family member or friend to let us know if this is the case. We will also attempt to rearrange any study visits which are still due for after you leave the hospital if possible.

What happens if there is a problem or if something goes wrong? If you have a concern about any aspect of this study, you should ask to speak with the research team who will do their best to answer your questions. Their contact details are given at the end of the document. If you remain unhappy and wish to complain formally, you can do this by contacting the research team or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480 or the head of CTRG on email at ctrg@admin.ox.ac.uk. The University of Oxford has arrangements in place in the unlikely event that harm arises to you from taking part in this research study.

Who is organising and funding the research study? The study is being organised by Professor Mona Bafadhel, funded by the Oxford NIHR Biomedical Research Centre, Respiratory Theme and sponsored by the University of Oxford.

Who has reviewed the study? All research is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the London Fulham Ethics Committee and the MHRA.

Thank you for taking the time to read this information

Please ask if you have any further questions

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