SNIFSII

Saline Nasal Irrigation For acute Sinusitis II

Research Project Protocol – REC: 19/LO/0620. IRAS: 253414

VERSION 1.2 – 09/05/2019

CONFIDENTIAL

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

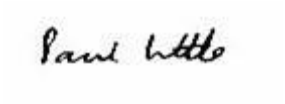
Signature: Date:...../...../....

Name: Dr Alison Knight

Position: Head of Research Integrity & Governance

Chief Investigator:

Signature: Date:09/05/2019



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Position: Professor of Primary Care

Title	**Saline Nasal Irrigation For acute Sinusitis (II): A Randomized Controlled Pilot Trial**
Abbreviated title	SNIFS (II)
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ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
BNF	British National Formulary
CI	Chief Investigator
CRF	Case Report Form
CRP	C-Reactive Protein
CTU	Clinical Trial Unit
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMP	Data Management Plan
DSMC	Data and Safety Monitoring Committee
DVS	Data Verification Site
EQ-5D	EuroQoL-5D
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HDPE	High-density polyethylene
HRQL	Health-related quality of life
HUI	Health Utility Index
IB	Investigators Brochure
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
LRTI	Lower Respiratory Tract Infection
MHRA	Medicines and Healthcare products Regulatory Agency
MIC	Minimum inhibitory concentration (*i.e.* the lowest concentration of antimicrobial that will inhibit the visible growth of a micro-organism after overnight incubation)
mls	Millilitres, volume of antibiotic or placebo to be taken by the child
ISF	Investigator Site File
NRES	National Research Ethics Service
PC-CTU	Primary Care – Clinical Trials Unit
PE	Pulmonary Embolism
PI	Principal Investigator
PSC	Programme Steering Committee
PSS	Personal Social Service

QALY	Quality-Adjusted Life-Years
QoL	Quality of Life
QP	Qualified Person
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

1. OVERVIEW OF RESEARCH

Design: Pilot RCT

Target population: Adults with uncomplicated acute rhinosinusitis: acute sinus discomfort (<=4 weeks), and 2 of reported nasal obstruction, reported purulent discharge, or pus visible).

Trial groups: a) Immediate antibiotics (this approximates usual care: currently nearly 95% of patients receive antibiotics) b) advice to use high volume hypertonic saline nasal irrigation with a delayed prescription for antibiotics.

Baseline measures: Structured history/examination. Nasal swabs for bacteriology (optional to maximise participation).

Feasibility outcomes: follow-up rates, recruitment rates, adherence/acceptability of the intervention.

Primary outcome: Antibiotic use.

Other outcomes: duration of moderately bad symptoms (using a validated symptom diary; variables (using 7 point Likert scales): nasal blockage, discharge, unpleasant taste/smell, facial pain, pain on bending, impaired activities, generally unwell, sleep disturbance.

Secondary outcomes: symptom duration until little/no problem; mean symptom score; development of new/worsening symptoms. Health related quality of life (EQ5D). Reconsultations/resource use during the next month.

Sample size: Feasibility estimates: to estimate follow-up rates in each group between 65% and 80% assuming we want to be reasonably sure that the follow-up rate is not 50% in each group (i.e.95% confidence intervals of +/- 15%) then 41 per group are needed. We also anticipate that it should be possible for the intervention group to achieve use of antibiotics of around 65% or less. To estimate this proportion with 95% confidence intervals of +/- 15% (i.e. that antibiotic use is 80% or less) 41 per group is also needed. To allow for loss to follow-up more than 100 patients are needed.

Feasibility. Our previous JAMA trial recruited 238 individuals/4 years with one RA (one centre), but recruitment is currently more challenging. We therefore estimate that with one RA at the coordinating centre and P/T RAs in two other centres will allow us to recruit our target efficiently in 2 winter seasons

2. LAY SUMMARY

Acute sinus infections are one of the commonest infections managed in primary care, Currently GPs prescribe antibiotics to most patients presenting with sinusitis, the highest of any of the common acute infections presenting in adults, at over 90%.The trouble with prescribing for most people is that we are using antibiotics too much which is causing the bacteria to become resistant, which is likely to lead in the future to serious infections becoming untreatable from ‘superbugs’. Alternatives to the initial management with antibiotics are needed.

Previous studies have tried nasal irrigation using salt solution for colds but the studies are small and not conclusive. There have also been studies of nasal irrigation in chronic sinus infections which do show some benefit. A large study in chronic or recurrent sinusitis in primary care showed that most people can learn to do nasal irrigation with simple advice and a short video to show how it is done, find it acceptable and will keep doing it over several weeks. However, there was some evidence that the approach to help people use nasal irrigation could be made more effective, dealing with key barriers or difficulties more effectively. There have been no good studies of saline irrigation in acute sinusitis.

In a separate study, we have worked together with patients to optimise how we help patients use sinus irrigation, making sure that we are providing all the necessary advice and materials to help deal with any issues or problems patients might have. The study will randomise more than 100 people with acute sinus infections presenting in primary care to either a) immediate antibiotics (current usual treatment in primary care) or b) advice to do nasal irrigation for up to 3 weeks with a 'back-up' or delayed antibiotic prescription (a prescription that can be used if the sinusitis does not settle). Participants will fill out a daily symptom diary which will allow us to see whether irrigation makes any difference to symptom severity, or to the duration of illness, and whether antibiotic were used.

Participants who are happy to have further tests will have a swab of the nose.

This study will provide evidence of recruitment and follow-up rates, and is also likely to provide preliminary evidence about whether antibiotic use is likely to be reduced, in order to provide sufficient evidence for a larger application for a full trial.

3. BACKGROUND AND RATIONALE

Acute sinusitis like complaints are a common presentation in primary care with GPs seeing 50 or more cases per year on average (1) and cause significant morbidity, anxiety, lost time from work and school, antibiotic consumption, and treatment costs (2). The costs of antibiotic prescribing for the condition has been estimated at approximately 10 million pounds per year in the UK, and 2.4 billion dollars per year in the USA(3). Increasing antibiotic resistance in the community is a matter of ongoing international concern, in considerable part driven by antibiotic prescribing in primary care (4, 5). In contrast to the limited benefit from antibiotics, antibiotic prescribing rates remain very high, especially for sinusitis where by far the highest percentage of patients receive antibiotics when compared with any other acute respiratory infection (6) - 91% of patients in the UK. The problem with limiting antibiotic prescribing in acute sinusitis is that the natural history is prolonged. A systematic review estimated a median duration of nearly 3 weeks (7) and a primary care trial in the UK for individuals more likely to have bacterial infections the illness lasted a median of 2 weeks (8). Faced with such an unpleasant condition where the GP has little else to offer it is not surprising that prescriptions for antibiotics remain the highest among all RTIs. Alternatives to the initial prescribing of antibiotics are sorely needed.

A Cochrane review of nasal irrigation for chronic or recurrent sinusitis (9) concluded that nasal irrigation was helpful. However most of the trials were small, mainly from secondary care settings, had high heterogeneity, and the review documented symptom data from only 129 participants. A more recent review with more selective inclusion criteria (2 studies)(10) concluded that there was some evidence of benefit with high volume nasal irrigation but that the quality of evidence was limited.

We are aware of two trials that have included some participants from primary care: Rabago et al(11) (n=76) assessed a gravity based high volume nasal irrigation device compared to routine care among mainly primary care participants, and Pynnonen et al.(12) (n=121) assessed a positive pressure squeeze bottle compared to saline nasal spray among volunteers from a variety of sources. Both the latter trials demonstrated effectiveness of irrigation, but included significant individual coaching in how to do nasal irrigation. More recently a large more pragmatic trial of a brief intervention to advise high volume nasal irrigation in recurrent or chronic sinusitis advised participants to use a Netipot, and provided simple instructions on a YouTube video. The trial documented some symptomatic benefit(13), but less than the previous more intensive studies. The pragmatic trial intervention was very simple, most participants even with recurrent/chronic sinusitis engaged well – most were still using nasal irrigation 6 months later, participants had fewer headaches, and they were less likely to use over the counter medication, or to report intending to see the doctor in the next attack. Nevertheless qualitative work with participants clarified that better information about overcoming initial problems could potentially have helped increase engagement in using nasal irrigation.

The literature on the use of saline irrigation for chronic or recurrent sinusitis is supported by some evidence for acute illness. A Cochrane review of trials in acute a upper respiratory illness(14) identified five RCTs (544 children (three studies); 205 adults (two studies)) which compared saline irrigation to routine care or other nose sprays. The authors concluded that nasal saline irrigation possibly has benefits for relieving the symptoms of acute URTIs, but that the trials were generally too small and had a high risk of bias, advocating larger numbers and clinically meaningful outcome measures.

Considering both the evidence from chronic/recurrent disease and acute RTIs, on balance it is plausible that a relatively simple intervention, high volume saline nasal irrigation, could help both symptoms and help reduce antibiotic use.

4. AIMS AND OBJECTIVES

Hypotheses

Our hypotheses for a full trial are that saline nasal irrigation for acute sinusitis will improve symptom management and reduce antibiotic use, and that for the feasibility trial nasal irrigation will reduce antibiotic use.

Aim of the feasibility trial: To estimate use of the intervention; acceptability of randomisation; rates of follow-up, recruitment and antibiotic use, in order to provide sufficient evidence for a full trial application

Objectives:

- To conduct a pilot trial of nasal irrigation for acute sinusitis

5. RESEARCH PLAN

Design: Parallel group randomised controlled pilot trial

5.1. Health Technologies being assessed

Sinus nasal irrigation

5.2. Target Population

Patients attending primary care with acute sinusitis

5.3. Recruitment

Recruitment will take place in Primary care, since this is where the vast majority of those presenting with sinusitis are managed**.** Eligible patients will be informed about the study by the consulting clinician or other staff at the General Medical Practice, who will explain the study and provide the patient with a patient information leaflet.

5.4. Inclusion criteria

Inclusion criteria

We will pragmatically define acute sinusitis as having sinus discomfort, and at least 2 other symptoms (2 of: patient reported nasal obstruction, patient reported purulent nasal discharge, or pus seen in the nasal cavity on inspection by the clinician). We do not propose using prior duration (e.g. the requirement for at least 7 days without improvement in the Canadian guidelines) since there is no good evidence for a particular cut-off, and our aim is to help people who are currently being treatment with antibiotics for sinusitis, many of whom present with 7 days.

5.5. Exclusion criteria

Inability to complete outcomes (reduced capacity: dementia, severe uncontrolled mental illness; terminal illness etc); head/neck cancer; HIV; immune-suppressive treatment; cystic fibrosis; pregnancy/breast feeding; other nasal disorders e.g. polyps; poor gag/swallow reflexes.

5.6. Consent

The patient will be asked to consent to the study after they have considered a patient information leaflet about the study (approved by an NHS Multi-Centre ethics committee) and had sufficient time to consider participation and ask questions. If necessary, clinicians will see other patients in order to allow sufficient time for patients to read materials and formulate questions.

5.7. Intervention

1) Control group: immediate antibiotic prescription. We wish to provide some estimate of the reduction in antibiotic possible compared with current practice. Since more than 90% of patients currently receive antibiotic for acute sinusitis the nearest approximation to usual care is a prescription for immediate antibiotics, combined with advice about the use of analgesics. Although the particular antibiotics used is not the focus of this investigation, in line with PHE guidance for primary care we will advise the use of Penicillin V 500mgs QDS (or alternatively Amoxicillin 500mg tds) for 1 week or Clarithromycin 500mg BD also for 1 week if participants are allergic to penicillin.

2) Advice to use nasal irrigation. In addition to the advice in the usual care arm to use simple analgesics participants will be given both written and verbal instructions and given a link to a video clip (uploaded on YouTube: http://www.youtube.com/watch?v=zgvoxkGYSU4) demonstrating how to perform irrigation. They will be asked to irrigate the nose (150 ml through each nostril) daily for up to 21 days or until symptoms settle, and a SinuCleanse 19 nasal cup ('Netipot') will be provided to each subject. Patients will make their own buffered saline irrigation solution every 1 to 2 days comprising: 1 heaped teaspoon salt, one half teaspoon baking soda and 1 pint (568 ml) tap water; how to do this will also demonstrated on the video clip. We chose this particular intervention based on the provisional evidence from a previous randomised controlled trial in primary care in chronic/recurrent sinusitis (11) and from our most recent large trial also in chronic or recurrent sinusitis (13), where most patients found it acceptable and the majority continued using nasal irrigation. Participants in this group will be offered a delayed antibiotic prescription as in our previous trials(19), and advised only to use it if symptoms are getting significantly worse or not even starting to settle a little after a further week.

All study participants in both groups will have access to usual care; further medication or referral will be at the discretion of the doctor according to the normal practice of that doctor.

5.8. Randomisation

Patients who consent to the study and agree to randomization will be randomized to either intervention or control group. We propose individual level randomisation to intervention or usual care, with stratification according to the prior duration of illness (> 7 days or less than 7 days).

5.9. Pilot phase

This is the protocol for the pilot phase: if successful we will apply to the HTA or other funding bodies to fund the main trial.

5.10. Eligible patients not recruited to the trial

Some patient will decline participation. The main concern for the trial data is that due to selection bias the trial may end up having limited generalisability. Hence we propose that GPs record reasons for non-participation where feasible to do so.

5.11. Data Collection - Measurements and follow-up

Nasal sampling (swabs to send for bacteriology/virology) will be optional to maximise the generalisability of the sample, but we envisage from our experience of the TARGET cohort and other studies a high level of acceptance of sampling (at least 80%). The key microbiology of interest is the bacteriology for the common bacterial pathogens since we are interested in exploring whether the presence of pathogens predicts response to antibiotics but we will also aim to store the viral samples for future analysis. Participants will keep a diary of symptoms and daily activities (including days away from work) for up to four weeks after inclusion, and will post the diary back once symptoms have settled. If no diary is received a brief questionnaire will be sent to document the key outcomes (antibiotic use; severity and duration of symptoms), and following this a phone call and/or text to individuals not returning the brief questionnaire.

5.12. OUTCOMES

Proposed feasibility outcomes.

- Recruitment rate
- Proportion of eligible patients who accept randomisation
- Proportion using nasal irrigation in the first week in the intervention group
- Proportion using their antibiotic prescription in the intervention group and in the control group
- Proportion followed up with a primary outcome in each group

Proposed clinical outcomes

Antibiotic use: Use of antibiotic prescriptions reported in the 4 weeks of the symptom diary. We anticipate that the intervention will help individuals both decide not to use an immediate prescription if they have been given one and particularly limit the redemption of any delayed prescription. We have shown that the use of delayed prescriptions reported in diaries matches whether they were collected from practices(17).

Secondary outcomes

- **Duration of moderately bad illness.** The duration of illness rated moderately bad or worse i.e. making an important difference to patients, and as used in our previous studies of respiratory infections (20, 21). It will be measured using the symptom diary and where the diary is not returned information from a brief follow-up questionnaire, and/or phone call as necessary. The 4 week diary includes 11 symptom variables, assessed on 7 point Likert scales. The score has been developed to have content validity by incorporating items which not only take account of proposed diagnostic criteria for bacterial rhinosinusitis(22) but also physicians' perceptions of the important clinical features (based on focus groups and a questionnaire study)(23). The format of the diary items has been developed in a variety of other respiratory infections and been shown to have construct and criterion validity, and also sensitivity to change.(8, 17, 24) We have also shown the total symptom score for sinusitis is internally reliable (Cronbach's alpha 0.77) and sensitive to change (standardized response mean 1.6 comparing day 0 with day 5).(8, 24)
- **The duration of any symptom until rated very little or no problem** (measured as above);
- **Reconsultation** with non-resolving, new, or worsening illness within 1 month of the index consultation documented from medical records, and which can be measured reliably(25);
- **EQ5D5L (at days 1,7,14,21,28 of the diary)**. In prior trials EQ5D has been shown to be adequate in detecting the decrement in QOL with RTIs - to allow cost-effectiveness modelling(26) should the main trial be funded;
- **Resource use.** Information on NHS resource usage will be collected for all participants from a notes review - including capturing resource use for rare major adverse events (e.g. anaphylaxis, complications, hospital admission) up to 28 days.

- **Self-reported adherence and reasons for non-adherence,** using the validated Problematic Experiences of Therapy Scale, across different aspects of intervention materials (written / video / online instructions).
- **Modified Patient Enablement Instrument(27)**

5.13. Health care resource use

The feasibility of collecting health care resource use over the 28 days post randomization will be assessed but no formal analysis is proposed for the pilot study

5.14. Cost-effectiveness

There are no plans to perform cost-effectiveness analysis for the feasibility study, but will be performed for the main trial

5.15. Sample size calculation

Feasibility estimates: to estimate follow-up rates between 65% and 80% assuming we want to be reasonably sure that the follow-up rate is not 50% in each group (i.e.95% confidence intervals of +/- 15%) then 41 per group are needed. We anticipate that it should be possible for the intervention group to achieve use of antibiotics of around 65% or less. To estimate this proportion with 95% confidence intervals of +/- 15% (i.e. to be sure the use of antibiotics is 80% or less) 41 per group is also needed.

Provisional estimates of antibiotic reduction. In addition to descriptive information of antibiotic in each group we can also provide very provisional estimates of the difference in antibiotic use compared with control: 43 individuals per group will detect a plausible 25% absolute reduction in antibiotic use (for alpha=0.05 and 80% power) to 65% assuming at least 90% of the control group use antibiotics. Allowing for 20% loss to follow-up we will recruit 108 participants.

5.16. Feasibility

In our previous one centre study we were able to assess and randomise 238 individuals who fulfilled the Berg and Carenfeldt criteria in 4 years with a full time RA, but recruitment in primary care in the current context is more challenging than previously. A GP will also not see a case of sinusitis every day so full time staff are difficult to justify in all centres. If the coordinating centre has a P/T trial manager to coordinate, and each centre has some RA support and part time administrative help, this should allow us to recruit our target in 2 winters.

5.17. Role of funders

The funder will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit for publication.

5.18. Nested qualitative study

AIMS:

To explore a range of patient views on study participation, seeking to understand positive and negative experiences from start to finish.

TIMING:

Will take place once participants have been randomized and participated.

METHODS:

Semi-structured in-depth interviews will be used, but will be flexible to permit patients to speak freely on topics they deem to be relevant to ensure key emerging issues are captured. A subtle realist approach will be employed throughout the project to help represent participants' views.

SAMPLE:

A purposive sampling approach will be designed to elicit views of a range of patients (including a mix of men and women/rural and urban settings).Between 15 and 30 interviews should be adequate to represent the views of a range of patients following participation. Additional interviews will be conducted if saturation has not been reached.

ANALYSIS:

We will follow the stages of Braun and Clarke's thematic analysis, assisted by NVivo (QSR international Pty Ltd) computerized analysis software as necessary. Analysis will aim to identify themes to help fulfil aims 1 and 2 whilst remaining flexible and open to emerging findings.

QUALITY:

Standard methodological strategies will be employed to help safeguard rigour and ensure we produce trustworthy, plausible, and relevant findings. These will include careful purposive sampling, a clear exposition of methods (including field notes, and audio recording of interviews and accurate transcription of interviews, regular discussion between the fieldworker and senior qualitative researcher (including double coding/discussion of codes). Negative case analysis will help to refine analysis/safeguard against premature completion and the researcher will be tutored in the importance of a 'reflexive' sensitivity to the relationship between the researcher and research process.

CONFIDENTIALITY:

We will abide by the University of Southampton's Data Protection Compliance Statement. The University of Southampton (the University) is a research-led university that takes its data protection responsibilities seriously. We support the aims of data protection legislation to strengthen the rights of

individuals in respect of data relating to them and we are committed to complying with our obligations when processing personal data (either as a data controller or as a data processer).

Interviews will be recorded, transcribed and destroyed on completion of transcription and then stored in accordance with the University's archiving process, which is 10 years. All data will be anonymised and/or stored on password protected and secure drives.

5.19 Discontinuation / withdrawal of participants from trial

Each participant has the right to discontinue their study medication or withdraw from the study at any time. In addition, the investigator may discontinue a participant's treatment or withdraw a participant from the study at any time if the investigator considers it necessary (e.g. the participant experiences an adverse reaction, the patient withdraws consent, or the investigator considers that further participation in the study would not be appropriate due to the personal circumstances of the participant).

Patients whose nasal irrigation is discontinued will still be required to complete their study diaries and questionnaires and will still receive telephone follow-up calls unless they choose to withdraw consent for these.

WITHDRAWAL

Once a participant withdraws or is withdrawn from the study, no actions will be taken to obtain data other than to monitor adverse events (see section 7.3. PROCEDURES FOR RECORDING ADVERSE EVENTS). Consent to proceed with reviewing the medical notes will be specifically confirmed for participants withdrawn from the study.

5.20 Definition of end of trial

The end of the trial will be the date of the last medical notes review of the last trial participant.

5.21 Thank you to patients

As a token of our thanks for helping with the study and the time doing the diary we will provide a £10:00 High Street shopping voucher.

6. NASAL IRRIGATION

6.1. Saline Description/delivery

Intervention component	Dosage form/method
SinuCleanse 19 nasal cup ('Netipot') will be provided to each subject. .	Irrigate the nose (150 ml through each nostril) daily for up to 21 days or until symptoms settle .

Buffered saline	Patients will make their own buffered saline irrigation solution every 1 to 2 days comprising: 1 heaped teaspoon salt, one half teaspoon baking soda and 1 pint (568 ml) tap water; how to do this will also demonstrated on the video clip.

TREATMENT BLINDING

Patients cannot be blinded to treatment allocation throughout the trial.

6.2. Storage of Saline

If Saline is made fresh every 1-2 days there is no need for special storage arrangements.

6.3. Compliance with Trial Treatment

Patients will be asked to record in their study diaries each time irrigation was used. Patients whose study diaries indicate that they received more than half the intended irrigations during the first week will be considered to be compliant with trial procedures. All randomised trial participants will be included in the intention-to treat population.

6.4. Monitoring Trial Treatment

The investigator or designee must maintain an accurate record of the provision of Netipots, salt and bicarbonate in the baseline CRF (to be completed during the consultation). The CRFs will be monitored for completeness by the RA or administrator running the trial, and missing data requested from clinicians.

6.5. Concomitant Medication

Trial participants will be advised to continue their usual regular medications while taking part in the trial. Healthcare professionals will record data at baseline on antibiotic prescriptions given during the consultation, also any other prescriptions (e.g. inhalers, analgesics). We will advise clinicians to prescribe an appropriate betalactam antibiotic when prescribing as a first line agent (unless allergic to beta-lactams in which case a macrolide will be advised) .

Patients will be advised that they can take over the counter medications for their sinusitis (e.g. analgesics). They will be asked to record these additional medications in the study diary from days 1 to 28.

Clinicians will treat trial participants who re-consult in whatever way they feel is clinically appropriate.

A member of the research team will provide the practice staff with instructions for extraction of data and a form to record the data from participants' medical notes on further antibiotics and other medications prescribed during the 28-day period after study entry.

6.6. Post-trial Treatment

Participants will only be asked to use nasal irrigation for the duration of the current episode of sinusitis. After this they can use nasal irrigation if they wish, based on the prior evidence of a preventive effect for chronic/recurrent sinusitis.

7. SAFETY REPORTING

All adverse events, for patients randomised into the trial, should be reported from the time the patient signs the informed consent form until one week after randomisation. Depending on the nature of the event the reporting procedures below should be followed.

Any questions concerning adverse event reporting should be directed to the Study coordination centre in the first instance. A flowchart will be provided to aid in the reporting procedures.

Adverse events presenting to the participants GP will be notified by the practitioner. In addition participants will carry a study card which highlights the need to notify their own doctor regarding adverse events. As a final check all participants will be asked to consent to a medical notes review which will take place after study recruitment at a time when any letters will have been returned from out-patient appointments. This enables us to be confident of detecting adverse events which have not been notified using the first two mechanisms. A member of the research team will provide the practice staff with instructions for extraction of data and a form to record the data from participants' medical notes on further antibiotics and other medications prescribed during the 28-day period after study entry.

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. These will not be collected for this study.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to a trial intervention" means that a causal relationship between a trial intervention and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation (i.e an overnight stay) or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

	NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the trial treatments, based on the information provided.

Hospitalisations for elective treatment of a pre-existing condition do not need reporting as Serious Adverse Events (SAEs).

The antibiotics used in SNIFSII (beta-lactams or macrolides) are licensed medicines whose most common side-effects are mucocutaneous candidosis (thrush), diarrhoea, nausea, vomiting and rash (occurrence >=1/100 to <1/10). If these occur and are non-serious and of mild to moderate severity (based on clinician's assessment) an Adverse Event Report form will not be necessary. We will collect data on events such as severe reactions to the antibiotics such as anaphylaxis, severe allergy requiring steroid administration, emergency hospitalization for chest problems and severe Clostridium (antibiotic related diarrhoea).

Unexpected adverse reactions to antibiotics will be highly unlikely amongst trial participants, as the vast majority of patients will have previously received antibiotics to treat other infections. For non-serious adverse reactions to trial medication, the Chief Investigator or a designated alternative study clinician will assess the urgency with which the participant's treatment allocation should be unblinded.

For Nasal Irrigation there have been no serious sides effects reported, the most common side effects being nasal stinging and sinus discomfort for some patients.

7.1. Definitions

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

7.2. Causality

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

Related: The adverse event follows a reasonable temporal sequence from trial intervention. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

7.3. Procedures for Recording Adverse Events

The side effects of interest will be collected through the completion of the daily diary only.

7.4. Reporting Procedures for Serious Adverse Events

Appendix E contains a flowchart summarising the procedure for SAE reporting. Healthcare professionals will report SAEs to the SNIFSII coordination centre within 24 hours of becoming aware of the event. A medically qualified individual will be responsible for assessing the relatedness of the SAE to the trial procedures . All SAEs will be reported using the SAE form either on line or by paper and reporting this to the SNIFSII coordinating centre. All SAEs will be reported using the. The will SNIFSII coordinator will maintain dedicated report lines with answerphone and fax facilities to allow reporting of SAEs. The answerphone and fax will be checked regularly during office hours.

The Chief Investigator (CI) or their designated representative will be responsible for assessing the expectedness of SAEs reported as being related to the trial. Assessment of expectedness will be based on the Summary of Product Characteristics or the previous evidence about side effects of nasal irrigation. Reporting procedures for Suspected Unexpected Serious Adverse Reactions (SUSARs) are described in section 10.6.

The CI or designated PI at each clinical site will supply any supplementary information as requested by the REC or SNIFSII coordination centre.

7.5. Expectedness

Expectedness will be determined according to the Summary of Product Characteristics for antibiotics and based on prior evidence of side effects of nasal irrigation.

7.6. SUSAR Reporting

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

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

7.7. Safety Monitoring Committee

The Trial Steering Committee will be responsible for reviewing SAEs after each recruitment season. The main aims of this review are as follows:

• To ensure the safety of each patient in the trial;

• To pick up any trends, such as increases in unexpected events, and take appropriate action;

• To seek additional advice or information from investigators where required;

• To evaluate the risk of the trial continuing and take appropriate action where necessary;

• To act or advise, through the Chairman or other consultant, on incidents occurring between meetings that require rapid assessment.

7.8. Development Safety Update Reports

In addition to the expedited reporting above, the CI shall submit once a year throughout the clinical trial, or on request, a safety report to the Ethics Committee, Host NHS Trust and Sponsor.

7.9 Criteria for the termination of trial

The TSC will review SAEs after each recruitment season. The TSC or Sponsor may advise on whether the trial should be terminated.

8. HEALTH ECONOMICS

We do not propose a formal Economic analysis for the feasibility study, but simply feasibility wok to ensure that cost/resource data can be collected.

We will measure the quality of life based on the EQ5D5L. The EQ5D5L will be included on the basis that it measures quality of life at a point in time, and will be used in conjunction with the clinical outcome measures at days (1,3,7,14,21,28). This is important for an acute condition, and EQ5D was very helpfully used in the GRACE studies in adults to document change over time (and did change significantly which suggests it is likely to be useful in this population too).

9. STATISTICS

9.1. Description of Statistical Methods

The pilot data will examine organisational difficulties, whether fewer than expected eligible patients were recruited, any issues reported by GP regarding patients eligibility, and concerns encountered from patients.(28) Unearthing the key problems for recruiters is of central importance in the piloting phase and we anticipate that the issues will become apparent, as they have in our previous studies, in the process of detailed and sensitive discussion/iteration between an experienced trial manager and the 20-30 recruiting clinicians who are likely to participate in piloting. Based on this we would then make any required adjustments to the recruitment procedures, but no forma statistical analysis will be undertaken.

Statistical analysis.

Analysis of the feasibility outcomes will be descriptive with 95% confidence intervals provided for all proportions of interest, and where relevant also subdivided by trial group (e.g. proportion followed-up; proportion of the intervention group using nasal irrigation, proportion in each group using antibiotics).

We will also provide a table of baseline characteristics by trial group also presented with their 95% confidence intervals, and a similar table of outcomes at follow-up in each trial group for all clinical outcomes with their 95% confidence intervals.

We will do an exploratory intention to treat analysis, blind to group allocation, of the difference in antibiotic use between trial groups using logistic regression controlling for the severity of baseline symptoms, and other potential confounding variables as appropriate. Analysis of duration of symptoms will be performed using Cox proportional hazard models, again controlling for baseline covariates. Kaplan Meier curves will be used to demonstrate the resolution of symptoms graphically. Analysis of symptom severity will use linear regression modelling controlling for baseline covariates.

9.2 The Level of Statistical Significance

A 5% significance level will be used for testing the effects as per the sample size calculation.

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

For the regression analyses we will impute missing data using multiple imputation if appropriate.

9.4. Inclusion in Analysis

The primary analysis will be an intention to treat basis. A per protocol analysis is unlikely to be very meaningful in the proposed modest sample but we can present estimates for individuals who irrigate more than 50% of the days during the first week.

10. DATA MANAGEMENT

10.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. Source documents will be comprised of the following:

• Case report forms (CRF) for baseline assessment, follow-up and study discontinuation (completed by researchers in consultation with participant or their healthcare professional)

• Medical records (from which medical history and previous and concurrent medication may be summarised into the CRF or entered directly into Research Online)

• Diaries (hard copies completed by parents/guardians/participants)

• Correspondence (provided by participants, their healthcare professional or researcher).

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, assent and baseline contact information page, the participant will be referred to by the study participant number/code, not by name.

10.2. Access to Data

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

Raw study data will be protected as far as is possible by the release being made following all investigations described in this Protocol and the associated study Publication Policy and Data Management Plan.

10.3. Data Recording and Record Keeping

Study data will be entered, or transferred, into a secure data base such as Research Online (RO). Participants will only be identified by a study-specific participant number and/or code in the Research Online database. Documents containing participant identifiable information will be stored separately from other study documents and saved within a securely hosted database separate from Research Online.

Our data base will manage and store clinical study data. Its usage enables compliance with Good Clinical Practice (GCP) and regulatory guidelines by offering differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, de-identification of protected health information and comprehensive auditing to record and monitor access and data changes.

Our databases meet the highest available standards for security. The servers are actively monitored to prevent failure, and backups of all data are made on a daily basis. Backups are stored in secured locations that are geographically dispersed. .

All Data Management functions will be performed in accordance with SOPs. A Data Management Plan (DMP) is in place for all hosted trials, outlining in detail the study specific procedures to ensure that high quality data is produced for statistical analysis. The DMP is reviewed and signed by all applicable parties, including the Study Manager and the Trial Statistician, prior to the first patient being enrolled.

Clinical study data will be collected in paper format, direct data capture, and also direct upload of study data. The final repository for all study data will be the study data base. All Study Data Documents (SDDs) in paper format are date stamped upon receipt and tracked within a study management database. A full pre-entry review ensures that all pages have been received, subject identifiers are consistent and obvious errors/missing data are appropriately addressed prior to entry. All paper SDDs are entered by independent data entry staff into the clinical database.

Data validation for all data entered into the clinical database is achieved by programming study specific checks at point of entry, or by execution of SQL based queries. The Clinical Data Manager will review all discrepancies and generated output. If clarification from a research site is required, the query is added to a Data Verification Site (DVS) Report, and subsequently issued. The Clinical Data Manager oversees the tracking of DVS reports until they are resolved, and applies any updates to the clinical database.

Prior to database lock, dataset review is performed by the Clinical Data Manager and the Trial Statistician. All critical data items are 100% checked against original SDDs (and subsequent updates) to ensure accuracy, and an error rate is established across all fields to ensure a consistently accurate dataset.

At the conclusion of the study and after the database has been locked, all essential documents will be archived for 15 years. The Chief Investigator is responsible for authorising retrieval and disposal of archived material.

11. QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures. Regular monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Healthcare professionals participating in our study will be asked to submit proof that they have completed GCP training, or be required to undertake GCP training (e.g. register for the online GCP course provided by the CRN team or attend local face to face training).

The Study Management Group (SMG) will be responsible for the monitoring of all aspects of the trial's conduct and progress and will ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the trial itself. The SMG will be comprised of individuals responsible for the study's day to day management (e.g. the CI, study manager, statistician, data manager) and will meet regularly.

The Trial Steering Committee (TSC) will provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC will review the accruing study data after each winter during the study recruitment period and assess whether there are any safety issues that should be brought to the REC or Sponsor's attention or any reasons for the study not to continue.

12. SERIOUS BREACHES

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

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

(b) the scientific value of the study.

In the event that a serious breach is suspected, the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed and, if appropriate, the Sponsor will report it to the REC and the NHS host organisation within 7 calendar days.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

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

13.2. ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

13.3. Approvals

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

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

13.4. Reporting

The CI shall submit once a year throughout the clinical study, or on request, an Annual Progress Report to the REC, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the REC, host organisation and Sponsor.

13.5. Participant Confidentiality

The study staff will ensure that the participants’ confidentiality is maintained. Other than on the contact information sheet, consent form and, if applicable, assent form, participants will be identified only by a participant ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data

Protection Act (and also the recent GDPR regulations) which requires data to be anonymised as soon as it is practical to do so.

14. FINANCE AND INSURANCE

14.1. Funding

The study is funded by a grant from the NIHR (National Institute for Health Research) School for Primary Care Research (SPCR).

14.2. Insurance

The University of Southampton has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research. NHS indemnity operates in respect of the clinical treatment which is provided.

15. PUBLICATION POLICY

The investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR SCPR. The publication policy for this Grant will state the lead author(s) and co-authors for each manuscript. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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17. Appendix A: Protocol Change Control

Version	Date	Summary of Changes	Author
V1.0	01/09/2018		Paul Little
V1.1	30/12/2018		Paul Little
V1.2	09/05/2019	• Youtube link added to paragraph 5.7.2 pp18 • Included a paragraph on transcription confidentiality pp21 • Saline solution measures altered from US to UK, pp22, 6.1 and pp18, 5.7.2	Paul Little

18. Appendix B: TIMETABLE

Study timetable:

0-3 months: ethics submission, RM+G. finalise RM+G; site preparation/training

3-20m pilot trial recruitment (2 seasons) and follow-up, data cleaning

20-23 months analysis, report writing

9. APPENDIX E. SAE FLOW