Trial Title: Treating COVID-19 infections with inhaled corticosteroids
Internal Reference Number / Short title: The STOIC Study (STerOids in COVID)

Ethics Ref: 20/HRA/2531

IRAS Project ID: 282772

EudraCT Number: 2020-001889-10

Date and Version No: V2.0_26May2020

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Sponsor: University of Oxford

Funder: Respiratory BRC & Investigator Initiated Grant from AstraZeneca

Chief Investigator Signature: 

No potential conflicts of interest

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

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1. KEY TRIAL CONTACTS

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2. LAY SUMMARY

At the time of writing over five million people have been infected by the SARS-CoV-2 coronavirus around the world. The severe clinical condition that leads to deaths is now called CoVID-19. Currently, there are no effective treatments for the early or late stages of this illness. Governments worldwide have undertaken dramatic interventions to try and reduce the rate of spread of this deadly coronavirus.

Early data from multiple studies in China, where the virus originated, show that severe cases of CoVID-19 are not as prevalent in patients with chronic lung diseases as expected. This is similar to findings from Italy and the US. We think that the widespread use of inhaled corticosteroids may be reducing the risk of severe CoVID-19 infection in patients with chronic lung disease. Early experimental data also shows that inhaled corticosteroids are effective at slowing down the rate of coronavirus replication on lung cells.

Inhaled corticosteroids are widely used to manage common lung conditions, such as asthma and chronic obstructive lung disease. This type of medicine is among the top 3 most common medication prescribed around the world. These medicines are safe, the way inhaled steroids work is well understood, and the potential side effects are mild and reversible.

We propose to test the idea that, in participants early in the course of CoVID-19 illness, daily inhaled corticosteroids for a maximum of 28 days, will reduce the chances of severe respiratory illness needing hospitalisation. We will also study the effect of this inhaled therapy on physiology, symptoms and the amount of virus that is shed.

3. SYNOPSIS

Trial Title	Treating COVID-19 infection with inhaled corticosteroids		
Internal ref. no. (or short title)	The STOIC Study (STerOids in COVID)		
Trial registration	INTENDED: CLINICAL TRIALS.GOV		
Sponsor	University of Oxford		
Funder	Oxford NIHR Biomedical Research Centre - Respiratory Theme & Investigator Initiated Grant from AstraZeneca		
Clinical Phase	Phase 2		
Trial Design	Randomised, open label parallel group controlled clinical trial		
Trial Participants	Adults ≥18, male and female, with clinical signs consistent with early COVID-19 illness		
Sample Size	478 participants		
Planned Trial Period	Participant duration with IMP: 28 days Participant duration with active follow up: 0 days Study period: May 2020 to Aug 2020		
Planned Recruitment period	60 days		
	Objectives	Outcome Measures	Timepoint(s)
Primary	Evaluate the efficacy of ICS therapy compared to standard care in participants with early COVID-19 illness	1.Hospitalisation or emergency department attendance related to COVID	Day 0 to 28
Secondary	Evaluate the effect of ICS therapy on physiology, symptoms, and viral load, compared to standard care in participants with early COVID-19 illness	1. Body temperature 2. Blood oxygen saturation level 3. Nasal/throat swab SARS-CoV-2 viral load	Day 0 to 28 Day 0 to 28 Day 0, 7 and 14

		4. Common cold questionnaire and FluPRO questionnaire	Day 0 to 28
Exploratory outcomes	Evaluate the effect of ICS therapy on whole blood, nasal and viral mediator responses compared to standard care in participants with early COVID-19 illness.	1. Nasal and viral mediator responses 2. Whole blood mediator responses	Day 0 and 14 Day 0 and 28
Intervention(s) • **IMP(s)**	Inhaled corticosteroids Budesonide dry powder inhaler 400mcg per actuation, 2 inhalations twice a day for maximum of 28 days		
Comparator	Standard care		

4. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CCG	Clinical Commissioning Group
CI	Chief Investigator
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
IMP	Investigational Medicinal Product
IRB	Independent Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
RES	Research Ethics Service
ORTU	Oxford Respiratory Trials Unit
ORTU SOG	ORTU Safety Oversight Group
PCR	Polymerase Chain Reaction
PE	Pulmonary embolism
PI	Principal Investigator

PPE	Personal Protective Equipment
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RMU	Respiratory Medicine Unit
RSI	Reference Safety Information
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

5. BACKGROUND AND RATIONALE

The global community is experiencing an unprecedented pandemic of the COVID-19 coronavirus. COVID-19 has spread across multiple nations around the world with a significantly higher number of cases and fatalities compared to previous coronavirus outbreaks in the last two decades (SARS and MERS). Although most people suffering COVID-19 experience either no symptoms or a mild/moderate self-limiting disease[1], the widespread nature of this pandemic, and the severity of disease experienced by a minority of those infected has led to several critical challenges, in particular, the huge pressures on available healthcare resources, in terms of equipment, facilities and staff.

In order to contain the spread of COVID-19, early treatment of potential cases and symptoms as soon as they occur may be critical. This is especially the case for patients at risk of deterioration. It is estimated that 20% of all COVID-19 infections will lead to hospitalisation and that 1 in 4 of those hospitalised will have a severe illness that needs intensive care and may result in death. At the moment, the majority of drug trials are being done in patients already admitted to hospital. So far no one drug has been proven to be effective[2].

5.1. Clinical course of COVID-19

The vast majority of patients with COVID-19 will develop a respiratory illness. Case series published from around the world of hospitalised patients show that almost all patients who develop severe COVID-19 illness report fever or respiratory tract symptoms (cough, sneezing, blocked nose, poor sense of smell or breathlessness)[1,3,4]. Governments around the world have undertaken very serious containment measures as there is a possibility that SARS-CoV-2 could be transmitted prior to symptom onset. However, the severe COVID-19 clinical syndrome is almost always preceded by typical respiratory viral illness symptoms.

Evidence from around the globe as it is being published, indicates that the majority of patients (80%) will have mild illness alone. In the minority of cases (up to 20%), COVID-19 can cause severe illness. There are some indicators in whom a severe illness may occur in[1,3-5]:

- Presence of a co-morbidity
- Male gender
- Late hospital presentation
- Black and ethnic minority persons

5.1.1 Under-representation of asthma and COPD patients

Surprisingly though, among patients with severe COVID-19 illness, there is a gross under representation of patients with asthma or COPD. This finding has been serially found in data from China, Europe and the US. In a study from China of 45,000 pooled patients, 900 (less than 2%) had a respiratory co-morbidity[5]. Using an estimate of 100 million people in China who have COPD, the prevalence of COPD in this cohort should be approximately 6% (a conservative estimate), whilst the prevalence of asthma is estimated to be 45 million (4%). It would be expected that in a study of 45,000 patients, 3000 should have COPD, whilst 1800 should have asthma. The expected and observed incidence difference is $p<0.0001$ in this pooled analysis. In a cohort of 1099 hospitalised COVID-19 patients, also in China[1], only 1.1% were noted to have COPD (and asthma was not noted at all). A further study demonstrated that less than 1% of patients hospitalised with COVID-19 had asthma[6], and was not listed as a common cause of illness in a large study investigating anti-virals[7]. These puzzling observations, while certainly not forming a complete picture, are impossible to ignore, particularly since the logical explanation is to expect patients with pre-existing, serious lung conditions to be over-, not under-represented in patients with COVID-19 requiring hospitalisation. The widespread use of inhaled corticosteroids (ICS) in asthma and COPD patients could be the reason for this under-representation of these patient groups in severe COVID-19 illness cohorts.

5.2. What are inhaled corticosteroids?

Inhaled corticosteroids (ICS) are a commonly prescribed class of medication throughout the world. They are cheap and have been used widely for the last 60 years. They have been shown to be very effective in improving asthma and COPD care over the long term. UK[8] and international[9] guidelines recommend that most, if not all, patients with asthma should be prescribed an inhaled corticosteroid and up to 90%[10] of patients with COPD in the UK are prescribed ICS.

5.2.1 Laboratory evidence of ICS effect on coronavirus

There is experimental evidence that inhaled corticosteroids inhibit coronavirus replication in vitro[11,12]. SARS-CoV-2 binds to cells via the angiotensin converting enzyme 2 (ACE2) receptor. ACE2 is highly expressed on epithelial cells in the oral mucosa and type 2 alveolar epithelial cells. The use of inhaled corticosteroids as a therapy suggests it would target cells of interest.

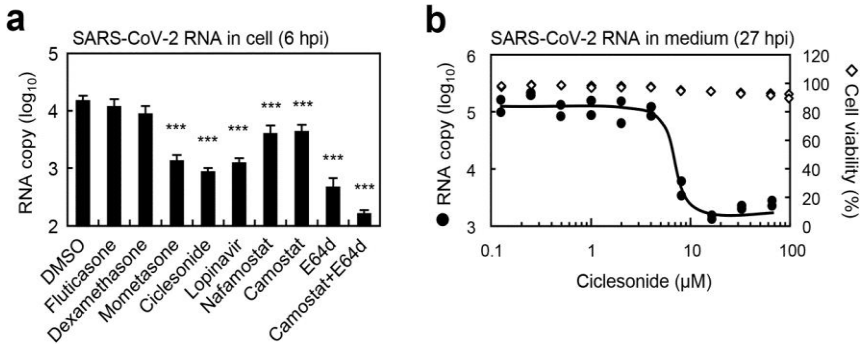

Figure 1. Matsuyama et al. bioRxiv 2020; 2020.03.11.987016. In-vitro analysis demonstrating that in epithelial cells, inhaled corticosteroids (mometasone and Ciclesonide) reduce viral replication greater that antivirals (Lopinovir, Nafamostat and Camostat)

5.2.2 Inhaled corticosteroids: benefits, risk consideration and dose justification

The World Health Organisation, recommends that there is no evidence to support the use of systemic corticosteroids in COVID-19 illness, extrapolated from studies during SARS and MERS; whilst in COVID-19, high dose systemic corticosteroids are associated with increased mortality[5]. However, inhaled corticosteroids have not been investigated during these past illnesses. We believe that the delivery of corticosteroids topically, in an inhaled formulation, means that we are locally targeting airway epithelial cells which are the initial site of infection of SARS-CoV-2 and this occurs before the development of interstitial pneumonia. Furthermore, the primary action of the inhaled steroids is on the type 2 pneumocytes where viral replication is going to be at its most, where we know that ACE2 receptor expression is high. Inhaled corticosteroids are used to reduce airway inflammation. By taking it in an inhaled form, patients derive the benefit of suppressing airway inflammation (the major driver of morbidity in asthma and COPD), while minimising the systemic absorption of these medications[13]. As mentioned in the previous section, early laboratory data show that ICS use reduces the replication of the SARS-CoV-2 virus, whilst recent data show that inhaled steroids are also able to reduce ACE2 expression[14]. This could potentially explain the epidemiological observations we have seen of the less than expected CoVID-19 hospitalisations in published cohorts.

Unlike systemic corticosteroids, there are fewer risks using inhaled corticosteroids. The potential risks of ICS administration include[13] cough, a hoarse voice and oral candidiasis from oral inhaled steroid deposition during inhalation. This will be mitigated with patient education on correct inhaler technique and advice to gargle after inhalation. These side effects are reversible and treatable. We propose to use the highest licensed dose of inhaled corticosteroids to try and maximise the clinical benefit for the participants. As the participants only take the investigational product for a short period of time (maximum of 4 weeks), the risk of harm is low. There is a described link between ICS use and the risk of pneumonia in patients with COPD[15] (~4% risk per annum). There is no evidence demonstrating any risk of

pneumonia in short-term use or in people without COPD, demonstrating that this short-term use is not associated with any adverse outcomes, in this study design or population studied.

5.3. Contraception and pregnancy

The British National Formulary advises that the general class of inhaled corticosteroids are safe to use in pregnancy and during breastfeeding and patients prescribed this for asthma are asked to continue this during pregnancy and breastfeeding. The duration of the IMP in this study is short in comparison to usual treatment for asthma and so any concern during pregnancy is minimal. Finally, the systemic absorption of ICS has been shown to be minimal. Women who are pregnant or who might be of childbearing age will not be excluded from this study. No extra contraception will be required of study participants and pregnancies will not be followed up following completion of the trial.

5.4. Rationale for study design

During this CoVID-19 pandemic, there are no effective treatments for mild or severe disease. To allow for better management of health resources during this pandemic, effective interventions to reduce the number of emergency department visits and hospitalisations are very important. Inhaled corticosteroids are accessible, cheap, safe, and widely prescribed. If effective, this would be the ideal class of medication to prescribe to reduce COVID-19 related morbidity and mortality.

During the coronavirus pandemic, it is felt that respiratory symptoms with a new cough, and/or fever and/or flu symptoms consistent with COVID-19 are going to be related to SARS-CoV-2 infection. Therefore, a positive COVID-19 test result is not a requirement of entry into the study. Furthermore, as is apparent in clinical practice, at best the sensitivity of the PCR testing is approximately 70% and significantly affected by testing practices. In this study design, a significant proportion will be self-swabbed, such that we believe that the sensitivity will reduce to 50% at best. This means there would be a risk of providing false negative results to potential participants and therefore providing false reassurance that they are not required to self-isolate due to their symptoms (as per Public Health Guidance). Finally, as per reports from government health committees, testing results can take up to 7 days to return, which is occurring both at a national and local level. Thus, this form of study design allows for recruitment of patients early in the course of the disease and give enough time for the intervention to be effective. Serum (from collected whole blood) will be taken to confirm antibodies to SARS-CoV-2 infection. We believe that any available antigen test, antibody test, in addition to inflammatory mediators, and symptoms as reported in the questionnairewill improve the external validity of the trial data.

The global evidence that patients with respiratory co-morbidity are not commonly found in patients with severe COVID-19 infection, implies that this is not specific to one inhaled corticosteroid and is likely a class effect. The STOIC study will be an open label, randomised controlled trial comparing, an inhaled corticosteroid against standard of care. Participants randomised to the inhaled corticosteroid arm will be given 1600 mcg of inhaled budesonide daily.

Hypothesis

The administration of inhaled corticosteroids at the onset of a new cough and/or symptoms consistent of SARS-CoV-19 infection during a pandemic, leads to improved outcomes following a COVID-19 illness. The mechanism underpinning this is via reduced viral replication.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Evaluate the efficacy of ICS therapy compared to standard care in participants with early CoVID-19 illness	1.Hospitalisation or emergency department attendance related to COVID	Day 0 to 28
Secondary Evaluate the effect of ICS therapy on physiology, symptoms, and viral load, compared to standard care in participants with early CoVID-19 illness	1. Body temperature 2. Blood oxygen saturation level 3. Nasal/throat swab SARS-CoV-2 viral load 4. Common cold questionnaire and FluPRO questionnaire	Day 0 to 28 Day 0 to 28 Day 0, 7 and 14 Day 0 to 28
Exploratory Evaluate the effect of ICS therapy on whole blood, nasal and viral mediator responses compared to standard care in participants with early COVID-19 illness.	1. Nasal and viral mediator responses 2. Whole blood mediator responses	Day 0 and 14 Day 0 and 28

7. TRIAL DESIGN

Study design: Randomised open label parallel group clinical trial, as described in study flowchart in Appendix A

Study setting: Community

Participants: Adults ≥18 years with recent onset of possible COVID-19 illness

Investigational medicinal product: Inhaled Budesonide

Study arms:

Participants who meet the inclusion criteria will be randomised to either the interventional arm or the standard care arm at a 1:1 ratio.

Interventional arm

Participants randomised to the interventional arm will be allocated to ICS: inhaled budesonide via dry powder inhaler, 1600mcg daily

Standard care arm

Participants randomised to the standard care arm will receive study visits but will not receive any additional intervention. All participants will be asked to follow 111 advice available as standard care, which is a series of questions on symptoms. Simple advice (that complies with NHS guidance) will be provided by the study nurses and physicians if needed.

Study Visits:

Following confirmation of eligibility and consent, participants will be recruited and randomly allocated to the interventional or standard care arms of the study. The day of recruitment will be designated as day 0 (visit 1). Participants will then be scheduled to have a visit on day 7 (visit 2), day 14 (visit 3) and day 28 (visit 4) to complete data collection and return study equipment.

8. PARTICIPANT IDENTIFICATION

8.1. Trial Participants

Adult participants ≥18 years with recent onset of symptoms suggestive of possible COVID-19 illness. Participants will be recruited from the community and primary care.

8.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial
- Male or Female, aged 18 years or above
- New onset of symptoms suggestive of COVID-19 e.g. new onset cough and/or fever, and/or loss of smell or taste within 7 or fewer days of participant being seen at visit 1
- In the Investigator's opinion, is able and willing to comply with all trial requirements

8.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- A known allergy to IMP
- Any known contraindication to IMP
- Patient currently prescribed inhaled or systemic corticosteroids
- Recent use, within the previous 7 days of inhaled or systemic corticosteroids
- Patient needs hospitalisation at time of study consent
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.
- Participants who have participated in another research trial involving an investigational product in the past 12 weeks.

9. TRIAL PROCEDURES

	V1	V2	V3	V4	Daily procedures
Time	Day 0	Day 7 ± 1	Day 14 ± 2	Day 28 -2/+ 7	
Consent	✓				
Eligibility check	✓				
Randomisation	✓				
Demographics	✓				
Medical history	✓				
Medication check	✓				
Dispensing of IMP	✓	✓	✓		
Administration of IMP*	✓	✓	✓		✓
CRF completion	✓	✓	✓	✓	✓
Blood sampling	✓¥			✓	
Nose and throat swab	✓	✓	✓		
Nasosorption sample	✓		✓		
Body temperature*	✓				✓
Pulse oximetry*	✓				✓
Medication adherence check*	✓	✓	✓	✓	✓
Phone calls					✓
Symptoms diary*	✓				✓
SAE/AE reporting	✓	✓	✓	✓	✓

*to be completed daily until symptom resolution or hospitalisation for COVID-19 ¥Not performed if home/doorstep visit

10. Recruitment

Patients will be recruited from participating primary care practices, the National Health Service 111 hotline, advertising and from close family contacts of participants of the study, who develop symptoms. For all recruitment avenues, once consent (initially via a telephone and then in person, or in person only depending on how the participant is being recruited) is obtained participants will be asked which type of visit (for visit 1-3) they would prefer (see section 10.6; for description of visit types).

Primary Care Practices: There are several avenues for recruitment from primary care:

a. All patients registered at a participating primary care practice will be contacted via mobile phone text message, e-mail, and/or post. On the invitation, they will be asked to contact the study team if they have symptoms suggestive of COVID-19 illness. Upon contacting the research team, a short pre-screening set of questions for study eligibility will be asked. Upon confirmation of eligibility, initial verbal (telephone) consent will be obtained (section 10.2) and Visit 1 as per participant preference (see section 10.6) will be arranged. At Visit 1, the participants will be asked to sign the informed consent form to re-confirm and document their agreement to take part in the study.

b. Patients attending their GP practice or Coronavirus Hubs (set up for management of COVID-19 infection in the community) who are being seen as per clinical practice and are then found to have symptoms of COVID-19 will be asked by their clinical team if they are interested in taking part in the study. Methods of recruitment from the GP surgery/Coronavirus Hubs will depend on whether the study team are on site at the time and are described below:

i. If the study team are on site, the GP will inform them that they have identified a potential trial participant. Potential participants will then be approached by the study team to discuss the study. The study team will then conduct the pre-screening set of questions. Upon confirmation of eligibility (section 10.1), the study team will obtain consent and continue to complete assessments for Visit 1 or if this is not convenient for the participant, Visit1 will be arranged at a different date (within the acceptable window) as a home or doorstep visit. If Visit 1 is happening on the day at the GP practice/Coronavirus Hub and the participant is randomised to IMP, the nurse will arrange the delivery of the IMP to participant's home on the same or next day (the day that the participant starts taking the IMP will be recorded in the CRF).

ii. If the study team are not on site, the clinical team will offer the PIS with the study team contact details. The participant will then be able to contact the study team (phone, email or via the website). Upon contacting the study team, the same process will be followed as described in section "a" above.

In addition to the above, participants may also be recruited via:

NHS 111 Hotline: Members of the public living in Oxfordshire who contact NHS 111 online, with symptoms suggestive of COVID-19 illness, will be automatically directed to contact the study team via the study website and to phone or e-mail for further information.

Family contacts of participants: Participants who have already been in contact with the study team will be asked to pass the details of the study on to members of their household or other people they may be in contact with so they can contact the study team if they start to have symptoms suggestive of COVID-19.

Social media, local media, study posters and website: The study will be advertised through the following channels: University of Oxford website, adverts, social media and local media (e.g. BBC Oxford). All advertising will include the website and study contact details.

Upon contacting the study team, the same process will be followed as described in section "a" above.

10.1. Pre-Screening & Eligibility Assessment

Potential participants will be pre-screened, via telephone or face-to-face, dependent on the mode of recruitment (as per section 10 details). The study staff (usually a research nurse) will ask a pre-screening questionnaire to assess study eligibility as per the study inclusion/exclusion criteria (section 8.2 and 8.3).

The study team (usually a research nurse) will contact the CI (or other delegated clinician) if the eligibility of any potential participants needs to be discussed further. Following confirmation of eligibility, informed consent will be obtained (section 10.2) and a trial visit will be organised.

10.2. Informed Consent

Informed consent will depend on initial participant interaction as per mode of recruitment. Participants recruited at the GP practices /Coronavirus Hubs as described in section 10 above, following confirmation of eligibility, will be asked to sign two copies of the current approved written informed consent form when they are approached at the practice/hub. One signed copy will be given to the participant and the other copy will be retained by the study team and stored at the RMU, University of Oxford.

Due to the pandemic, suitably qualified research study staff (including research nurses) will also be able to obtain the initial verbal (telephone) consent from participants who approach the study team via phone/website (or those who are unable to provide consent straight away when approached at the GP practice/Coronavirus Hub). Upon confirmation of eligibility, potential participants will be asked if they have read the patient information sheet online, otherwise verbal versions of the patient information sheet will be provided over the phone. If the potential participant requires more time, they will be given the PIS by referring them to the study website or by email. The potential participant will be informed that they will be contacted within the 7-day time limit from onset of symptoms for study enrolment to see if they have made a decision. If the participant verbally agrees to participate in the trial, the study team will obtain the initial verbal (telephone) consent and this will be signed, dated and timed as such by the researcher on the ICF which at Visit 1 the participant will also be asked to sign. If Visit 1 is arranged as a doorstep visit, the study team will leave the study pack, including the patient information sheet and two copies of the informed consent form on the doorstep (see further details of doorstep visits section 10.6). Participants will be asked to sign two copies: one signed copy will be retained by the participant and the other copy will be collected by the study team and stored at the RMU, University of Oxford.

As part of the informed consent process, written, and/or verbal versions of the Participant Information Sheet and Informed Consent will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal. Participants will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Participants will be informed that they will need to make a decision within the first 7 days of their illness to fit with the study inclusion criteria. The PIS and ICF will be available in paper formats; electronic formats to review will be available on the study website; verbal formats will be discussed with participants as part of telephone consent.

10.3. Randomisation

Randomisation sequence will be created prior to study commencement using Microsoft Excel and the random number generation function. The randomisation sequence will be held in a secure network location at the University of Oxford. Randomisation blocks will be minimised as per section 13. Allocation sequence to inhaled corticosteroids or standard care will be generated through block randomisation and will be allocated to inhaled corticosteroids or standard care on a 1:1 ratio.

Once a participant has been consented to the study (verbal or in person consent), a research nurse will contact the study team member responsible for randomisation (or delegated back-up, in the event of sickness) in person or by phone, provide the minimisation details and request randomisation. The randomiser will then communicate the randomisation allocation and the participant ID number to the research nurse. The record of the randomisation allocation will be saved at a secure network location with a date and time stamp.

10.4. Blinding and code-breaking

No blinding or code-breaking is required.

10.5. Assessments

The following assessments will be performed according to the schedule in table 1.

Eligibility check: Inclusion and exclusion criteria will be checked with the participant. The responsibility of confirming eligibility will be delegated by the CI to a member of the research team. All study nurses will be designated the responsibility for eligibility confirmation. The study nurses will contact the CI (or other delegated clinician) if the eligibility of any potential participants needs to be discussed further.

Demographic history: Participant demographics including age, smoking history and past medical history will be collected.

Medication history: Full medication history will be collected, including the use of as required and over the counter medication. Any drug allergy will be documented and dates of flu vaccination, S. pneumoniae and H. influenzae B vaccinations will be recorded from the participant and/or medical records as necessary.

Past medical history: Full medical history will be collected from the participant. Additional data can also be collected from electronic medical records if available.

History of current illness: This will include predominant symptoms suggestive of COVID-19 illness, length of symptoms and use of any treatment (over the counter or prescribed) to treat current illness.

Symptom daily diary: Participants will be asked to complete a daily diary using the common cold questionnaire[16] and the FluPRO[17] questionnaire, for a maximum duration of 28 days following randomisation.

Venous blood sampling¥: Study staff will collect up to a maximum of 60ml of venous blood at Visit 1 (only from patients being seen at the GP practice or coronavirus Hub) and at Visit 4 which will take place at the Respiratory Medicine Unit (RMU) at the John Radcliffe Hospital

Nose/throat swab and nasosorption¥: For participants who have attended the GP surgery or Hub at the time of recruitment, study staff will collect nasosorption, nasal and throat swabs from participants at visit 1. At home visits (visit 1, 2 and 3) study staff will perform the sampling. At doorstep visits (visit 1, 2 and 3), information sheets will be provided for sampling technique and participants asked to watch the self-taught videos available on the study website if possible prior. At doorstep visits participants will be asked to perform these tests themselves.

Body temperature: Participants will be asked to measure their own temperature with their allocated thermometer on a daily basis until symptom resolution. The participant will be given a thermometer to record their temperature daily.

Blood oxygen saturations: Participants will be asked to measure their own saturations with their allocated pulse oximeter on a daily basis until symptom resolution. The participant will be loaned a pulse oximeter to record their saturations daily.

Emergency department presentation/hospital admission: Participants will be asked if they have attended an emergency department or if they have been hospitalised at all visits and at daily phone calls.

Medication adherence: Participants will be asked of their adherence to study medication. Inhaler count if available, will be checked at all visits and at daily phone calls. Participants will be asked to stop taking the medication either when their CoVID-19 symptoms disappear or when the 28 day point is reached, whichever is soonest.

Self-testing, using nasal, throat swab, nasosorption, pulse oximetry, body temperature, and how to take the inhaler will be provided for all participants via information sheets and also via videos on the study website.

¥PPE availability – In the unlikely event that study staff are unable to access PPE, these study investigations will not be performed and will not affect the primary outcome.

10.5.1 Visit 1 Baseline assessments (GP surgery/hub visit, home visit or doorstep visit)

The assessments that will be conducted are:

- Consent
- Eligibility check
- Demographics
- Medication check
- Medical history
- Body temperature
- Blood oxygen saturation
- Nasosorption, nose and throat swab (will be performed by nurse unless doorstep visit preferred)
- Blood sampling (only at GP surgery/hub visits)
- Symptom daily diary
- Randomisation to IMP or standard care
- Dispense and administer IMP
- SAE/AE reporting

10.5.2 Visit 2 (Day 7 ± 1 day) (home visit or doorstep visit)

The assessments that will be conducted are:

- Nose and throat swab (will be performed by nurse unless doorstep visit preferred)
- Medication and questionnaire adherence reminder
- Dispense IMP (if required)
- SAE/AE reporting

10.5.3 Visit 3 (Day 14 ± 2 days) assessments (home visit or doorstep visit)

The assessments that will be conducted are:

- Nasosorption, nose and throat swab (will be performed by nurse unless doorstep visit preferred)
- Medication and questionnaire adherence reminder
- Dispense IMP (if required)
- SAE/AE reporting

10.5.4 Visit 4 (Day 28, -2/+ 7 days) assessments (GP surgery or study centre visit at RMU)

The assessments that will be conducted are:

- Venous blood sampling
- Final medication adherence data collection
- SAE/AE reporting

If outstanding, collection of:

- equipment
- symptom diary

10.5.5 Daily phone call

The assessments that will be conducted are:

- Body temperature
- Blood oxygen saturation
- SAE/AE check
- Medication and questionnaire adherence reminder

10.5.6 Study Visits and Hospitalisation

For participants who have been admitted to hospital (for any reason) within the study period and are unable to complete their scheduled study visit, an alternative visit date will be arranged at a convenient time if possible. The daily phone calls will continue to be attempted by the research team during the participant's hospitalisation (until it is known that the IMP is stopped).

Continued attempts will be made to contact the participant via phone throughout the study period. At the start of the study, the participant will be asked if they would be happy for a family member/friend to contact the study team to inform them of any developments such as disease progression/hospitalisation if the participant is unable to do so. If the participant cannot be contacted up until the end of their study period, they will be deemed lost to follow-up.

Participants who are admitted for a non COVID-19 related reason will be asked to continue taking the IMP if they are still suffering from COVID-19 symptoms (unless advised by their clinical care team to stop).

If they are admitted for a COVID-19 related reason, it may not be known that they do have COVID-19 until later in the course of their admission (until their test results are available) and initially it may not be obvious whether their admission is COVID-19 related. Therefore, they could continue taking the IMP even when admitted (unless their clinical team

advises them to stop). However, following a confirmed COVID-19 related admission they have reached the primary outcome and they would be asked to stop taking the IMP at that point.

10.6. Location of study visits

Due to the quickly changing healthcare delivery paradigm during the COVID-19 pandemic, the study visits can be performed in different ways/locations. As listed above, some assessments will only be done at certain study settings. None of these will limit the primary outcome of the study. The location/settings options will be:

- GP surgery or Hub visit (only for participants recruited on the day they visit the GP practice/Coronavirus Hub for clinical purposes) – Visit 1 only

- Home visit – Visit 1, 2 and 3
  Study nurses will attend the homes of participants who provided telephone consent. Study nurses will enter the participant's home to obtain written informed consent and to complete study assessments. This will allow participants to undergo study investigations without needing to perform it on themselves. No blood sampling will be performed in the participant's home

- Doorstep visit – Visit 1, 2 and 3
  Study nurses will attend the doorstep of participants who provided telephone consent. Study nurses will not enter the participant's home. The attending research nurse will leave a study pack (containing ICF, patient information sheets and study equipment) on the doorstep. The study nurse will then return to an appropriate distance (being mindful of social distancing rules) while being aware of participant confidentiality (e.g. to their car). The study nurse will remain at an appropriate distance until the participant is able to complete the self-performed study investigations and be available on the phone to answer any queries the participant may have. When the participant has completed the self-performed study investigations, they will contact the nurse to return to pick up the study samples. No blood sampling will be performed at doorstep visits. The nurse will then return to an appropriate distance (being mindful or social distancing rules) while being aware of participant confidentiality (e.g. to their car) to conduct the rest of visit 1 via telephone.

- GP practice or RMU – Visit 4 only
  The final study visit will be performed at the study centre at the RMU, part of the University of Oxford or at a local GP surgery if it is one of the participating practices (neither of which contravene social isolation guidance). The location of Visit 4 will be dependent on participant preference and/or whether participants are registered at the participating GP surgeries and room availability at the practice.
  At this final visit, the study assessments will be completed as described in 10.5.4 above including a blood test for SARS-CoV-2 antibodies to demonstrate that participants truly had the COVID-19 infection (owing to the fact that the viral swab has a sensitivity of 70% and that self-collected swabs are approximately 50% sensitive).

If potentially eligible patients are not able to be seen due to staff capacity they will be logged in the screening log and reported in final publication. In addition to the study visits, daily phone calls will take place to complete data collection.

10.7 Sample Handling

Whole blood will be collected and sent in a pseudoanonymised form to the Respiratory Medicine Lab, part of the University of Oxford at the John Radcliffe Hospital. Blood will be processed for granulocyte separation, cell sorting,

antibodies, and flow cytometry for analysis of cell receptor expression, function, and morphology. Supernatant and sorted cells will be stored in a pseudoanonymised format for exploratory objective cytokine analysis with Industry and Academic Partners (to whom the samples will be anonymous).

Nasal and throat swabs collected will be used for viral quantitative PCR at the end of the study. Nasosorption samples will also be collected. All samples will be sent in a pseudoanonymised form to the Respiratory Medicine Lab, part of the University of Oxford at the John Radcliffe Hospital. SARS-CoV-2 viral quantitative PCR (qPCR) will be performed on the viral swabs. For the nasosorption samples, supernatant and sorted cells will be stored in a pseudoanonymised format for exploratory objective cytokine analysis with Industry and Academic Partners (to whom the samples will be anonymous). Samples taken from patients who have tested or are reasonably expected to test positive for SARS CoV-2 must be handled by trained, authorised users at containment level 3 using a microbiological safety cabinet until they have been inactivated or deemed virus free. This will be performed by appropriately trained study personnel in accordance with SOP's, in facilities provided locally at the University of Oxford.

Following the end of the trial, participants who provide appropriate consent will donate their remaining blood, nose, throat and nasosorption samples to be stored for a maximum of 10 years in a facility with an appropriate HTA license to be used for future studies with appropriate ethical approval .Any remaining samples provided by the participants who had only consented to provide their samples for the purpose of this study will be destroyed within 1 year after the study completion.

10.8. Early Discontinuation/Withdrawal of Participants

During the trial, a participant may choose to discontinue trial treatment at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE
- Inability to comply with trial procedures
- Participant decision
- Clinical care team decision unrelated to COVID-19

In addition, the Investigator may withdraw a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (for example, arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements
- Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures

If the participant discontinues treatment due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised. Participants who prematurely discontinue treatment, following the administration of IMP will be asked to return at the scheduled study visits to complete study specific assessments. If participants refuse, they will be asked to attend the equivalent of the end-of-trial visit at 4 weeks post first IMP administration to complete study specific assessments.

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up. Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. In the case of withdrawal from both treatment and active follow up, participants can withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data or samples would be collected after withdrawal. The reason for premature discontinuation and decision of continuation will be

recorded in the CRF if the participant consents to disclose. Withdrawal from the study will not exclude data analysis. Withdrawn participants will be replaced if withdrawal or discontinuation occurs

- before the administration of IMP
- or if withdrawal/discontinuation occurs before Visit 2 (day-7 follow-up visit)

10.9. Definition of End of Trial

The end of trial is date of last analysis of data from the last participant.

11. TRIAL INTERVENTIONS

11.1. Investigational Medicinal Product(s) (IMP) Description

Participants will be randomised to either standard care or inhaled corticosteroids (Inhaled Budesonide 400mcg as described below)

-Inhaled Budesonide 400mcg

Inhaled budesonide comes in a polyethylene container consisting of a white cover screwed onto a brown bottom plate. Inside this is the inhaler with its main parts: a mouthpiece, a dosing mechanism and a substance store. The device will have 50 actuations of 400mcg/actuation. This product has marketing authorisation in the UK (PL 17901/0164). This product is manufactured by AstraZeneca UK Ltd, 600 Capability Green, Luton, LU1 3LU, UK. This IMP will be taken as 2 puffs twice a day and up to 3 inhalers will be provided at study visits.

The participants will be advised to take the IMP until i) the COVID-19 symptoms (such as, but not limited to, high temperature, new continuous cough, and/or loss of sense of smell or taste) cease; ii) they are hospitalised for a COVID-19 related reason; iii) they are advised by their clinical care team to stop; iv) or for a maximum of 28 days. Any part-used or un-used treatment should be returned to the RMU at Visit 4. The undesirable effects of inhaled budesonide are as described in the SmPC.

11.2. Side effects of inhaled corticosteroids

Potential side effects from IMP include:

- Cough immediately after inhaling
- Mouth and throat pain
- Hoarse voice
- Oral candidiasis (thrush)

11.3. Blinding of IMPs

IMP will not be blinded.

11.4. Storage of IMP

The study drugs will be shipped by AstraZeneca Ltd to Stockport Pharmaceuticals (Stepping Hill Hospital, Poplar Grove, Stockport, SK2 7JE, UK) for labelling and QP release. The labelled IMP packs will be transferred to the RMU at the University of Oxford for storage and use in the study. IMP will be stored in temperature monitored and locked facilities within RMU under 30 degrees centigrade.

Following randomisation, a study prescription will be completed by study doctors (paper or electronic format, as per study TSP) and provided to the study nurse to collect IMP (if randomised to IMP arm). The IMP will be transported in the study team's cars (in locked boxes) to the appropriate visit. There will be no temperature monitoring of the medications when they are being transported by the nurses. IMP collection and unused IMP returned to the RMU will be logged daily by the study nurses who will also monitor the stock levels.

11.5. Compliance with Trial Treatment

Participants will receive a daily phone call to remind them to take the IMP. As this is a short study duration, we expect adherence to be high. The ICS device has a dose indicator which can be recorded at Visit 4 when IMP is returned for

destruction. These will be destroyed by the research team as per standard procedure. IMP compliance could also be a reflection of symptom resolution; participants may thus stop IMP earlier than 28 days. The date that IMP cessation will be recorded on the CRF.

11.6. Concomitant Medication

Medication history and concomitant medication will be taken at every visit. Widespread use of the IMPs in this study suggests that potential risk of interaction with other drugs is low.

11.7. Post-trial Treatment

There will not be provision of the IMP beyond the trial period.

11.8. Other Treatments (non-IMPS)

All participants who participate in the trial will be reminded of the NHS guidance on recognising and managing the symptoms of CoVID-19. This will form the advice that is provided to the participants randomised to the standard of care. The provision of the pulse oximeter will provide another trigger for participants to seek medical advice. If the participant's blood oxygen saturation is below 92%, they will be advised to contact their GP or call 111 or attend the local ED.

If participants have very severe difficulty breathing, they will be asked to call 999.

11.9. Other Interventions

There are no additional interventions in the trial design.

12. SAFETY REPORTING

12.1. Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect*. Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

12.2. Assessment results outside of normal parameters as AEs and SAEs

There are no standard tests included in this study. Any tests undertaken during clinical care will be dealt with according to best practice. Adverse Events and Serious Adverse Events will be recorded and reported as described below.

12.3. Assessment of Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Unrelated – Where an event is not considered to be related to the IMP / intervention

Possibly Related – although a relationship to the IMP / intervention cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Probably Related – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP / intervention

Definitely Related – the known effects of the IMP, its therapeutic class or based on challenge testing suggests that the IMP / intervention is the most likely cause.

All SAEs labelled possibly, probably or definitely related will be considered as related to the IMP.

12.4. Procedures for Reporting Adverse Events

Adverse events listed below at 12.5.1, as foreseeable, will be collected in CRFs in the daily questionnaire and as scheduled visits. Any other AEs will be recorded on an Adverse Event CRF. The following information will be reported on the CRF: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

Non-serious AEs considered related to the trial medication as judged by a medically qualified investigator will be followed up until the event resolves or is considered stable. It will be left to the Investigator’s clinical judgment to decide whether or not an AE is of sufficient severity to require the participant’s removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant will be asked to continue with scheduled visits to enable full data collection and to monitor resolution of the AE.

12.5. Reporting Procedures for Serious Adverse Events

The safety reporting window will be from consent until Visit 4 (28 days from beginning of IMP administration). Safety reporting after day 28 is not required due to the well-established safety profile of the intervention.

All SAEs that are not foreseeable in this patient population (see 12.5.1), occurring in the safety reporting period as described above must be reported on the ORTU reporting form to ORTU within 24 hours of the Site Study Team becoming aware of the event being defined as serious. See 12.5.2. for further details.

The development of a pregnancy during the study, for participants in the interventional arm (i.e. following the administration of IMP) will not be followed up or monitored due to the well-established safety profile of the IMP and due to its routine use in pregnancy and due to the short study duration of IMP (less than 28 days) with minimal systemic absorption.

12.5.1 Events exempt from immediate reporting as SAEs

Foreseeable Adverse Events in this study are those associated with the progression of COVID-19 related symptoms. Severe forms of all these adverse events have been reported in some patients with COVID 19. There is no measure of severity specified in this table as this is currently unknown in this new disease and all levels of severity for these adverse events are considered to be foreseeable. These will be collected in CRFs for analysis but do not require expedited reporting. The list below details these events:

Respiratory	Haematological	Neurological	Gastrointestinal	Cardiovascular	Renal
Fever	Disseminated intravascular coagulopathy	Headache	Diarrhoea	Myocarditis	Dehydration
Cough	Abnormal liver function tests	Stroke	Vomiting	Chest pain	Kidney failure
Nasal congestion	Abnormal clotting	Neurological disturbances	Loss of taste	Heart attack	
Chills	Pancytopenia	Fatigue	Abdominal pain	Heart failure	
Sore throat	Thrombocytopenia				
Coughing up sputum	Lymphopenia				
Shortness of breath					
Coughing up blood					
Muscle aches					
Loss of sense of smell					
Pulmonary Embolism					

12.5.2 Procedure for immediate reporting of Serious Adverse Events

All SAEs (other than those defined in the protocol as not requiring reporting) must be reported on the ORTU SAE reporting form via the trial database within 24 hours of the Site Study Team becoming aware of the event. The entry of the SAE report onto the database by the nurse and the assessment of the event by a doctor will trigger an email which will be automatically sent to ORTU to inform them of the SAE. If it is not possible for the site study staff to report the SAE on the database straight away (within 24 hours) for logistical reasons, a word version of the ORTU SAE form should be completed and then emailed to respiratorytrialsunit@ouh.nhs.uk. The research team will then complete data entry for this event on the database as soon as possible. ORTU will perform an initial check of the report, request any additional information, and ensure it is reviewed by a nominated Medical Reviewer (including Expectedness

Assessment). It will also be reviewed at the next Trial Safety Oversight Group meeting. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form submitted through the trial database. See Appendix B.

12.6. Expectedness

Expectedness will be determined by a nominated Medical Reviewer according to the appropriate SmPC currently approved for use in this trial by the Sponsor and MHRA at the time of the event.

12.7. SUSAR Reporting

All SUSARs will be reported by the sponsor delegate to the relevant Competent Authority and to the REC and other parties, including AstraZeneca (as funder and ICS licence holder) as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

12.8. Development Safety Update Reports

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, with copies sent to the Sponsor.

If approved under the notification scheme, the HRA Annual Progress Report (APR) form should be used as a template for the DSUR, and should include a list of all SARs in Section 6. The cover letter must state that this is an APR in lieu of a full DSUR, and include the EudraCT number and CTA reference number.

For assessment of SARs in the DSUR, the RSI that was approved at the start of the safety reporting period will be used. When there has been approved changes to the RSI by substantial amendment during the reporting period, the RSI used for the DSUR will differ to the RSI used to assess expectedness at the time of SAR occurrence for SARs which require expedited reporting.

13. STATISTICS

13.1. Statistical Analysis Plan (SAP)

The plan for the statistical analysis of the trial are outlined below. There is a separate SAP document in use for the trial.

13.2. Description of Statistical Methods

Randomisation by minimisation for gender, age (18-40 or >40) and presence of co-morbidities (1 or less or >1) will be performed. Primary outcome analysis will be performed on an intention to treat analysis. Descriptive statistics will be used to describe variables between the groups in the interventional arm and the standard care arm. Tests of normality will be applied and appropriate parametric or non-parametric statistical tests will be performed. For continuous variables, the difference in the means or medians and the corresponding 95% confidence interval or interquartile range will be reported for each treatment group and overall. For continuous variables, t-tests will be applied to compare the intervention and observational group. For categorical variables, including the primary outcome, the number (and percentage) of patients in each category will be reported for each treatment group and overall and chi-squared tests will be used for comparing treatment groups, with adjustment for the minimisation criteria as applicable[18]. Secondary analysis will be undertaken using logistic regression with adjustment for minimisation and other important prognostic factors and time to hospitalisation using Kaplan-Meier curves. Characteristics of response (clinical, physiological and biological) will be identified following generation of receiver operator characteristic curves and correlation coefficients. Unsupervised K-means (or equivalent) cluster analysis statistical techniques will be used to interrogate characteristics predictive of recovery. Generalised mixed and linear regression models including time as a covariate will be imputed to analyse longitudinal variable data[19]. Data will also be explored using linear-effects modelling for repeated and longitudinal measures. Predetermined sub analyses will include analysis of outcomes based on gender, age at consent, time of onset and number of days symptoms present prior to visit 1. No interim analyses are planned. Statistical analysis will be conducted using suitable statistical software including STATA version 14 and above (StataCorp, Texas USA) and R (R-Project.org).

13.3. Sample Size Determination

As discussed above, we assume that 20% of all COVID-19 illness is severe and will require hospitalisation needing respiratory support. Using 80% power at 0.05 level, 199 patients in each arm are required to demonstrate a 50% reduction of hospitalisations (from 20% to 10%). This will also test to see if there is a difference in effect size on the common cold questionnaire of 0.8 points[16] (large clinical effect). We will recruit a total of 478 patients to include 20% drop out.

13.4. Analysis Populations

A per protocol and intention to treat analysis will be performed.

13.5. Decision Points

No interim analysis will be performed.

13.6. Stopping Rules

No formal stopping rules apply.

13.7. The Level of Statistical Significance

All tests will be completed at a 5% 2-sided significance level. All comparative outcomes will be presented as summary statistics with 95% confidence intervals and reported in accordance with the CONSORT Statement (http://www.consort-statement.org). P-values will be reported to a minimum of 3 decimal places or as required by specific journals for publication.

13.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data will be minimised by careful data management. Missing data will be described with reasons given where available; the number and percentage of individuals in the missing category will be presented by treatment arm. All data collected on data collection forms will be used, since only essential data items will be collected. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis. The nature and mechanism for missing variables and outcomes will be investigated, and if appropriate multiple imputation will be used. Sensitivity analyses will be undertaken assessing the underlying missing data assumptions.

13.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviations from the statistical plan will be described in the final report.

13.10. Health Economics Analysis

No health economics analysis is to be performed.

14. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

14.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to CRFs, questionnaires, clinical and office charts, laboratory records, diaries, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

14.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

14.3. Data Recording and Record Keeping

Trial staff will collect data from direct patient questioning and from clinical laboratory software which will be written on to approved paper CRFs (stored at RMU). Data will then be entered onto eCRFs (OpenClinica, a secure, validated, GCP-compliant electronic data management system). Daily diary data will be completed by participants on printed study diaries. This will also be entered onto the database. All staff performing data entry will be appropriately trained prior to access being granted. Study staff's access to all systems is controlled by individual user accounts, and a full audit trail is kept of all modifications made to data. The study database will be hosted on a secure server. The database will be backed up at least daily.

Standard Operating Procedures (SOPs) will be followed to ensure quality control. The processes for validation of study data will be detailed in the data management plan, and other associated documents. The Chief Investigator will facilitate access to study records for the purpose of monitoring, audits, and regulatory inspections. Patients' consent to this will be sought at the time of enrolment into the study. Both paper and electronic trial data will be retained through an archiving service as per the sponsoring institute's policy, and data will be retained for a minimum of 10 years after termination of the trial.

The participants will be identified by a unique trial specific number and/or code in any database. Participant identifiable details from consented participants (name and telephone number) will be stored in a password protected file secure University of Oxford server, accessed only by nominated research staff, to facilitate contact with participants at the non-face-to-face follow-up visit.

15. QUALITY ASSURANCE PROCEDURES

15.1. Risk assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment will be prepared before the study opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

15.2. Monitoring

The study will be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures by the representatives of the University of Oxford or delegate. A detailed Risk Assessment will be conducted by ORTU before the trial starts and an appropriate Monitoring Plan will be developed by CTRG.

15.3. Trial committees

15.3.1 Trial management group (TMG)

The TMG will meet on a monthly basis throughout the trial to discuss the day-to-day management of the trial, assess any recurring safety issues and escalate these if necessary. A TMG charter will be written further detailing the roles and responsibilities of this committee. This will include the CI, the responsible study research team (e.g. lead research nurse), the data coordinator and the trial manager.

15.3.2 Safety Oversight Group

The Oxford Respiratory Trials Unit (ORTU) Trial Safety Oversight Group will conduct a review of all SAEs for the trial reported during the reporting period and cumulatively. The ORTU Safety Oversight Group requires at least three clinicians to attend each meeting (this may include the Chief Investigator). The Group will provide advice to the TMG and may correspond directly with the Sponsor if potential safety concerns are raised. The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

The content and timings of the ORTU Safety Oversight Group will be detailed in a Safety Oversight Group Charter, which is agreed with the members.

16. PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and assessed appropriately as per the ORTU SOP and filed in the trial master file.

17. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

18.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

18.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

18.4. Other Ethical Considerations

As a study investigating a commonly used medication, there is a risk of patients in the standard care arm seeking a prescription for this from their general practitioner. There could be significant crossover from the standard care arm to the interventional arm. However, there is significant equipoise with regards to inhaled corticosteroids. It is important to conduct this study to definitively answer this question during this pandemic.

Another ethical issue is if this class of medication works to control the severity of symptoms associated with COVID-19, there may be a shortage of this medication worldwide. At the time of writing, there are at least 4 other clinical trials studying the effect of ICS on COVID-19 and are using at least 2 other ICS medicines. Thus, the combined effect of these studies and this one, will be able to demonstrate a class effect. Furthermore, Budesonide is available in generic formulation (off patent) and will thus reduce manufacturing pressure.

Home visits are an integral part of the study in order to optimise swab and inhaler technique and to help participants with the study assessments. We do not feel that home visits present increased risk to participants or other household members. If a participant is symptomatic, all household members are already considered to be exposed. The definition of a close contact, as NHS guidelines, is spending more than 2 hours in a room with another person. The home visit will not last this long therefore will not meet the definition of close contact. Nevertheless, participants can opt for

doorstep visits if this is their preference. Research nurses will operate under the guidance of appropriate lone working and home visit policies and procedures (e.g. working under the buddy system so that someone else if aware of their whereabouts) and will wear appropriate PPE.

18.5. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

18.6. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Results will be uploaded to the European Clinical Trial (EudraCT) Database within 12 months of the end of trial declaration by the CI or their delegate.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

18.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

Doorstep and home visits carry with it a risk of breaching confidentiality. During this pandemic, we feel that this risk is minor.

18.8. Expenses and Benefits

As this is a trial conducted during a pandemic, there will be no re-imbursement to the patient beyond the provision of their personal thermometer and oximeter to be used during the study period.

19. FINANCE AND INSURANCE

19.1. Funding

This study is funded by the Oxford NIHR Biomedical Research Centre - Respiratory Theme & Investigator Initiated Grant from AstraZeneca.

19.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

19.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

20. PUBLICATION POLICY

The final results of the study will be submitted for publication in peer-reviewed scientific journals for publication and dissemination. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. All data will be anonymised for publication. Funders will be acknowledged in any publication format.

21. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable.

22. ARCHIVING

All trial documents will be archived for at least 10 years following the end of the trial. Documents will be stored in a secure archiving facility as required by ORTU SOPs. The informed consent forms and paper CRFs will be archived in locked cupboards in the Respiratory Medicine Unit (RMU).

23. REFERENCES

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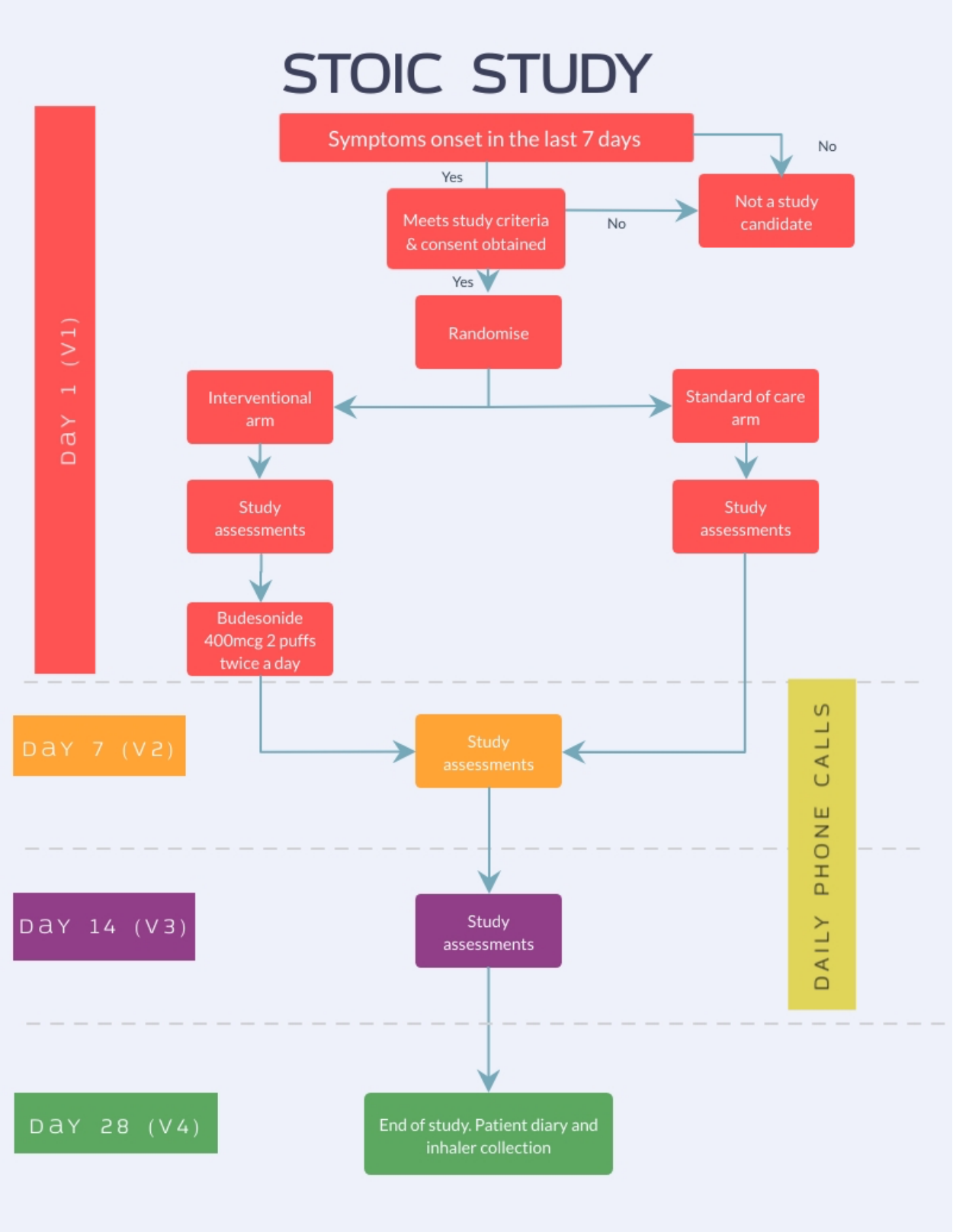
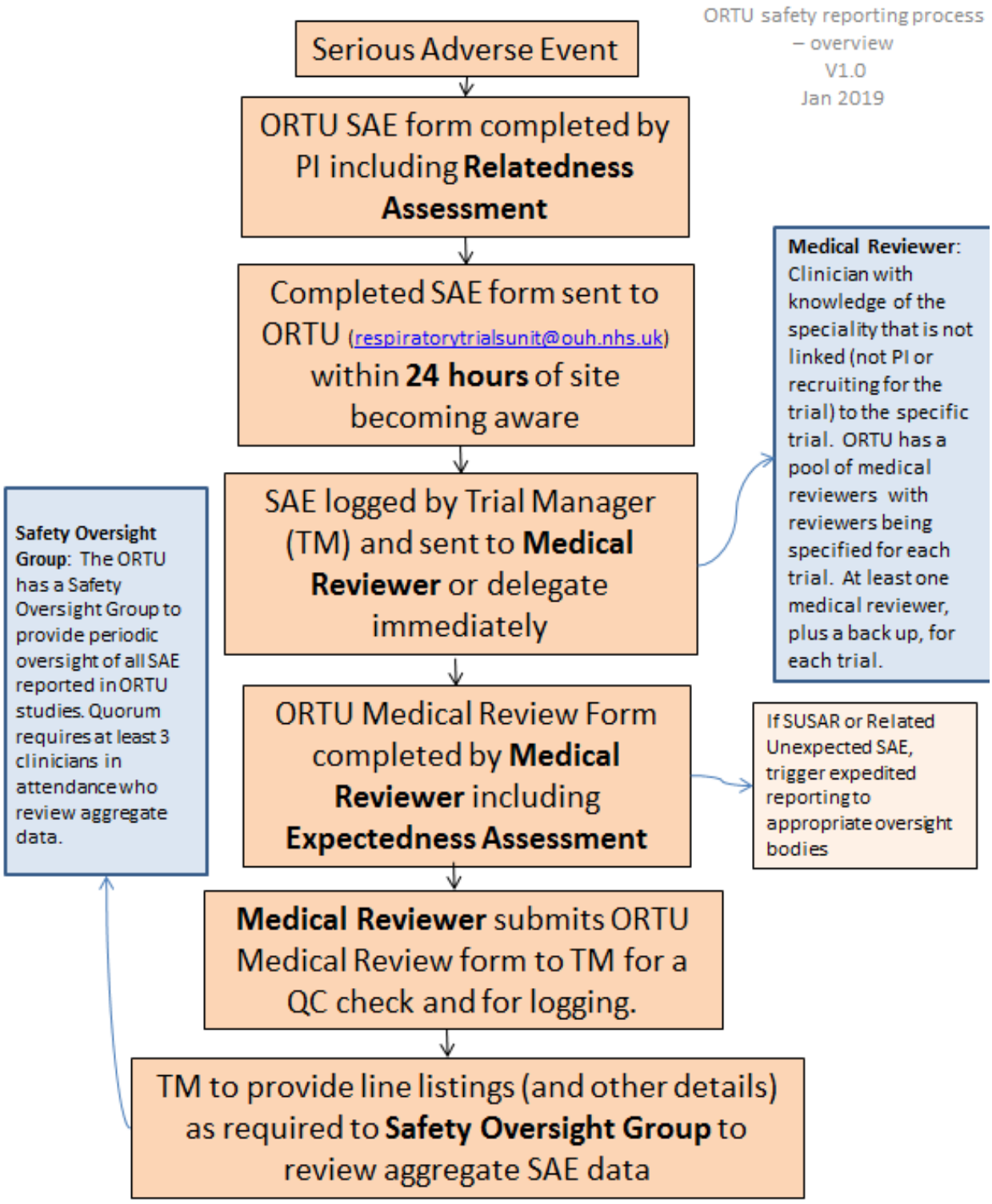
24. APPENDIX A: TRIAL FLOW CHART



25. APPENDIX B: SAE REPORTING FLOW CHART



26. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version	Date issued	Author(s) of changes	Details of Changes made
SA01 (MHRA only) including changes requested by the initial REC review	No.2.0	26May2020	Prof Mona Bafadhel	a. Removal of Ciclesonide b. Correction of how long the samples will be kept for future research (max 10 years). c. Update to the list of COVID19 symptoms d. Corrections to the stats and analysis sections. e. Updates to the rationale and risk/benefits sections.

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.