CLINICAL INVESTIGATION PLAN

Best Assessment of Sore Throat and Antibiotic prescribing (BASTA)

Version 1.1 dated 2023-03-17

Principal Investigator:

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Sponsor:

Allmänmedicinskt Centrum, The Västra Götaland Region, and

Institute of Medicine, University of Gothenburg

Synopsis

Title:	Best Assessment of Sore Throat and Antibiotic prescribing (BASTA)
Aim:	This project aims to investigate if an organisational change of patient flow away from medical practitioners can reduce unnecessary antibiotic prescribing in patients attending with a sore throat as the main complaint.
Primary Objective:	Will the proportion of patients attending for an uncomplicated acute sore throat being managed according to prevailing guidelines differ if the initial assessment is made by a medical practitioner, a trained nurse or a trained pharmacist?
Secondary Objectives:	1) What proportion of patients attending PHC centres or pharmacies are classified as apparently uncomplicated, potentially complicated or potentially critically ill? (see appendix 1)1) 2) Will patient characteristics differ if the patient first appears to the medical practitioner, a trained nurse or a trained pharmacist? 3) To what extent do patients attending Primary Health Care/Pharmacies due to an acute sore throat harbour the SARS-CoV-2 virus?
Study Design:	A pragmatic controlled clinical trial design with three study arms. A total of 12 primary health care centres and 12 Pharmacies will function as study sites. One primary health care centre and one Pharmacy will be paired to form one cluster. 12 clusters will be allocated to one of three study arms: a) Patients will be first assessed by General practitioner. b) Patients will be first assessed by Nurse. c) Patients will be first assessed by Pharmacist.
Study Population:	Patients aged ≥6 years of age contacting a primary health care centre or a Pharmacy with the main complaint being an acute sore throat will be asked for participation.
Number of Subjects:	Approximately 450 subjects will be included altogether.
Eligibility Criteria:	Patients contacting the PHC centre or nearby Pharmacy with the main complaint, being an acute sore throat will be asked to participate. **Inclusion criteria** • The patient is contacting/attending PHC centre or Pharmacy presenting with a sore throat as the main complaint. • Male or female, aged ≥6 years. • Fluent in Swedish (reading, writing, conversational) (applicable to caregivers/parents/guardians in case of children). • Mental state such that he or she can understand and give informed consent to participation in the study by signing the Information and Consent Form. • Provision of signed and dated Informed Consent Form. **Exclusion criteria** • The illness episode is classified as potentially complicated or potentially critically ill (see appendix 1)

	• Presence of SARS-CoV-2 virus in a patient first appearing at the PHC in a cluster where the assessment is supposed to be done by the pharmacists. The patient will not be sent to the pharmacist in case of presence of SARS-CoV-2-virus. • Patient request to be withdrawn from the study.
Study Period:	Jan 2023 – December 2025
Sponsor:	Allmänmedicinskt Centrum, The Västra Götaland Region, Sweden and Institute of Medicine, University of Gothenburg
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Version number and date:	Version 1.1 dated 2023-03-17
Investigation sites:	12 Primary Health Care Centres in the region of Västra Götaland 12 Pharmacies in the region of Västra Götaland
Identification number of the clinical investigation:	Universal Trial Number (UTN): U1111-1278-6025 ClinicalTrials.gov Identifier: TBA CIP code: BASTA

Changes to the clinical investigation plan

Date	Changes
2022-06-23 Version 1.0	Initial version
2023-03-17 Version 1.1	**Change 1:** The previous version of Appendix 1 in this clinical investigation plan was inspired by ongoing discussions between researchers from different countries. These discussions has since been slightly refined and resulted in a published paper (https://doi.org/10.1080/23744235.2023.2191714). Hence, the table in Appendix 1 stating the differences between apparently uncomplicated, potentially complicated and potentially critical illness had a minor revision to make some clarifications and two new figures taken from the now published manuscript is added. The new figure 2 is revised compared to the published manuscript in that the wait-and-see policy for patients with an apparently uncomplicated acute sore throat and 3-4 Centor criteria was removed to make figure 2 to comply exactly with the current Swedish national guidelines for managing patients with an acute sore throat. **Change 2:** More than 50% of pharmacies do not have space allocated making physical examination of patients possible. Hence, the pharmacies having this space has to be allocated to the arm where patients are assessed by pharmacists while the other pharmacies have to be allocated to one of the other two arms. This means we have to eliminate the random allocation of pharmacies to arms. This resulted in minor changes throughout the clinical investigation plan. **Change 3:** End of study is extended from June 2025 to December 2025.

Protocol Agreement

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing the sponsors with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Title: Best Assessment of Sore Throat and Antibiotic prescribing (BASTA)

Protocol Number: 1.1

Protocol Date: 2023-03-17

Investigator Signature	*Date*

Ronny Gunnarsson, Professor in General Practice

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1 List of Abbreviations

ARTI	Acute Respiratory Tract Infection
CIP	Clinical Investigation Plan
COVID-19	Coronavirus Disease that emerged 2019
eCRF	electronic Case Report Form
GAS	Group A Streptococci
ICF	Informed Consent Form
ISF	Investigator Site File
PHC	Primary Health Care
PI	Principal Investigator
PMG	Project Management Group
SIC	Subject Identification Code

2 Introduction

A sore throat is one of the common reasons people attend primary health care (PHC).[1] It is a special kind of acute upper respiratory tract infection (ARTI) commonly caused by various viruses and group A beta-haemolytic Streptococci (GAS). A viral origin should not be treated with antibiotics. However, the opinions on antibiotic use when the cause is GAS varies [2].

2.1 Antibiotic stewardship

ARTI is the most common cause for antibiotic prescribing in PHC [3] with an overprescribing of 2-4 times compared to guidelines.[4] Growing use of antibiotics is nowadays one of the biggest public health challenges, which require immediate action to prevent antibiotic resistance. Guidelines aim to reduce antibiotic prescribing for uncomplicated ARTI and may theoretically be beneficial but they have a tendency to work less well in PHC.[5] It has been challenging to implement the required organizational and behavioural changes needed into the clinical praxis of PHC. Inadequate time, resources and support are common factors explaining the lack of success.[6] The main problem seen is that guidelines are ignored by many medical practitioners who instead develop their own unique behaviour of antibiotic prescribing that does not resemble any guideline.[7, 8, 9]

2.2 Antibiotic stewardship interventions

A multitude of interventions has been done to change medical practitioners' prescribing of antibiotics. Some of these studies show a modest short-term benefit[10] but it seems difficult to prove that any of the attempts so far has any long term benefit.[10]

A possible alternative is to let other health care providers than medical practitioners manage otherwise healthy patients at their first visit for an uncomplicated acute sore throat. These patients are already today initially screened by not only medical practitioners, but also nurses and pharmacists. Studies evaluating nurse's management of patients with sore throat are, due to methodological problems, inconclusive. A study by Thornley et al[11] tested the outcome of

letting community Pharmacies manage patients with an uncomplicated acute sore throat. The pharmacists aimed to adhere to a guideline identical to the current Swedish guideline and managed to prescribe antibiotics to only 9.8% of patients, which is much less compared to the prescribing pattern of medical practitioners. However, it is unclear if these patients had a milder illness compared to those seen by medical practitioners.

2.3 Current management of patients attending with an acute uncomplicated sore throat

Today patients appear either at a PHC centre or at the Pharmacy. The Pharmacy may provide advice on analgesic or refer the patient to a PHC centre. At the PHC centre, the patient may first appear to the medical practitioner or a nurse pending on local routines. The current Swedish guideline recommends no antibiotics and no testing for patients with 0-2 Centor criteria. For patients with 3-4 Centor criteria the guideline recommends testing and only consider antibiotics if GAS is present.

2.4 COVID-19

Key symptoms associated with COVID-19 include cough, fever, headache, breathlessness and loss of sense of smell and taste.[12] A sore throat, which can be an early sign of the disease, is a less known symptom of COVID-19. However, 5-17% of patients with COVID-19 will experience a sore throat[13, 14] and attend their local PHC centres and Pharmacies.

2.5 The remaining unresolved problem

COVID-19 has gradually transformed from expressing itself as a severe lower respiratory tract infection to be more of an upper respiratory tract infection. Furthermore, COVID-19 is likely to transform from a pandemic to an endemic state with a low continuous incidence. Hence, in response to COVID-19 it seems crucial to identify to what extent the common sore throat is caused by the SARS-CoV-2.

Furthermore, a large controlled clinical trial is required to sort out if patients attending with a sore throat as the main complaint are best managed by medical practitioners, nurses or pharmacists. This study aims to perform such a controlled clinical trial comparing the outcome of sore throat patients management by medical practitioner, nurses and pharmacists. This study also aims to investigate to what extent the SARS-CoV-2 virus is identified in these patients.

2.6 Rationale and justification of study

Antibiotic prescribing in PHC is influenced by the following factors:

1) The patient propensity to visit a medical practitioner when ill. This is partly a personality factor[15] and partly influenced by competing, more or less accurate, information available from the government, friends, relatives, the press and on the Internet.
2) The degree of access to an appointment with a medical practitioner. The number of doctors is increasing both in absolute numbers and on a per capita basis in most high-income countries.[16] However, this is a double edged sword. There is a correlation between attendance rates and antibiotic prescribing[3, 4] so lowering the threshold to see a medical practitioner is likely to increase antibiotic prescribing.
3) The threshold for the medical practitioner the patient encounter to prescribe antibiotics. This vary due to different perceptions and personal preference[17] and can be labelled as the doctor risk factor.

4) The actual health of the patient with symptoms and signs. This may be a less important factor in the decision to prescribe antibiotics.

Overprescribing of antibiotics suggests our health care system is a risk factor for population health. Several high-income countries have failed in addressing the issue of overuse of antibiotics.[16] Although Sweden has so far been more successful than most other high-income countries in its use of antibiotics[16], there is scope for further improvements.[4] The "low hanging fruit" for the health care system is to review and eliminate unnecessary use of antibiotics, especially in PHC.

2.7 A risk/benefit assessment and ethical considerations

The study will be approved by the Swedish Ethical Review Authority before recruiting study subjects. All subjects included in the study will sign an informed consent form.

Participants are not expected to have any short-term health benefits from participating in the proposed study. Potentially, in the long term, participants might contribute to the implementation of new and enhanced antibiotic stewardship in health care.

3 Aims and objectives

3.1 Primary objective

Will the proportion of patients attending for an uncomplicated acute sore throat being managed according to prevailing guidelines differ if the initial assessment is made by a medical practitioner, a trained nurse or a trained pharmacist?

3.2 Secondary objectives

1) What proportion of patients attending PHC centres or pharmacies are classified as apparently uncomplicated, potentially complicated or potentially critically ill? (see appendix 1)
2) Will patient characteristics differ if the patient first appears to the medical practitioner, a trained nurse or a trained pharmacist?
3) To what extent do patients attending PHC/Pharmacies due to an acute sore throat harbor the SARS-CoV-2 virus?

4 Methods and study procedures

4.1 Study design

This study is a pragmatic controlled clinical trial. The duration of this study for each subject will be a maximum of approximately 1 month from inclusion to follow-up assessment.

4.2 Setting

The study will be conducted at PHC centres and Pharmacies in region Västra Götaland, Sweden. A total of 12 PHC centres and 12 Pharmacies will function as study sites. One PHC centre and one Pharmacy will be paired to form one cluster. These two are located near each other.

4.3 Allocation

Invited PHC centres and Pharmacies will be allocated to one of three arms. Some pharmacies will have space to assess patients, and some won't. PHC centres and pharmacies expressing a wish to participate will be given thorough study information by the trial manager (or a person delegated

this task by the trial manager). When three PHC centres and pharmacies have remaining interest where at least one of the pharmacies have the space to assess patients they will be allocated to one of three arms, either to study arm 1, 2 or 3.
Arm 1: participants get allocated for first assessment by a medical practitioner
Arm 2: participants patients get allocated for first assessment by a Nurse
Arm 3: participants patients get allocated for first assessment by a Pharmacist
It is our ambition to allocate in total 12 PHC centres and 12 pharmacies.

4.4 Study population and selection criteria

This study is aiming to include 450 eligible study participants, 150 participants per study arm.

4.4.1 Pre-screening and recruitment methods

Patients contacting the PHC centre or nearby Pharmacy with the main complaint being an acute sore throat will be asked to participate in the study. If they agree, they will be asked to answer a few control questions (pre-screening), to assure they are eligible for inclusion. Eligibility criteria are described in detail elsewhere.

4.4.2 Consenting subjects

Following approval from the Swedish Ethical Review Authority, and before any investigation related procedure, potential subjects will sign the Informed Consent Form (ICF). The subjects will be given time to read and understand the contents of the ICF. The subjects will also have the chance to ask any questions that may have emerged. Research nurses may be delegated to obtain informed consent. If a subject is younger than 18, informed consent will be sought from a parent/guardian. Since this research involves no more than minimal risk, the consent of one parent/guardian will be considered sufficient.

4.4.3 Screening and eligibility criteria

Only subjects who fulfill all inclusion criteria will be enrolled in the investigation. Once the ICF is signed, each subject will be allocated a Subject Identification Code (SIC). The SIC will be recorded in the electronic Case Report Form (eCRF) associated with each subject as well as in patient's chart/medical history. A Screening and Enrolment Log, that identifies everyone who has been pre-screened, screened and enrolled in the clinical investigation, will be kept in the Investigator Site File (ISF).

4.4.4 Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. The patient is contacting/attending PHC centre or Pharmacy presenting with a sore throat as the main complaint.
2. Male or female, aged ≥6 years.
3. Fluent in Swedish (reading, writing, conversational) (applicable to caregivers/parents/guardians in case of children).
4. Mental state such that he or she can understand and give informed consent to participation in the study by signing the Information and Consent Form.
5. Provision of signed and dated Informed Consent Form.

4.4.5 Exclusion criteria

Patients fulfilling any single exclusion criteria will be withdrawn from the study. Any data obtained before the withdrawal will be kept and included in analysis. Exclusion criteria to be applied after inclusion:

- The illness episode is classified as potentially complicated or potentially critically ill (see appendix 1)
- Presence of SARS-CoV-2 virus in a patient first appearing at the PHC in a cluster where the assessment is supposed to be done by the pharmacists. The patient will not be sent to the pharmacist in case of presence of SARS-CoV-2-virus.
- Patient request to be withdrawn from the study.

4.5 Study Assessments

4.5.1 Inclusion (Day 0)

Eligible subjects will be referred and assessed according to the planned allocation arm for the cluster, i.e. Arm 1/Arm 2/Arm 3. According to the protocol a standard assessment of sore throat is followed by a throat swab in order to detect GAS as well as the SARS-CoV-2 virus. The subject's body temperature will be measured with an ear thermometer and any previous intake of fever medication will be recorded in the eCRF. Assessment of the Centor criterium fever will be based on either of:

1) subject's body temperature measured at site
2) patient history on subject's body temperature measured at home
3) patient history on a high probability of fever even if the temperature is not measured (e.g. sweating, chills and shivering, headache, muscle aches, general weakness).

Testing for GAS as well as SARS-CoV-2 virus will be performed at the PHC centre in all participants regardless of investigator's clinical decision concerning the need of a throat swab for further management.

The informed consent process, assessment and throat swab is estimated to take approximately 15-20 minutes. For safety reasons all participants who, according to their allocation, will be primarily assessed by either a nurse or pharmacist will also receive an additional final assessment conducted by a medical practitioner. Hence, a medical practitioner is making the final decision as to antibiotic prescribing. For details see Table 1 (next page).

Table 1. Study procedures at the different study arms.

	Arm 1 (primary assessment by medical practitioner)	**Arm 2** (primary assessment by Nurse)	**Arm 3** (primary assessment by Pharmacist)
Patient first appear to medical practitioner	1) Informed consent by medical practitioner	1) Informed consent by medical practitioner	1) Informed consent by medical practitioner
	2) Assessment by medical practitioner	2) Assessment by nurse	2) Throat swab (presence of SARS-CoV-2 virus → staff is informed and patient is excluded)
	3) Throat swab (presence of SARS-CoV-2 virus → staff is informed)	3) Throat swab (presence of SARS-CoV-2 virus → staff is informed)	3) Assessment by medical practitioner (patient asked to conceal any information provided by the medical practitioner)
	4) Assessment again by medical practitioner if the medical practitioner requested a throat swab.	4) Assessment again by nurse if the nurse requested a throat swab.	4) Transfer PHC → Pharmacy
		5) Assessment by medical practitioner	5) Assessment by pharmacist
			6) Assessment again by pharmacist if the pharmacist requested a throat swab*
Patient first appear to the nurse at the PHC	1) Informed consent by nurse	1) Informed consent by nurse	1) Informed consent by nurse
	2) Assessment by medical practitioner	2) Assessment by nurse)	2) Throat swab (presence of SARS-CoV-2 virus → staff is informed and patient is excluded)
	3) Throat swab (presence of SARS-CoV-2 virus → staff is informed)	3) Throat swab (presence of SARS-CoV-2 virus → staff is informed)	3) Assessment by medical practitioner (patient asked to conceal any information provided by the medical practitioner)
	4) Assessment again by medical practitioner if the medical practitioner requested a throat swab.	4) Assessment again by nurse if the nurse requested a throat swab.	4) Transfer PHC → Pharmacist
		5) Assessment by medical practitioner	5) Assessment by pharmacist
			6) Assessment again by pharmacist if the pharmacist requested a throat swab*
Patient first appear at the Pharmacy	1) Informed consent by pharmacist	1) Informed consent by pharmacist	1) Informed consent by pharmacist
	2) Transfer Pharmacy → PHC	2) Transfer Pharmacy → PHC	2) Assessment by pharmacist
	3) Assessment by medical practitioner	3) Assessment by nurse)	3) Transfer Pharmacy → PHC
	4) Throat swab (presence of SARS-CoV-2 virus → staff is informed)	4) Throat swab (presence of SARS-CoV-2 virus → staff is informed)	4) Throat swab (presence of SARS-CoV-2 virus → staff is informed)
	5) Assessment again by medical practitioner if the medical practitioner requested a throat swab.	5) Assessment again by nurse if the nurse requested a throat swab.	5) Assessment again by pharmacist if the pharmacist requested a throat swab*
		6) Assessment by medical practitioner	6) Assessment by medical practitioner

*pharmacist phone the PHC to obtain the test outcome and register a decision on management

Indicates relocation of the participant from the Pharmacy to the PHC or from the PHC to the Pharmacy.

Indicates assessment by a medical practitioner (every patient is assessed at least once by a medical practitioner).

4.5.2 Follow-up

Approximately one month after inclusion, all participants who were assessed according to their allocation to study arms will be asked to fill out a Follow-up Questionnaire (Appendix 2). The subject will be either prompted by a text message (SMS) or an email or, alternatively, will be contacted via telephone, depending of the way of communication chosen by the subject on Day 0 (Inclusion).

4.5.3 Collection of POCT test

For the purpose of this study each participating PHC centre will receive Abbott ID NOW Strep A, a small device which will be used for the detection of GAS as well as the SARS-CoV-2 virus. It is a CE approved, easy to use device which is in alignment with ordinary routines and standards at PHC. This device uses a nucleic acid test with LAMP technology which is an isothermal PCR (similar to ordinary PCR). The test has a >95% sensitivity and >95% specificity to detect GAS and SARS-CoV-2 virus in comparison to ordinary PCR [18]. The test takes up to eight minutes to analyze. Test result will be available to the Investigator on request. The result of testing as well as Investigator's clinical decision concerning antibiotic treatment with justification will be recorded in the eCRF. Study personnel, responsible for collecting the swab tests, will undergo an onsite training session on how to run the test.

4.6 Management of suspected or confirmed COVID-19 cases

It is recommended to assume that every patient is potentially infected with a pathogen that could be transmitted to study personal or other patients. Attempts should be made to isolate all patients with suspected symptoms of any respiratory infection using remote office areas (separate waiting areas, separate entrance). For the direct patient interactions, personal protective equipment must be available including gloves, an apron, a surgical mask and a visor/goggles.
The practitioner performing the final assessment at PHC is responsible for informing the pharmacist about potential exposure to SARS-CoV-2 virus if a study participant is tested positive for SARS-CoV-2 virus after being consented or assessed at a Pharmacy.

4.7 Early Termination and withdrawal of subjects

Subjects first presenting to medical practitioners or nurses at the PHC centre but allocated to Arm 3 (assessment at Pharmacist) and tested positive for SARS-CoV-2 virus at PHC will be withdrawn from the study (Table 1). This group of participants will not be transferred to Pharmacy for assessment.

Since the decision to take part in this study is entirely voluntary the subject is free to withdraw from the study at any time and for any reason, without the need to justify their decision. However, the Investigator should record the reason for the patient's withdrawal, if possible. If withdrawal occurs for other reasons than subject's decision, the primary reason for withdrawal will be documented in the eCRF.

5 Data collection and Data Management

5.1 Case Report Forms (CRF)

Electronic Case Report Forms (eCRF), provided by REDCap consortium, will be used for data capture. Data will be collected at the following points: Screening and Inclusion (Day 0), Follow-up (approximately Day 30), Early Termination and Withdrawal (alternatively). Data should be entered into the system timely after the patient has attended a visit or after the data become

available, as applicable. The Investigator will approve the eCRF entries for each patient with an electronic signature which is equivalent to a handwritten signature. The information entered in the eCRF is described in appendix 3.

5.2 Data management of personal data

The personal data collected in the electronic case report form (eCRF) is described in appendix 3. The study data managers, all working for the Sponsor, will have access to the data stored in the eCRF. Paper documentation containing personal data (i.e. signed Informed Consent Forms) will be stored at site in a locked cabinet or room within a secure area. Personal data stored electronically will only be accessible by authorized members of the study/clinical care team. A unique login name and password will be required to access electronic personal data. Personal data will be stored for at least 15 years. The Sponsor will be contacted before any paper documentation is destroyed.

5.3 Data Processor

The Data Processor is the Principal Investigator (PI). Processing of data may be delegated to a qualified member(s) of the research team.

5.4 Data Controller

The Data Controller is the study Sponsor. The Data Controller is the organization who determines the purposes for which, and the manner in which, any personal data are processed.

5.5 Training the investigation team on the data management plan

All members of the trial team, both management and clinical, will be informed and trained on the data management plan.

5.6 Procedures used for data review and database cleaning

After the trial database is declared clean and released for statistical analysis, a final copy of the database will be stored at the Sponsor. Errors occurring in the eCRF will be corrected electronically.

5.7 Procedures for verification and securing of electronic clinical data systems

To ensure an appropriate audit trail is present, the Investigator will make sure to maintain documentation that allows reconstruction of the course of events, that any and all data changes will be documented and that there will be no deletion of entered data. The revision history of all files and data will be maintained and repeatedly verified. A time-stamped electronic record that allows reconstruction of the course of events relating to the creation and modification of data will be created and maintained for this purpose.

5.8 Procedures for data retention

The PI and the Sponsor have agreed on policies and procedures that prevent unauthorized access to the data, both internally and externally. The PI will maintain a list of individuals who have access to the electronic data system as well as the dates of access and privileges granted to each user. This Data Access and Privileges List will be found in the Trial Master File (TMF). The signed Informed Consent Forms will be archived in clearly labelled and sealed plastic boxes

stored in a locked cabinet located in a locked room. The labels will contain the CIP title, as well as the contact information of the PI. Data will be stored for at least 15 years.

6 Statistics and data analysis

The primary objective will be answered by comparing groups using a multivariable binary logistic mixed model analysis where cluster will be a random effect and group allocation a fixed effect. Patients age, gender and Centor score will be effect modifiers and treated as fixed effects. For the secondary objectives the following methods will be used:

1 Chi-square will be used to estimate any difference in illness severity between the arms.
2 Characteristics of patients, defined as age, gender, number of Centor criteria and presence of SARS-CoV-2 virus will be compared between the groups first attending a PHC centre or a Pharmacy using one way ANOVA (for age), Kruskal-Wallis test (for number of Centor criteria) and chi-square (for binary variables).
3 Chi-square will be used to estimate any difference in prevalence of SARS-CoV-2 virus between the arms

6.1 Sample size calculation

The primary hypothesis is that a primary assessment by pharmacists slightly more adhere to the desired guideline compared with assessments made by medical practitioners or nurses at PHC. A secondary, less likely, hypothesis is that nurses adhere better than medical practitioners to the desired guideline.

A sample size calculation for the primary hypothesis assume that the proportion of patients correctly managed according to the desired guideline is 60% among patients primarily assessed at a PHC (by medical practitioners or nurses) and 80% if primarily assessed by pharmacists require 143 patients in each of these two groups when assuming a level of significance of 0.05 and a power of 0.95. We aim to include 150 patients in each of our three groups, in total 450 patients.

6.2 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) will not be asked for nor registered.

7 Trial management and oversight arrangements

7.1 Project Management Group

The trial will be coordinated by a Project Management Group (PMG), consisting of the PI, prof. Ronny Gunnarsson, MD PhD, the Trial Manager (Carl Wikberg), a. prof. Pär-Daniel Sundvall and dr Patrycja Woldan-Gradalska. The Trial Manager will oversee the study and will be accountable to the PI. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team. A Delegation Log will be prepared for the investigation site, detailing the responsibilities of each member of staff working on the trial.

7.2 Inspection of records

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

8 Statements of compliance

Good Clinical Practice (GCP) is the ethical and practical standard to which all clinical research is conducted. The GCP guidelines were developed by the International Conference on Harmonisation (ICH) and are applicable to the conduct of all research including clinical trials which do not involve an Investigational Medicinal Product. The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

8.1 Approvals before commencement of clinical investigation

The clinical investigation shall not begin until the required approval/favourable opinion from the Swedish Ethics Review Authority have been obtained. Any additional requirements imposed by the Swedish Ethics Review Authority shall be followed, if appropriate.

9 Investigator responsibilities

The Investigator is responsible for the overall conduct of the study at the site and compliance with the CIP and any Clinical Investigational Plan Amendments. Responsibilities may be delegated to an appropriate member of study site staff.

9.1 Clinical investigational plan amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the subject in the case of an urgent safety measure, must be reviewed and approved by the PI. The updated CIP will be signed by the Investigator(s) and the Sponsor. Amendments will be notified to (non-substantial amendments) or approved by the Swedish Ethics Review Authority before the implementation.

9.2 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a subject to participate in clinical research is voluntary and should be based on a clear understanding of what is involved. Subjects must receive adequate oral and written information – appropriate Subject Information and Informed Consent Forms (ICF) will be provided. The oral explanation to the subject will be performed by the Investigator or qualified delegated person and must cover all the elements specified in the Subject Information and Consent Form. The subject must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The subject must be given sufficient time to consider the information provided. It should be emphasized that the subject may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled. The Investigator or delegated member of the trial team and the subject will sign and date

the ICF(s) to confirm that consent has been obtained. The subject will receive a copy of this document and a copy will be filed in the ISF.

9.3 Study Site Staff

The Investigator must be familiar with the CIP and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed and trained about the CIP and their trial related duties.

10 Data recording and confidentiality

The Trial Manager is responsible for the quality of the data recorded in the eCRF at each study site. The PI will ensure that the required documentation is available in local ISFs. All evaluation forms, reports, and other records must be identified in a manner designed to maintain subject confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.1 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information. Access to collated subject data will be restricted to those individuals from the research team treating the subjects, representatives of the Sponsor and representatives of regulatory authorities. Computers used to collate the data will have limited access measures via usernames and passwords. Published results will not contain any personal data that could allow identification of individual subjects.

11 Deviations from Clinical Investigational Plan

Any change, divergence, or departure from the study design or procedures defined in the CIP is considered a deviation. The investigator shall not deviate from this CIP except in situations that affect the subject's rights, safety and well-being, or the scientific integrity of the clinical investigation.

11.1 Procedures for recording, reporting and analysing CIP deviations

CIP deviations will be recorded in a deviation log maintained by the study site. Any deviations from the CIP that are identified will be reported to the Sponsor within 24 hours of being identified.

11.2 Notification requirements and time frames

Requests for deviations by the Investigator will be responded to within 48 hours of receipt. The Corrective and Preventive Action (CAPA) document will be created for every deviation. The

CAPA will focus both on the immediate noncompliance and the broader scope of the problem. It involves investigating and understanding the issue, correcting the issue, and preventing the root cause. The CAPA will describe reactive steps to correct the immediate problem (corrective), describe the measures taken to understand and underlying cause(s) and extent of the problem(s) and list proactive steps to prevent future recurrence of the problem(s) (preventive). The PI, in collaboration with the PMG and study site staff, will strive to develop effective corrective and preventive actions focusing on eliminating the cause of the detected deviation.

11.3 Disqualification of a clinical investigator

The Investigator is disqualified if the Investigator has repeatedly or deliberately deviated from the CIP, or failed to comply with applicable regulatory requirements, or has repeatedly or deliberately submitted false information to the Sponsor, or the Swedish Ethics Review Authority, in any required report.

12 Serious breach requirements

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

1) the safety or physical or mental integrity of the subjects of the trial; or
2) the scientific value of the study.

If a potential serious breach is identified by the Investigator or delegates, the Sponsor must be notified within 24 hours. It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to the Swedish Ethics Review Authority as necessary.

13 Study record retention

All study documentation will be kept for a minimum of 15 years from the end of study point defined in the CIP. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the Sponsor. Following publications, a de-identified individual subject data set will be submitted for public data archiving for sharing purposes.

14 Insurance and indemnity

The Clinical investigational plan has been designed by the PI and researchers employed by the Västra Götaland Region and collaborators. All patients will meet a medical practitioner. Hence, the national “Patientskadeförsäkringen” is valid for this study.

15 Renumeration

15.1 Renumeration to participating clinics

Participating PHC centres as well as pharmacies are paid for their job as follows:

- Inform patient about the study and obtain informed consent: 300 SEK.
- Doing the first assessment of the patient and propose management: 400 SEK.

- Obtain the throat swab and perform laboratory analysis: 300 SEK (test apparatus and test kits are supplied by the sponsor).
- Doing the final assessment by a medical practitioner and deciding about management: 400 SEK (for patients allocated to do their first assessment by a medical practitioner the first assessment and the final assessment will be the same and together result in a renumeration of 400 SEK).

15.2 Renumeration to participating patients

All participants included in the study will have a longer physical visit than they excepted. A throat swab will be taken on all patients, even when it is not motivated by current guidelines. Furthermore, they are required to answer a short survey 30 days after the first visit. All participants will be offered a small renumeration of 300 SEK for the extra time they have to put in and for the discomfort of obtaining a throat swab sample. Parents / guardians will decide if the renumeration goes to their child or to themselves (not all children have own bank accounts). Information about renumeration is included in the patient information for adults and older children. For young children this information is not included in the written information but will be passed on verbally to their guardian.

16 End of study, reporting, publications and notification of results

16.1 End of Study

The end of study is defined as when all data for the follow-up at 30 days after the visit is collected. The Investigators or the Sponsor also have the right at any time to terminate the study for clinical or administrative reasons.

16.2 Suspension or premature termination of the clinical investigation

Both the Sponsor and the PI reserve the right to terminate the clinical investigation at any time. Should this be necessary, the procedures will be arranged on an individual basis after review and consultation by both parties. In terminating the clinical investigation, the Sponsor and the PI will assure that adequate consideration is given to the protection of the subject's interests.

16.3 Authorship policy

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with university guidelines.

16.4 Registration in a publicly accessible database

In accordance with the Declaration of Helsinki, this research will be registered in a publicly accessible database before recruitment of the first subject.

16.5 Publication

The Clinical Study Report (CSR) will be submitted to the Sponsor within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. All proposed publications and presentations must be discussed with the PI prior to their release. Summaries of results will also

be made available to Investigators. The data will be disseminated at local, national level via publication in peer review journals and at international meetings. Results, links to study outputs and a general summary of the results will be available for the public. The study report will undergo independent peer review prior to publication in a scientific Journal.

17 Expected outcome

Previous studies suggests that pharmacists may reduce antibiotic prescribing by up to 50%. However, this has not been investigated in any high-quality study. We do expect that pharmacists will recommend less antibiotic prescribing than medical practitioners and most likely adhere better to national guidelines.

18 Conflict of interest

No conflict of interest to declare.

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20 Description of appendices

List of appendices:

1) Appendix 1 – Criteria for estimating illness severity
Contains criteria to classify the illness episode as one of
a) apparently uncomplicated,
b) potentially complicated,
c) potentially critically ill.

2) Appendix 2 - Follow-up Questionnaire
The Follow-up Questionnaire is attached as a separate pdf-file.

3) Appendix 3 - eCRF
The content of the eCRF is described in a separate pdf-file

4) Appendix 4 - Payment of remuneration to included participants
Procedure and forms for paying remuneration to participants.

20.1Appendix 1 – Criteria for estimating illness severity

Any single item fulfilled in the rightmost column makes the patient "potentially critically ill" (Inspired by the NICE Sepsis guidelines from 2017). Similarly, any single item fulfilled in the orange column rules out that the patient is "apparently uncomplicated".

	Apparently uncomplicated	**Potentially complicated**	**Potentially critically ill**
===== History =====			
Impaired immune system	No	Yes	
History of peritonsillar abscess	No	Yes	
Visits	First visit	Re-visiting health care for the same illness episode	
===== Acute symptoms from the throat =====			
Worsening	No worsening after day 3.	Worsening after day 3.	
Total duration	Duration <5 days OR 5-8 days with noticeable improvement the last 1-2 days	Duration ≥5 days without noticeable improvement OR duration ≥8 days (HIV or mononucleosis?)	
Intensity of pain	Mild to moderate intensity or initially severe with very good effect of fast acting paracetamol	Severe intensity and poor or moderate effect of paracetamol	
Location of pain	Mainly bilateral	Unilateral	
===== Acute symptoms from locations other than the throat =====			
Neck stiffness and/or torticollis	No	No	Yes
Swelling of the face or neck	No	No	Yes
Chest pain	No	No	Yes
New altered mental state	No	No	Yes
Passing of urine	Adults: Yes within 12 hours	Adults: No urine in 12-17 hours	Adults: No urine in ≥18 hours
Inability to open the mouth fully	No	Yes	
Difficulty swallowing saliva, drooling	No	No	Yes (epiglottitis?)

Severe local pain on neck, torso or extremities	No	No	Yes (necrotizing fasciitis?)
Abdominal symptoms	No	No	Vomiting OR diarrhoea (toxins?)
===== Physical examination =====			
General appearance	Mildly but not significantly affected	Significantly affected	
Mottled or ashen appearance of skin OR Non-blanching rash	No	No	Yes
Red non-blanching skin rash that has a sandpaper feel or a "strawberry tongue"	No	Yes	
Rigors (severe shivering)	No	No	Yes
Cyanosis	No	No	Yes on skin, lips or tongue
Respiratory distress OR stridor	No	No	Yes (epiglottitis)
Very thick, gray membrane covering the throat and tonsils	No	No	Yes (diphtheria?)
Heart rate	Children 3-5 years: <120 Children 6-7 years: <110 Children 8-11 years: <105 All patients ≥ 12 years: ≤90	Children 3-5 years: 120-129 Children 6-7 years: 110-119 Children 8-11 years: 105-114 All patients ≥ 12 years: 91-130	Children 3-4 years: sustained >140 Children 5 years: >130 Children 6-7 years: >120 Children 8-11 years: >115 All patients ≥ 12 years : >130
Systolic blood pressure (mm Hg)	All patients ≥ 12 years: > 100	All patients ≥ 12 years: 91 - 100	All patients ≥ 12 years: ≤90 mmHg OR ≥40 mmHg below normal for the patient (if known)
Respiratory rate	Children 3-7 years: <24 Children ≥ 8 years + adults: <21	Children 3-5 years: 24-28 Children 6-7 years: 24-26 All patients ≥ 8 years: 21-24	Children 3-5 years: ≥29 Children 6-7 years: >27 All patients ≥ 8 years: ≥25
Body temperature (tympanic)	≥36°C AND <39.5°C	<36°C OR ≥39.5-41°C	>41°C
Oxygen saturation in room air (%)	Children 6-12 years: ≥97% All patients ≥ 13 years: ≥96%	Children 6-12 years: 95-96% All patients ≥ 13 years: 92-95%	Children 6-12 years: <95 All patients ≥ 13 years: <92% (<88% in COPD)

Potentially critically ill patients should be admitted to nearest hospital as soon as possible for further evaluation. Potentially complicated patients should not be included in the study but instead be referred to their medical practitioner for immediate assessment. Only patients whose illness episode is apparently uncomplicated are to be included in the study.

Physical examination of patients that at first glance seem to have an apparently uncomplicated acute sore throat:
Take history (including acute symptoms) and evaluate the general appearance of the patient. Do inspection of the throat, palpation of cervical glands and estimate body temperature. In the meantime, obtain oxygen saturation and the heart rate (to be done with the same device). No need to obtain blood pressure or respiratory rate if all these indicate an apparently uncomplicated illness episode. Practical instructions are provided in figure 1 and 2 below.

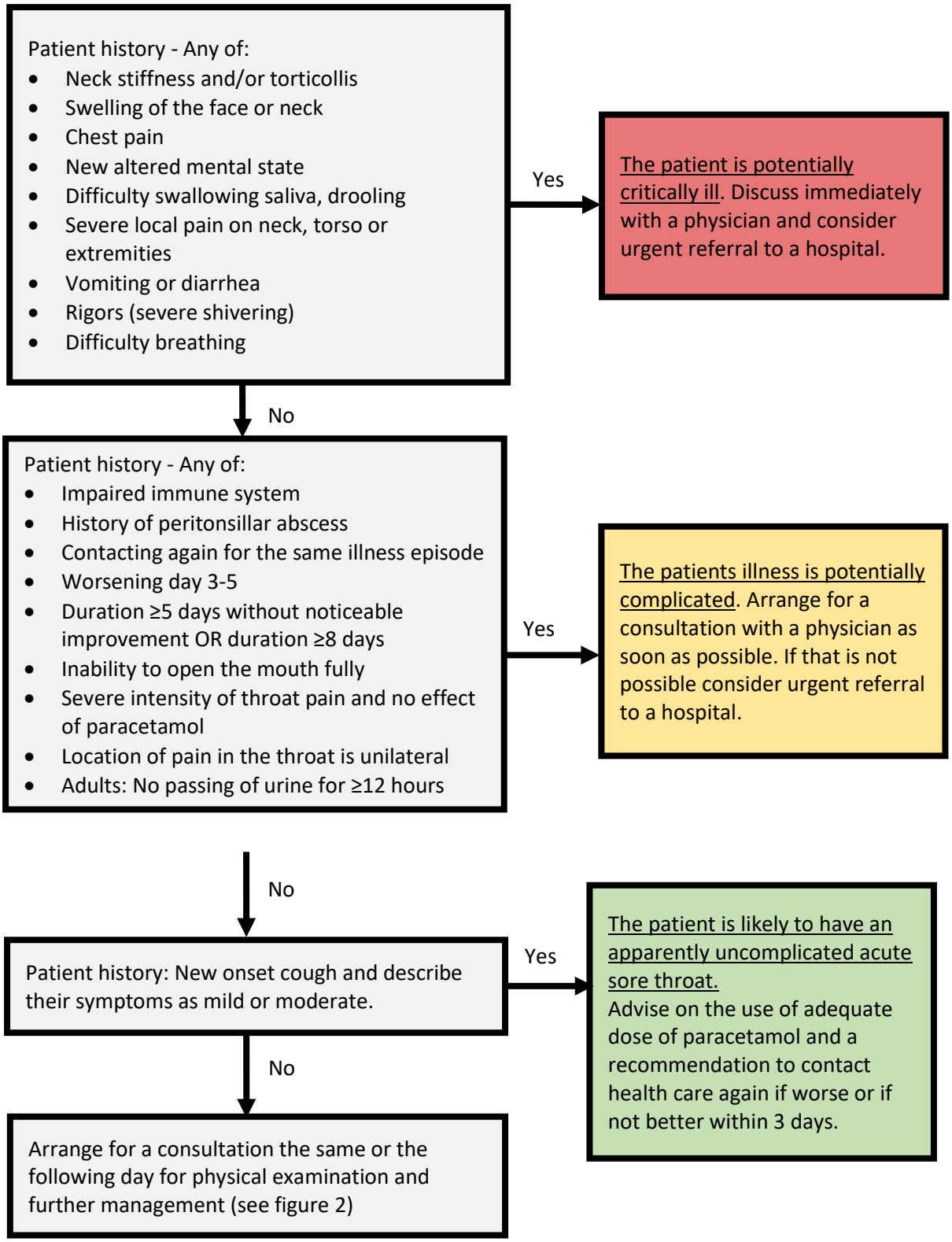

Figure 1 – Initial triage of patients (can be done in a phone or video consultation)

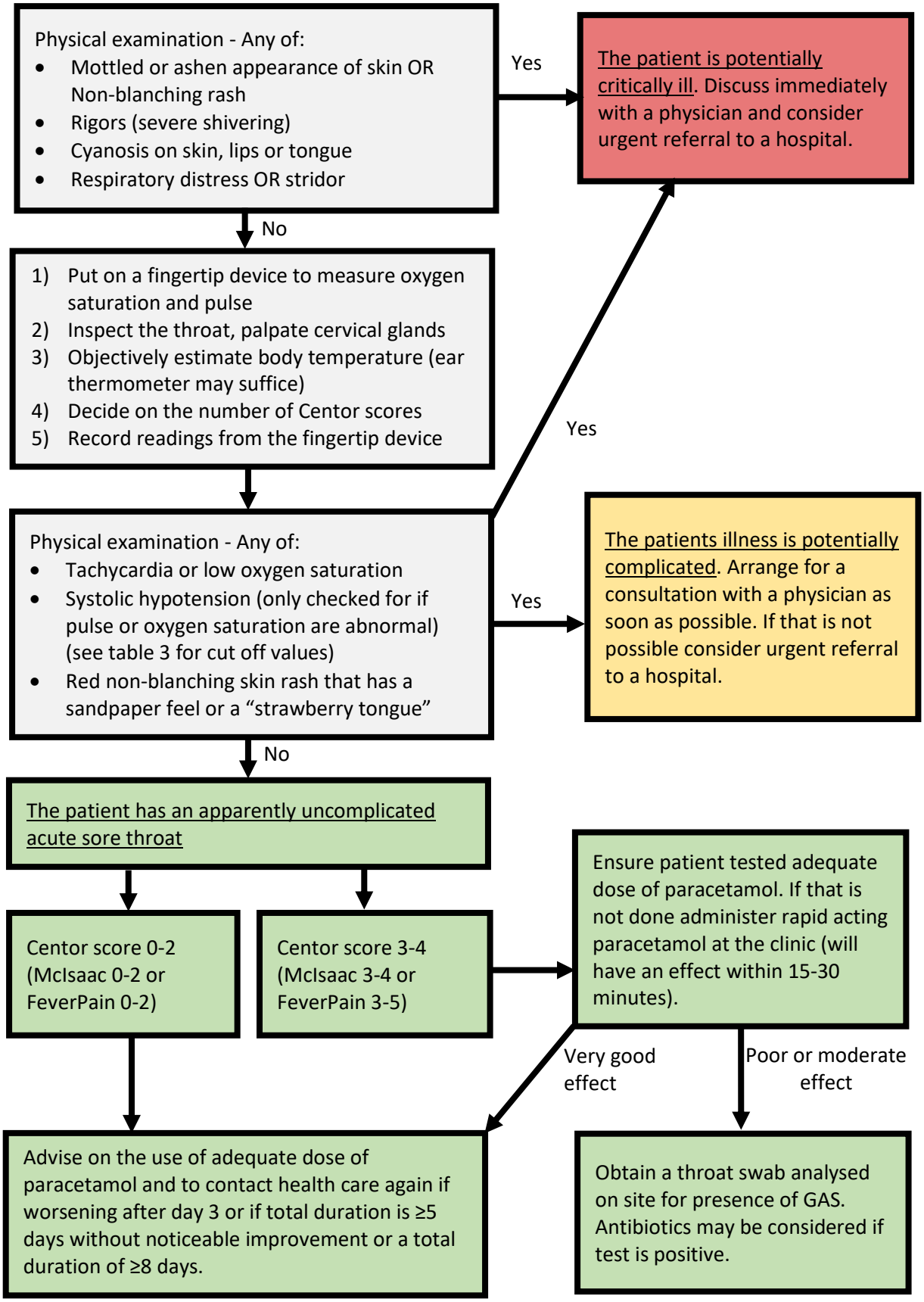

Figure 2 – Further assessment and management of patients (requires a physical visit)

20.2 Appendix 2 - Follow-up Questionnaire

(The follow-up questionnaire is delivered either as an electronic survey prompted by a text message, as an email or a telephone interview pending on patients request. Only relevant questions are prompted. Hence, patients stating they have not attended any health care provider again for the same illness vill not see the subsequent questions.)

(The follow-up questionnaire is is Swedish and is therefore omitted here. It can be requested from the principal investigator.)

20.3Appendix 3 – eCRF

An electronic case report form (eCRF) will be used containing the information below. The eCRF-system will use the information to automatically evaluate if the patient fulfill the inclusion criteria or if the exclusion criteria illness severity is fulfilled.

Inclusion criteria
The patient is contacting/attending PHC centre or Pharmacy presenting with a sore throat as the main complaint
Age (the eCRF will not accept patients <6 years)
Fluent in Swedish (reading, writing, conversational) (applicable to caregivers/parents/guardians in case of children) (yes/no)?
Mental state such that he or she can understand and give informed consent to participation in the study by signing the Information and Consent Form (yes/no)?
Provision of signed and dated Informed Consent Form (yes/no)?
Basic information
Site where the patient first attends with a complaint of a sore throat
Biological sex (male/female)
Place of birth (in Sweden, in Europe but not Sweden, outside Europe)
Preferred method for contact about the 30-day follow-up (phone or email is stored)
Patient history
Known impaired immune system (yes/no)?
History of peritonsillar abscess (yes/no)?
First visit for this illnes episode (yes/no)?
Duration of the sore throat (days)?
Noticable improvement in symptoms last 1-2 days?
Intensity of pain in the throat (mild, moderate or severe)?
Has taken over the counter analgetic medication in adequate dose (yes or no)
Location of pain in the throat (unilateral or bilateral)?
Presence of neck stiffness and/or torticollis (yes/no)?
Swelling of the face or neck (yes/no)?
Chest pain (yes/no)?
New altered mental state (yes/no)?
Passing of urine (hours since last time)
Inability to fully open the mouth (yes/no)
Difficulty swallowing saliva, drooling (yes/no)?

Severe local pain on neck, torso or extremities (yes/no)?
Abdominal symptoms such as vomiting / diarrhoea (yes/no)?
Used over the counter pain medication before arriving to the clinic? (yes/no)?
Measured body temperature at home? (yes/no and if yes what was it)
Cough during this illness episode (yes/no)?
Patients general condition at assessment
General appearance (unaffected, mildly affected or significantly affected)
Mottled or ashen appearance of skin OR Non-blanching rash (yes/no)?
Red non-blanching skin rash that has a sandpaper feel typical for scarlet fever (yes/no)
Rigors (severe shivering) (yes/no)?
Cyanosis (yes/no)?
Respiratory distress OR stridor (yes/no)?
Heart rate (beats/ minute)
Oxygen saturation in room air (%)
Tympanic body temperature (Celcius)
Patients throat status at assessment
Any tonsillar excudate (yes/no)?
Very thick, gray membrane covering the throat and tonsils (yes/no)?
Tender cervical lymph nodes (yes/no)?
Presence of Strawberry tounge typical for scarlet fever (yes/no)
Proposed evaluation and management (before any throat swab)
Suspected aetiologic agent (viral/bacterial/unsure)?
Your recommended management (No action/obtain a throat swab/prescribe antibiotics)?
Outcome of throat swab analysis
Presence of group A Streptococci (yes/no)?
Presence of Sars-Cov-2 virus (yes/no)?
Proposed management (after throat swab for those ordering it)
Would you recommend antibiotics (yes/no?)

Final assessment by medical practitioner (only if primary assessment by nurse or pharmacist)
Your recommended management (No action/prescribe antibiotics)?
Was the outcome of the throat swab of any help? (yes/no)

20.4Appendix 4 – Payment of remuneration to included participants

Participants are asked to fill in a form with the information shown below to receive remuneration of SEK 300 (before tax). The research team sends the form to the finance department Regionhälsan, Västra Götalandsregionen who make the payment. The Swedish social security number is requirered on this form to enable payment of preliminary tax. The payment will be made after the 30-day follow-up questionnaire is completed.