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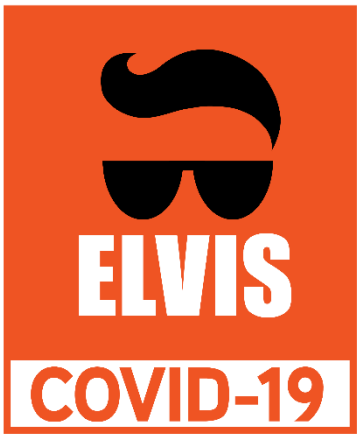

Non-CTIMP Study Protocol

Hypertonic saline nasal irrigation and gargling for suspected or confirmed COVID-19: pragmatic web-based Bayesian adaptive randomised controlled trial (ELVIS COVID-19)

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Amendment classification and number:	**Summary of change(s)**
Response to REC	Minor change to study title Clarification surrounding diary completion and reminders and process for missing data Clarification of process for contacting the study team Update to eligibility criteria following government isolation guidelines for COVID-19
Response to REC	Addition of “People ≤17 years” to exclusion criteria
Amendment 1	Addition of plan to actively monitor participants condition and symptoms during their participation in the study Addition of section 5.3 to clarify randomisation procedure
Amendment 2	Adapting documents to be UK wide appropriate Update to section recruitment strategies

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
BREATHE	Health Data Research Hub for Respiratory Health
CI	Chief Investigator
CRF	Case Report Form
COVID-19	Coronavirus Disease-19
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ELVIS	Edinburgh and Lothians' Viral Intervention Study
GCP	Good Clinical Practice
GP	General Practitioner
HOCl	Hypochlorous acid
HSNIG	Hypertonic Saline Nasal Irrigation and Gargling
ICH	International Conference on Harmonisation
NaCl	Sodium Chloride
OOH	Out-of-hours
PI	Principal Investigator
QA	Quality Assurance
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RNA	Ribonucleic Acid
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
URTI	Upper Respiratory Tract Infection
WURSS-24	Wisconsin Upper Respiratory Symptom Survey-24 questionnaire

INTRODUCTION

1.1 BACKGROUND

Post-hoc secondary analysis of data from our recent Edinburgh and Lothians Viral Intervention Study (ELVIS) pilot randomised controlled trial (RCT) indicates that hypertonic saline nasal irrigation and gargling (HSNIG) reduced the duration of coronavirus upper respiratory tract infection (URTI) by an average of two-and-a-half days.[1] As such, it may offer a potentially safe, effective and scalable intervention in those with Coronavirus Disease-19 (COVID-19) following infection with the betacoronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[2]

ELVIS was undertaken in 66 adults with an URTI. Results have been reported in detail elsewhere.[3] Briefly, volunteers with URTI were, within 48 hours of symptom onset, randomised to intervention (n=32) or control (n=34) groups. The intervention group made hypertonic saline at home and performed HSNIG as many times as needed (maximum of 12 times/day). Control group participants dealt with their URTI as they normally did. Nose swabs collected at recruitment and first thing in the morning on four consecutive days were sent to the laboratory for testing. Both groups kept a diary (which included the Wisconsin Upper Respiratory Symptom Survey-21 questionnaire) for a maximum of 14 days or until they were well for two consecutive days. Follow-up data were available for 92% of individuals (intervention group: n=30; control group: n=31). HSNIG reduced the duration of URTI by 1.9 days (95% CI = 0.4 to 3.3) (p=0.01), over-the-counter medication use by 36% (p=0.004), transmission within household contacts by 35% (p=0.006) and viral shedding by ≥0.5 log10/day (p=0.04) in the intervention group when compared to controls.[3]

We also recently reported that epithelial cells mount an antiviral effect by producing hypochlorous acid (HOCl) from chloride ions.[4] HOCl is the active ingredient in bleach. Epithelial cells have this innate antiviral immune mechanism to clear viral infections. Since bleach is effective against all virus types,[5] we tested to see if a range of DNA, RNA, enveloped and non-enveloped viruses were inhibited in the presence of chloride ions supplied via salt (NaCl). All the viruses we tested were inhibited in the presence of NaCl. The human viruses we tested were: DNA/enveloped: herpes simplex virus; RNA/enveloped: human coronavirus 229E (HCoV-229E), respiratory syncytial virus, influenza A virus; and RNA/non-enveloped: coxsackievirus B3.[4]

In COVID-19, high titres of SARS-CoV-2 are detectable in the upper respiratory tract of asymptomatic and symptomatic individuals.[6] The titres are higher in the nose than the throat suggesting measures that control the infection and viral shedding will help reduce transmission.[6] In the context of the COVID-19 pandemic, we have undertaken a post-hoc re-analysis of the ELVIS data with a focus on those infected with coronaviruses. Coronaviruses were the second most common cause of URTI (after rhinoviruses). Fifteen individuals were infected by a coronavirus (intervention group (n=7), control group (n=8)). In the intervention

group, four participants were infected by an alphacoronavirus (HCoV 229E=3, HCoV NL63=1) and three by a betacoronavirus (HCoV HKU1=3). In the control group, two were infected by an alphacoronavirus (HCoV NL63=2) and six by a betacoronavirus (HCoV OC43=1, HCoV HKU1=5). An individual in the control group with HCoV HKU1 had dual infection with rhinovirus.

The duration of illness was lower in the intervention group compared to the control group in the subset of patients infected with coronavirus (mean days (SD): 5.6 (1.4) vs 8.1 (2.9)). Using a two-sample t-test, this was difference of -2.6 days (95%CI -5.2, 0.05; p=0.054). The difference in the duration of blocked nose was -3.1 days (95%CI -6.0, -0.2; p=0.04), cough -3.3 days (95%CI -5.9, -0.7; p=0.02) and hoarseness of voice -2.9 days (95%CI -5.6, -0.3; p=0.03) in favour of HSNIG.

In the absence of a suitable antiviral agent or a vaccine, we need a safe and effective intervention that can be globally implemented. Our in-vitro data gives the evidence that NaCl has an antiviral effect that works across viral types. The findings from this post-hoc analysis of ELVIS need to be interpreted with caution. These data do however suggest that HSNIG may have a role to play in reducing symptoms and duration of illness in COVID-19.

1.2 RATIONALE FOR STUDY

The mucolytic effect of NaCl is the current accepted rationale for saline irrigation in URTI. However, we recently reported that human epithelial (cervical-HeLa, respiratory-A549) cells utilise NaCl to mount a broad spectrum antiviral effect against both DNA and RNA viruses enveloped and non-enveloped viruses (enveloped DNA viruses: herpes simplex virus, varicella zoster virus; enveloped RNA viruses: respiratory syncytial virus and influenza A virus; non enveloped RNA virus: Coxsackievirus B3).[4] The antiviral effect is dependent on the entry of chloride (not sodium) ions into the cell and the production of intracellular hypochlorous acid (HOCl). The antiviral effect was reversed when chloride (not sodium) channels were blocked. HOCl is the active ingredient of bleach, a broad spectrum anti-infective agent which can inactivate most viruses.[7-10] A polymorphism causing reduction in HOCl production has been reported in individuals with cervical cancer.[11] Since cervical cancer follows infection with high-risk types of human papilloma viruses, it suggests a key role for local antiviral mechanisms. HOCl production is an important anti-bacterial mechanism in human neutrophils[12]. Increased HOCl production is reported within gut epithelial cell of fruit flies after bacterial lysate ingestion[13]. These data suggest an anti-infective role of HOCl and its precursor NaCl in epithelial cells.

Recently, it has been shown that accumulation of Na^+ ions in human skin helps fight bacterial/parasitic infections.[14,15] A high salt diet increased Na^+ in skin leading to a hypertonic environment, increased Nitric Oxide (NO) production in macrophages and thereby pathogen removal.[14,15] Whilst our laboratory data points to the importance of Cl^- in combating viral infections, Jantsch et al have shown the importance of Na^+ in fighting bacterial infections. Taken

together, it suggests that innate immunity may be dependent on NaCl in epithelial cells helping to clear bacterial and viral infection.

Given the laboratory evidence supported by our demonstration of clinical benefits in adults (i.e. duration of symptoms, over the counter medication, viral shedding and transmission within households in Edinburgh and Lothians' Viral Intervention Study (ELVIS)), we believe a RCT in adults with COVID-19 symptoms to study the effects of HS on duration of illness and viral shedding is now needed.

We have recently completed ELVIS, an open label pilot RCT of hypertonic saline nasal irrigation and gargling (HSNIG) in 66 adults with an URTI (www.elvisstudy.com). Most participants were infected with rhinovirus/coronavirus. The intervention arm had a 22% reduction in duration of illness (mean (SD) of intervention arm: 6.8 days (2.2) and control arm 8.7 days (3.3), difference of 1.9 days; p=0.01). 93% believed HSNIG helped improve symptoms of the cold. There was 36% reduction in over-the-counter medication use (p=0.003), transmission within household was reduced by 35% (p=0.006), and viral shedding by ≥0.5 $\log_{10}$/day (p=0.04).[3] The reduction in viral shedding and transmission within household are both in keeping with our laboratory results suggesting that NaCl induces an antiviral response within the cell. Since HSNIG reduced duration of illness, viral shedding, over the counter medication use and transmission within households in adults, we propose a RCT of HSNIG in adults with suspected or confirmed COVID-19. Since normal saline (a commonly used, safe, placebo) has NaCl in it, and sodium bicarbonate can be uncomfortable (PI's personal experience) and plain water is hypotonic and hence painful, the study will not be placebo controlled.

1.2.1 Hypotheses

Primary: HSNIG is effective in reducing the duration of illness in those with clinically suspected or confirmed COVID-19 being managed at home.

Secondary: HSNIG is effective in reducing complications of COVID-19 and onward household transmission.

1.2.2 Intervention

Self-isolated participant with suspected or confirmed COVID-19: HSNIG made at home (instructions and study videos are available to be viewed by the intervention group in the study website) and used as required to a maximum of 12 times/day for a maximum of 14 days. Participants are informed that symptoms might reduce after HSNIG, but the symptoms may return after a while. Symptoms could hence return as early as 30 minutes to many hours later after HSNIG. Participants are requested to perform HSNIG as soon as symptoms return. Participants are expected to perform HSNIG as many times as needed (but not more than 12 times/day) until well or until the end of their study participation (either on day 14 or on admission to hospital or on withdrawal from the study) and follow standard advice from NHS on personal

and household hygiene and social distancing: https://www.nhs.uk/conditions/coronavirus-covid-19/self-isolation-advice/

1.2.3 Control

Those randomised to the control arm will be asked to follow the guidance on personal and household hygiene and social distancing as advised by the NHS: https://www.nhs.uk/conditions/coronavirus-covid-19/self-isolation-advice/

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To investigate whether the use of HSNIG performed by adults with symptoms consistent with COVID-19 reduces the duration of symptoms when compared to participants managed using standard care.

2.1.2 Secondary Objectives

To determine the effect of HSNIG on:

1. Severity of all symptoms
2. Duration and severity of individual symptoms
3. Over-the-counter medication use
4. Contact with primary care, NHS 24/111 and out-of-hours (OOH) primary care, COVID-19 hubs
5. Hospital attendance (i.e. A&E attendance and/or hospital admission) and diagnosis
6. Number of household contacts infected
7. Side-effect of HSNIG.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

Self-reported time to resolution as assessed by completion of the validated self-reported UK-adapted short form of the Wisconsin Upper Respiratory Symptom Survey (WURSS-24), which will be used to collect daily symptom data[16,17].

2.2.2 Secondary Endpoints

1. Severity of all symptoms

2. The length of time for individual symptoms to resolve

3. Severity of individual symptoms

4. Contacting healthcare (NHS 24, OOH, GP) (Number of participants and frequency of contacts)

5. Participants needing GP appointments (Number of participants and frequency of contacts)

6. Participants attending hospital (Number of participants)

7. Length of stay in hospital if admitted

8. Number of participants reporting over the counter medication use

9. Reduction in transmission to household contacts

10. Number of participants reporting side effects of nasal irrigation

11. Types and severity of side effects reported

12. Cost of over the counter medication used

3 STUDY DESIGN

ELVIS COVID-19 is a pragmatic, non-CTIMP, web-based, Bayesian adaptive randomised controlled trial (RCT) of HSNIG vs. standard care in adults >18 years of age with suspected or confirmed COVID-19. The study will run throughout the course of the COVID-19 pandemic until numbers have been recruited for sufficient analysis. Participants are recruited within 48 hours of developing COVID-19 symptoms by use of study advertising through traditional media such as radio and internet advertisements, as well as social media. For the purposes of this study, symptoms or diagnosis of COVID-19 are defined as at least one of the following symptoms: recent onset of (i) new continuous cough and/or (ii) high temperature) and/or (iii) loss of, or change in, sense of smell or taste (anosmia) or those with virologically confirmed SARS-CoV-2 infection and clinical symptoms indicative of COVID-19.

Willing participants will be directed by the study advertising to access a study specific webpage where they will be able to access further study information and documents. The affected individual (one per household at any one time) will be centrally randomised through an easy to access web-based randomisation schedule hosted at the study data centre (the Edinburgh Clinical Trials Unit, University of Edinburgh). All pre- and post-randomisation data will be collected through mobile phone/web-based questionnaires (see daily diary, end of illness questionnaire and day 14 questionnaire). Participants will be randomised to either a Control arm of standard symptomatic care, or an Intervention arm of HSNIG up to 12 times per day for a maximum of 14 days or until asymptomatic, alongside standard symptomatic care. All participants will be required to complete a daily symptom diary (WURSS-24 questionnaire) until asymptomatic or Day 14 and all participants will be asked to complete the Day 14 questionnaire, which will establish if other members of the participant's household have developed symptoms of COVID-19. If a participant's symptoms clear before Day 14, they will be invited to complete

the End of Illness questionnaire (healthcare use, adverse events, acceptability, infection in household contacts) on the day that these symptoms resolve.

Participants who have been randomised to the Intervention arm, will be allowed access to a webpage featuring videos and instructions on how to prepare the hypotonic saline solution and how to perform HSNIG.

At consent, participants will be given the option to consent to the future collection of samples for COVID-19 serological analysis.

3.1 ELVIS COVID-19 Study Patient Pathway

Adults who are self-isolating contact the study team

Case definition:
Adult patients (≥18 years) who are self-isolating at home within 2 days of the start of the illness with:
(a) clinical symptoms suggestive of COVID-19 (i.e. those who have at least one of the following symptoms: recent onset of (i) new continuous cough and/or (ii) high temperature) and/or (iii) loss of, or change in, sense of smell or taste (anosmia) **or**
(b) those with virologically confirmed SARS-CoV-2 infection and clinical symptoms indicative of COVID-19 (as detailed in (a) above).

↓

Eligibility confirmed, Details on individual and family contacts collected and consent taken (Online)

↓

Randomisation (Online)
Intervention groups taught how to prepare hypertonic saline (HS) and perform hypertonic saline nasal irrigation and gargling (HSNIG). Both groups taught to fill an online daily diary using a web link sent directly to their email address.

↓

Control Group	**Intervention Group**
Standard personal, household hygiene and social distancing advice: https://www.nhs.uk/conditions/coronavirus-covid-19/self-isolation-advice/	**HSNIG started within 48 hours of symptom onset** *Number of times HSNIG should be done:* As many times as needed (but not more than 12 times/day) PLUS **Standard personal, household hygiene and social distancing advice:** https://www.nhs.uk/conditions/coronavirus-covid-19/self-isolation-advice/

↓

Information to be collected during study period (14 days)
Daily diary – to be completed daily
End of illness diary – To be completed the day participant reports feeling well or Day 14
Day 14 questionnaire – To be completed by those whose symptoms resolved before Day 14

↓

Post-trial: Data to be linked to NHS records to enable assessment of virological/serological status

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We aim to recruit a total of 405 participants from within the UK. 50% of these patients will be randomised to the study intervention and 50% will be randomised to standard care.

This sample size will be re-estimated from blinded internal data (via the independent Data Monitoring Committee) when the first n=100 have completed the study, and also from any updated relevant external data on the pathway for recovery in COVID-19.

4.2 INCLUSION CRITERIA

- Adults (≥18 years)
- Those living within the UK
- Those self-isolating at home within 48 hours of the start of the illness with:
  - (a) Clinical symptoms suggestive of COVID-19 (i.e. those who have at least one of the following symptoms: recent onset of (i) new continuous cough and/or (ii) high temperature) and/or (iii) loss of, or change in, sense of smell or taste (anosmia) OR
  - (b) Those with virologically confirmed SARS-CoV-2 infection and clinical symptoms indicative of COVID-19 (as detailed in (a) above).
- Provision of informed consent

4.3 EXCLUSION CRITERIA

- Onset of illness >48 hours
- People ≤17 years
- Inability to consent
- Pregnancy
- Immunosuppression
- Inability to perform HSNIG
- Those taking part in another interventional medical trial
- Those without access to a supply of salt
- Those who have had a negative COVID-19 swab result for the present symptoms
- Those with suspected/confirmed COVID-19 in whom hospital admission is recommended
- Those who do not have access to email/internet
- Those living in a household with another person currently participating in this study

4.4 CO-ENROLMENT

Co-enrolment is permitted for non-interventional trials that involve data collection only. Co-enrolment should only be considered if it is not expected to put an unnecessary burden on the participant and their family and does not compromise the end point of either trial. Any co-enrolment will follow the Sponsor Guidelines GL001. Enrolment in another interventional trial is not permitted and is an exclusion criterion.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

We propose to advertise the study via traditional and social media, using videos, advertisements and posters. We will also promote the study via NHS Lothian and University of Edinburgh email lists and through collaboration with other COVID-19 studies on their websites and apps, with agreement from their Chief Investigators. Potential participants will be approached via health research registers and SHARE (within Scotland).GP networks and care homes may also be utilised to promote the study. Promotional material will be utilised in COVID-19 testing centres, GP practices and on their websites, where possible, to raise awareness of the study. Workplace email lists will also be used to distribute information about the study, with agreement from the relevant management staff. We will contact volunteer groups (e.g. https://covidmutualaid.org/) both for help in promoting the study and for local help to participants (e.g. top-up supply of salt, if needed).

Participants will identify themselves and access the study specific website for more information and to view the Participant Information Sheet. If they consider themselves to be suitable and willing to participate in the study, they will be able to click through to the public facing pages of the REDCap database where they will confirm that they are eligible before consent.

Contact information for the study team will be made available to participants in the PIS and the study website. This information will include the study team email address for general queries and this will be monitored Monday-Friday during normal working hours. If a participant has an urgent query regarding their participation in the study, they will be advised to contact the study doctor using the contact details stated on the website and PIS.

5.2 CONSENTING PARTICIPANTS

Participants will complete an online eligibility baseline check before being directed to an online consent. Participants will consent themselves after having time to read the patient information sheet and any study information on the study website. There is no set time given to the participant to consider the information however at consent they must still be <48 hours of start of illness.

5.2.1 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point, without giving a reason. If the participant chooses to withdraw they can document this by selecting this option on the daily questionnaires. This will trigger the End of Illness form and we ask participants to complete this however, this is optional. Participants will also be asked if they are happy for the study team to use data collected before the time of withdrawal.

5.3 RANDOMISATION

5.3.1 Randomisation Procedures

Participants will be allocated in 1:1 ratio to either HSNIG or standard care. The randomisation will be performed using a web-based system utilising a block randomisation with varying block sizes and will be stratified on the variables: age (<50, 50-<70, ≥70) and gender (male, female).

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

Study timepoints	Screening	Baseline	Days 1-13	Day 14
Self-screening	X			
Informed Consent		X		
Eligibility Criteria		X		
Randomisation/Treatment Allocation		X		
Baseline CRF		X		
Intervention arm – HSNIG up to 12 times daily			X	
Daily diary			X	
Adverse Events			X	X
End of illness diary			X	X
Day 14 Questionnaire (if symptoms resolve before Day 14)				X

All participants

Online Daily Diary: Participants in both intervention arm and control arm will complete an online daily diary which will be emailed directly to them first thing in the morning. The diaries will be maintained until the participant reports that they are well or a maximum of 14 days or if they withdraw or are hospitalised. If participants have not completed their online daily diary by approximately 11am, a reminder will automatically be generated by the REDCap database and sent to the participant's email address. Reminders will subsequently be sent approx. every 5 hours until the diary is completed. If the diary is not completed by the participant by the end of

the day, their link to that daily diary will expire. Participants will continue to receive daily emails with diary links until they either withdraw from the study, they report they are well, or they reach Day 14. If the diaries are not maintained regularly, a member of the trial team may contact the participant to remind them to document the diary. All data points in the daily diaries and the end of illness questionnaires will be made mandatory on the study database where possible, limiting the risk of missing data. In each daily diary and in the end of illness questionnaire, participants will be asked if they have been tested for COVID-19 and if so, what the result of this test is. Therefore, data regarding COVID-19 testing can be captured if a participant is tested or the results are not returned until after they have consented to participate and completed the initial testing question. There will be a number of participants who are not tested for their illness. The study team have taken a pragmatic approach in addressing this and therefore participants who deem themselves eligible for the study can take part'

All participants will be advised to continue with UK Government advised personal and household hygiene as recommended by:

https://www.nhs.uk/conditions/coronavirus-covid-19/self-isolation-advice/

All participants will be asked within their daily diary if they think their condition or symptoms have worsened significantly. If they answer yes this will prompt an email to the study clinicians advising that a participant has reported a worsening of symptoms. If deemed clinically necessary, the study clinician will then contact the participant via email or phone to discuss their condition or symptoms further and advise an appropriate course of action. This might involve contacting their GP or other clinical care, stopping the study intervention or withdrawing from the study.

Intervention (HSNIG) Group Only

Participants will have access to an online video on how to prepare the hypertonic saline solution and perform nasal irrigation and gargling. Participants will be asked to make use of bowls/cups/containers and equipment available in their own house. They can either make the solution fresh every time or make it in bulk and use it for up to 24 hours. Participants will be asked to perform the nasal irrigation and gargling at home. The number of times the participant will need to perform the nasal washout and gargling will depend on the severity of their symptoms (maximum of 12 times/day). The participant could expect to perform the procedure 6-12 times a day in the first few days, and thereafter 3-12 times a day until or until day 14.

6.2 LONG TERM FOLLOW UP ASSESSMENTS

There are no long term follow up assessments after day 14 of COVID-19 symptoms developing. If a suitable antibody test becomes available in the next 6 months, we propose to contact those who have consented to provide further samples as part of the study.

7 DATA COLLECTION

Data will be collected directly from the participant on an online REDCap database. Participants will complete a baseline eligibility check prior to consent. Eligible participants will then be randomised then complete a daily diary which includes the Wisconsin Upper Respiratory Symptom Survey (WURSS-24) – Daily Symptom Report to analyse length and severity of symptoms. Participants will be asked to complete the End of Illness diary the first day they feel well or on day 14. Those who complete the end of illness diary before day 14 will be asked to answer a few questions on day 14 (day 14 questionnaire).

Participants will be sent a daily reminder and link to the diaries via email. If participants miss the completion of a daily diary, the trial team will contact them with an email reminder.

8 DATA MANAGEMENT

8.1 PERSONAL DATA

The following personal data will be collected as part of the research:

Name
Date of Birth
Sex
Address
Phone number
Email
GP Address

Personal Data will be entered by each participant onto the REDCap database using forms that have been generated and accessed by individualised links sent via email to participants. Electronic personal data will be stored securely on the REDCap database hosted on the University of Edinburgh server. Only certain members of the study team, including Data Management and Trial Management teams, can access the study database using individual logins. The Statistician will be given access to personal data where necessary for analysis and only as and when required.

The data will be stored in a secure server in the University of Edinburgh for at least the archiving period.

8.2 TRANSFER OF DATA

Data collected or generated by the study will be transferred securely via BREATHE (Health Data Research Hub for Respiratory Health) to be stored as an anonymised data set in the SAIL (Secure Anonymised Information Linkage) databank hosted on secure servers at the University of Swansea. SAIL is trusted data repository for BREATHE, a collaboration led by the University of Edinburgh.

All datasets held by SAIL are accessed using a secure remote desktop, after an application to view the dataset has been reviewed by the SAIL Information Governance Review Panel.

8.3 DATA CONTROLLER

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site)

8.4 DATA BREACHES

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

There are considerable uncertainties around the dynamics of the primary outcome (self-reported time to resolution using WURSS-24) in the context of COVID-19. There are as yet very little substantive data on time to recovery (despite, as at 27th March 2020, over 132,440 people globally defined as recovered from COVID-19 infection). However, we intend to set out our best assumptions based on what we know to date, and then re-estimate the required sample size when we have completed data on the first n=100 participants.

For 90% power and 5% level of significance, using a two-sided two-sample t-test, the study will require 170 participants in total to detect a difference in time to recovery of 2 days between intervention and control groups assuming a common standard deviation of 4 days. Since there is only 1 respondent per household (the index case) there is no adjustment for clustering required (i.e. ICC=0). If we assume there is 25% crossover from control to active (i.e. 1 in 4 of the control group work out how to use the intervention) the sample size increases to 304. We then allow that potentially 25% will fail to provide sufficient data for the primary outcome to be ascertained, leading to a final sample size (total) of 405. As indicated, this sample size will be re-estimated from blinded internal data (via the independent Trial Steering Committee) when the first n=100 have completed the study, and also from any updated relevant external data on the pathway for recovery in COVID-19.

9.2 PROPOSED ANALYSES

The study will be monitored in a flexible way using a Bayesian approach. Full details of the Bayesian monitoring and the final analysis will be pre-specified in a comprehensive Statistical Analysis Plan (SAP), authored by the study statistician, Dr Cat Graham, with the assistance of Professor John Norrie, Chair of Medical Statistics at The University of Edinburgh.

In summary we will perform an intention to treat analysis with a sensitivity analysis of the primary outcome using those considered to be compliant with the study protocol. The primary outcome of 'time to resolution of symptoms' will be defined by the single question 'how unwell do you feel today' will be presented descriptively by treatment with a comparison made between intervention and control using a two-sample t-test. The change over the study duration will also be presented graphically.

Time to resolution of individual symptoms will be analysed in the same way as the primary outcome.

The number of participants contacting healthcare, attending GPs, being hospitalised and using over the counter medications will be compared between groups using a binomial test for the comparison of proportions. Where participants are admitted to hospital comparison in the length of hospital stay will be made between groups using a Mann-Whitney test. Where over the counter medications have been used the comparison will be made between groups using a two-sample t-test.

Registration and reporting

The trial will be registered with ClinicalTrials.gov. The SAP will be published in advance of commencing any analysis. The trial will be reported using the CONSORT reporting guidelines for randomised controlled trials[18] together with the COVID-19 reporting guidelines, which are currently in development (Sinead Langan, personal communication, 29 March 2020). Trial meta-data will be deposited in the HDRUK Gateway and trial data will be made available through the BREATHE Hub, which sits on the ISO accredited SAIL Databank UK Secure Research Platform (SeRP).

10 ADVERSE EVENTS

A few individuals reported irritation of nose and throat in ELVIS study. Information on these adverse events will be gathered. There is a remote possibility that HSNIG could by itself increase transmission, which will be assessed once we have gathered data for the first 100 participants by analysing the data for increase in illness amongst household contacts.

Symptoms and side effects from the Daily Diary will be recorded in the CRF but will not be recorded as AEs/ARs on the AE log. Hospitalisation is a study outcome and is exempt from reporting to the Sponsor as an SAE.

11 OVERSIGHT ARRANGEMENTS

11.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and documentation.

11.2 PROJECT MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group (PMG), consisting of the Chief Investigator, Trial Managers, and Statistician.

The Trial Managers will oversee the study and will be accountable to the Chief Investigator.

The trial will be led by Professor Aziz Sheikh, an experienced clinical trialist and Director of the Usher Institute. Dr Sandeep Ramalingam, Consultant Virologist at the Royal Infirmary Edinburgh and affiliate of the Usher Institute at the University of Edinburgh will support the study as Co-Investigator. The trial statistician will be Dr Cat Graham, who will work under the oversight of Professor John Norrie, Director of the Edinburgh Clinical Trials Unit. The study will be supported by the Edinburgh Clinical Trials Unit (a fully registered UKCRC Clinical Trials Unit #15) for all its data management and web programming needs, and trial management.

A Delegation Log will be prepared, detailing the responsibilities of each member of staff working on the trial.

11.3 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct progress and safety of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details are detailed in CR015 DMC & TSC Charters.

11.4 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial.

11.5 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by

the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

12.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

12.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out and therefore eligibility is confirmed and consent is given online before participants enter any personal information. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants will receive adequate written information – appropriate Participant Information and Informed Consent Forms will be provided.

The participant will be given sufficient time to consider the information provided. The participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

As the consent for the study is done by the participant online, the study team will not sign the consent forms. Instead, PDF copies of the participants' consent forms will be stored securely on the REDCap database and a PDF of the participant consent will be made available to download or print for their files.

12.2.2 Confidentiality

All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study.. Prior written agreement from the sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

12.2.3 Data Protection

All Investigators and study staff involved with this study must comply with the requirements of GDPR with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities. Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

The website for the study will include a GDPR statement for the participant to review before consenting. Caldicott approval will be sought where necessary.

STUDY CONDUCT RESPONSIBILITIES

12.3 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

12.4 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this will be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. . An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

12.5 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

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

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

12.6 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.7 END OF STUDY

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the RECand co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

A summary report of the study will be provided to the REC within 1 year of the end of the study.

12.8 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

The ECTU Publication Policy will be followed. Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

13.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the European clinical trials database within 1 year of the end of the study.

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