4S Study

Scores and **S**wabs to **S**elf-assess **S**ore Throat Feasibility Study

Full Title	4S Throat Feasibility Study – Scores and Swabs to Self-assess Sore Throat
Sponsor	University of Southampton
Sponsor Reference Number	TBC
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Study Site	GP practices in Wessex / community
Total Number of Sites	5-10
Funder	National Institute of Health Research School for Primary Care Research FR 18. £111,295
Start Date **Duration of Grant**	01/07/2020 9 months
ERGO reference	TBC
REC Number	TBC
Aims	• Understand the feasibility of, and barriers and facilitators to, conducting a study to evaluate the diagnostic properties of home assessment of sore throat using clinical prediction rules and self/parental throat swabbing. • Explore participant/parent views about (self)-assessment and swabbing/saliva tests for sore throat. • Assess the feasibility of participants using their smart phone to photograph their throat. • Develop tools to support patients/parents in (self)-assessment and testing for sore throat. • Describe the population agreeing to participate in the study and compare it to data already collected on participants presenting with sore throat.

	• Assess the participant clinical feature assessment and testing technique via video observation. • Describe the detection of bacterial and viral respiratory pathogens, including Group A streptococcus, from throat swab and saliva samples using culture and PCR. • Determine whether candidate inflammatory markers can be measured from samples taken from the mouth in the study population; and quantify potential sources of variation in marker concentrations.
Rationale	Most throat infections are caused by viruses. Antibiotics confer little benefit but are prescribed frequently, contributing to antimicrobial resistance. Clinical prediction rules (Centor and FeverPAIN) are frequently used in general practice for identifying streptococcal sore throat. Group A streptococcal rapid antigen detection tests (GAS RADT) may be useful when there is diagnostic uncertainty, but require a throat swab. Since the onset of the COVID-19 pandemic people with sore throat are commonly assessed remotely (telephone and video consultations) and taking a throat swab has been discouraged because of the risk of transmission. Self-assessment using prediction rules and self-testing could play an important role in helping target antibiotics appropriately. The feasibility of (self/parental)-assessment using clinical rules and (self/parental-)testing (for GAS and inflammatory markers) has not been assessed.
Hypothesis	We will be evaluating the hypothesis that it is feasible to conduct studies in participants with sore throat who are at home, to evaluate the diagnostic properties of home assessment of sore throat using clinical scores, and (self) -testing for pathogenic streptococci, and inflammatory markers and other pathogens including COVID-19 using throat swabs and saliva tests.
Study Design	1) Exploratory interview study and co-developing participant support materials. 2) Prospective observational feasibility study set in participant's homes.
Study Population	1) Developing Materials: Approximately 10 adult participants, 10 parents of young children (3-5) and 10 parent of older children (6-15) recruited directly from the public via advertising (social media 2) Feasibility Study: 20-40 adults with acute sore throat, and 20-30 parents of children (10-15 younger and 10-15 older children) with acute sore throat, recruited from participating general practices and directly from the general public.
Timeline	**Set-up:** During the initial 4-6 weeks (Aug-Sep 2020), study materials will be developed (including PIS, consent, CRFs) a scoping review will be performed and ethical approvals applied for (faculty and HRA NRES) **Stage 1 – Develop Materials:** 6-8 weeks (Sep-Oct 2020). Draft materials will be developed; participants will be recruited using social media and posters. The participants will then be interviewed and materials iteratively modified. **Stage 2 – Feasibility Study:** 16-20 weeks (November 2020 – Feb 2021). Participants will be recruited to the feasibility study

	Analysis: 8 weeks (Feb – Mar 2021). Data cleaning, analysis and writing up of quantitative and qualitative work.
Biological Samples	2 x throat swabs + 2 x saliva samples 1. Throat culture (group A, C or G streptococcus) 2. Viral swab + saliva samples for respiratory viral panel PCR, covid-19 PCR and exploratory cytokine analysis.
Quantitative feasibility outcomes	• The recruitment rate (recruited participants / month) overall and by approach (GP or direct). • Data completion rates. • The proportion of participants able to assess each clinical feature and able to obtain an adequate throat swabs + saliva samples. • Description of participants, including the proportions with a positive throat swab culture for group A, C and G streptococcus, and demographics (age gender, ethnicity, etc.). • The proportion of participants willing to provide a second throat swab +/- saliva samples for inflammatory marker testing. • The distribution of inflammatory marker concentrations by presence / absence of pathogenic streptococci, and by adequacy of swabbing achieved. • The impact of sample storage/transport time on inflammatory marker concentrations.
Qualitative feasibility outcomes	• Views of participating participants/parents on acceptability, barriers and facilitators to assessing clinical features and obtaining home (self-)tests. • Assessment of the quality of participant assessment of features (such as lymph node enlargement and tenderness) and swabbing / saliva tests.
Sample Size	We will aim to recruit 40-70 participants (20-40 adults and 20-30 children) with sore throat. With a sample size of 50 participants, we would be able to estimate a participation rate of 50% (this is the most conservative proportion to use) to within a 95% confidence interval of +/- 9.8%. 40 participants would allow us to estimate a participation rate of 50% to within a 95% confidence interval of +/- 11%. For the development of the assessment tools, we anticipate needing to recruit 10-20 participants in order to gain sufficient information about their experiences of participating in the research.
Statistical Analysis	<u>Description of participants</u> We will use descriptive statistics to report recruitment rates and describe the characteristics of recruited participants. We will also describe how well they meet pre-specified criteria for assessing clinical prediction rules and taking throat swabs, using standardised scoring of video-recorded observations. <u>Description of participants using with swab cultured streptococcus</u> We will use descriptive statistics to report proportions of participants with group A, C or G streptococcus and by subgroup of symptom score classification. We will a

	Respiratory Panel PCR and SARS-CoV-2 PCR to assess the feasibility of detecting common respiratory pathogens from a self-swab and saliva samples. Description of the test characteristics of the inflammatory markers We will describe biomarker detection rates and the distribution of biomarker concentrations by presence of group A, C and G streptococci, by FeverPAIN and Centor score, and by reported adequacy of swabbing. We will also explore the effect of sample storage/transport time in a subset of samples by comparing concentrations of markers from samples stored for 0, 2 and 4 days.
Questionnaire and Qualitative data	Interviews with adults and participants in stage 1 will be audio-recorded, transcribed verbatim and analysed using thematic analysis. Analysis will include reading and familiarisation with the transcripts, noting and recording initial themes and then conducting systematic and detailed open coding using NVivo. The coding of the first set of interviews will generate an initial coding framework, which will be discussed with the members of the research team. This will be further developed and refined as analysis proceeds. The research team will also critically discuss the categories and themes emerging from the data, to ensure trustworthiness and increase rigour. During stage 2, we will collect questionnaire data about the materials and study procedures. We will also interview a mixed purposive sample of between 10 and 30 participants to obtain views on the study material and procedures.
Procedures and Assessments	**All study procedures will be carried out remotely in the community** **Stage 1:** • Participant contacts study team via study website or email address. • Participant will be provided with a link for Lifeguide by the study team (if contacted by email) or will be to access the Participant Information Sheet and Informed Consent Form directly on the website. • Research fellow arranges to call the participant after having received the study information to answer any questions and confirm that the test kit will be sent to participant and a time for video consult is arranged. • Participant is consented online using LifeGuide. • Participant is contacted by the research fellow for a scheduled video call. The think aloud method will be explained fully to the participant. • Participant is observed making an assessment by the study research fellow via video call. Participants will be interviewed using the think aloud method during this procedure. • Participant is offered a break between the assessment and swab or this may be requested for clinical reasons so another call may be scheduled. • Participant is observed and rated taking self swab(s) and saliva sample(s). Participants will be interviewed using the think aloud method during this procedure. • Participant completes the sample forms and is observed by research fellow to ensure these are added into the correct pre-paid envelope to be sent directly to the correct laboratory. (All samples are optional)

	• Participant sends a photograph of their throat to the study team. **Stage 2:** • Participant with sore throat contacts clinician at their GP surgery. The clinician informs participant about the study and takes consent to pass contact details to the study team. • GP provided details of the Lifeguide system to the participant to access the Participant Information Sheet and Informed Consent Form. • Research fellow arranges to call the participant after having received the study information to answer any questions and confirm that the test kit will be sent to participant and a time for video consult is arranged. • Participant is consented online using LifeGuide. • Participant is contacted by the research fellow for a scheduled video and is observed making an assessment as soon as possible after referral and consent. • A further video call will be planned once the participant has received the test kit and participant is observed and rated taking self swab(s) + saliva sample(s). • Participant completes the sample forms and is observed by research fellow to ensure these are added into the correct pre-paid envelope to be sent directly to the correct laboratory. (All samples are optional) • Participant is interviewed (using semi-structured interviews) and completes questionnaire. • Participant sends a photograph of their throat to the study team.

Contents

1. Introduction

Acute sore throat is a common illness and a common reason for patients to see a general practitioner. Most throat infections are caused by viruses, but a minority are caused by streptococcal infections (primarily Group A strep (GAS), but also Group C and Group G strep).[1] Overall, antibiotics confer little benefit for people with sore throat, and yet they continue to be prescribed for around 60% of people presenting with sore throat.[2] Use of antibiotics causes side effects, wastes resources, promotes the development of antimicrobial resistance, and can lead to changes in gut flora which may have longer-term effects.[3,4]

Two clinical prediction rules, Centor and FeverPAIN (which are recommended by NICE[5]), have been shown to have moderately good diagnostic properties for identifying streptococcal sore throat in general practice (positive predictive value 37-47%, negative predictive value 72-90%)[6], and have become widely used in the UK. Streptococcal rapid antigen detection tests (RADT) are point of care tests that have been around for many years and have good sensitivity and specificity for detecting GAS.[7] However, the largest evaluation of their use in the U.K. (in a GP setting) concluded that they did not improve decision making over use of the FeverPAIN clinical decision rule.[8]

In the past couple of years, there have been pilot schemes set up in Wales and London that encourage people with sore throat to consult with a community pharmacist under a Sore Throat Test and Treat (STTT) service.[9,10] This involves managing patients with sore throats based upon an algorithm that uses a GAS RADT and clinical prediction rule. The COVID-19 pandemic has resulted in the STTT service being suspended in order to reduce the risk of transmission. Taking a throat swab has been identified as a high-risk procedure for transmission of COVID-19 infection, and therefore, the service as it was is unlikely to re-start any time soon. Furthermore, the COVID-19 pandemic has resulted in a large proportion of general practice consultations being conducted remotely.

Supporting remote and self-management are key priorities for the NHS. A significant proportion of patients with sore throat could potentially be managed at home. In order to facilitate safe home management of patients with sore throat, it is important to determine how well patients, and parents of patients, can (self-)assess sore throat, and how they can best be supported to take a throat (self-)swab.

Most of the criteria included in the FeverPAIN and modified Centor scores should be relatively easy for patients/parents to asses (history of fever, recent onset, no cough or coryza, age). It may be possible for patients to assess tender anterior cervical nodes, and it is unlikely that they will be able to accurately assess pus and inflammation on examination of the throat. It may therefore be necessary to combine the accessible criteria from the two scoring systems, but the validity of this, especially in this population, has not yet been assessed.

An approach that may supplement or replace testing for GAS is measuring markers of inflammation from the throat mucosa.[16] Bacterial and viral infections produce different inflammatory responses, and molecules associated with these inflammatory responses can be detected using molecular techniques, which could potentially be developed into new rapid diagnostic tests. However, although the potential for using biomarkers to differentiate bacterial from viral infections is substantial,[16-18] research into using biomarkers from throat mucosal samples as a tool for guiding antibiotic prescribing for sore throat is at an early stage. We have previously demonstrated that Calprotectin, a marker of neutrophil activity, can be measured from throat swab samples and that there is some evidence of an association with streptococcal infection.[16] The next step in exploring the utility of this novel approach is to assess barriers to accurately measuring a range of biomarkers from throat swab samples in this population, assessing the impact of potential sources of variability, and identifying candidate biomarkers to take forward to an adequately powered diagnostic study.

As sore throats are prevalent in younger populations including children, throat swabbing may not be as practical and convenient as saliva sampling which can be performed using several methods such as buccal swabbing with sponges or spitting. It is believed that with appropriate techniques salivary biomarkers can be accurately measured for diagnostic studies.[21] Research has indicated that saliva may be less reliable than throat culture for detecting group A streptococcus.[22] However, more research is needed to validate the utility of saliva testing and sampling methods for respiratory viruses and cytokines and a multi-marker approach may be required.[23]

There is therefore a need to: 1) evaluate the feasibility and diagnostic accuracy of home assessment of sore throat, and 2) evaluate the feasibility of using inflammatory markers from throat swab samples to guide antibiotic prescribing decisions. However, before we can conduct an adequately powered study, we need to identify the barriers and facilitators to undertaking research in this setting, and asses the feasibility of conducting a larger study.

Our overall aims are therefore to evaluate the feasibility of conducting a study assessing the properties of current diagnostic strategies (clinical scores and throat swabbing) and novel inflammatory marker diagnostic testing including using saliva samples in the home setting. This will allow us to develop a future study based around a clear understanding of the barriers and facilitators to undertaking this research, and determine candidate biomarkers to take forward to the next study.

2. Study objectives and outcomes

This is a pilot feasibility study that could underpin a larger trial. We aim to determine if it is feasible to conduct studies in patients with sore throat who are at home, to evaluate the diagnostic properties of home assessment of the clinical features used in clinical scores, and (self-) throat swab testing for pathogenic streptococci, common respiratory viruses and COVID-19 in addition to inflammatory markers.

2.1. Quantitative feasibility outcomes

- The recruitment rate (recruited participants / month) overall and by approach (GP or direct).
- Data completion rates.
- The proportion of participants able to assess each clinical feature and able to obtain an adequate throat swab.
- Description of participants, including the proportions with a positive throat swab culture for group A, C and G streptococcus, and demographics (age gender, ethnicity, etc.) and by presence of group A, C and G streptococcus on throat swab culture.
- The proportion of participants willing to provide a second throat swab /- saliva samples for inflammatory marker testing.
- The distribution of inflammatory marker concentrations by presence/absence of pathogenic streptococci, and by adequacy of sampling achieved.
- The impact of sample storage/transport time on inflammatory marker concentrations.

2.2. Qualitative feasibility outcomes

- Views of participants/parents on acceptability, barriers and facilitators to assessing clinical features and obtaining home (self-) throat swabs + saliva samples.
- Assessment of the quality of participant assessment of features (such as lymph node enlargement and tenderness) and swabbing + saliva sampling.

3. Study design

3.1. Preliminary development work

We will conduct a brief scoping review of scientific literature and patient materials on self-assessment of sore throat and throat swabbing + saliva sampling and as a study team decide on the most useful aspects in consultation with PPI. We will then develop an online support tool (which can be adapted to be paper-based) to support self-assessment of sore throat with clinical scores and swabs which will be hosted using the Lifeguide or a similar platform.

3.2. Stage 1 – iterative development work

During this stage, we will recruit (using social media snowball sampling) up to 10 adults, 10 parents of young children (3-5 years) and 10 parents of older children (6-15 years) to iteratively co-develop the tools to support self-assessment. Participants who have become aware of the study via social media will contact the study team via the study website or email address. The study research fellow will email the link to Lifeguide and call the patient to check if any questions and to arrange for video call/confirm sample kit will be sent. Swabs + saliva collection kits and tongue depressors will be sent to the participants by next day delivery. During the video consult, the research fellow will:

- Explain the study.
- Obtain informed consent online using Lifeguide before the video consultation.
- Collect demographic data (including age, gender, ethnicity) and symptoms (including presence, duration, and severity)
- Observe the participant making an assessment and interview the participant about the procedure and study materials using the think aloud method.
- Observe the participant performing self-swabbing/sampling (optional) and interview the participant about the procedure and materials using the think aloud method. Samples will be returned by participants using pre-paid envelopes directly to the correct laboratory for processing accompanied by a sample form with the participant ID – this will be observed by research fellow to ensure sent to the correct one. We expect to find a clinically significant difference in the range of inflammatory markers between stage 1 and stage 2 participants.
- Observe the participant attempting to photograph their or their child's throat

Qualitative research is invaluable in enabling researchers to improve the acceptability of an intervention. We will elicit and observe reactions to every element of the intervention, using think-aloud techniques [19], which enable researchers to observe people using the intervention while saying their thoughts out loud. This has provided valuable insight into people's views and experiences of an intervention [20]. We will then iteratively modify the intervention to improve acceptability.

3.3. Stage 2 – feasibility study.

In stage 2, the feasibility study, we will recruit 20-40 adults with acute sore throat and 20-30 parents of children (3-5 younger and 6-15 older children) with acute sore throat from participating general practices. We will ask GPs to discuss the study with patients presenting in consultation with sore throats to pass on contact details to the study team and provide the link to the Lifeguide website. If recruitment via this

strategy alone is not successful, we will also recruit patients with acute sore throat via social media and posters in participating GP surgeries. The study research fellow will contact participants to arrange a suitable time for the video call and to carry out the sore throat clinical assessment as soon as possible after referral and arrange sending the sample kit. Swabs + saliva sampling kits and tongue depressors will be sent to the participants by next day delivery. If there is a delay in arrival of the swabs, two video calls may be arranged in order for clinical features to be assessed more rapidly and then a second call for the swabbing/saliva sampling. During the video call(s), the research fellow will:

- Explain the study.
- Obtain informed consent online using Lifeguide before the video consultation.
- Collect demographic data (including age, gender, ethnicity) and symptoms (including presence, duration, and severity)
- Observe the participant making an assessment.
- Observe the participant performing self-swabbing / collecting samples (optional). Samples will be returned by participants using pre-paid envelopes directly to the correct laboratory for processing accompanied by a sample form with the participant ID – this will be observed by research fellow to ensure sent to the correct one. We will perform stability testing on up to ten sets of samples, which will be collected by a courier / taxi service.
- Interview the participant about the study procedures using semi-structured interviews and questionnaire.
- Observe the participant attempting to photograph their or their child's throat.

4. Selection of study population

4.1. Inclusion criteria

- Sore throat < 2 weeks duration (for stage 2 only; stage one participants are not required to have an acute sore throat).
- Fully conversant in the English language
- Able to communicate easily by video consultation
- Able and willing (in the investigator's opinion) to comply with all study requirements
- Informed consent to participate in the trial
- Adults aged > 16 years <= 65 years
- Parents of children aged 3-16 years

4.2. Exclusion criteria

- Any significant disease, disorder, or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data, for example recent surgery to the pharynx or acute illness which would contraindicate swabbing e.g. epiglottis.
- Current or recent (within 3 months) involvement in a clinical trial.

5. Recruitment

5.1. Number of participants

We aim to recruit approximately 10 adult participants and 10 parents of children > 5 years and 10 children aged 3-5 with a history of sore throat for phase 1 of the study. We aim to recruit 20-40 adults and 10-20 parents of children with acute sore throat, from 3-5 participating general practices and directly from the general public for phase 2 of the study.

5.2. Recruitment process

Stage 1 participants will be recruited directly from the public via advertising (social media, posters) following University of Southampton ERGO approval (stage 1 participants are not required to have an acute sore throat).

Stage 2 participants will be recruited from participating general practices following NHS REC approval.

GPs will be asked to inform patients who are consulting with acute sore throat about the study and with the patient's consent; they will pass on patient details to the study team. If sufficient recruitment rates are not achieved, also directly from the general public, via advertising (social media, posters in participating surgeries). Participants who make contact with the study team to express interest in taking part will be emailed participant information sheets.

6. Withdrawal

All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further treatment. If participants do not want their data to be used, we will delete their database records and dispose of biological samples.

If the research fellow deems that the participant is unsuitable for study following consent, for example because of ill health or on discovery that any of the exclusion criterias are met the participant will also be withdrawn.

7. Intervention

We will develop on-line tools to support self-assessment of clinical features and self-testing for participants with acute sore throat. Initial development will include a scoping review of the literature and consultation with PPI to construct an on-line tool, which can then be iteratively refined during stage 1 of the trial. The clinical features are often assessed using FeverPAIN and modified Centor scores (Appendix 1). Most of the criteria included in the scores should be relatively easy for participants/parents to assess (history of fever, recent onset, no cough or coryza, age). We will also develop materials to support self-swabbing of the throat + saliva collection.

The intervention will be hosted using the Lifeguide (or a similar) platform.

8. Serious Adverse Events/Adverse Events

Since the study will use existing widely practiced strategies there should be minimal risk to participants.

8.1 Definitions

For this study, "Serious Adverse Event" (SAE) is defined as any untoward medical occurrence or effect that:

- Results in death
- Is life-threatening[1]
- Requires hospitalisation[2], or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Other important medical events[3]

8.2 Causality

An SAE occurring to a research participant will be reported to the study team where, in the opinion of the Chief Investigator, the event was related to administration of any of the research procedures, and was an unexpected occurrence. The causality assessment of the event should always be undertaken by a medically qualified doctor who is delegated to do so as indicated on the trial delegation log.

8.3 Expectedness

For the purposes of this trial no SAE's are considered expected

8.4 Non serious AEs and exemptions

- Non-serious AEs will not be collected.
- SAEs NOT DIRECTLY related to the Trial are not required to be reported, this includes deaths and hospital admissions as assessed by CI as being not related to the trial. In such cases deaths will be reported using an End of Study form and will be sent directly to the trial team.
- Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, elective procedures for a pre-existing condition will not be classed as an SAE unless deemed related to the trial. Hospital admissions that are not directly related to the trial do not need to be reported

9. Trial procedures

9.1. Location

All trial procedures will be carried out by participants (or parents of children) at home in the community.

9.2. Consent

Participants will be provided with a participant information sheet and asked to consent remotely via Lifeguide before the video consultation having had the opportunity to discuss any questions with the

[1] 'Life-threatening' in the definition of 'serious' refers to an event in which the patient 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.
[2] Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
[3] Other important medical events that may not result in death, be life threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

study Research Fellow. Parents will be asked to give consent on behalf of children. Some of the older children may be able to understand child specific participant information leaflet and we will collect assent from the children who are able to understand the study procedures. All sites who are due to take part will have a requirement for the PI to have GCP (Good Clinical Practice) training valid within the last 2 years.

9.3. Data collection

For each participant we will collect demographic data (including age, gender, ethnicity) and clinical data including symptoms (including presence, duration, and severity) using the tools developed in the first stage to help with assessment of features. Only authorised persons have access to the Lifeguide (or similar) platform and to the data. Data backups must occur regularly and automatically. We will adhere to GPDR guidance and all data will be pseudonymised. For data that cannot be pseudonymised, please see below.

9.3.1 Video

As the video consults will include PID, these files will be encrypted and stored securely separately from any other participant data collected to ensure anonymity in line with GDPR legislation. This information will only be able to be accessed by relevant members of the study team. These videos will have all identifiable information is removed from the videos prior to storage for the study period before archiving (10 years). We will also distort the image of the video using Microsoft Moviemaker (or equivalent, freely available software) so the participants faces are distorted. This extra layer of security serves to preserve participant confidentiality while in storage.

9.4. Collection of biological samples

The throat culture samples will be sent to the laboratory directly from the participant as soon as possible after the sample is taken in a pre-paid envelope supplied by the study team, along with a sample form which will reference the participant's anonymised study ID and should be processed within 24 hours. The lab results analysed at the site will be used for the purpose of gathering data to support research and will not be used for diagnostic purposes. The throat culture samples will be processed on receipt and destroyed by the pathology laboratory after analysis in keeping with standard procedures.

The viral swab and saliva samples will be used to obtain both the viral PCR analysis and the cytokine analysis. 200 micolitres of the 3mL transport medium will be used for respiratory PCR (Targets = Influenza A, Influenza B, RSV A/B (does not distinguish), Metapneumovirus, Parainfluenza 1, 2 and 3 (does distinguish), Rhinovirus, Adenovirus) and COVID-19. The viral / cytokine swab and saliva samples will be frozen and batch analysed at the end of the study. The samples will be destroyed after processing. We will courier / taxi up to ten samples in stage 2 to be frozen as soon as possible for the stability analysis.

Future studies could include a wider range of inflammatory markers but for this feasibility study, we are including a few key inflammatory markers that have been shown to be useful in differentiating bacterial from viral infections in the past,[16-18] or are known to be associated with bacterial or viral inflammatory processes. We plan to use ELISA assays to measure concentrations of:

- Calprotectin
- Neutrophil elastase

In addition, we will measure the concentrations of the following markers using Luminex Mulitplex assays:

- Interleukin 1 beta (IL-1β)

- IL-6
- IL-17A
- IL-21
- Neutrophil lipocalin
- Matrix metalloproteinase-8 (MMP-8) / neutrophil collagenase
- Matrix metallopeptidase-9 (MMP-9)
- Interferons (α, β, γ)
- C-X-X motif chemokine 10 (CXCL10) / interferon gamma-induced protein 10 (IP-10)

If concentrations are above the standard curve, then we will use serial dilutions until we achieve results within the standard curve. We will also explore the effect of sample storage time by testing a subset of thawed samples (couriered to lab) within 4 hours and after they have been stored at room temperature for 1, 2 and 4 days.

9.4.1 Destruction of Samples

Samples will be stored in accordance with Human Tissue Act requirements at the processing laboratory with no patient identifying information (a study ID number will have been allocated prior to receipt by the laboratory). Samples will only be kept for the duration of the sample analysis (upon receipt or frozen for analysis at the end of the study) and no analysis on DNA will take place. All sample destruction will be carried out according to GLP following the laboratory procedures by trained laboratory staff.

9.5. Summary of procedures

The trial procedures during stage 1 are listed below in Table 1 with an estimated time taken of 1 hour and 5 minutes.

Procedure	Description	Estimated time taken
Participant contacts study team	Participant contacts study team via study website or email address to register interest for the study. Participant is emailed link to the Lifeguide website for Participant Information Sheet and Informed Consent Form.	10 minutes
Participant accesses study material	Participant accesses study tools / training material via website.	10 minutes
Consent	Participant (or parent of child) is called by research fellow to discuss any questions and consents using Lifeguide. Arrangements are made to send through sample kit and arrange for video consult.	15 minutes
Participant makes clinical assessment & is interviewed	Participant is observed making a clinical assessment by the study research fellow via video consult. Participant will be	15 minutes (followed by break prior to swab if required)

	interviewed using the think aloud method during this procedure.	
Participant takes self-swab(s) & is interviewed.	Participant is observed and rated taking a throat swab. If in agreement, they will take further samples (swab + saliva sample) for viral pathogen and cytokine analysis. Participants will be observed completing sample form and putting sample(s) in pre-paid envelope to send directly to the correct laboratory with a sample form detailing study ID only. Participant will be interviewed using the think aloud method during/after the procedure.	15 minutes

Table 1 – Phase 1 study procedures

The procedures during stage 2 are listed below in Table 2 with an estimated time taken of 50 minutes.

Procedure	**Description**	**Estimated time taken**
Participant contacts study team	Participant develops sore throat and contacts their GP surgery. The assessing clinician informs patient about the study and with consent passes patient's information onto the study team. The GP provides the link for the Lifeguide website to the patient.	10 minutes
Participant accesses study material	Participant accesses study tools / training material via website.	10 minutes
Consent	Participant (or parent of child) is called by research fellow to discuss any questions and consents using Lifeguide. Arrangements are made to send through sample kit and arrange for video consult.	15 minutes
Participant makes clinical assessment	Participant is observed making a clinical assessment by the study research fellow via video consult.	5 minutes

Participant takes self-swab(s) (This procedure may be performed on a different day from the other procedures)	Participant is contacted via video consult to be observed by research fellow and rated taking a throat swab. If in agreement, they will take further samples (swab + saliva sample) for viral pathogen and cytokine analysis. Participants will be observed completing sample forms and adding to prepaid envelopes to return sample(s) directly to the correct laboratory with a sample form detailing study ID only. Up to ten samples will be collected by taxi / courier.	10 minutes
Participant is interviewed about the study procedures	Participant is interviewed using semi-structured interviews and questionnaire about their views on the study procedures.	10-15 minutes

Table 2 – Phase 2 study procedures

10. Statistics and analysis

10.1. Sample size

For the development of the assessment tools, we anticipate needing to recruit 10-20 participants in order to gain sufficient information about their experiences of participating in the research.

For stage 2, we will aim to recruit 40-60 participants (20-40 adults and 10-20 children) with sore throat. With a sample size of 50 participants, we would be able to estimate a participation rate of 50% (this is the most conservative proportion to use) to within a 95% confidence interval of +/- 9.8%. 40 participants would allow us to estimate a participation rate of 50% to within a 95% confidence interval of +/- 11%.

10.2. Study feasibility data

We will use descriptive statistics to describe:

- The recruitment rate (recruited participants / month) overall and by approach (GP or direct). If we do not recruit sufficient participants (3 per week) after one month of the stage 2 trial, we will also recruit using social media and review recruitment strategies.
- Data completion rates.
- The proportion of participants able to assess each clinical feature and able to obtain an adequate throat swab.
- The proportion of participants willing to provide a second throat swab + saliva sample for inflammatory marker testing.

10.3. Description of participants

We will use descriptive statistics to describe the characteristics of recruited participants. We will also describe how well they meet pre-specified criteria for assessing clinical prediction rules and taking throat samples, using standardised scoring of video-recorded observations.

10.4. Description of participants with swab cultured streptococcus

We will use descriptive statistics to report proportions of participants with group A, C or G streptococcus and by subgroup of symptom score classification. We will also use a standard respiratory panel and SARS-CoV-2 PCR to assess the feasibility of detecting common respiratory pathogens from a self-swab sample.

10.5. Inflammatory biomarker testing

Swabs will be transported in Amies transport media. Upon arrival in the laboratory, they will be stored at -80^{o}C until ready for batch processing. Future studies could include a wider range of inflammatory markers but for this feasibility study we are including a few key inflammatory markers that have been shown to be useful in differentiating bacterial from viral infections in the past,[16-18] or are known to be associated with bacterial or viral inflammatory processes. We plan to use ELISA assays to measure concentrations of:

- Calprotectin
- Neutrophil elastase

In addition, we will measure the concentrations of the following markers using R&D Mulitplex:

- Interleukin 1 beta (IL-1β)
- IL-6
- IL-17A
- IL-21
- Neutrophil lipocalin
- Matrix metalloproteinase-8 (MMP-8) / neutrophil collagenase
- Matrix metallopeptidase-9 (MMP-9)
- Interferons (α, β, γ)
- C-X-X motif chemokine 10 (CXCL10) / interferon gamma-induced protein 10 (IP-10)

If concentrations are above the standard curve, then we will use serial dilutions until we achieve results within the standard curve. We will also explore the effect of sample storage time by testing a subset of samples after they have been stored at room temperature for 2 and 4 days.

10.6. Description of the test characteristics of inflammatory markers

We will describe biomarker detection rates and the distribution of biomarker concentrations by presence of group A, C and G streptococci, by FeverPAIN and Centor score, and by reported adequacy of swabbing. We will also explore the effect of sample storage/transport time in a subset of samples by comparing concentrations of markers from samples stored for 1, 2 and 4 days.

10.7. Qualitative data

The think aloud interviews gathered during stage 1 will be used to iteratively develop the study material used to guide the assessments and swab / sample taking. Interviews with adults and participants in stage

2 will be audio-recorded, transcribed verbatim and analysed using thematic analysis. Analysis will include reading and familiarisation with the transcripts, noting and recording initial themes and then conducting systematic and detailed open coding using NVivo. The coding of the first set of interviews will generate an initial coding framework, which will be discussed with the members of the research team. This will be further developed and refined as analysis proceeds. The research team will also critically discuss the categories and themes emerging from the data, to ensure trustworthiness and increase rigour.

11. Trial closure

The end of trial is considered the date of the last participant recruited into the 4S trial has completed the study and laboratory analysis has been completed.

12. Archiving

All research data will be stored in accordance with the University of Southampton Research Data Policy and will be held for a period of 10 years from collection, creation or generation of the Research Data or publication of the research results (whichever is the later).

13. Regulatory Issues

The study will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 as amended.

The protocol, informed consent form, participant information sheets, and any proposed advertising material will be submitted for written approval to an appropriate Research Ethics Committee (REC); host institution(s); and for Research governance approval, prior to any trial procedures taking place. The Health Research Authority guidance on consent and participant information sheets will be followed as appropriate. The Chief Investigator (CI) or delegate will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.1. Confidentiality

The CI will ensure all trial staff are fully trained and adhere to the principles of Good Clinical Practice (GCP) and the Data Protection Act, 1998. Participants will only be identified on trial documents by use of a unique trial ID which cannot be used to identify individual participants. Electronic data will be pseudonymised and GPDR guidance will be adhered to. Any information which contains PID (such as video consults) will be encrypted and stored securely separately from any other participant data collected to ensure anonymity. This information will only be accessed by relevant members of the study team.

13.2. Indemnity

University of Southampton will provide indemnity and compensation in the event of a claim by, or on behalf of participants, for negligent harm as a result of the study design and/or in respect of the protocol authors/research team. The University of Southampton does not provide compensation for non-negligent harm.

13.3. Study sponsorship

University of Southampton will act as sponsor for study.

13.4. Funding

The trial will be funded by the School for Primary Care Research (SPCR) (round 18) administered by the National Institute for Health Research by means of a research grant to the Primary Care and Population Science department. The research funding will be administered by the University of Southampton.

13.5. Audits and inspections

The study is participant to inspection by National Institute for Health Research SPCR as the funding organisation. The trial may also be participant to inspection and audit by University of Southampton under their remit as sponsor.

14. Publication policy

The trial protocol will be published and the trial registered with the ISRCTN. The trial results will be published and all who meet the criteria for authorship will be listed as authors. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. Papers will be shared with the funders prior to submission. Funders will have 14 days in which to respond and to bring any matters of factual accuracy relating to the attention of the trial team. The funders will have no role in decisions on publication. The funding source and other support will be acknowledged.

14.1. **Feedback to participants and other stakeholders**

Participants, and associated GPs will receive summaries of the trial findings and they will be made available to the general public via the trial website. The PPI representatives will be asked for their assistance in ensuring the material prepared for the general public is comprehensive and appropriate.

15. Study Gantt chart

	1	2	3	4	5	6	7	8	9
Task	**Jul-20**	**Aug-20**	**Sep-20**	**Oct-20**	**Nov-20**	**Dec-20**	**Jan-21**	**Feb-21**	**Mar-21**
Develop and refine protocol									
Develop phase 1 documents (consent +PIS)									
Apply for stage 1 faculty ethics									
Scoping literature review									
Develop & revise materials									
Apply for HRA NRES									
Develop Online CRFs and database									
Recruit stage 1 participants									
Interview Stage 1 participants									
Recruit GP surgeries									
Recruit Stage 2 participants									
Data cleaning and analysis									
Report writing and dissemination									

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17. Appendices

17.1. Appendix 1 – clinical scores

FeverPAIN criteria

- **F**ever (during previous 24 hours)
- **P**urulence (pus on tonsils)
- **A**ttend rapidly (within 3 days after onset of symptoms)
- Severely **I**nflamed tonsils
- **N**o cough or coryza (inflammation of mucus membranes in the nose)

Each of the FeverPAIN criteria score 1 point (maximum score of 5). Higher scores suggest more severe symptoms and likely bacterial (streptococcal) cause. A score of 0 or 1 is thought to be associated with a 13 to 18% likelihood of isolating streptococcus. A score of 2 or 3 is thought to be associated with a 34 to 40% likelihood of isolating streptococcus. A score of 4 or 5 is thought to be associated with a 62 to 65% likelihood of isolating streptococcus

Centor criteria

- Tonsillar exudate
- Tender anterior cervical lymphadenopathy or lymphadenitis
- History of fever (over 38°C)

- Absence of cough

  Each of the Centor criteria score 1 point (maximum score of 4). A score of 0, 1 or 2 is thought to be associated with a 3 to 17% likelihood of isolating streptococcus. A score of 3 or 4 is thought to be associated with a 32 to 56% likelihood of isolating streptococcus