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Study protocol of the Edinburgh and Lothian Virus Intervention Study in Kids: A randomised controlled trial of hypertonic saline nose drops in children with upper respiratory tract infections (ELVIS Kids)

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Abstract

Introduction: ELVIS Kids is a parallel, open-label, randomised controlled trial (RCT) of hypertonic saline (HS) nose drops (~2.6% sodium chloride; NaCl) vs. standard care in children <7 years of age with symptoms of an upper respiratory tract infection (URTI).

Methods and analysis: Children are recruited prior to URTI or within 48 hours of developing URTI symptoms by advertising in areas such as local schools/nurseries, health centres/hospitals, recreational facilities, public events, workplaces, local/social media. Willing parents/guardians, of children <7 years of age will be asked to contact the research team at their local site. Children will be randomised to either a control arm (standard symptomatic care), or intervention arm (3 drops/nostril of HS, at least 4 times a day, until 24 hours after asymptomatic or a maximum of 28 days). All participants are requested to provide a nasal swab at the start of the study (intervention arm: before HS drops) and then daily for 4 more days. Parent/guardian complete a validated daily symptom diary, an end of illness questionnaire, and a wheeze questionnaire (day 28). The parent/guardian of a child in the intervention arm is taught to prepare HS nose drops. Parent/guardian of children asymptomatic at recruitment are requested to inform the research team within 48 hours of their child developing an URTI and follow the instructions already provided. The day 28 questionnaire determines if the child experienced a wheeze following illness. Participation in the study ends on day 28.

Ethics and dissemination: The study has been approved by the West of Scotland Research Ethics Service (REC) (18/WS/0080). It is co-sponsored by Academic and Clinical Central Office for Research and Development (ACCORD) - a partnership between the University of Edinburgh and NHS Lothian Health Board. The findings will be disseminated through peer-reviewed publications, conference presentations and via the study website.

Trial registration number: Clinicaltrials.gov: NCT03463694

Strengths and limitations of this study

- Open label community-based randomised controlled study investigating the effectiveness of HS vs standard treatment in children under 7 years of age with a common cold
- Parents in the intervention arm are taught to safely make HS at home
- Nose swabs are collected to identify the virus(es) and to measure change in viral shedding
- A validated symptom score diary (CARIFS) is used as part of the daily diary
- There is no placebo arm

Introduction:

Viral upper respiratory tract infections (URTI) are very common in childhood resulting in a significant burden on the population and health services[1]. The annual incidence rate of URTI in childhood can vary between 6-12 episodes[2 3]. Children have a longer duration of illness (mean 1.8 weeks; standard deviation: 1.3 weeks) compared to adults[3 4]. In Scotland, URTI is the leading cause of general practitioner (GP) visits in children <5 years (n=84710, 574/1000 population) and the fourth most common cause of consultation in children aged 5-14 (n=33790, 116.5/1000 population)[5]. In secondary care, in 2015-16, 13.3% (n=16,644) and 19.7% (14,600) of all admissions/emergency admissions respectively in children were due to upper/lower respiratory tract infections[6]. 12-14% of children who develop an URTI will go on to develop lower respiratory tract disease (viral induced wheeze: 80/1000[7], bronchiolitis: 46/1000[8], and pneumonia: 0.27 episodes/child year[9]). Hence interventions that reduce URTI severity may considerably benefit patients/carers and reduce pressure on the NHS. Since >200 viruses[10] can cause an URTI, individually targeted antiviral therapy is impractical and measures that work against all viruses are required.

New data suggest that hypertonic saline (HS) may be able to suppress viral replication, regardless of viral type and hence be a potential respiratory antiviral agent with clinical application. Saline irrigation is commonly used in clinical practice, mostly to deliver a mucolytic effect. However, we have recently identified that human epithelial (cervical-HeLa, respiratory-A549) cells utilise NaCl to mount a broad-spectrum antiviral effect against representative DNA, RNA enveloped and non-enveloped viruses[11]. The antiviral effect is dependent on the entry of chloride ions into the cell and the production of intracellular hypochlorous acid (HOCl)[11]. HOCl is the active ingredient of bleach, which can inactivate most viruses[12-15]. A polymorphism causing reduction in HOCl production has been reported in individuals with cervical cancer[16]. 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[17]. Increased HOCl production is reported within gut epithelial cell of fruit flies after bacterial lysate ingestion[18]. These data suggest an anti-infective role of HOCl and its precursor NaCl in epithelial cells.

In addition, it has recently been shown that accumulation of Na^+ ions in human skin helps fight bacterial/parasitic infections[19 20]. A high salt diet increased Na^+ in skin leading to a hypertonic environment, increased Nitric Oxide (NO) production in macrophages and thereby pathogen removal[19 20]. Whilst our laboratory data point to the importance of Cl^- in combating viral infections, Jantsch et al have shown the importance of Na^+ in fighting bacterial infections. Taken together, these data suggest that innate immunity may be dependent on NaCl in epithelial cells helping to clear bacterial and viral infection.

Nebulised HS has been used to treat bronchiolitis; an acute viral infection of young children caused by a variety of respiratory viruses. Meta-analyses of current trials suggest a possible reduction in length of hospital stay[21 22], but the association is weak and there have been concerns about the replicability of this finding[23-27] potentially as HS has been given at the peak of disease when viral load is maximum and lower respiratory tract disease (with potential

dysregulated immune response) is established. More positive signals have been demonstrated when HS has been administered in accident and emergency department contexts to reduce hospital admission rates: data remain conflicting and a systematic review has been started to analyse data as they emerge [26-28].

The role of saline (isotonic or hypertonic) in children with viral URTI has been explored in two published studies. In children aged 6-10 years administered isotonic saline as a spray (6 times/day) there was a significant reduction in reported sore throat, nasal secretions, and use of nasal decongestants/mucolytic (vs. standard care, no placebo)[29]. In children <2 years treated with saline/sea water drops (thrice a day for 5 days) there was a significant reduction in URTI symptoms reported when compared to untreated children[30]. However, a Cochrane review concluded that no definitive conclusions could be drawn as the available studies were small and had major methodological limitations: baseline symptom score was calculated over 7 days (not at the point of entry) and groups had different characteristics at baseline[31].

We recently completed the Edinburgh and Lothians' Viral Intervention Study (ELVIS), an open label pilot randomised controlled trial (RCT) of hypertonic saline nasal irrigation and gargling (HSNIG) in 66 adults with an URTI (www.elvisstudy.com)[4]. Most participants were infected with rhinoviruses/coronaviruses. 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 reduced at a faster rate of ≥0.5 $\log_{10}$/day in those receiving HSNIG (p=0.04) [4]. The reduction in viral shedding and transmission within household were supportive of our laboratory data and consistent with a direct cellular antiviral action by NaCl.

Given the laboratory evidence supported by our demonstration of clinical benefits in adults an RCT in children with URTI to study the effects of HS on duration of illness and viral shedding is now needed. No suitable placebo is available: Sodium bicarbonate and plain water cause discomfort when administered to nasal mucosa and normal saline, a commonly used, safe, placebo contains NaCl and so may not act as a placebo. For these reasons, the study will not be placebo controlled.

Methods and analysis:

Study objectives

Primary objective:

To investigate whether the use of parent/guardian-initiated HS nose drops administered to children with symptoms consistent with acute viral URTI reduces the duration of symptoms when compared to children managed using standard care.

Secondary objectives:

To determine the effect of HS nose drops on:

1. Severity of all symptoms

2. Duration and severity of individual symptoms
3. Contact with NHS 24, out of hours primary care (OOH), and primary care (GP)
4. Hospital attendance (i.e. A&E attendance and/or hospital admission) and diagnosis
5. Reduction in wheeze
6. Over the counter medication use
7. Duration, reduction or rate of reduction in viral shedding
8. Transmission within the household
9. Side effects associated with the use of saline nose drops
10. Adverse events associated with the use of saline nose drops
11. Time off from school/nursery for child and workdays lost for parent/guardian
12. Cost associated with illness (over the counter medication costs and NHS costs)

Study design and sample size:

ELVIS Kids is a parallel, open label, RCT of HS nose drops (~2.6% NaCl) vs. standard care in children <7 years of age with symptoms of an URTI. The aim is to recruit a total of 480 children (240/arm).

The study will run over ~42 months at participating sites in Scotland (sites are as listed on clinicaltrials.gov). Children are recruited prior to, or within 48 hours of developing URTI symptoms by advertising in areas such as local schools, nurseries, health centres, hospitals, recreational facilities,workplaces public events and the community as well as local and social media. For the purposes of this study an URTI is defined as: at least two respiratory symptoms (nasal congestion, runny nose, cough, sore throat) OR one respiratory symptoms and at least one systemic symptom (low energy/tired, muscle aches/pains, headache, fever ≥38°C). Willing parents/guardians, will be directed by the study advertising to contact the research team at their local site) if they are interested in participating.

Children will be randomised to either a control arm of standard symptomatic care, or an intervention arm of 3 drops each nostril of HS at least 4 times a day and up to a maximum of 12 times a day until asymptomatic or maximum of 28 days. All parents/guardians will be requested to obtain a mid-turbinate nasal swab from the participant first thing in the morning (before nose drops in the intervention arm) for five for 5 consecutive days (unless the child is well before then), a daily symptom diary (a global severity question, CARIFS[32], a validated illness measure in the UK, side effects and compliance with trial procedures) until they report the child as “not unwell”, an end of illness questionnaire (infection in household contacts, ease of use and acceptability of intervention, medication and healthcare use, acceptability, time taken off usual activities, wheezing and whistling in the chest), a satisfaction questionnaire and adverse events. Parents/guardians of the children allocated to the intervention arm will be taught how to prepare the HS (including sterilization instructions for children under a year). Parents/guardians of children who are asymptomatic at recruitment are requested to inform their local research team

when the child develops an URTI (within 48 hours) and follow the instructions already provided to them. On day 28, parents/guardians will be contacted to determine if their child suffered from wheezing or whistling in the chest either during the illness or at any point until day 28. Participation in the study will end on day 28.

Eligibility and consent:

Pre-screening for eligibility to participate will be completed by a member of the research team at the clinical trials unit when parents/guardians phone to express interest in the study. If parents/guardians attend an appointment and take part in the study, the study number will be recorded on the screening log and details of eligibility will be recorded in the study database.

Inclusion criteria:

1. Children between corrected gestational age of ≥40 weeks and <7 years of age
2. Children without URTI OR ≤48 hours of URTI* starting.

*A URTI being defined as at least two respiratory symptoms (nasal congestion (i.e. stuffy nose), runny nose, cough, sore throat) OR one respiratory symptom + at least one systemic symptom (Low energy/tired, muscle aches/pains, headache, fever 38°C).

Exclusion criteria:

1. Children needing immediate medical attention
2. Children using saline drops/sprays at the time of randomisation
3. Children on immunosuppressive medication, regular oral/inhaled steroids, regular antibiotics (use of antibiotics is allowed as long as the child does not need regular antibiotics)
4. Children with a known chronic illness (e.g. cystic fibrosis, cardiac, renal, liver, lung, neurological conditions) apart from wheeze or asthma which are not exclusions if the child is otherwise well and not on regular steroids)
5. Children being followed up for developmental delay
6. Children receiving the nasal flu vaccine ≤14 days ago
7. Children taking part in another interventional trial
8. If parents/guardians indicating that they are unable to comply with the study protocol prior to randomisation
9. If parents/guardians are unable to understand written or spoken English
10. Children randomised to ELVIS KIDS on a previous episode of URTI
11. Children with a concurrently participating sibling

All ineligible and non-recruited participants will be recorded on the ELVIS Kids screening log with a reason given.

Obtaining consent:

Only trained and delegated members of the trial team will take consent – this will usually be the research nurse. The participant information sheet (PIS), which will explain the aims of the study and the potential risks and benefits of the study treatment, are provided to parents/guardians when they meet the research team (also available online). A children's PIS will be available to discuss with older children attending the appointment with the option of giving their assent. (Supplement)

If the parent/guardian wishes to participate in the study, then they will be asked to sign the Informed Consent Form (ICF) (Supplement). Both the parent/guardian and the person delegated to take consent will sign and personally date the ICF. The original signed ICF must be kept by the Investigator in the investigator site file, 1 copy is provided to the parent/guardian, 1 copy is placed in TRAK. The same would apply in the case of assent being given.

Randomisation and treatment allocation:

A member of the research team from the clinical research facility will perform the randomisation using a web-based randomisation service managed by the Edinburgh Clinical Trials Unit (ECTU). Children will be allocated to receive either HS nose drops or standard care in a 1:1 ratio using minimisation based on age (0-2, >2 year) and sex and allocated to receive the treatment which minimises the imbalance with a probability 0.8. The study is not blinded apart from those carrying out lab assessments of nasal swabs.

Sea salt will be provided by Cornish Sea Salt company in 225g pots. They will be supplied to local pharmacies where they will be labelled and stored. A working stock will be issued to the research team. If a child is allocated to an intervention arm, the parent/guardian will be given instructions on the preparation and use of HS nose drops using instructional video, verbal and written information. Parents/guardians will be asked to add 1 level measure of sea salt to a fixed volume of freshly boiled water using the measuring spoon and clean glass jar provided. This provides a NaCl concentration of ~2.6% and the drops can be used once cooled. Two glass jars are provided so that the parent / guardian could use one and have a clean spare to prepare solution the next day. Two dropper bottles are provided with which nose drops can be applied (one in use, and a clean spare).

Withdrawal of study participants:

Parents/guardians are free to withdraw their child from the study at any point. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if given. All data and swabs collected before withdrawal will be retained for analysis in cases where participants withdraw.

Study assessments:

The protocol is designed in accordance with the standard protocol items: recommendations for interventional trials (SPIRIT). The trial overview of the study assessments is available as a SPIRIT figure (Table 1). At the appointment, a member of the research team will train the parent/guardian how to identify a URTI, how to measure temperature, how to complete the diaries and how to collect and return the mid-turbinate swabs. In addition, those in the intervention arm will be given instructions on how to prepare and apply nose drops. Baseline information on the child, contact details of parent / guardian and number of household members at the time of recruitment will be collected in the electronic case report form (eCRF). If recruited when symptomatic, parents will be instructed to start the study assessments the same day. If recruited when asymptomatic, and there are no changes to the child's medical information, parent/guardians will be asked to start the study assessments and to inform the study team the same day if possible or at least within 2 days of onset of illness. If recruited when asymptomatic, and there are changes to the child's medical information, parent/guardians will be asked to contact the study team to ensure the child still meets the eligibility criteria before starting the study procedures. If it is not suitable for the child to take part during this URTI (e.g. received the flu vaccine in the past 2 weeks) they will remain on study and be asked to contact the team at the onset of the next URTI.

Parents/guardians are requested to collect a nasal (mid-turbinate) swab as soon as possible on day 1 and first thing in the morning (and prior to HS nose drops being applied) on days 2-5 if children remain unwell. These samples are to be packed in the transport box provided, stored in the fridge and returned in the pre-paid envelope or as soon as possible after completing collection. If samples are not received by day 10, a reminder will be sent to the parent/guardian.

Parents/guardians will complete a daily diary (Supplement) which records any symptoms the child is experiencing, compliance to nasal swabs and HS drops, any side effects and use of healthcare services. Parents will be taught how to measure temperature with TempaDot. Parents are advised to measure the temperature only if they think the child has a fever. If the child has an axillary temperature of ≥38°C, it should be recorded as a fever in the daily diary. The diaries will be provided as an online form (unless parents cannot access this in which case a paper copy can be provided). If the online Daily Diary is not completed a reminder will be sent.

An end of Illness diary (Supplement) and satisfaction questionnaire (Supplement) will be completed by the parent/guardian once the child is asymptomatic for >24hours or after a maximum of 28 days. On day 28, the parent/guardian will be contacted by email and sent a text message to ask if their child has experienced any wheeze since the end of illness diary was completed (Supplement).

Participants will be sent a £30 voucher by email as compensation for any inconvenience once they have returned the study data.

Analysis and storage of samples:

Up to five nasal swabs will be collected and posted to the Department of Laboratory Medicine, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4SA, where they will be stored and processed. Day 1 samples will be analysed by the respiratory panel and the cycle threshold (CT) of positive samples recorded. If the day one sample is missing, the first available sample will be tested to identify the virus. If an agent is identified, all samples (days 1-5) will be tested in parallel to estimate change in viral shedding and the CT recorded. If a sample is positive on day 1 and negative on subsequent days, they may be tested for human DNA to confirm a sample was collected. Log conversion of each positive result will be done using the following formula: (40-CT of specimen)/3.3 to estimate change in shedding. All nucleic acid extracts and remaining original samples will be stored in the Lothian NHS research Scotland BioResource biobank (REC reference 15/ES/0094) in future ethically approved studies.

Outcomes / endpoints:

Primary endpoint:

Duration of illness (measured as the number of days until the parent reports the child to be well)

Secondary endpoints:

1. Severity of all symptoms as measured by CARIFS
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 and diagnosis (Number of participants and frequency of contacts)
7. Length of stay in hospital if admitted
8. Number of participants reporting wheeze during illness and between end of illness to 28 days.
9. Number of participants reporting over the counter medication use
10. Duration of viral shedding
11. Reduction in viral shedding
12. Rate of reduction in viral shedding
13. Reduction in transmission to household contacts
14. Number of participants reporting side effects associated with nasal drops
15. Number of participants reporting adverse events associated with nasal drops
16. Types and severity of side effects/adverse events reported
17. Number of days lost from school/nursery for child
18. Number of days lost from work for parent/guardian
19. Cost of over the counter medication used

20. NHS costs associated with illness

Participant timeline:

The participant pathways can be seen in figures 1 and 2. Participants will be active in the study for 28 days. There are no long term follow up assessments after day 28 of URTI developing.

Data collection:

Baseline data will be collected on the baseline electronic CRF (eCRF) by a member of the research team. Parents/guardians will record study data onto either an online form which will be saved into the eCRF. A paper CRF (pCRF) option is available if a parent/guardian prefers it. pCRF will be returned to the local research team and transcribed by a member of the research team into the database and cross-checked by another.

Virological results are downloaded (identifiable by study number) on a weekly basis on to a specific drive by the Laboratory Information Management & Technology team. These will be emailed to the ECTU on a monthly basis and uploaded into the study database.

The trial database will be created and maintained by ECTU. Trained and delegated members of the research team will be given password-protected logins to the database to complete data entry. Data completed online by parents/guardians will be transmitted into the study database. The data will be stored in a secure server in the University of Edinburgh for at least the archiving period.

Adverse events:

Symptoms and side effects from the Daily Diary will be recorded in the CRF but will not be recorded as an adverse event (AE) or adverse reaction. Hospitalisation is a study outcome and is exempt from reporting to the Sponsor as a serious adverse event.
Any other adverse events identified between Day 1 and Day 28 of the study will be recorded. Any events reaching seriousness criteria will be reported to the sponsor within 24 hours.

Sample size calculation and statistical analysis:

Sample size calculation is based on mean (SD) duration of illness values in a control population from Gruber et al of 13 (9) days. To detect a 20% difference in mean duration, i.e. 3 days, using a two-sided, two-sample test with 5% level of significance, 90% power and common standard deviation of 9 days we will need a sample of 191 per treatment arm, without drop-outs. Hence, we will recruit 240 participants per arm to allow for up to 20% drop-outs.

Statistical analysis will be conducted according to, and full of the details will be specified in, the pre-specified Statistical Analysis Plan (SAP). Differences in illness duration between treatment arms will be compared using a two-sample t-test or non-parametric equivalent, as appropriate. This method will also be employed to examine differences between treatment arms for other continuous outcome measures such as average symptom score, viral shedding between treatment arms. For binary categorical data, for example the proportion of participants per arm

attending their GP, attending hospital, etc we will compare the treatment arms using a binomial test for the comparison of proportions. Where we have categorical data with more than 2 categories a Chi-squared test will be used to examine the relationships between treatment arms. If the number of cases of individual viruses are sufficient, the above analysis will be repeated by virus type.

Oversight arrangements:

The study is co-sponsored by ACCORD, a partnership between the University of Edinburgh and NHS Lothian Health Board based at QMRI, 47 Little France Crescent, Edinburgh Email: enquiries@accord.scot. The trial will be coordinated by a Project Management Group (PMG), consisting of the Chief Investigator, Co-investigators, Trial Manager, Statistician and Coordinating Nurse. The Trial Manager will oversee the study and will be accountable to the Chief Investigator. ECTU is responsible for trial management and oversight of data collection. The Edinburgh Clinical Research Facility are responsible for the statistical analysis. A Delegation Log will be prepared, detailing the responsibilities of each member of staff working on the trial. A Trial Steering Committee (TSC) has been established to oversee the conduct progress. As there will be no Data Monitoring Committee for this project, the TSC will review safety information as part of their remit.

Ethics and dissemination:

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP). The study has been approved by the West of Scotland Research Ethics Service (reference: 18/WS/0080) and registered on Clinicaltrials.gov (NCT03463694). 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, will be reviewed and approved by the Chief Investigator. Amendments will be submitted to the sponsor 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. The findings will be disseminated through peer-reviewed publications, conference presentations and on the study website.

Confidentiality:

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant's parent/guardian. The Investigator and study site 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, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

All Investigators and study site staff involved with this study must comply with the requirements of General Data Protection Regulations 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.

Patient and Public involvement (PPI): Feedback was obtained from PPI representatives on the study protocol, information sheets, diaries and consent forms and necessary modifications made prior to starting the study. A PPI representative is also invited to attend the trial steering committee meetings.

Access to data:

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.

Trial status:

This paper describes study protocol version V4 (06/01/2020). The trial opened on 02 November 2018. The first participant was recruited on 6th November 2018. The planned study end date is 30 November 2021. At the time of submission, study recruitment was suspended due to the COVID-19 pandemic.

Discussion:

The study is based on the recently discovered evidence that epithelial cells have an innate antiviral effect [11]. This effect can be augmented by supplying the cells with chloride ion through NaCl. Saline, commonly used as a placebo cannot be used in that role here as it contains NaCl – the substrate being tested. We are hence measuring viral shedding as an independent measure of any antiviral effect. The results from this trial will help determine if a simple and low-cost intervention could help reduce the duration of symptoms of URTI in children. Changes to the duration of individual symptoms, wheeze, transmission within the household, over-the-counter medication use, need for further treatment, days lost and cost of illness are all secondary outcomes.

Conclusion:

Since numerous viruses can cause URTI and in the absence of an antiviral agent/vaccine against the vast majority of viruses, if successful, this low cost and easily accessible intervention can easily be rolled out globally.

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Authors' contributions:

Sandeep Ramalingam – Planned the study and wrote the protocol

Catriona Graham – Planned the study, revised protocol and approved the final manuscript.

Katherine Oatey – Revised protocol, obtained approvals and approved the final manuscript.

Phillip Rayson – Revised protocol, obtained approvals and approved the final manuscript.

Andrew Stoddart – Revised protocol and approved the final manuscript.

Aziz Sheikh – Planned the study and revised protocol and approved the final manuscript.

Steve Cunningham - Planned the study and revised protocol and approved the final manuscript.

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Usher Institute: Aziz Sheikh

Edinburgh Clinical Research Facility: Emily Evans, Catriona Graham

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Competing interests statement: No conflicts of interest to declare

Table 1:

Study timepoints	Pre- Screen ing	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 5-8	Days 5-28 (as applicable)	Day 28
Pre-Screening	X									
Informed Consent		X								
Eligibility Criteria		X								
Eligibility review if change in health information			X							
Randomisation/Treatment Allocation		X								
Baseline Case Report Form		X								
Nose Swab collection (if child remains unwell)			X	X	X	X	X			
Nose Swab return								X		
Intervention arm - HS Drops			X	X	X	X	X		X	
Daily diary			X	X	X	X	X		X	
Adverse Events			X	X	X	X	X		X	
End of illness diary				◄	—	—	—	—	—	►
Satisfaction questionnaire				◄	—	—	—	—	—	►
Return of diaries									X	
Day 28 Wheeze question										X

Figure 1: ELVIS Kids Patient Pathway when the child has a URTI at recruitment

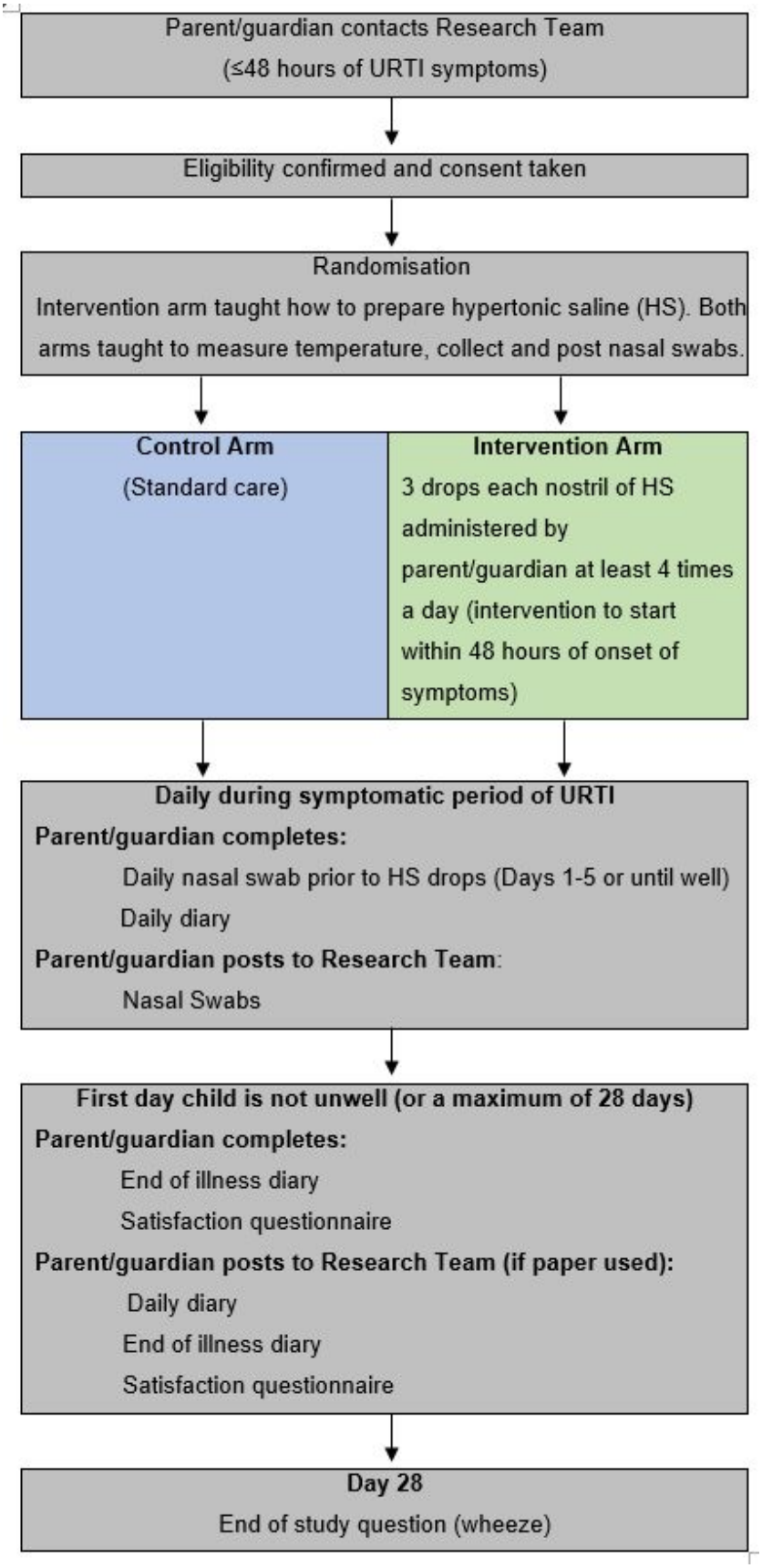
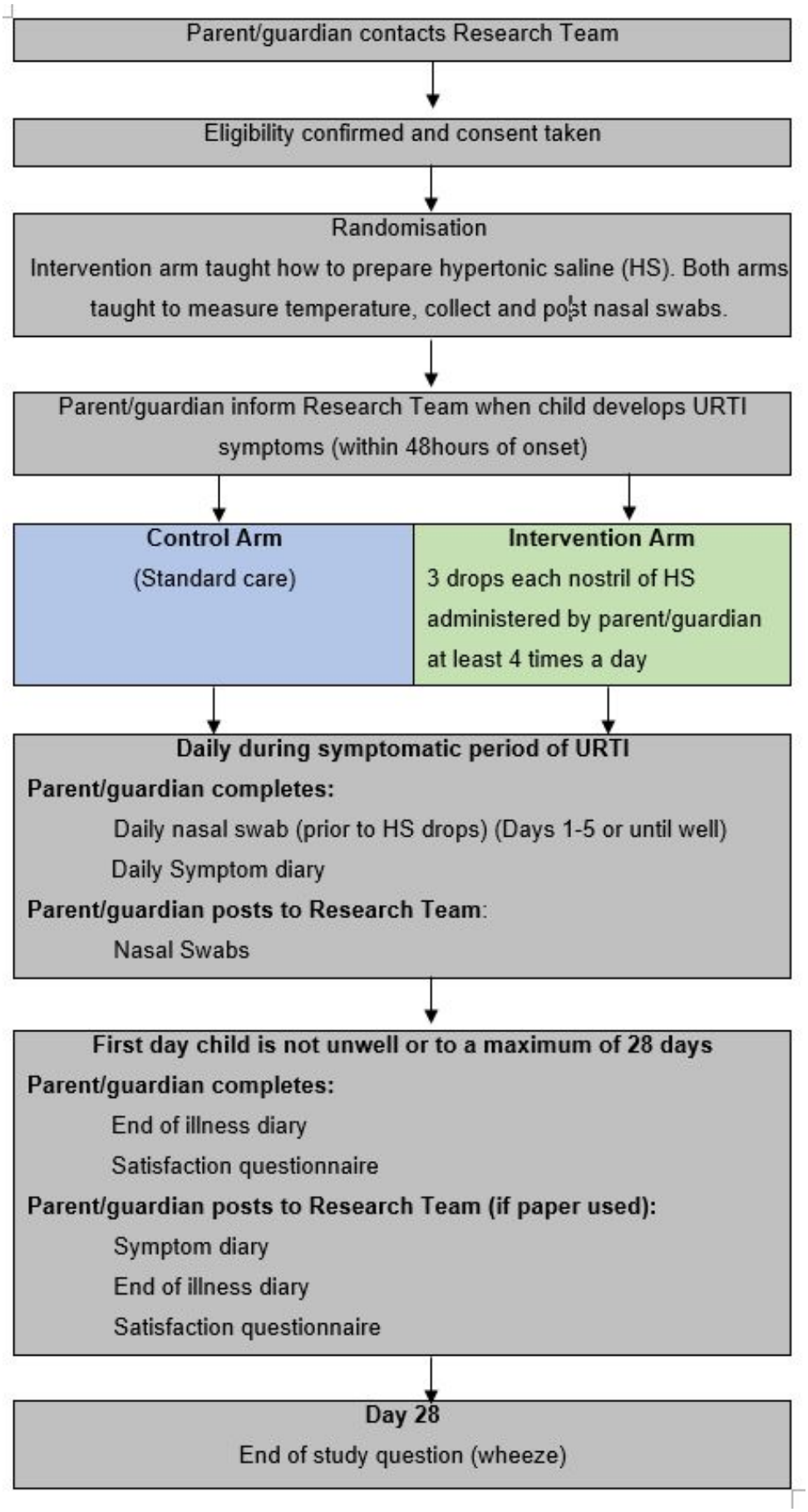


Figure 2: ELVIS Kids Patient Pathway when the child does not have a URTI at recruitment



<INSERT TRUST LOGO>

ELVIS Kids: Information Sheet for children

Hello, this is ELVIS. He has a Cold!

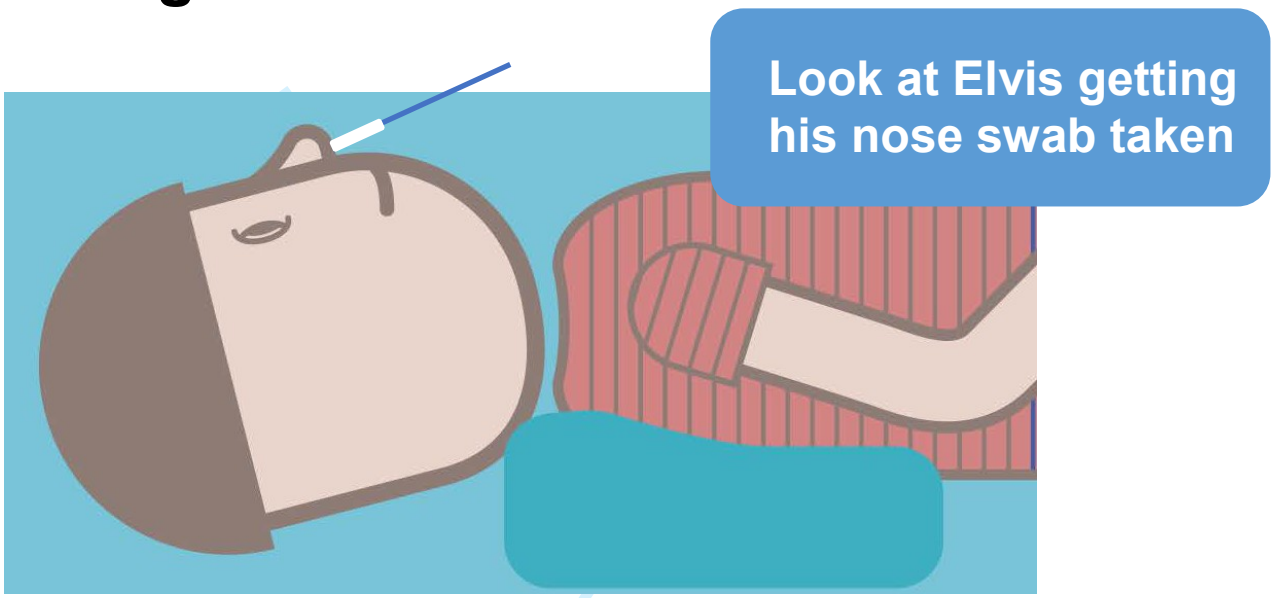
Elvis does not like a cold.

It makes him cough, his nose runs, and he is too tired to play.

He wishes there was a cure for the cold!

So, Elvis goes to meet the nurse in the hospital to take part in a study.

The nurse tells Elvis that he will need to take a swab from his nose for a few days. This is like a cotton bud wiping the inside of his nose. This won't hurt but might tickle a bit!



The nurse tells Elvis that he may be in the group of children that need nose drops for their cold until they are well.

If he is, he will lie down and a few drops of water will be put up his nose by a grown up in his family. This might be tickly or make him want to blow his nose. He will do this every day until his cold gets better.

Look at Elvis's Mum putting in his nose drops. He is good at lying still!

Not all the children helping with the study will use nose drops. The nurse will look at their computer to see which children will get them.

The nurse tells Elvis that he doesn't have to take part if he doesn't want to and he can change his mind later if he wants. He just needs to tell a grown up.

The nurse thanks Elvis for his interest in the study.

Do you want to be like Elvis and help the nurse too?

What is your name: _____

Colour in this picture of Elvis's Teddy who is visiting the nurse too:

<INSERT TRUST LOGO>

ELVIS Kids: Assent Form for children

Child to tick all they agree with:

Participant Number:	
Do you understand what this study is about?	Yes ☐ No ☐
Have you asked all the questions you want?	Yes ☐ No ☐
Have you had your questions answered in a way you understand?	Yes ☐ No ☐
Are you happy to take part?	Yes ☐ No ☐

If any answers are 'no' or you don't want to take part, don't sign your name!

If you do want to take part, you can write your name below:

Your name_____

Date_____

The nurse who explained this project to you needs to sign too:

Print Name_____

Sign_____

Date_____

Thank you for your help!

<INSERT TRUST LOGO>

Participant Number: _____

CONSENT FORM: ELVIS Kids		Please **initial** box
1.	I confirm that I have read and understand the information sheet (Dated: _____ and Version Number_____) for the above study. I have had the opportunity to consider the information, ask questions and have had these questions answered satisfactorily.	☐
2.	I understand that my participation and my child's participation is voluntary and that I am free to withdraw at any time without giving any reason and without my child's medical care and/or legal rights being affected.	☐
3.	I give permission for the study team to access my child's medical records if needed, to collect data on visits to hospital, and treatment received and to check whether they are suitable to take part in the study.	☐
4.	I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by individuals in the study team, from the Sponsor (University of Edinburgh and/or NHS Lothian), from NHS <INSERT TRUST NAME> or other regulatory authorities where it is relevant to my child taking part in this study. I give permission for these individuals to have access to my child's data and/or medical records.	☐
5.	I give permission for my personal information and my child's personal information (including my child's date of birth, and my telephone number and email address) to be passed to the University of Edinburgh for administration of the study.	☐
6.	I understand that the nose swabs collected from my child will be tested to see which bacteria or viruses have caused my child's cold.	☐
7.	I understand that the nose swabs collected from my child may be tested for human DNA to check the samples have been taken correctly.	☐
8.	I agree to my child's anonymised data and nose swabs being kept for use in future ethically approved studies and I understand the samples will be held securely in the Lothian NRS BioResource.	Yes ☐ No ☐
9.	I understand that as part of future ethically approved studies the samples may be tested for human DNA to identify why some children get more infections or why some children have mild and others have severe illness and consent to it.	Yes ☐ No ☐
10.	I agree to my child's General Practitioner being informed of their participation in the study.	☐
11.	I give permission for the trial researchers to contact me by email, phone and text message during the study.	☐
12.	I agree that my child will take part in the above study.	☐

Name of Person Giving Consent		Date		Signature
Name of Person Receiving Consent		Date		Signature

1x original – into Site File; 1x copy – to Participant; 1x copy – into medical record

ELVIS Kids Daily Diary (Intervention Arm)

Thanks for your help with ELVIS Kids!

Participant ID: ☐☐☐☐☐

Does my child have a cold?

Your child should have at least two of the cold symptoms listed **OR** one cold symptom and one symptom affecting the whole body to start the study. Please record the symptoms your child has for this cold below.

Cold Symptoms			Whole body Symptoms			
Stuffy nose	O Yes	O No	Fever (≥ 38°C)	O Yes	O No	
Runny nose	O Yes	O No	Low energy/tired	O Yes	O No	
Cough	O Yes	O No	Muscle aches/pains	O Yes	O No	O Don't Know
Sore throat	O Yes	O No	Sore head	O Yes	O No	O Don't Know

When did the illness start?

(Please do not start the study if the cold started more than 48 hours ago)

Date Started: *(DD-MMM-YYYY)* ☐☐-☐☐☐-☐☐☐☐ **Time Started:** *(24 hour clock)* ☐☐:☐☐

If your child's medical details have changed since you first saw the study nurses, please contact the study nurses on STUDY NUMBER before starting the study

Did your child receive the nasal flu vaccine within the last 4 weeks?

O Yes, my child received the nasal flu vaccine O No my child has not received the nasal flu vaccine

If you answered YES, please contact the study nurses on STUDY NUMBER before starting the study

Date Flu Vaccine Received: *(DD-MMM-YYYY)* ☐☐-☐☐☐-☐☐☐☐

ELVIS kids

Participant ID: ☐☐☐☐☐

Daily Diary: Day 1

Date: ☐☐-☐☐☐-☐☐☐☐ **Time** *(24 hour clock)*: ☐☐:☐☐

Select one option	**Not unwell** 0		**Very mildly** 1	2	**Mildly** 3	**Moderately** 4	5	**Severely** 6	7
How unwell is your child today?									

If you ticked 'Not unwell', please skip the next section and go to the 'Other Questions' section

Are these symptoms a problem for your child today? Tick the most appropriate box for each question:

Symptom	No Problem	Minor Problem	Moderate Problem	Major Problem	Don't Know or N/A
Poor appetite					
Not sleeping well					
Irritable, cranky, fussy					
Feels unwell					
Low energy, tired					
Not playing well					
Crying more than usual					
Needing extra care					
Clinginess					
Headache					
Sore throat					
Muscle aches or pains					
Fever					
Cough					
Nasal congestion, runny nose					
Vomiting					
Not interested in what's going on					
Unable to get out of bed					

Other Questions:

How many times did you give the drops in the last day (24 hours)? ☐☐

Were there any side effects? O Yes O No

If yes, please indicate the severity of symptoms by ticking the following where 0 is none and 5 is the worst it can be.

Symptom	None 0		**Score** 1	2	3	4	Max 5
Runny nose							
Sneezing							
Pain / Sore							
Other symptom 1: _____							
Other symptom 2: _____							
Other symptom 3: _____							

Was a nose swab collected this morning? O Yes O No

If no, what was the reason? O I forgot O My child refused O I had problems doing it
O Other: _____

ELVIS Kids Daily Diary (Control Arm)

Thanks for your help with ELVIS Kids!

Participant ID: ☐☐☐☐☐

Does my child have a cold?

Your child should have at least two of the cold symptoms listed **OR** one cold symptom and one symptom affecting the whole body to start the study. Please record the symptoms your child has for this cold below.

Cold Symptoms			Whole body Symptoms			
Stuffy nose	O Yes	O No	Fever (≥ 38°C)	O Yes	O No	
Runny nose	O Yes	O No	Low energy/tired	O Yes	O No	
Cough	O Yes	O No	Muscle aches/pains	O Yes	O No	O Don't Know
Sore throat	O Yes	O No	Sore head	O Yes	O No	O Don't Know

When did the illness start?

(Please do not start the study if the cold started more than 48 hours ago)

Date Started: *(DD-MMM-YYYY)* ☐☐-☐☐☐-☐☐☐☐ **Time Started:** *(24 hour clock)* ☐☐:☐☐

If your child's medical details have changed since you first saw the study nurses, please contact the study nurses on STUDY NUMBER before starting the study

Did your child receive the nasal flu vaccine within the last 4 weeks?

O Yes, my child received the nasal flu vaccine O No my child has not received the nasal flu vaccine

If you answered YES, please contact the study nurses on STUDY NUMBER before starting the study

Date Flu Vaccine Received: *(DD-MMM-YYYY)* ☐☐-☐☐☐-☐☐☐☐

Participant ID: ☐☐☐☐☐

Daily Diary: Day 1

Date: ☐☐-☐☐☐-☐☐☐☐ **Time** *(24 hour clock)*: ☐☐:☐☐

Select one option	Not unwell 0	Very mildly 1	2	Mildly 3	Moderately 4	5	Severely 6	7
How unwell is your child today?								

If you ticked 'Not unwell', please skip the next section and go to the 'Other Questions' section

Are these symptoms a problem for your child today? Tick the most appropriate box for each question:

Symptom	No Problem	Minor Problem	Moderate Problem	Major Problem	Don't Know or N/A
Poor appetite					
Not sleeping well					
Irritable, cranky, fussy					
Feels unwell					
Low energy, tired					
Not playing well					
Crying more than usual					
Needing extra care					
Clinginess					
Headache					
Sore throat					
Muscle aches or pains					
Fever					
Cough					
Nasal congestion, runny nose					
Vomiting					
Not interested in what's going on					
Unable to get out of bed					

Other Questions:

Was a nose swab collected this morning?	O Yes O No
If no, what was the reason?	O I forgot O My child refused O I had problems doing it O Other: _____

Participant ID: ☐☐☐☐☐

End of Illness Diary *(Intervention Arm)*

END OF ILLNESS DETAILS

Please complete this on the first day your child is well after their cold or after 28 days if your child remains unwell

Date Diary Completed: ☐☐-☐☐☐-☐☐☐☐
(DD-MMM-YYYY)

How many adults and children live in the house (including your child who's taking part in ELVIS Kids)?

Adults ☐☐ Children ☐☐

Did anybody at home develop the cold after your child?

O Yes O No

If yes, how many were adults?

☐☐

If yes, how many were children?

☐☐

How easy was it to apply the nose drops

Very Easy	Easy	Moderate	Difficult	Very Difficult	Did Not

What was your preferred option?

O Cradle child in arms O Lay child on bed O Other: _____

Do you think applying nose drops made a difference to your child's symptoms?

O Yes O No

Would you do it again if your child had a cold in the future?

O Yes O No

If no, what is the reason? (tick all that apply)

No improvement O Yes O No

Too difficult O Yes O No

Child did not like it O Yes O No

There were side effects O Yes O No

Other O Yes O No Other:_____

Participant ID: ☐☐☐☐☐

End of Illness Diary *(Intervention Arm)*

END OF ILLNESS DETAILS *(continued)*

Did your child take over-the-counter medication for their cold?

O Yes O No

If yes, approximately how much did you spend?

£ ☐☐.☐☐

Did you seek further medical attention related to the cold?

O Yes O No

If yes, how many times did you use each of the following?

a. Telephone contact GP? ☐☐

b. Telephone contact out of hours GP? ☐☐

c. Telephone contact NHS 24? ☐☐

d. Attended GP? ☐☐

e. Attended out of hours GP? ☐☐

f. GP Home visit? ☐☐

g. Attended hospital? ☐☐

h. Was your child admitted to hospital?

O Yes O No

If yes, number of days and what was the reason

Number of days: ☐☐ Reason: _____

Does your child attend nursery/school?

O Yes O No

If yes, number of days your child missed nursery/school during this cold

☐☐

Number of days or work missed by adults to take care of your child

☐☐

Has your child had wheezing or whistling in the chest while they had this cold?

O Yes O No

If yes, how many days did your child have wheezing or whistling?

☐☐

Participant ID: ☐☐☐☐☐

End of Illness Diary *(Control Arm)*

END OF ILLNESS DETAILS

Please complete this on the first day your child is well after their cold or after 28 days if your child remains unwell

Date Diary Completed: ☐☐-☐☐☐-☐☐☐☐
(DD-MMM-YYYY)

How many adults and children live in the house (including your child who's taking part in ELVIS Kids)?

Adults ☐☐ Children ☐☐

Did anybody at home develop the cold after your child?

O Yes O No

If yes, how many were adults?

☐☐

If yes, how many were children?

☐☐

Did you use salt water nose drops/sprays for your child's cold?

O Yes O No

If yes, what is the name of the drops/sprays you used?

_____

How many days did you use the drops/sprays?

☐☐

How many times per day did you use the drops/sprays?

☐☐

Did your child take over-the-counter medication for their cold?

O Yes O No

If yes, approximately how much did you spend?

£☐☐.☐☐

Participant ID: ☐☐☐☐☐

End of Illness Diary *(Control Arm)*

END OF ILLNESS DETAILS *(continued)*

Did you seek further medical attention related to the cold?

O Yes O No

If yes, how many times did you use each of the following?

a. Telephone contact GP? ☐☐

b. Telephone contact out of hours GP? ☐☐

c. Telephone contact NHS 24? ☐☐

d. Attended GP? ☐☐

e. Attended out of hours GP? ☐☐

f. GP Home visit? ☐☐

g. Attended hospital? ☐☐

h. Was your child admitted to hospital?

O Yes O No

If yes, number of days and diagnosis

Number of days: ☐☐ Diagnosis: _____

Does your child attend nursery/school?

O Yes O No

If yes, number of days your child missed nursery/school during this cold

☐☐

Number of days or work missed by adults to take care of your child

☐☐

Has your child had wheezing or whistling in their chest while they had this cold?

O Yes O No

If yes, how many days did your child have wheezing or whistling?

☐☐

Participant ID: ☐☐☐☐☐

Satisfaction Questionnaire

About the Study

Q1. How easy was it to collect the swabs?

Very Easy	Easy	Moderate	Difficult	Very Difficult	Did Not

Q2. How would you rate the comfort level of your child with the swabs?

Very Comfortable	Comfortable	Moderately Comfortable	Uncomfortable	Very Uncomfortable	Did Not

Q3. How easy was it to return samples?

Very Easy	Easy	Moderate	Difficult	Very Difficult	Did Not

Q4. How easy was it to complete the daily diary?

Very Easy	Easy	Moderate	Difficult	Very Difficult	Did Not

Q5. Based on your experience, do you have any suggestions for improving the trial procedures in the future?

Participant ID: ☐☐☐☐☐

Day 28 Wheeze Details

DAY 28 WHEEZE DETAILS	
Between your child's cold ending and today, did your child develop wheezing or whistling in their chest?	O Yes O No
If yes, how many days did your child have wheezing or whistling? *(Please enter a number, e.g. 4)*	☐☐

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1-18
Protocol version	3	Date and version identifier	12
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	2,11
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11,12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5,6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9,10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10,16

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8,10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7,8,10-12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6,10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10,11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5,10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6,7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6,7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11,12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10-12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	7-9
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Study protocol of the Edinburgh and Lothian Virus Intervention Study in Kids: A randomised controlled trial of hypertonic saline nose drops in children with upper respiratory tract infections (ELVIS Kids)

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Study protocol of the Edinburgh and Lothian Virus Intervention Study in Kids: A randomised controlled trial of hypertonic saline nose drops in children with upper respiratory tract infections (ELVIS Kids)

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Abstract

Introduction: ELVIS Kids is a parallel, open-label, randomised controlled trial (RCT) of hypertonic saline (HS) nose drops (~2.6% sodium chloride; NaCl) vs. standard care in children <7 years of age with symptoms of an upper respiratory tract infection (URTI).

Methods and analysis: Children are recruited prior to URTI or within 48 hours of developing URTI symptoms by advertising in areas such as local schools/nurseries, health centres/hospitals, recreational facilities, public events, workplaces, local/social media. Willing parents/guardians, of children <7 years of age will be asked to contact the research team at their local site. Children will be randomised to either a control arm (standard symptomatic care), or intervention arm (3 drops/nostril of HS, at least 4 times a day, until 24 hours after asymptomatic or a maximum of 28 days). All participants are requested to provide a nasal swab at the start of the study (intervention arm: before HS drops) and then daily for 4 more days. Parent/guardian complete a validated daily diary, an end of illness diary, a satisfaction questionnaire, and a wheeze questionnaire (day 28). The parent/guardian of a child in the intervention arm is taught to prepare HS nose drops. Parent/guardian of children asymptomatic at recruitment are requested to inform the research team within 48 hours of their child developing an URTI and follow the instructions already provided. The day 28 questionnaire determines if the child experienced a wheeze following illness. Participation in the study ends on day 28.

Ethics and dissemination: The study has been approved by the West of Scotland Research Ethics Service (REC) (18/WS/0080). It is co-sponsored by Academic and Clinical Central Office for Research and Development (ACCORD) - a partnership between the University of Edinburgh and NHS Lothian Health Board. The findings will be disseminated through peer-reviewed publications, conference presentations and via the study website.

Trial registration number: Clinicaltrials.gov: NCT03463694

Strengths and limitations of this study

- Open label community-based randomised controlled study investigating the effectiveness of HS vs standard treatment in children under 7 years of age with a common cold
- Parents in the intervention arm are taught to safely make HS at home
- Nose swabs are collected to identify the virus(es) and to measure change in viral shedding
- A validated symptom score diary (CARIFS) is used as part of the daily diary
- There is no placebo arm

Introduction:

Viral upper respiratory tract infections (URTI) are very common in childhood resulting in a significant burden on the population and health services[1]. The annual incidence rate of URTI in childhood can vary between 6-12 episodes[2 3]. Children have a longer duration of illness (mean 1.8 weeks; standard deviation: 1.3 weeks) compared to adults[3 4]. In Scotland, URTI is the leading cause of general practitioner (GP) visits in children <5 years (n=84710, 574/1000 population) and the fourth most common cause of consultation in children aged 5-14 (n=33790, 116.5/1000 population)[5]. In secondary care, in 2015-16, 13.3% (n=16,644) and 19.7% (14,600) of all admissions/emergency admissions respectively in children were due to upper/lower respiratory tract infections[6]. 12-14% of children who develop an URTI will go on to develop lower respiratory tract disease (viral induced wheeze: 80/1000[7], bronchiolitis: 46/1000[8], and pneumonia: 0.27 episodes/child year[9]). Hence interventions that reduce URTI severity may considerably benefit patients/carers and reduce pressure on the NHS. Since >200 viruses[10] can cause an URTI, individually targeted antiviral therapy is impractical and measures that work against all viruses are required.

New data suggest that hypertonic saline (HS) may be able to suppress viral replication, regardless of viral type and hence be a potential respiratory antiviral agent with clinical application. Saline irrigation is commonly used in clinical practice, mostly to deliver a mucolytic effect. However, we have recently identified that human epithelial (cervical-HeLa, respiratory-A549) cells utilise NaCl to mount a broad-spectrum antiviral effect against representative DNA, RNA enveloped and non-enveloped viruses[11]. The antiviral effect is dependent on the entry of chloride ions into the cell and the production of intracellular hypochlorous acid (HOCl)[11]. HOCl is the active ingredient of bleach, which can inactivate most viruses[12-15]. A polymorphism causing reduction in HOCl production has been reported in individuals with cervical cancer[16]. 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[17]. Increased HOCl production is reported within gut epithelial cell of fruit flies after bacterial lysate ingestion[18]. These data suggest an anti-infective role of HOCl and its precursor NaCl in epithelial cells.

In addition, it has recently been shown that accumulation of Na^+ ions in human skin helps fight bacterial/parasitic infections[19 20]. A high salt diet increased Na^+ in skin leading to a hypertonic environment, increased Nitric Oxide (NO) production in macrophages and thereby pathogen removal[19 20]. Whilst our laboratory data point to the importance of Cl^- in combating viral infections, Jantsch et al have shown the importance of Na^+ in fighting bacterial infections. Taken together, these data suggest that innate immunity may be dependent on NaCl in epithelial cells helping to clear bacterial and viral infection.

Nebulised HS has been used to treat bronchiolitis; an acute viral infection of young children caused by a variety of respiratory viruses. Meta-analyses of current trials suggest a possible reduction in length of hospital stay[21 22], but the association is weak and there have been concerns about the replicability of this finding[23-27] potentially as HS has been given at the peak of disease when viral load is maximum and lower respiratory tract disease (with potential

dysregulated immune response) is established. More positive signals have been demonstrated when HS has been administered in accident and emergency department contexts to reduce hospital admission rates: data remain conflicting and a systematic review has been started to analyse data as they emerge [26-28].

The role of saline (isotonic or hypertonic) in children with viral URTI has been explored in two published studies. In children aged 6-10 years administered isotonic saline as a spray (6 times/day) there was a significant reduction in reported sore throat, nasal secretions, and use of nasal decongestants/mucolytic (vs. standard care, no placebo)[29]. In children <2 years treated with saline/sea water drops (thrice a day for 5 days) there was a significant reduction in URTI symptoms reported when compared to untreated children[30]. However, a Cochrane review concluded that no definitive conclusions could be drawn as the available studies were small and had major methodological limitations: baseline symptom score was calculated over 7 days (not at the point of entry) and groups had different characteristics at baseline[31].

We recently completed the Edinburgh and Lothians' Viral Intervention Study (ELVIS), an open label pilot randomised controlled trial (RCT) of hypertonic saline nasal irrigation and gargling (HSNIG) in 66 adults with an URTI (www.elvisstudy.com)[4]. Most participants were infected with rhinoviruses/coronaviruses. 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 reduced at a faster rate of ≥0.5 $\log_{10}$/day in those receiving HSNIG (p=0.04) [4]. The reduction in viral shedding and transmission within household were supportive of our laboratory data and consistent with a direct cellular antiviral action by NaCl.

Given the laboratory evidence supported by our demonstration of clinical benefits in adults an RCT in children with URTI to study the effects of HS on duration of illness and viral shedding is now needed. No suitable placebo is available: Sodium bicarbonate and plain water cause discomfort when administered to nasal mucosa and normal saline, a commonly used, safe, placebo contains NaCl and so may not act as a placebo. For these reasons, the study will not be placebo controlled.

Methods and analysis:

Study objectives

Primary objective:

To investigate whether the use of parent/guardian-initiated HS nose drops administered to children with symptoms consistent with acute viral URTI reduces the duration of symptoms when compared to children managed using standard care.

Secondary objectives:

To determine the effect of HS nose drops on:

1. Severity of all symptoms

2. Duration and severity of individual symptoms
3. Contact with NHS 24, out of hours primary care (OOH), and primary care (GP)
4. Hospital attendance (i.e. A&E attendance and/or hospital admission) and diagnosis
5. Reduction in wheeze
6. Over the counter medication use
7. Duration, reduction or rate of reduction in viral shedding
8. Transmission within the household
9. Side effects associated with the use of saline nose drops
10. Adverse events associated with the use of saline nose drops
11. Time off from school/nursery for child and workdays lost for parent/guardian
12. Cost associated with illness (over the counter medication costs and NHS costs)

Study design and sample size:

ELVIS Kids is a parallel, open label, RCT of HS nose drops (~2.6% NaCl) vs. standard care in children <7 years of age with symptoms of an URTI. The aim is to recruit a total of 480 children (240/arm).

The study will run over ~42 months at participating sites in Scotland (sites are as listed on clinicaltrials.gov). Children are recruited prior to, or within 48 hours of developing URTI symptoms by advertising in areas such as local schools, nurseries, health centres, hospitals, recreational facilities,workplaces public events and the community as well as local and social media. For the purposes of this study an URTI is defined as: at least two respiratory symptoms (nasal congestion, runny nose, cough, sore throat) OR one respiratory symptoms and at least one systemic symptom (low energy/tired, muscle aches/pains, headache, fever ≥38°C). Willing parents/guardians, will be directed by the study advertising to contact the research team at their local site) if they are interested in participating.

Children will be randomised to either a control arm of standard symptomatic care, or an intervention arm of 3 drops each nostril of HS at least 4 times a day and up to a maximum of 12 times a day until asymptomatic or maximum of 28 days. All parents/guardians will be requested to obtain a mid-turbinate nasal swab from the participant first thing in the morning (before nose drops in the intervention arm) for five for 5 consecutive days (unless the child is well before then), a daily diary (a global severity question, CARIFS[32], a validated illness measure in the UK, side effects and compliance with trial procedures) until they report the child as “not unwell”, an end of illness diary (infection in household contacts, ease of use and acceptability of intervention, medication and healthcare use, acceptability, time taken off usual activities, wheezing and whistling in the chest), a satisfaction questionnaire and adverse events. Parents/guardians of the children allocated to the intervention arm will be taught how to prepare the HS (including sterilization instructions for children under a year). Parents/guardians of children who are asymptomatic at recruitment are requested to inform their local research team when the child

develops an URTI (within 48 hours) and follow the instructions already provided to them. On day 28, parents/guardians will be contacted to determine if their child suffered from wheezing or whistling in the chest either during the illness or at any point until day 28. Participation in the study will end on day 28.

Eligibility and consent:

Pre-screening for eligibility to participate will be completed by a member of the research team at the clinical trials unit when parents/guardians phone to express interest in the study. If parents/guardians attend an appointment and take part in the study, the study number will be recorded on the screening log and details of eligibility will be recorded in the study database.

Inclusion criteria:

1. Children between corrected gestational age of ≥40 weeks and <7 years of age
2. Children without URTI OR ≤48 hours of URTI* starting.

*A URTI being defined as at least two respiratory symptoms (nasal congestion (i.e. stuffy nose), runny nose, cough, sore throat) OR one respiratory symptom + at least one systemic symptom (Low energy/tired, muscle aches/pains, headache, fever 38°C).

Exclusion criteria:

1. Children needing immediate medical attention
2. Children using saline drops/sprays at the time of randomisation
3. Children on immunosuppressive medication, regular oral/inhaled steroids, regular antibiotics (use of antibiotics is allowed as long as the child does not need regular antibiotics)
4. Children with a known chronic illness (e.g. cystic fibrosis, cardiac, renal, liver, lung, neurological conditions) apart from wheeze or asthma which are not exclusions if the child is otherwise well and not on regular steroids)
5. Children being followed up for developmental delay
6. Children receiving the nasal flu vaccine ≤14 days ago
7. Children taking part in another interventional trial
8. If parents/guardians indicating that they are unable to comply with the study protocol prior to randomisation
9. If parents/guardians are unable to understand written or spoken English
10. Children randomised to ELVIS KIDS on a previous episode of URTI
11. Children with a concurrently participating sibling

All ineligible and non-recruited participants will be recorded on the ELVIS Kids screening log with a reason given.

Obtaining consent:

Only trained and delegated members of the trial team will take consent – this will usually be the research nurse. The participant information sheet (PIS), which will explain the aims of the study and the potential risks and benefits of the study treatment, are provided to parents/guardians when they meet the research team (also available online). A children's PIS will be available to discuss with older children attending the appointment with the option of giving their assent. (Supplement)

If the parent/guardian wishes to participate in the study, then they will be asked to sign the Informed Consent Form (ICF) (Supplement). Both the parent/guardian and the person delegated to take consent will sign and personally date the ICF. The original signed ICF must be kept by the Investigator in the investigator site file, 1 copy is provided to the parent/guardian, 1 copy is placed in TRAK. The same would apply in the case of assent being given.

Randomisation and treatment allocation:

A member of the research team from the clinical research facility will perform the randomisation using a web-based randomisation service managed by the Edinburgh Clinical Trials Unit (ECTU). Children will be allocated to receive either HS nose drops or standard care in a 1:1 ratio using minimisation based on age (0-2, >2 year) and sex and allocated to receive the treatment which minimises the imbalance with a probability 0.8. The study is not blinded apart from those carrying out lab assessments of nasal swabs.

Sea salt will be provided by Cornish Sea Salt company in 225g pots. They will be supplied to local pharmacies where they will be labelled and stored. A working stock will be issued to the research team. If a child is allocated to an intervention arm, the parent/guardian will be given instructions on the preparation and use of HS nose drops using instructional video, verbal and written information. Parents/guardians will be asked to add 1 level measure of sea salt to a fixed volume of freshly boiled water using the measuring spoon and clean glass jar provided. This provides a NaCl concentration of ~2.6% and the drops can be used once cooled. Two glass jars are provided so that the parent / guardian could use one and have a clean spare to prepare solution the next day. Two dropper bottles are provided with which nose drops can be applied (one in use, and a clean spare).

Withdrawal of study participants:

Parents/guardians are free to withdraw their child from the study at any point. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if given. All data and swabs collected before withdrawal will be retained for analysis in cases where participants withdraw.

Study assessments:

The protocol is designed in accordance with the standard protocol items: recommendations for interventional trials (SPIRIT). The trial overview of the study assessments is available as a SPIRIT figure (Table 1). At the appointment, a member of the research team will train the parent/guardian how to identify a URTI, how to measure temperature, how to complete the diaries and how to collect and return the mid-turbinate swabs. In addition, those in the intervention arm will be given instructions on how to prepare and apply nose drops. Baseline information on the child, contact details of parent / guardian and number of household members at the time of recruitment will be collected in the electronic case report form (eCRF). If recruited when symptomatic, parents will be instructed to start the study assessments the same day. If recruited when asymptomatic, and there are no changes to the child's medical information, parent/guardians will be asked to start the study assessments and to inform the study team the same day if possible or at least within 2 days of onset of illness. If recruited when asymptomatic, and there are changes to the child's medical information, parent/guardians will be asked to contact the study team to ensure the child still meets the eligibility criteria before starting the study procedures. If it is not suitable for the child to take part during this URTI (e.g. received the flu vaccine in the past 2 weeks) they will remain on study and be asked to contact the team at the onset of the next URTI.

Parents/guardians are requested to collect a nasal (mid-turbinate) swab as soon as possible on day 1 and first thing in the morning (and prior to HS nose drops being applied) on days 2-5 if children remain unwell. These samples are to be packed in the transport box provided, stored in the fridge and returned in the pre-paid envelope or as soon as possible after completing collection. If samples are not received by day 10, a reminder will be sent to the parent/guardian.

Parents/guardians will complete a daily diary (Supplement) which records any symptoms the child is experiencing, compliance to nasal swabs and HS drops, any side effects and use of healthcare services. Parents will be taught how to measure temperature with TempaDot. Parents are advised to measure the temperature only if they think the child has a fever. If the child has an axillary temperature of ≥38°C, it should be recorded as a fever in the daily diary. The diaries will be provided as an online form (unless parents cannot access this in which case a paper copy can be provided). If the online Daily Diary is not completed a reminder will be sent.

An end of Illness diary (Supplement) and satisfaction questionnaire (Supplement) will be completed by the parent/guardian once the child is asymptomatic for >24hours or after a maximum of 28 days. On day 28, the parent/guardian will be contacted by email and sent a text message to ask if their child has experienced any wheeze since the end of illness diary was completed (Supplement).

Participants will be sent a £30 voucher by email as compensation for any inconvenience once they have returned the study data.

Analysis and storage of samples:

Up to five nasal swabs will be collected and posted to the Department of Laboratory Medicine, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4SA, where they will be stored and processed. Day 1 samples will be analysed by the respiratory panel and the cycle threshold (CT) of positive samples recorded. If the day one sample is missing, the first available sample will be tested to identify the virus. If an agent is identified, all samples (days 1-5) will be tested in parallel to estimate change in viral shedding and the CT recorded. If a sample is positive on day 1 and negative on subsequent days, they may be tested for human DNA to confirm a sample was collected. Log conversion of each positive result will be done using the following formula: (40-CT of specimen)/3.3 to estimate change in shedding. All nucleic acid extracts and remaining original samples will be stored in the Lothian NHS research Scotland BioResource biobank (REC reference 15/ES/0094) in future ethically approved studies.

Outcomes / endpoints:

Primary endpoint:

Duration of illness (measured as the number of days until the parent reports the child to be well)

Secondary endpoints:

1. Severity of all symptoms as measured by CARIFS
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 and diagnosis (Number of participants and frequency of contacts)
7. Length of stay in hospital if admitted
8. Number of participants reporting wheeze during illness and between end of illness to 28 days.
9. Number of participants reporting over the counter medication use
10. Duration of viral shedding
11. Reduction in viral shedding
12. Rate of reduction in viral shedding
13. Reduction in transmission to household contacts
14. Number of participants reporting side effects associated with nasal drops
15. Number of participants reporting adverse events associated with nasal drops
16. Types and severity of side effects/adverse events reported
17. Number of days lost from school/nursery for child
18. Number of days lost from work for parent/guardian
19. Cost of over the counter medication used

20. NHS costs associated with illness

Participant timeline:

The participant pathways can be seen in figure 1 and figure 2. Participants will be active in the study for 28 days. There are no long term follow up assessments after day 28 of URTI developing.

Data collection:

Baseline data will be collected on the baseline electronic CRF (eCRF) by a member of the research team. Parents/guardians will record study data onto either an online form which will be saved into the eCRF. A paper CRF (pCRF) option is available if a parent/guardian prefers it. pCRF will be returned to the local research team and transcribed by a member of the research team into the database and cross-checked by another.

Virological results are downloaded (identifiable by study number) on a weekly basis on to a specific drive by the Laboratory Information Management & Technology team. These will be emailed to the ECTU on a monthly basis and uploaded into the study database.

The trial database will be created and maintained by ECTU. Trained and delegated members of the research team will be given password-protected logins to the database to complete data entry. Data completed online by parents/guardians will be transmitted into the study database. The data will be stored in a secure server in the University of Edinburgh for at least the archiving period.

Adverse events:

Symptoms and side effects from the Daily Diary will be recorded in the CRF but will not be recorded as an adverse event (AE) or adverse reaction. Hospitalisation is a study outcome and is exempt from reporting to the Sponsor as a serious adverse event.

Any other adverse events identified between Day 1 and Day 28 of the study will be recorded. Any events reaching seriousness criteria will be reported to the sponsor within 24 hours.

Sample size calculation and statistical analysis:

Sample size calculation is based on mean (SD) duration of illness values in a control population from Gruber et al of 13 (9) days. To detect a 20% difference in mean duration, i.e. 3 days, using a two-sided, two-sample test with 5% level of significance, 90% power and common standard deviation of 9 days we will need a sample of 191 per treatment arm, without drop-outs. Hence, we will recruit 240 participants per arm to allow for up to 20% drop-outs.

Statistical analysis will be conducted according to, and full of the details will be specified in, the pre-specified Statistical Analysis Plan (SAP). Differences in illness duration between treatment arms will be compared using a two-sample t-test or non-parametric equivalent, as appropriate. This method will also be employed to examine differences between treatment arms for other continuous outcome measures such as average symptom score, viral shedding between

treatment arms. For binary categorical data, for example the proportion of participants per arm attending their GP, attending hospital, etc we will compare the treatment arms using a binomial test for the comparison of proportions. Where we have categorical data with more than 2 categories a Chi-squared test will be used to examine the relationships between treatment arms. If the number of cases of individual viruses are sufficient, the above analysis will be repeated by virus type.

Oversight arrangements:

The study is co-sponsored by ACCORD, a partnership between the University of Edinburgh and NHS Lothian Health Board based at QMRI, 47 Little France Crescent, Edinburgh Email: enquiries@accord.scot. The trial will be coordinated by a Project Management Group (PMG), consisting of the Chief Investigator, Co-investigators, Trial Manager, Statistician and Coordinating Nurse. The Trial Manager will oversee the study and will be accountable to the Chief Investigator. ECTU is responsible for trial management and oversight of data collection. The Edinburgh Clinical Research Facility are responsible for the statistical analysis. A Delegation Log will be prepared, detailing the responsibilities of each member of staff working on the trial. A Trial Steering Committee (TSC) has been established to oversee the conduct progress. As there will be no Data Monitoring Committee for this project, the TSC will review safety information as part of their remit.

Ethics and dissemination:

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP). The study has been approved by the West of Scotland Research Ethics Service (reference: 18/WS/0080) and registered on Clinicaltrials.gov (NCT03463694). 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, will be reviewed and approved by the Chief Investigator. Amendments will be submitted to the sponsor 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. The findings will be disseminated through peer-reviewed publications, conference presentations and on the study website.

Confidentiality:

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant's parent/guardian. The Investigator and study site 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, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

All Investigators and study site staff involved with this study must comply with the requirements of General Data Protection Regulations 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.

Patient and Public involvement (PPI): Feedback was obtained from PPI representatives on the study protocol, information sheets, diaries and consent forms and necessary modifications made prior to starting the study. A PPI representative is also invited to attend the trial steering committee meetings.

Access to data:

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.

Trial status:

This paper describes study protocol version V4 (06/01/2020). The trial opened on 02 November 2018. The first participant was recruited on 6th November 2018. The planned study end date is 30 November 2021. At the time of submission, study recruitment was suspended due to the COVID-19 pandemic.

Discussion:

The study is based on the recently discovered evidence that epithelial cells have an innate antiviral effect [11]. This effect can be augmented by supplying the cells with chloride ion through NaCl. Saline, commonly used as a placebo cannot be used in that role here as it contains NaCl – the substrate being tested. We are hence measuring viral shedding as an independent measure of any antiviral effect. The results from this trial will help determine if a simple and low-cost intervention could help reduce the duration of symptoms of URTI in children. Changes to the duration of individual symptoms, wheeze, transmission within the household, over-the-counter medication use, need for further treatment, days lost and cost of illness are all secondary outcomes.

Conclusion:

Since numerous viruses can cause URTI and in the absence of an antiviral agent/vaccine against the vast majority of viruses, if successful, this low cost and easily accessible intervention can easily be rolled out globally.

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Authors' contributions:

Sandeep Ramalingam – Planned the study and wrote the protocol

Catriona Graham – Planned the study, revised protocol and approved the final manuscript.

Katherine Oatey – Revised protocol, obtained approvals and approved the final manuscript.

Phillip Rayson – Revised protocol, obtained approvals and approved the final manuscript.

Andrew Stoddart – Revised protocol and approved the final manuscript.

Aziz Sheikh – Planned the study and revised protocol and approved the final manuscript.

Steve Cunningham - Planned the study and revised protocol and approved the final manuscript.

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The ELVIS Kids Trial Investigators are:

Chief Investigator: Sandeep Ramalingam

Children's Clinical Research Facility (Edinburgh): Brittney Abernathy, Julie Baggot, Ruaridh Buchan, Gillian Black, Steve Cunningham, Louise Frampton, Naomi Matos, Elinore McGivern, Rachel McKernan, Debbie Miller, Margaret Millar, Sheila Mortimer, Finny Paterson, Maxine Ramsay, Joan Thomson, Emma Ward, Jacqueline Waters.

Department of Laboratory Medicine, Royal Infirmary of Edinburgh: Alistair Scott, Jenny Dove, Marianne Cunningham, Lisa Marie Wilson

Edinburgh Clinical Trials Unit (ECTU): Ruth Armstrong, Christine Campbell, Gina Cranswick, Ronnie Harkess, Lynsey Milne, Katherine Oatey, Phillip Rayson, Pamela Sinclair, Michelle Steven, Andy Stoddart.

Pharmacy NHS Lothian. Ruaridh Buchan, Jacqueline Waters

Usher Institute: Aziz Sheikh

Edinburgh Clinical Research Facility: Emily Evans, Catriona Graham

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Competing interests statement: No conflicts of interest to declare

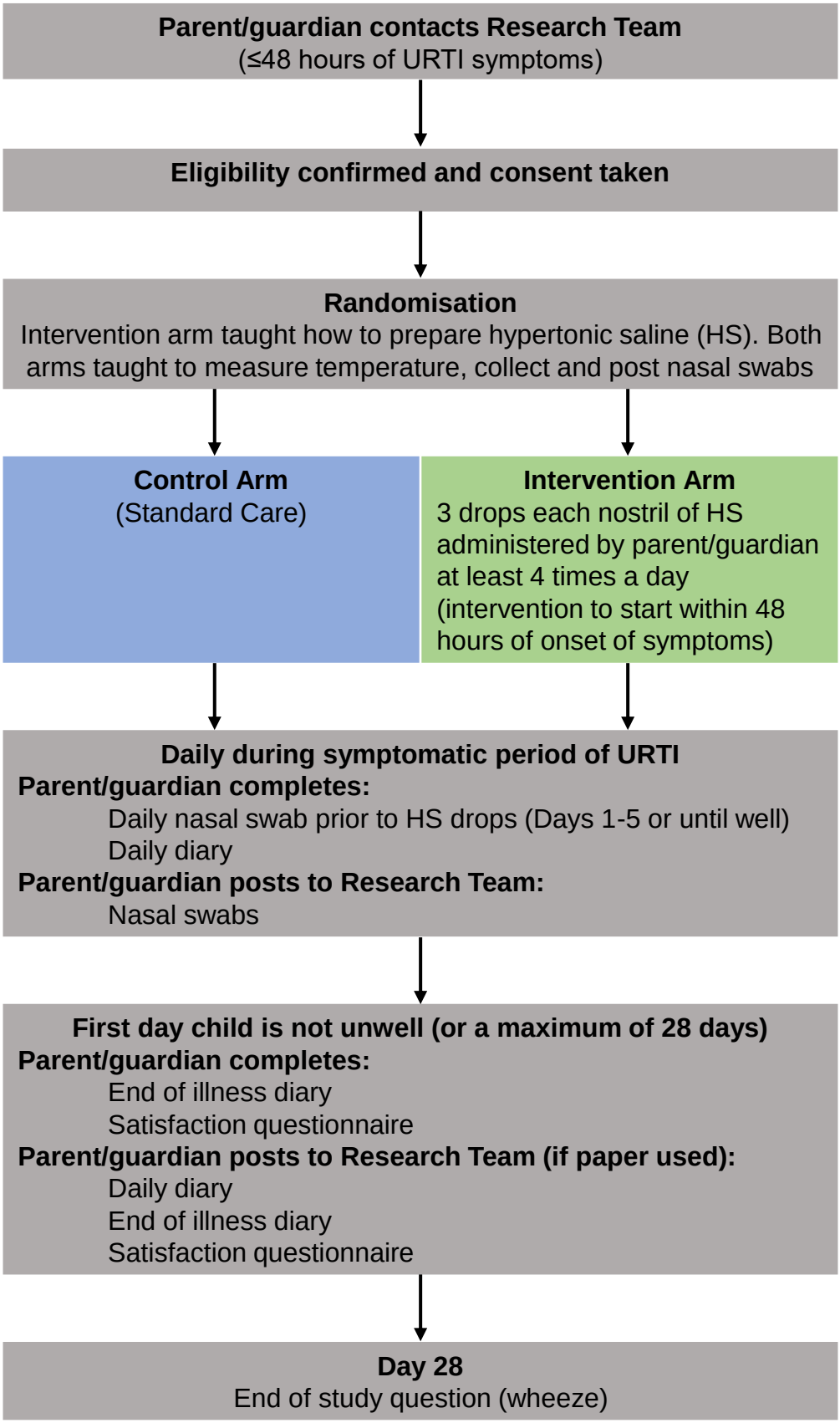
Figure Legends:

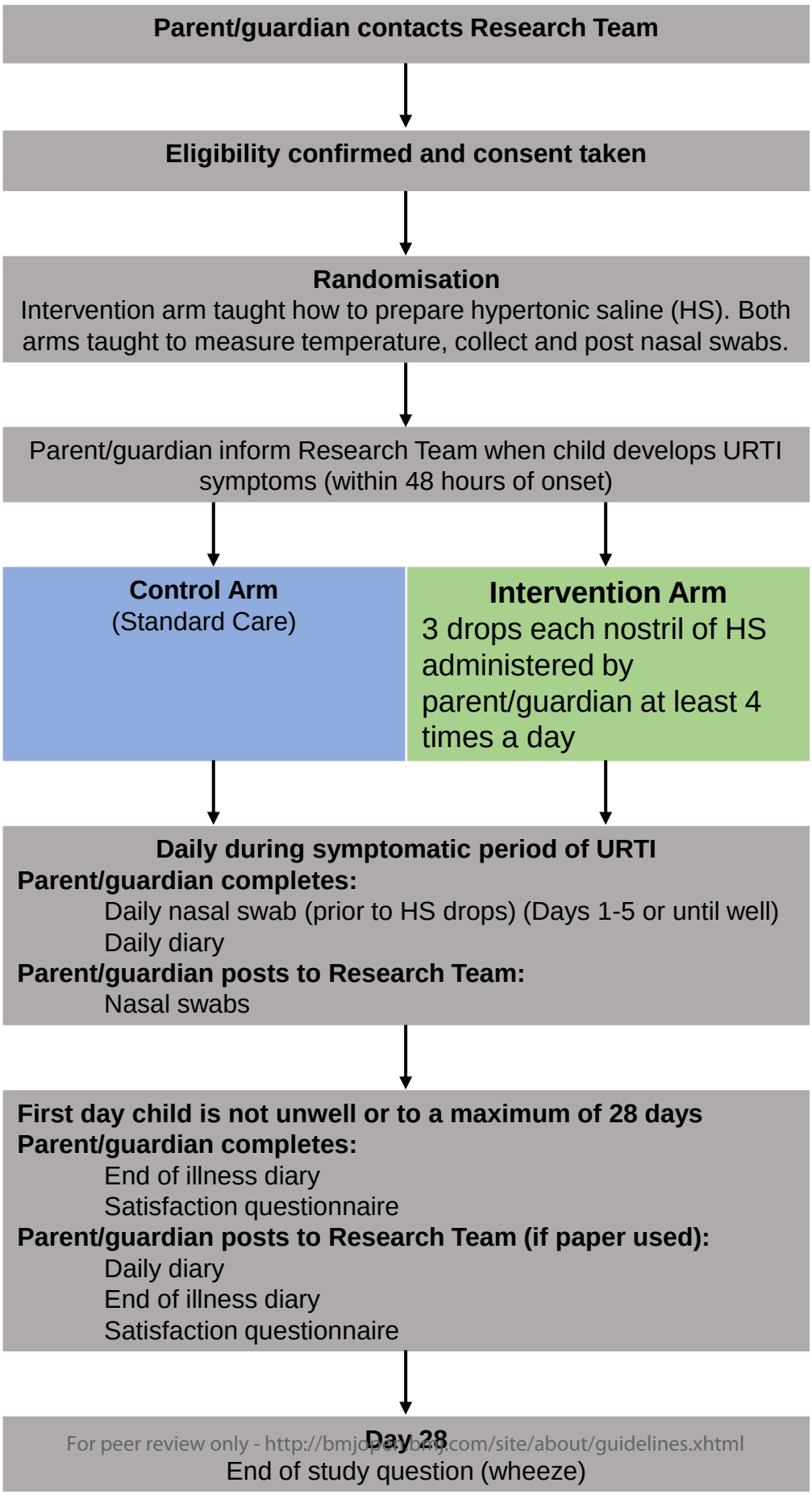
Figure 1: ELVIS Kids Patient Pathway when the child has a URTI at recruitment.

Figure 2: ELVIS Kids Patient Pathway when the child does not have a URTI at recruitment.

Table 1:

Study timepoints	Pre- Screen ing	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 5-8	Days 5-28 (as applicable)	Day 28
Pre-Screening	X									
Informed Consent		X								
Eligibility Criteria		X								
Eligibility review if change in health information			X							
Randomisation/Treatment Allocation		X								
Baseline Case Report Form		X								
Nose Swab collection (if child remains unwell)			X	X	X	X	X			
Nose Swab return								X		
Intervention arm - HS Drops			X	X	X	X	X		X	
Daily diary			X	X	X	X	X		X	
Adverse Events			X	X	X	X	X		X	
End of illness diary				←	—	—	—	—	—	→
Satisfaction questionnaire				←	—	—	—	—	—	→
Return of diaries									X	
Day 28 Wheeze question										X


Parent/guardian contacts Research Team
(≤48 hours of URTI symptoms)
Eligibility confirmed and consent taken
Randomisation
Intervention arm taught how to prepare hypertonic saline (HS). Both arms taught to measure temperature, collect and post nasal swabs
Control Arm
(Standard Care)
Intervention Arm
3 drops each nostril of HS administered by parent/guardian at least 4 times a day (intervention to start within 48 hours of onset of symptoms)
Daily during symptomatic period of URTI
Parent/guardian completes:
Daily nasal swab prior to HS drops (Days 1-5 or until well)
Daily diary
Parent/guardian posts to Research Team:
Nasal swabs
First day child is not unwell (or a maximum of 28 days)
Parent/guardian completes:
End of illness diary
Satisfaction questionnaire
Parent/guardian posts to Research Team (if paper used):
Daily diary
End of illness diary
Satisfaction questionnaire
Day 28
End of study question (wheeze)



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ELVIS Kids: Information Sheet for children

Hello, this is ELVIS. He has a Cold!

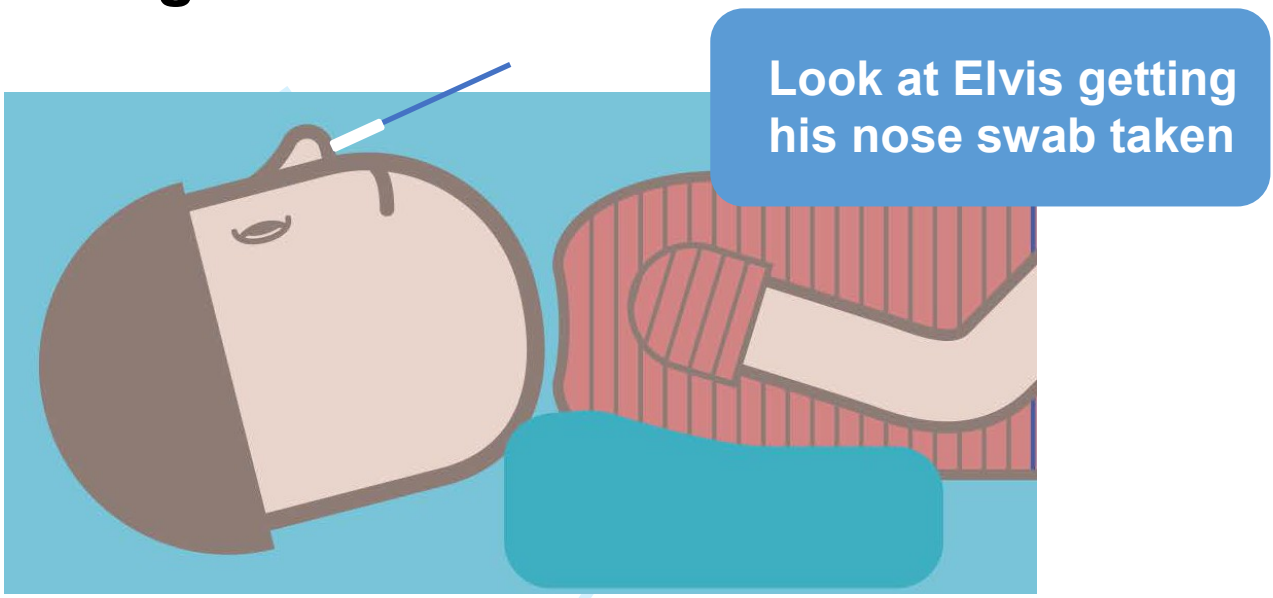
Elvis does not like a cold.

It makes him cough, his nose runs, and he is too tired to play.

He wishes there was a cure for the cold!

So, Elvis goes to meet the nurse in the hospital to take part in a study.

The nurse tells Elvis that he will need to take a swab from his nose for a few days. This is like a cotton bud wiping the inside of his nose. This won't hurt but might tickle a bit!



The nurse tells Elvis that he may be in the group of children that need nose drops for their cold until they are well.

If he is, he will lie down and a few drops of water will be put up his nose by a grown up in his family. This might be tickly or make him want to blow his nose. He will do this every day until his cold gets better.

Look at Elvis's Mum putting in his nose drops. He is good at lying still!

Not all the children helping with the study will use nose drops. The nurse will look at their computer to see which children will get them.

The nurse tells Elvis that he doesn't have to take part if he doesn't want to and he can change his mind later if he wants. He just needs to tell a grown up.

The nurse thanks Elvis for his interest in the study.

Do you want to be like Elvis and help the nurse too?

What is your name: _____

Colour in this picture of Elvis's Teddy who is visiting the nurse too:

<INSERT TRUST LOGO>

ELVIS Kids: Assent Form for children

Child to tick all they agree with:

Participant Number:	
Do you understand what this study is about?	Yes ☐ No ☐
Have you asked all the questions you want?	Yes ☐ No ☐
Have you had your questions answered in a way you understand?	Yes ☐ No ☐
Are you happy to take part?	Yes ☐ No ☐

If any answers are 'no' or you don't want to take part, don't sign your name!

If you do want to take part, you can write your name below:

Your name_____

Date_____

The nurse who explained this project to you needs to sign too:

Print Name_____

Sign_____

Date_____

Thank you for your help!

<INSERT TRUST LOGO>

Participant Number: _____

CONSENT FORM: ELVIS Kids		Please **initial** box
1.	I confirm that I have read and understand the information sheet (Dated: _____ and Version Number_____) for the above study. I have had the opportunity to consider the information, ask questions and have had these questions answered satisfactorily.	☐
2.	I understand that my participation and my child's participation is voluntary and that I am free to withdraw at any time without giving any reason and without my child's medical care and/or legal rights being affected.	☐
3.	I give permission for the study team to access my child's medical records if needed, to collect data on visits to hospital, and treatment received and to check whether they are suitable to take part in the study.	☐
4.	I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by individuals in the study team, from the Sponsor (University of Edinburgh and/or NHS Lothian), from NHS <INSERT TRUST NAME> or other regulatory authorities where it is relevant to my child taking part in this study. I give permission for these individuals to have access to my child's data and/or medical records.	☐
5.	I give permission for my personal information and my child's personal information (including my child's date of birth, and my telephone number and email address) to be passed to the University of Edinburgh for administration of the study.	☐
6.	I understand that the nose swabs collected from my child will be tested to see which bacteria or viruses have caused my child's cold.	☐
7.	I understand that the nose swabs collected from my child may be tested for human DNA to check the samples have been taken correctly.	☐
8.	I agree to my child's anonymised data and nose swabs being kept for use in future ethically approved studies and I understand the samples will be held securely in the Lothian NRS BioResource.	Yes ☐ No ☐
9.	I understand that as part of future ethically approved studies the samples may be tested for human DNA to identify why some children get more infections or why some children have mild and others have severe illness and consent to it.	Yes ☐ No ☐
10.	I agree to my child's General Practitioner being informed of their participation in the study.	☐
11.	I give permission for the trial researchers to contact me by email, phone and text message during the study.	☐
12.	I agree that my child will take part in the above study.	☐

Name of Person Giving Consent		Date		Signature
Name of Person Receiving Consent		Date		Signature

1x original – into Site File; 1x copy – to Participant; 1x copy – into medical record

ELVIS Kids Daily Diary (Intervention Arm)

Thanks for your help with ELVIS Kids!

Participant ID: ☐☐☐☐☐

Does my child have a cold?

Your child should have at least two of the cold symptoms listed **OR** one cold symptom and one symptom affecting the whole body to start the study. Please record the symptoms your child has for this cold below.

Cold Symptoms			Whole body Symptoms			
Stuffy nose	O Yes	O No	Fever (≥ 38°C)	O Yes	O No	
Runny nose	O Yes	O No	Low energy/tired	O Yes	O No	
Cough	O Yes	O No	Muscle aches/pains	O Yes	O No	O Don't Know
Sore throat	O Yes	O No	Sore head	O Yes	O No	O Don't Know

When did the illness start?

(Please do not start the study if the cold started more than 48 hours ago)

Date Started: *(DD-MMM-YYYY)* ☐☐-☐☐☐-☐☐☐☐ **Time Started:** *(24 hour clock)* ☐☐:☐☐

If your child's medical details have changed since you first saw the study nurses, please contact the study nurses on STUDY NUMBER before starting the study

Did your child receive the nasal flu vaccine within the last 4 weeks?

O Yes, my child received the nasal flu vaccine O No my child has not received the nasal flu vaccine

If you answered YES, please contact the study nurses on STUDY NUMBER before starting the study

Date Flu Vaccine Received: *(DD-MMM-YYYY)* ☐☐-☐☐☐-☐☐☐☐

ELVIS kids

Participant ID: ☐☐☐☐☐

Daily Diary: Day 1

Date: ☐☐-☐☐☐-☐☐☐☐ **Time** *(24 hour clock)*: ☐☐:☐☐

Select one option	**Not unwell** 0		**Very mildly** 1	2	**Mildly** 3	**Moderately** 4	5	**Severely** 6	7
How unwell is your child today?									

If you ticked 'Not unwell', please skip the next section and go to the 'Other Questions' section

Are these symptoms a problem for your child today? Tick the most appropriate box for each question:

Symptom	No Problem	Minor Problem	Moderate Problem	Major Problem	Don't Know or N/A
Poor appetite					
Not sleeping well					
Irritable, cranky, fussy					
Feels unwell					
Low energy, tired					
Not playing well					
Crying more than usual					
Needing extra care					
Clinginess					
Headache					
Sore throat					
Muscle aches or pains					
Fever					
Cough					
Nasal congestion, runny nose					
Vomiting					
Not interested in what's going on					
Unable to get out of bed					

Other Questions:

How many times did you give the drops in the last day (24 hours)? ☐☐

Were there any side effects? O Yes O No

If yes, please indicate the severity of symptoms by ticking the following where 0 is none and 5 is the worst it can be.

Symptom	None 0		**Score** 1	2	3	4	Max 5
Runny nose							
Sneezing							
Pain / Sore							
Other symptom 1: _____							
Other symptom 2: _____							
Other symptom 3: _____							

Was a nose swab collected this morning? O Yes O No

If no, what was the reason? O I forgot O My child refused O I had problems doing it
O Other: _____

ELVIS Kids Daily Diary (Control Arm)

Thanks for your help with ELVIS Kids!

Participant ID: ☐☐☐☐☐

Does my child have a cold?

Your child should have at least two of the cold symptoms listed **OR** one cold symptom and one symptom affecting the whole body to start the study. Please record the symptoms your child has for this cold below.

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Runny nose	O Yes	O No	Low energy/tired	O Yes	O No	
Cough	O Yes	O No	Muscle aches/pains	O Yes	O No	O Don't Know
Sore throat	O Yes	O No	Sore head	O Yes	O No	O Don't Know

When did the illness start?

(Please do not start the study if the cold started more than 48 hours ago)

Date Started: *(DD-MMM-YYYY)* ☐☐-☐☐☐-☐☐☐☐ **Time Started:** *(24 hour clock)* ☐☐:☐☐

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Did your child receive the nasal flu vaccine within the last 4 weeks?

O Yes, my child received the nasal flu vaccine O No my child has not received the nasal flu vaccine

If you answered YES, please contact the study nurses on STUDY NUMBER before starting the study

Date Flu Vaccine Received: *(DD-MMM-YYYY)* ☐☐-☐☐☐-☐☐☐☐

Participant ID: ☐☐☐☐☐

Daily Diary: Day 1

Date: ☐☐-☐☐☐-☐☐☐☐ **Time** *(24 hour clock)*: ☐☐:☐☐

Select one option	Not unwell 0	Very mildly 1	2	Mildly 3	Moderately 4	5	Severely 6	7
How unwell is your child today?								

If you ticked 'Not unwell', please skip the next section and go to the 'Other Questions' section

Are these symptoms a problem for your child today? Tick the most appropriate box for each question:

Symptom	No Problem	Minor Problem	Moderate Problem	Major Problem	Don't Know or N/A
Poor appetite					
Not sleeping well					
Irritable, cranky, fussy					
Feels unwell					
Low energy, tired					
Not playing well					
Crying more than usual					
Needing extra care					
Clinginess					
Headache					
Sore throat					
Muscle aches or pains					
Fever					
Cough					
Nasal congestion, runny nose					
Vomiting					
Not interested in what's going on					
Unable to get out of bed					

Other Questions:

Was a nose swab collected this morning?	O Yes O No
If no, what was the reason?	O I forgot O My child refused O I had problems doing it O Other: _____

Participant ID: ☐☐☐☐☐

End of Illness Diary *(Intervention Arm)*

END OF ILLNESS DETAILS

Please complete this on the first day your child is well after their cold or after 28 days if your child remains unwell

Date Diary Completed: ☐☐-☐☐☐-☐☐☐☐
(DD-MMM-YYYY)

How many adults and children live in the house (including your child who's taking part in ELVIS Kids)?

Adults ☐☐ Children ☐☐

Did anybody at home develop the cold after your child?

O Yes O No

If yes, how many were adults?

☐☐

If yes, how many were children?

☐☐

How easy was it to apply the nose drops

Very Easy	Easy	Moderate	Difficult	Very Difficult	Did Not

What was your preferred option?

O Cradle child in arms O Lay child on bed O Other: _____

Do you think applying nose drops made a difference to your child's symptoms?

O Yes O No

Would you do it again if your child had a cold in the future?

O Yes O No

If no, what is the reason? (tick all that apply)

No improvement O Yes O No

Too difficult O Yes O No

Child did not like it O Yes O No

There were side effects O Yes O No

Other O Yes O No Other:_____

Participant ID: ☐☐☐☐☐

End of Illness Diary *(Intervention Arm)*

END OF ILLNESS DETAILS *(continued)*

Did your child take over-the-counter medication for their cold?

O Yes O No

If yes, approximately how much did you spend?

£ ☐☐.☐☐

Did you seek further medical attention related to the cold?

O Yes O No

If yes, how many times did you use each of the following?

a. Telephone contact GP? ☐☐

b. Telephone contact out of hours GP? ☐☐

c. Telephone contact NHS 24? ☐☐

d. Attended GP? ☐☐

e. Attended out of hours GP? ☐☐

f. GP Home visit? ☐☐

g. Attended hospital? ☐☐

h. Was your child admitted to hospital?

O Yes O No

If yes, number of days and what was the reason

Number of days: ☐☐ Reason: _____

Does your child attend nursery/school?

O Yes O No

If yes, number of days your child missed nursery/school during this cold

☐☐

Number of days or work missed by adults to take care of your child

☐☐

Has your child had wheezing or whistling in the chest while they had this cold?

O Yes O No

If yes, how many days did your child have wheezing or whistling?

☐☐

Participant ID: ☐☐☐☐☐

End of Illness Diary *(Control Arm)*

END OF ILLNESS DETAILS

Please complete this on the first day your child is well after their cold or after 28 days if your child remains unwell

Date Diary Completed: ☐☐-☐☐☐-☐☐☐☐
(DD-MMM-YYYY)

How many adults and children live in the house (including your child who's taking part in ELVIS Kids)?

Adults ☐☐ Children ☐☐

Did anybody at home develop the cold after your child?

O Yes O No

If yes, how many were adults?

☐☐

If yes, how many were children?

☐☐

Did you use salt water nose drops/sprays for your child's cold?

O Yes O No

If yes, what is the name of the drops/sprays you used?

_____

How many days did you use the drops/sprays?

☐☐

How many times per day did you use the drops/sprays?

☐☐

Did your child take over-the-counter medication for their cold?

O Yes O No

If yes, approximately how much did you spend?

£☐☐.☐☐

Participant ID: ☐☐☐☐☐

End of Illness Diary *(Control Arm)*

END OF ILLNESS DETAILS *(continued)*

Did you seek further medical attention related to the cold?

O Yes O No

If yes, how many times did you use each of the following?

a. Telephone contact GP? ☐☐

b. Telephone contact out of hours GP? ☐☐

c. Telephone contact NHS 24? ☐☐

d. Attended GP? ☐☐

e. Attended out of hours GP? ☐☐

f. GP Home visit? ☐☐

g. Attended hospital? ☐☐

h. Was your child admitted to hospital?

O Yes O No

If yes, number of days and diagnosis

Number of days: ☐☐ Diagnosis: _____

Does your child attend nursery/school?

O Yes O No

If yes, number of days your child missed nursery/school during this cold

☐☐

Number of days or work missed by adults to take care of your child

☐☐

Has your child had wheezing or whistling in their chest while they had this cold?

O Yes O No

If yes, how many days did your child have wheezing or whistling?

☐☐

Participant ID: ☐☐☐☐☐

Satisfaction Questionnaire

About the Study

Q1. How easy was it to collect the swabs?

Very Easy	Easy	Moderate	Difficult	Very Difficult	Did Not

Q2. How would you rate the comfort level of your child with the swabs?

Very Comfortable	Comfortable	Moderately Comfortable	Uncomfortable	Very Uncomfortable	Did Not

Q3. How easy was it to return samples?

Very Easy	Easy	Moderate	Difficult	Very Difficult	Did Not

Q4. How easy was it to complete the daily diary?

Very Easy	Easy	Moderate	Difficult	Very Difficult	Did Not

Q5. Based on your experience, do you have any suggestions for improving the trial procedures in the future?

Participant ID: ☐☐☐☐☐

Day 28 Wheeze Details

DAY 28 WHEEZE DETAILS	
Between your child's cold ending and today, did your child develop wheezing or whistling in their chest?	O Yes O No
If yes, how many days did your child have wheezing or whistling? *(Please enter a number, e.g. 4)*	☐☐

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1-18
Protocol version	3	Date and version identifier	12
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	2,11
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11,12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5,6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9,10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10,16

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8,10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7,8,10-12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6,10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10,11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5,10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6,7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6,7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11,12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10-12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	7-9
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.