STUDY PROTOCOL

COORDINATE

CRP f**O**r respirat**OR**y **DI**agnosis i**N** Kyrgyz pedi**AT**ric practic**E**

BISHKEK - COPENHAGEN 2021

BRIEF PROTOCOL TITLE: CRP for respiratory diagnosis in Kyrgyz pediatric practice

FULL PROTOCOL TITLE: Using the CRP test in children under 12 years with respiratory symptoms in Kyrgyz Republic

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AI	Assistant Investigator
CA-ARTI	Community Acquired Acute Respiratory Tract Infection
CRF	Case Report Form
CRP	C-reactive protein
CRP POCT	C-reactive protein point-of-care testing
COVID-19	Coronavirus disease 2019
FMC	Family Medicine Centre
FOP	Feldsher-Obstetric Point
FPG	Family physicians groups
GP	General Practitioner
HCW	Healthcare Workers
IC	Informed Consent
ICU	Intensive care unit
IMCI	Integrated management of childhood Illness
IRCT	Individual Randomised Controlled Clinical Trial
PI	Principal Investigator
RCT	Randomised Controlled Clinical Trial
RTI	Respiratory Tract Infection
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2 (virus causing COVID-19 disease)
SD	Standard deviation
SMG	Study Management Group
UCPH	University of Copenhagen
WHO	World Health Organisation

SUMMARY

Rationale: Respiratory tract infections are the most common cause to contact to the healthcare system worldwide and the most common cause of inappropriate use of antibiotics. And while lower respiratory tract infections are still the main cause of death for children under 5 globally, only a small proportion of children with airway disease need antibiotics.
Overuse of antibiotics globally is leading to increasing rates of antibiotic resistance and may lead to a 'post-antibiotic' era. Case fatality rates for pneumonia in children remain high in Central Asia and there is a lack of knowledge of which viruses and bacteria cause the disease. Antibiotic resistance patterns of common bacteria remain largely unknown in Central Asia which makes it challenging for clinicians to choose the right antibiotic to treat children with suspected bacterial pneumonia and sometimes healthcare workers overuse an antibacterial therapy even when the child does not need it.
Randomised trials of using CRP point of care test (POCT) to guide antibiotic prescription for respiratory tract infections has been successful in lowering unnecessary antibiotic prescriptions in adults in high income countries but left a small concern for safety in the form of possibly slightly increased risk of hospitalisation in the CRP group.

Objective: This study seeks to gain evidence on whether use of C-reactive protein point-of-care test can safely decrease prescription of antibiotics for children under 12 with acute respiratory symptoms in primary level healthcare centres in Kyrgyzstan.

Study design: Multicentre, open-label, individual randomised controlled clinical trial with 14 days blinded follow-up in rural Chui and Naryn regions of Kyrgyz Republic. Healthcare workers from ten selected healthcare centres will be trained in the CRP POCT and in interpreting the results in the field.

Study population: Children aged from 6 month to 12 years attending the primary level healthcare centres during normal business hours with acute respiratory symptoms.

Main study parameters: The proportion of patients in the two groups prescribed an antibiotic within 14 days of index consultation; length of disease, antibiotics given at index consultation, admissions and vital status.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Risks, inconvenience and burden associated with participating in this observational study are low. As part of the inclusion children in the CRP cluster group will have a finger-prick test performed. This may be unpleasant and course transient discomfort but poses no risks to the child. Follow-up will be three short phone calls day 3, 7 and 14 after inclusion. Risks includes possible undertreatment of serious disease, however previous studies have not found safety issues with CRP testing in children. There is no direct benefit to participants, but side effects and non-necessary medications are likely minimised.

1. INTRODUCTION AND RATIONALE

Respiratory tract infections are the most common cause of contact to the health system and are the main reason for antibiotic overuse at the primary care level globally [1–3]. At the same time, acute lower respiratory infections (ALRI) are the most common cause of death among children under 5 globally [4], costing the lives of almost 1 million children annually [5]. Unfortunately, there is substantial overlap in the presentation of different causes of acute lower respiratory illness in young children, including bacterial pneumonia, viral infections and wheezing [6,7] and with increasing coverage of pneumococcal and Haemophilus influenza type b vaccination, only a smaller proportion of these need antibiotics [8,9]. At the same time, globally, most children are diagnosed and treated at a primary care clinic, primarily by mid-level providers with only limited access to diagnostic equipment [3]. To assist healthcare providers in diagnosing under these conditions, various algorithms have been used, e.g. WHO's Integrated Management of Childhood Illness, which bases diagnosis of respiratory diseases in children mainly on presence of cough and elevated respiratory rate [10]. This approach has been shown to severely over-diagnose pneumonia and thus result in unnecessary prescription of antibiotics [11]. Therefore, new approaches to diagnosing and treating respiratory infections in children are urgently needed.

Concurrently, antimicrobial resistance is now what WHO calls a global health emergency and warns that 'A post-antibiotic era—in which common infections and minor injuries can kill—far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century [12] (Figure 1). Unnecessary prescription of antibiotics is extensive globally [2,12] and most healthcare providers are aware of the global threat of antimicrobial resistance but express the need for support for prescribing differently, such as knowledge of local resistance patterns of pathogens and better diagnostics to support a decision not to treat with an antibiotic [13].

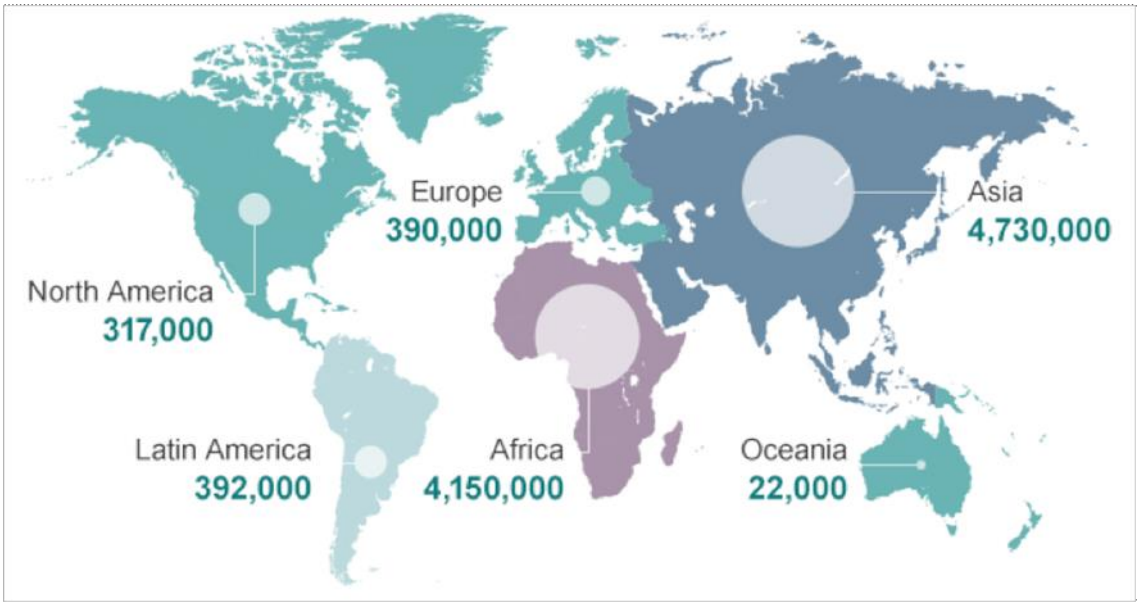

Figure 1: Deaths attributable to antimicrobial resistance every year by 2050 (Source: BBC and Review on Antimicrobial Resistance – Tackling a Crisis for the Health and Wealth of Nations (2014)).

C-reactive protein (CRP) is an acute phase reactant produced by the liver which can be used as a marker of serious infection. Randomised trials of using CRP point of care test (POCT) to guide antibiotic prescription for respiratory tract infections has been successful in lowering unnecessary antibiotic prescriptions in adults in high income countries but left a small concern for safety in the form of possibly slightly increased risk of hospitalisation in the CRP group [14]. Trials of CRP POCT in children have been performed in Tanzania as part of an intervention package with a strict prescription limit of > 80 mg/L CRP with a reduction in antibiotic prescriptions from 40% to 2% [15]. In South-East Asia with a small but statistically significant effect (5% reduction) when used as either above or below a certain threshold (40 mg/L) in Thailand and Myanmar [16]. In a sub-group analysis from a trial in Vietnam with both children and adults where the numeric value of CRP was used after a short training in CRP interpretation along with clinical evaluation resulted in a 20% reduction from 64% to 44% [17]. A cross-cutting qualitative study of the above-mentioned studies in Thailand, Myanmar, and Vietnam showed that lack of non-antibiotic alternatives to prescribe led to lower adherence to the CRP POCT result [18].

As the intervention of supplying CRP POCT to healthcare providers is more a behavioural than biomedical, previous trials have recommended that further trials are done in different contexts and that qualitative studies of reasons for success or failure [17].

Central Asian countries have been underrepresented in health science, especially in primary care research. The clinical context of primary care in South-East Asian countries, like Vietnam, Thailand, and Myanmar, and Central-Asian countries, like Kyrgyzstan, are vastly different with different caseloads, different human resources, and varying time for consultations available [3]. At the same time, case fatality rates for pneumonia in children remain high in Central Asia (Figure 2) and there is a lack of knowledge of which viruses and bacteria cause the disease. Antibiotic resistance patterns of common bacteria remain largely unknown in Central Asia, which makes it challenging for clinicians to choose the right antibiotic to treat children with suspected bacterial pneumonia.

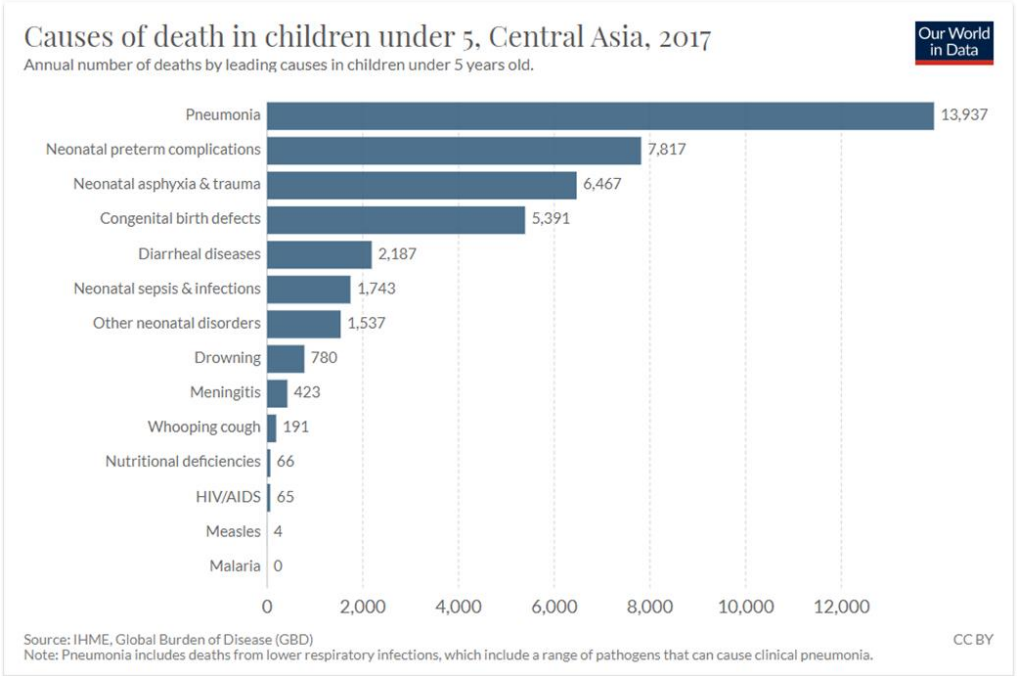

Figure 2: Causes of Death in Children under 5 in Central Asia.

Figure 3 shows a graph of the distribution of morbidity in children aged 0 to 14 years in the Kyrgyz Republic (http://cez.med.kg/) with respiratory diseases being the most common (49,7%). Among all acute respiratory diseases in children, upper respiratory tract infections are the most common, as shown in Figure 4. The number of cases per 100,000 population seems to de-crease by 2020, but it is still quite high (http://cez.med.kg/).

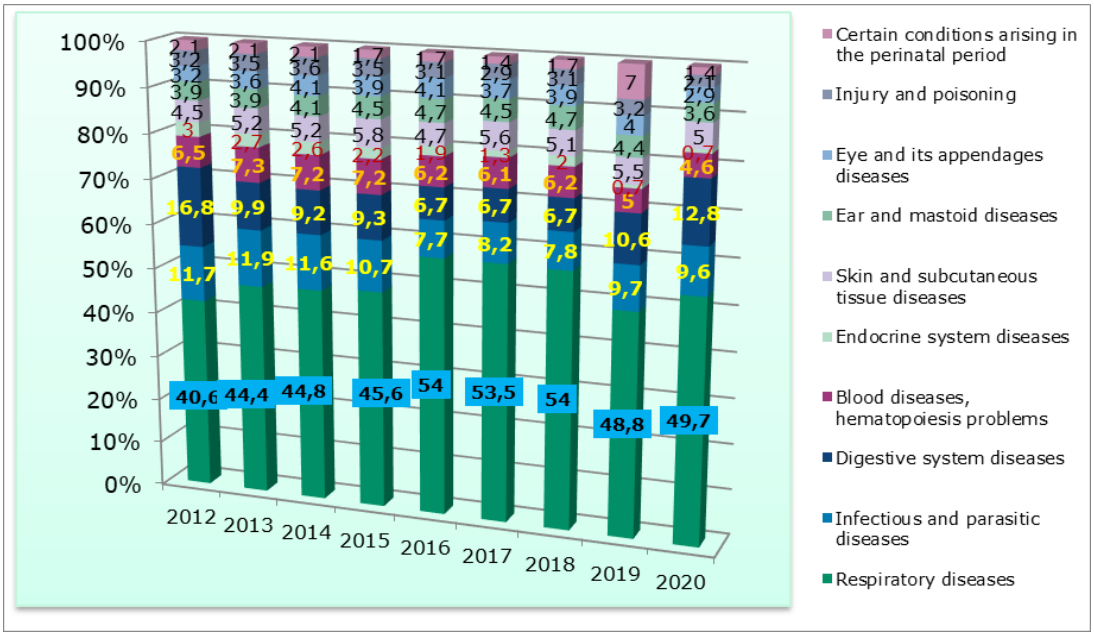

Figure 3: The structure of morbidity in children from 0 to 14 years old in the Kyrgyz Republic (%) 2012-2020

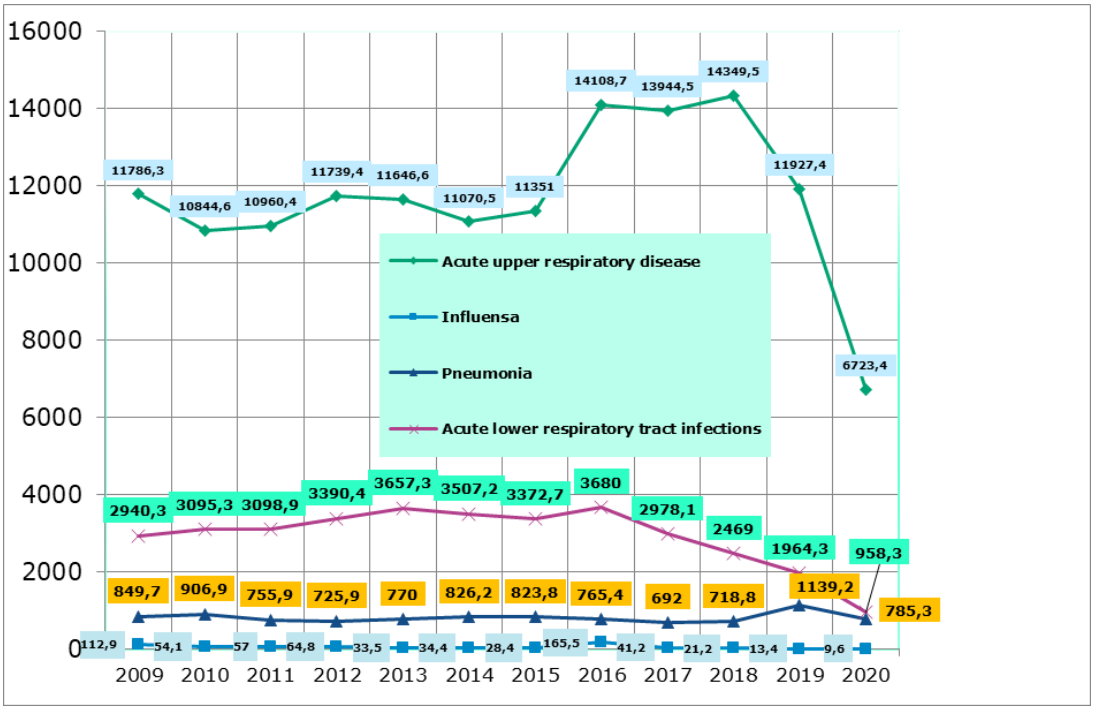

Figure 4: Dynamics of the prevalence of acute respiratory diseases in children under 14 years of age (per 100,000 child population) in the Kyrgyz Republic (2009-2020)

2. OBJECTIVES

The aim of this project is to find out if the overuse of antibiotics in children with acute respiratory symptoms can be reduced by effectively identifying children at increased risk of infections who require antibiotic therapy and children who will not benefit from antibiotics. This is done by implementing CRP POCT at the primary healthcare level.

Hypotheses:

Supplying CRP POCT equipment to primary healthcare providers will help them identify the majority of children who suffer from viral infections and assist in withholding antibiotic treatment when no benefit can be expected and will help identify the severely sick children in need of urgent referral, thus lowering unnecessary use of antibiotics and improving primary care management by studying supplying supportive medication for those not in need of antibiotics.

It will be an individually randomised clinical trial where CRP POCT is supplied to approximately 14 healthcare centres. All children up to 12 years with respiratory symptoms have basic clinical data recorded as well as data needed to classify according to WHO IMCI pneumonia diagnostic criteria. CRP POCT is used at intervention sites and CRP results, diagnosis, and treatment is recorded. Follow-up phone calls will be made 3, 7 and 14 days after the health centre visit to record recovery, antibiotics use, hospitalisation and vital status of the participating children.

3. STUDY DESIGN

Multicentre, open-label, individual randomised controlled clinical trial with 14 days blinded follow-up will be conducted in low altitude Chui and high altitude Naryn regions of Kyrgyz Republic. Healthcare workers (HCW) from 14 randomly selected healthcare centres will be trained in the CRP POCT and in interpreting the results in the field.

Children will be screened at 14 randomly selected primary healthcare centres using a screening form (see Appendix A). The 14 healthcare centres will consist of a combination of Family Medical Centres, Family Physician Groups and Feldsher-obstetric points. Screening will be performed by an assistant investigator (AI) prior to the children being examined by a local HCW. The screening form will include a list of symptoms from the eligibility criteria. If a child has at least one symptom from the inclusion criteria, the AI will receive a rapid diagnostic test for SARS-CoV-2 at the HCW's office. In case the test is negative, AI will ask the parent/caregiver about their child's participation in the study and offer to read and sign the informed consent (IC) form. Otherwise (the test is positive), the child will not be included in the study. If the parents agree to their child's participation in the study and have signed IC, the child is enrolled in the study and randomised to Group A or Group B. The randomisation will be carried out by a responsible person located in the Bishkek office through the Sealed Envelop™ programme (www.sealedenvelope.com). This person will be in touch with AIs by telephone and, upon the request of the AIs, will remotely randomise and report the result to AIs. The principal investigator will not to be aware of the results of the randomisation and follow-up will be blinded as well.

Group A:

Participants assigned to Group A will take CRP POCT during a check-up with their HCW. The AI will attend the child's consultation with the local HCW and complete the case report form (CRF) (see Appendix C). Consequently, the CRP result will be recorded in the CRF, which will be the basis for choosing a treatment, depending on its result.

Group B:

HCWs will also consult children who have been randomised to Group B. The AI will complete the CRF for these children, but no CRP POCT test will be perform in this control group. They will receive the treatment prescribed by the HCW as usual care in an intention-to-treat model.

Both groups will be assessed additionally on the 3rd, 7th and 14th day by phone calls from another AI who is blinded to the group allocation using Follow-up questionnaires (see Appendix E).

The RCT study design is depicted in figure 5:

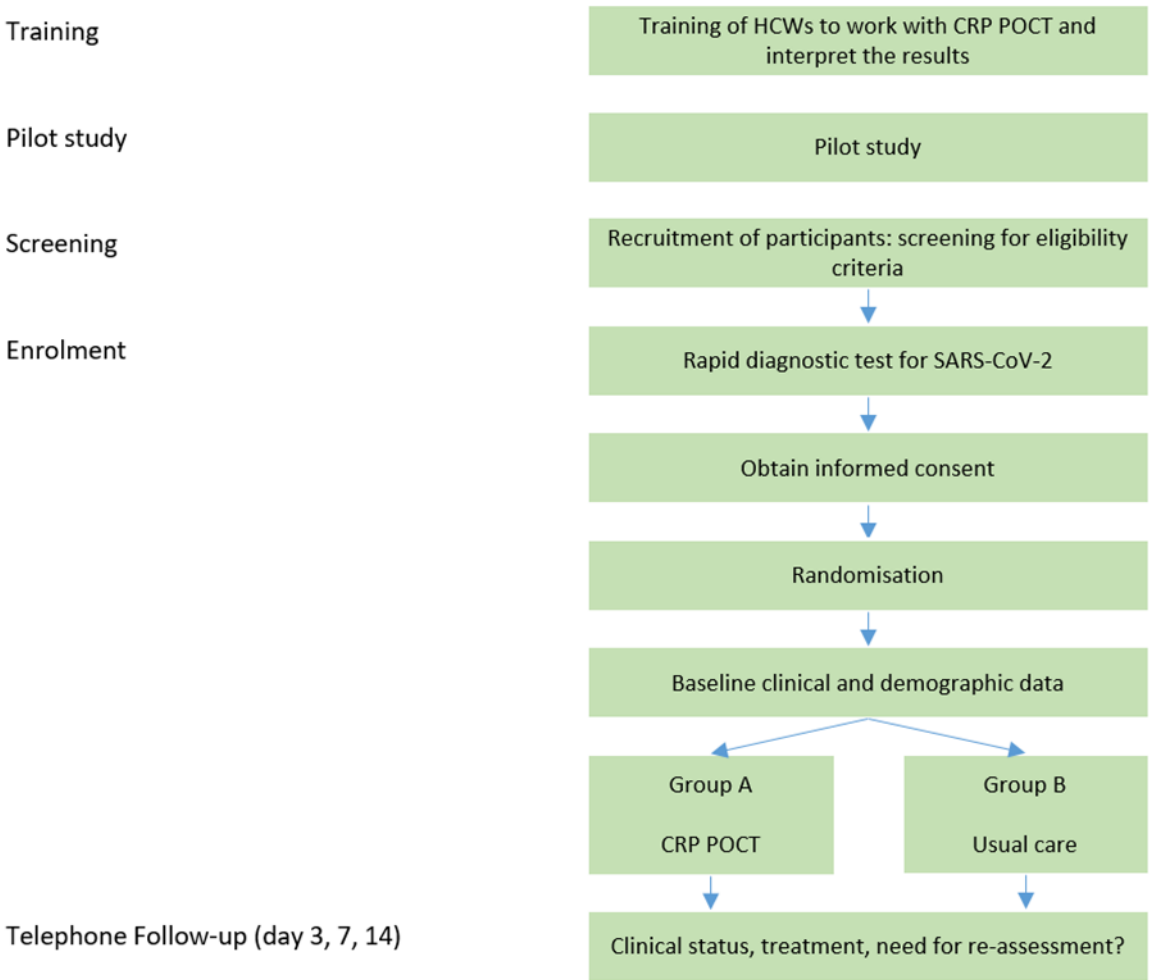

Figure 5: Multicentre, open-label, individual randomised controlled clinical trial with 14 days blinded follow-up.

PILOT STUDY

Prior to the start of the Main Study, a pilot study will be conducted to qualify and ensure practicality and acceptability of the main study. We aim to include 5-10 % of the original sample size calculation, approximately 60-75 (5%) children. The pilot study will access the number of eligible children and determine the number of caregivers willing to provide the informed consent form.

In the pilot study we will see how the CRFs and follow-up interviews are executed in regard to time to complete, understanding the questions and ease of use, completeness and loss to follow-up.

The pilot study will also involve qualitative interviews in the form of focus groups with healthcare workers and child caregivers.

The pilot study will be carried out in the three different first level of healthcare system in Chui region of Kyrgyzstan, in three randomly selected villages. This will inform how the trial will work, whether or not the project will be acceptable and feasible and likely to provide the results within the designated time.

4. STUDY POPULATION

4.1 Population (base)

All patients aged from 6 month to 12 years attending the primary care health clinics during normal business hours with symptoms as described in the inclusion criteria.

Patients of both sexes and all ethnic background can be included.

4.2 Inclusion criteria

Inclusion criteria is:

- Between 6 month and 12 years of age;
- Parents/caregivers of a child are able and willing to comply with all study requirements;
- Parents/caregivers of a child is able and willing to give Informed Consent;
- Having at least one of the following focal symptoms lasting for less than 2 weeks:
  - Cough;
  - Fast/difficult breathing;
  - Sore throat;
  - Shortness of breath;
  - Wheezing

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Severely ill and in need of urgent referral where measurement of CRP POCT would delay the process;
- Terminally ill patients;
- Patients with ear ache only;
- Patients with known immunosuppression or severe chronic disease (HIV, liver disease, history of neoplastic disease, long term systemic steroid use or similar conditions as assessed by the health worker or AI);
- Parents/caregivers who are not able to participate in follow-up procedures (lack of telephone etc);
- Positive rapid diagnostic test for SARS-CoV-2;
- Haven taken antibiotics within 24 hours before the index consultation

4.4 Sample size calculation

Provisional calculations show that a power of 90% to detect a 10% reduction in antibiotic use (from 55% to 45%) at a statistical significance level of 0.05 is achievable with the available resources resulting in recruitment of approximately 1046 children, 523 in each arm. With an expected dropout rate of 15% we aim to include 1204 children in total, 602 in each arm.

We expect to be able to include a sufficient number of patients in approximately three months. Each clinic has a patient flow of approximately 10 – 25 children per week. With 14 clinics, the weekly flow of potential participants is 100 – 250 even if only less than 1 in 2 patients are enrolled; we will still keep our schedule.
There has not been a diminished flow of patients at the healthcare centres curing the COVID-19 pandemic, so the study should be able to move ahead on schedule even in the face of the pandemic.

5. TREATMENT OF SUBJECTS

Children with the relevant age and symptoms will be consulted by a researcher, and with the consent of the parent / caregivers the child will be included in the study. In this case, the child in the control group will receive treatment according to the usual recommendations of the health workers. A child in the intervention group will receive an antibiotic only in accordance with the results of the CRP and the assessment of the health worker. If the child does not need antibiotic therapy, treatment will be prescribed in accordance with the recommendations for the management of acute respiratory viral infections without prescribing antibiotics, prescribing e.g. acetaminophen or other supportive treatment.

6. Intervention

CRP POCT equipment will be supplied at healthcare centres, along with a short training in use and interpretation supporting the clinical evaluation of the child. It will be communicated that CRP levels less than 10 indicate that the disease is not severe, and antibiotics is most likely not needed, if between 10 and 50, that antibiotics might be needed, and if more than 50 that it

is likely that they are needed. With CRP between 10-50 the HCW are instructed to take the clinical picture into account together with the value of the test. With obvious symptoms of bacterial infection such as high fever, very affected general condition, purulent sputum, signs of acute otitis media, persisting rhinosinusitis over 10 days etc. The training will also include knowledge of CRP pharmacodynamics and cases where a low CRP might need to be interpreted cautiously, e.g. a history of fever lasting less than 24 hrs. HCWs will be instructed to use CRP POCT for all patients in the intervention group and use the information to guide diagnosis and treatment choice. We will use Aidian (Copenhagen, Denmark) QuickRead go CRP POCT set-up (Figure 3).

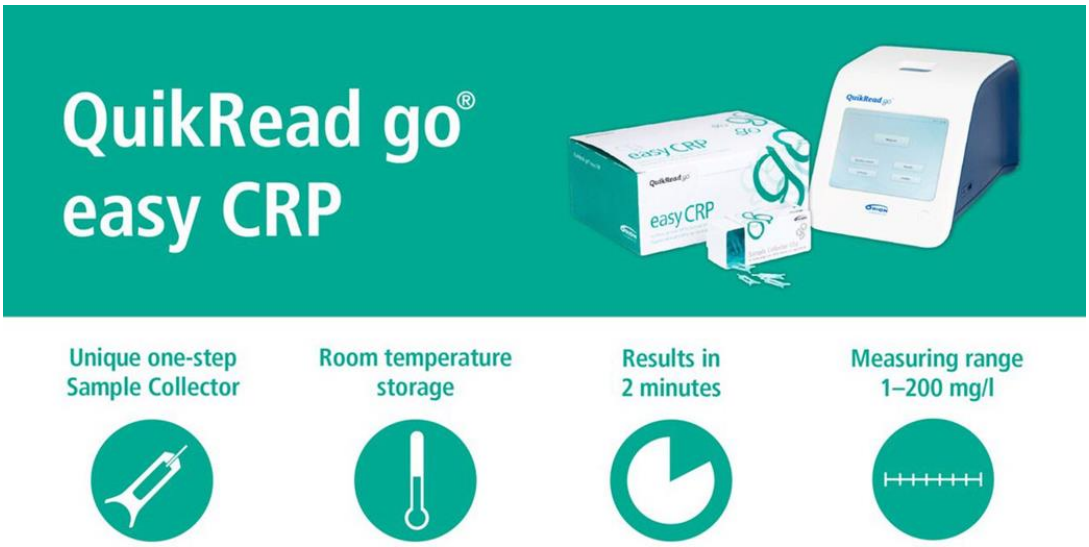

Figure 3: Aidian CRP POCT.

7. METHODS

7.1 Study parameters/endpoints

The primary outcome of the randomised trial is antibiotic prescription within 14 days from the index consultation, measured as proportion of children in each study group who receive an antibiotic (superiority analysis).
However, any reduction in antibiotic use must be balanced without any compromise to patient safety and the study will therefore include two primary outcomes. The second primary study outcome is patient safety measured as the number of days until recovery (non-inferiority analysis).

Secondary outcomes include other treatment, antibiotics given at index consultation, re-consultations, admissions and vital status.

7.2 Study setting

The study will be conducted in primary care in the rural areas in Chui region of Kyrgyz Republic, a Central Asian mountainous lower middle-income country with 6.2 million inhabitants (Figure

3). The study will be conducted in 14 randomly selected healthcare centres and consist of villages with between 590 and 10764 inhabitants. From previous research in the areas, we know that during winter-time on average, approximately 25 children visit a health centre with respiratory symptoms per week [3].

7.3 Types of medical centres in Kyrgyzstan

The Family Medicine Centre (FMC) is a unified complex, which employs doctors of all specialties and provides outpatient treatment for patients belonging to the area. The FMC also provides basic diagnostic services (general and biochemical blood tests, urine tests, stool analysis, electrocardiography, echocardiography, X-ray and ultrasound).

Family physician groups (FPG) is a medical institution that brings together family doctors, therapists, pediatricians, obstetrician-gynecologists, nurses and paramedics (depending on the population in the area and staffing), providing primary health care for patients related to the area. If it is necessary to take clinical tests, blood, urine or stool are taken from the patient and sent to the FMC. Results come in a few days. If it is necessary to pass biochemical tests or to undergo an instrumental examination, the patient is sent for this to the FMC or, if necessary, for a consultation with a narrow specialist.

A feldsher-obstetric point (FOP) is a structural unit of a medical and preventive institution that provides pre-hospital primary health care in rural areas, where feldshers and nurses act as medical personnel. In FOPs, pre-medical examination of patients belonging to this village is carried out. If it is necessary to consult a family doctor, the patient is referred to the FPG. There is no diagnostic equipment in FOPs.

A feldsher is a medical specialist who occupies an intermediate position between a doctor and a nurse. He can work both under the guidance of a doctor and independently.

7.4 Randomisation, blinding and treatment allocation

Randomisation will occur through a web based service Sealed Envelope™ https://www.sealedenvelope.com/ and conducted in a designated room by a dedicated member of the research team. Participants will be randomised (1:1) to either standard care or care according to CRP POCT. A dedicated member of the research team will inform the assessors of group allocations via telephone.

7.5 Study procedures

Recruitment:

The recruitment of participants will be carried out at 14 selected health centres among the children in attendance. AI screening will be used to select patients with the symptoms described in the STUDY POPULATION section. Further, in case the child is eligible for the

study, the AI will ask the parent / guardian about their child's participation in the study and offer to read and sign the IC form.

Special requirements during the COVID-19 Pandemic:

Given the COVID-19 pandemic, a Safety Concept for the COORDINATE Project has been developed. Due to the current situation with COVID-19, the following requirements must be observed for the study:

1. Participants and HCWs must wear disposable masks;
2. The consultation room and corridors should be equipped with alcohol-based wall sanitisers;
3. Cleaning in the room and in the corridors should be carried out strictly using chlorine solution;
4. Participants (children and caregivers), hospital stuff and research group must maintain social distance and refrain from close contact;
5. All children included in the study will receive a rapid diagnostic test for SARS-CoV-2

Screening and Eligibility Assessment

Children aged 6 month to 12 years will be assessed against the inclusion criteria by an AI and if eligible, be included upon signing of an IC by their parents/caregivers and have their CRF completed on paper. The AI will have a screening form. (See Appendix A) The selected children will then be randomised via a web programme (www.sealedenvelope.com) into two groups: Group A, who will receive antibiotics prescribed according to CRP POCT and provision of alternative non-antibiotic supportive treatment (e.g. paracetamol and/or salbutamol as relevant) for children with respiratory diseases that do not need antibiotics and Group B, who will receive the usual care.

Informed Consent

When the patient consults at the healthcare centres, explanation of the study, provision of study-related information, patient information sheet and IC will be performed at the practice. All study personnel will be trained by the national network facilitator or Principal Investigator (PI), detailing no less than: the exact nature of the study, implications and constraints of the study, and risks and benefits of participation. The study will provide a patient information sheet (appendix D) that includes all necessary information available in the official national language. 10 minutes will be given to the parents/caregivers to consider the information given to them and to ask any questions they may have about the study to decide whether their child will participate in the study. As participants are not of legal age of consent in their jurisdiction, consent will be provided by their parent/caregiver. It will be clearly stated in the patient information sheet and verbally explained to the participant that they are free to withdraw from the study at any time for any reason without impacting their future care, and with no obligation to provide the reason for withdrawal.

Study Visit – Inclusion

Patients will be included when they attend the health clinic upon fulfilment of the above-mentioned criteria. During the consultation and upon IC the baseline CRF data will be gathered (see appendix A, for the exact information that will be recorded). The CRF will be completed by the AI; the examination will be carried out by the clinic's HCW.

- Demographic details including: sex, age, co-morbidities, BMI category;
- Duration of CA-ARTI symptoms prior to consulting;
- Presence of specific RTI and general symptoms;
- Overall severity rating (HCW perception);
- Clinical assessments and results of clinical examination (oxygen saturation, respiratory rate, blood pressure, heart rate, body temperature);
- All diagnostic tests performed or ordered;
- Management: antibiotic, antiviral prescription, other (symptomatic) medication prescribed and advised;
- Additional advices: preventive measures for themselves and their family members, time-off, home isolation, hygienic measures;
- Referral to hospital or public health authority;
- During this visit a swab will be taken see below;
- COVID-19-specific questions;
- Participants randomised to a control group will receive routine care. Participants randomised to the CRP group will take the CRP test

Follow-up with Phone Calls

There will be no scheduled follow-up visit at the health clinic required by the study. Parents/caregivers will be phoned 3, 7 and 14 days after the index consultation to record outcomes. Phone calls will be blinded and performed by another AI (see appendix D):

- Number of symptomatic days after the consultation;
- Duration of specific symptoms;
- Return to school/work and usual activities;
- Additional contacts with HCWs;
- Any medicine bought over-the-counter or prescribed by other HCWs including the name of the drug(s);
- Additional diagnostic testing, including SARS-CoV-2 and outcomes;
- Complications (hospitalisation -days in hospital, ICU, medication/oxygen/ventilation received there-, pneumonia, death);
- Infections in their households;
- General well-being;
- Diarrhea

7.6 Withdrawal of individual participants

Participants can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. If any subjects are withdrawn, the reason(s) will be recorded in the CRF.

7.7 Follow-up of subjects withdrawn from study

The phone numbers of the parents/caregivers of the withdrawn or abandoned participants, if they wish, will be recorded and later called to find out the child's condition. The reasons for the refusal will also be recorded in a special section in the CRF.

7.8 Premature termination of the study and interim analysis

Since we are planning to include all subjects within two to three months, we do not plan to make an interim analysis. If the inclusion period will be longer than 3 months we will do an interim analysis or when 500 participants are included which ever comes first. The interim analysis will assess our primary outcome, safety outcome and adverse events. The PI will present the results of interim analysis to the Data Safety Monitoring Board (DSMB) / Safety Committee (see section 7.11).

SAFETY REPORTING

7.9 Temporary halt for reasons of subject safety

The study maybe halted for various reasons such as an urgent safety measures, further to a serious breach, serious sickness of researcher. A temporary halt applies when the suspension is imposed on all sites; suspension of the study at a single site due to logistical reasons is not considered a temporary halt.

The decision on whether a temporary halt should be imposed on a study will ultimately be a steering committee decision (and the decision-making process should be evidenced on file).

7.10 AEs, SAEs and SUSARs

7.10.1 Adverse events (AEs)

Adverse events may include the following:

- Allergic reaction to an antibiotic or any other drug during treatment (skin rash, lacrimation, flushing)
- Individual intolerance to an antibiotic or any other drug.
- Positive a rapid diagnostic test for SARS-CoV-2

7.10.2 Serious adverse events (SAEs)

As part of the study, we will collect the following outcomes at day 3, 7 and 14:

- Death
- Inpatient hospitalisation

SAE data will also be recorded in the CRF.

7.11 Data Safety Monitoring Board (DSMB) / Safety Committee

If need be a Data Safety Monitoring Board or Steering/Safety Committee will be activated and interim analysis including SAE will be presented and discussed. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to Principal Investigator concerning the continuation, modification, or

termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.
Items reviewed by the DSMB include: Interim/cumulative data for evidence of study-related adverse events; Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines, if appropriate; Data quality, completeness, and timeliness; Performance of individual centres; Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities; Adherence to the protocol; Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.);
The Data Safety Monitoring Board (DSMB) will consist of PI, coordinators from Denmark and Kyrgyz Republic and Professor Muhtar Asheraliev (paediatrician).

STATISTICAL ANALYSIS PLAN

7.12 General principles

This study is designed as an RCT to test effectiveness of CRP POCT in lowering prescription of antibiotics to children from 6 month to 12 years of age in 14 primary health clinics in Kyrgyzstan presenting with acute respiratory tract infection (see protocol for inclusion criteria) without compromising patient safety. The children will be randomised into two groups: in the intervention group CRP POCT will be measured and used to guide clinical decision-making regarding antibiotic use, in the control group standard care will be performed without CRP measurement. The primary outcome is the proportion of children receiving antibiotics within 14 days from the index consultation in each study arm. The main statistical analysis will follow an intention to treat (ITT) principle, in which all enrolled children will be analysed in the groups they are randomised to. Safety outcomes as well as other secondary outcomes will be assessed as described in 1.2.

The statistical analysis will be performed after data from the last follow up has been entered. Analysis will be performed by the investigators of the study using SAS statistical software. Data will be stored in REDcap.

7.13 Randomisation

The children will be randomised into two groups using the online randomisation tool ‘Sealed Envelope’ (www.sealedenvelope.com). Randomisation will be stratified by male/female as well as age<5 years and age>5 years.

7.14 Primary study outcomes

The primary study outcome is the proportion of included children in each study arm that are prescribed an antibiotic within 14 days from the index consultation (superiority analysis).

However, any reduction in antibiotic use must be balanced without any compromise to patient safety and the study will therefore include two primary outcomes. The second primary study outcome is patient safety measured as the number of days until recovery (non-inferiority analysis).

7.15 Secondary study parameters/outcomes

- Antibiotics prescribed at the index consultation

- Antiviral treatment at follow up
- Reconsultation within 14 days from index consultation
- Hospital referral at index consultation
- Hospital admission at follow up
- Mortality

7.16 Power calculation

As the study employs a combined superiority and non-inferiority approach based on the two related primary study outcomes; we provide two power calculations and opt for the conservative number of participants to ensure the adequate sample size for answering both primary outcomes. Power calculations are performed using sample size calculators provided by Sealed Envelope™.

Superiority power calculations show that for a power of 90% to detect a 10% reduction in antibiotic use (from 55% to 45% based on previous pilot registrations in the area) at a statistical significance level of 0.05 a total of 1046 children, 523 in each arm are necessary.

In our non-inferiority power calculation, we apply a margin of non-inferiority of one day (24 hours), i.e. the intervention arm is allowed to have a mean time to recovery that is one day longer than the mean recovery time in the control arm without being deemed inferior. The duration of acute respiratory tract infection in children is approximately 7 days with a standard deviation of 5 days. Hence, for a power of 90% and a statistical significance level of 0.05 a total of 858 children are needed.

To be able to assess both outcomes we will opt for the conservative measure, e.g. the superiority measure.

With an expected dropout rate of 15% we aim to include 1204 children in total, 602 in each arm. This is deemed achievable with the available resources. We expect to be able to include a sufficient number of patients in approximately three months. Each clinic has a patient flow of approximately 10 – 25 children per week. With 10 clinics, the weekly flow of potential participants is 100 – 250 even if only less than 1 in 2 patients are enrolled; we will still keep this schedule.

7.17 Data cleaning and data checking

Before unblinding and analysis the data will be checked for outlying, missing and/or otherwise faulty values. Faulty input and/or extreme outliers will be corrected, and it will be attempted to trace missing values.

7.18 Analysis of baseline variables

An unadjusted comparison will be done between baseline variables of the intervention and non-intervention group. Baseline variables to be compared include age, sex, comorbidities, number of siblings, smoking in household, study site and speciality of health worker.

7.19 Analysis of main outcomes

The main superiority outcome of antibiotic reductions at day 14 will be assessed by a multivariate logistic regression model and results presented both as odds ratio and as the absolute risk difference of antibiotic exposure in the two study arms. This analysis will be done as intention to treat (ITT).

The main non-inferiority outcome of patient safety will be assessed by a multivariate, generalised, linear model to calculate an adjusted 95% confidence interval (CI) for the

difference between CRP-guided and standard therapy in the number of days until recovery. This analysis will both be done as ITT and per-protocol (PP).

7.20 Missing data and lost to follow up

To correct for potential differences in between the groups with regard to missing data and patients that are lost to follow up the main analysis will be done with inverse probability weighing (IPW).

7.21 Analysis of secondary outcomes

Antibiotic treatment at follow up

Using linear regression we will compare how many in the intervention and non-intervention group are prescribed antibiotics at the index consultation.

Antiviral treatment at follow up

Using linear regression we will compare how many in the intervention and non-intervention group start antiviral treatment (prescribed or bought over-the-counter) within 14 days after the index consultation.

Reconsultations

Using linear regression we will compare how many in the intervention and non-intervention group come for reconsultations (planned and unplanned) within 14 days after the index consultation.

Hospital referral at index consultation

Using linear regression we will compare how many in the intervention and non-intervention group are referred to hospital at the index consultation.

Hospital admission at follow up

Using linear regression we will compare how many in the intervention and non-intervention group are or have been admitted into hospital until day 14 after the index consultation.

Mortality

Using linear regression we will compare mortality status in the intervention and non-intervention group.

Secondary outcomes will be expressed with 95% two-sided confidence intervals.

7.22 Adjustment for baseline variables

The analyses of the outcomes will be adjusted for the stratification variables – age and sex – so as to boost the power of the analyses. Additionally, clinical relevant variables such as respiratory frequency, fever and other severity markers will be included.

7.23 Presentation of data

Descriptive data will be presented either by means and standard deviations, or medians and interquartile ranges -as appropriate- for continuous data, or by numbers and percentages for categorical data. Data may also be investigated using visual tools (e.g. histogram, box-plot, scatter plot, Kaplan-Meier curves).

7.24 Interim analysis

Since we are planning to include all subjects within two to three months, we do not plan to make an interim analysis. If the inclusion period will be longer than 3 months we will do an interim analysis or when 500 participants are included which ever comes first. The interim analysis will assess our primary outcome, safety outcome and adverse events. The PI will present the results of interim analysis to the Data Safety Monitoring Board (DSMB) / Safety Committee (see section 7.11).

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted in accordance with the latest version of the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO) and other applicable privacy laws, local guidelines, regulations and Acts.

The team will ensure the correct regulatory approvals are gained prior to initiation of study. The protocol, and attached documents (ICFs, patient information sheets, CRF and phone questionnaire) will be submitted to an appropriate Research Ethics Committee (REC), and, if needed, additional regulatory authority. If necessary, approvals for all substantial amendments to the original approved documents will be obtained. Any substantial amendment to the protocol must be approved by all collaborating parties before they are submitted for national REC and regulatory approvals.

No patients will be enrolled in a country until all approvals have been obtained for that country's primary care network and sites.

Medical management of participants in this study must never be compromised by study procedures. At all times, priority will be given to samples required for medical management.

8.2 Recruitment and consent

Recruitment

All children presenting or consulting the primary care health clinic for their CA-ARTI symptoms described above can be included in the study. Therefore, the HCWs from primary care health clinics (doctors, nurses, practice assistants and medical students) may be involved in the inclusion procedures.

Screening and Eligibility Assessment

Any child aged from 6 month to 12 years contacting the participating health clinics and who meets the eligibility criteria will potentially be included. Patients will be assessed against the

inclusion criteria by the HCWs and if eligible, be included upon signing of an IC by their parents/caregivers and have their CRF completed on paper or online.

Informed Consent
When the patient consults at the health clinic, explanation of the study, provision of study-related information, patient information sheet and IC will be performed at the practice. Al study personal will be trained by the national network facilitator or PI, detailing no less than: the exact nature, implications and constraints of the study, and risks and benefits of participation. The study will provide a patient information sheet (appendix B) that includes all necessary information available in the official national language. Half a day will be given to the parents/caregivers to consider the information given to them and to ask any questions they may have about the study to decide whether their child will participate in the study. As participants are not of legal age of consent in their jurisdiction, consent will be provided by their parent/legal guardian. It will be clearly stated in the patient information sheet and verbally explained to the participant that they are free to withdraw from the study at any time for any reason without impacting their future care, and with no obligation to provide the reason for withdrawal.

8.3 Objection by minors or incapacitated subjects

Not applicable

8.4 Benefits and risks assessment, group relatedness

For the children being managed at participating health centres during the intervention period, the study adds a finger prick and, for some, a tracheal swab, which does give some discomfort for the child. On the other hand, it is the intention that the improved diagnosis will lead to better treatment for the child's condition. There is a slight risk that a child has a severe infection with eg. a short prodrome before presenting to the clinician leading to a CRP that is not yet elevated, and if the CRP levels are followed strictly that such a child is not treated with antibiotics. To counter this, part of the training given with the CRP POCT intervention will address such issues and highlight that if the clinician is worried for the child despite a low CRP count, antibiotic therapy should be started. It will also be emphasized that if in doubt, the clinician should re-evaluate the child eg. the next day or what is clinically meaningful. Previous studies very similar to this have shown to be safe for participants.

Sample analyses will become available weeks after the samples were taken, and thereby don't and can't influence patient care or management. Upon request, the national coordinator can supply the sample results to the health clinics after full data analysis, if participants wants to inquire their results.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

All study-specific documents and laboratory outcomes will be coded with the participant ID, a unique number incorporating the country (one letter K), healthcare centre (two letters) and sequential numbers, so not by name or personal identifiers of the patient. The CRF, swab, contact form and information from phone calls will be identified with this ID. All study documents will be stored securely and only accessible by study staff: PI and designated members of the research team, recruiters in the practices and personnel specifically dedicated for patient follow-up. After completion of follow-up the contact form will be destroyed. The participant code-list (name, birthdate and study ID) will be stored at the healthcare centre.

All paper patient-related documents (ICF, CRF, registration of phone calls) will be stored safely in a locked cabinet in the practice, or office of the PI. The eCRF and electronic entries stored securely at the REDCap online system maintained by the Rigshospitalet and Danske Regioner, Denmark. The REDCap system meets all International Conference on Harmonisation on Good Clinical Practice requirements safeguarding data integrity and electronic data security regulations. Data traffic within REDCap over the internet is encrypted using secured data communication protocols. The central databases and web servers are hosted in a secure data centre. The database (PostgreSQL) is backed up every day. Users will have a role-based access to RO after they log-in using their own personal username and password. This role-based access to the system will avoid unauthorised data access and prevents users from performing actions that they do not have authorisation for. The system logs all data entry steps with timestamps and user information, thereby creating an audit trail. Electronic data will be stored for at least 5 years. See Data Management Plan for further details.

Direct access to source, patient and REDCap data and will be granted to authorised representatives from the Colaborating parties, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections to ensure compliance with regulations. Coded data can be made available for research purposes after permission from the study responsibles.

With the procedures described the the personnel dedicated for participant follow-up will ensure that the patients' privacy is maintained.
All documents will be stored securely and are only accessible by the national network coordinator and dedicated study personnel. At the healthcare centres, all staff will safeguard the privacy of patients' personal data.

9.2 Monitoring and Quality Assurance

Monitoring
Monitoring will be implemented as soon as the study starts, checking study procedures, swab taking and storage, patient inclusion and data entry. Central monitoring will be performed by a responsible delegate from Copenhagen University. This procedure will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of any monitoring activities.

No on-site monitoring visits are planned during the study due to the short inclusion period, vast number of clinics and travel constraints. If required health clinics may be monitored at the end of the study, or afterwards by the PI or a responsible delegate.

Quality Assurance Procedures
The study will be conducted and executed in accordance with the approved protocol, and relevant regulations. Prior to starting the study, all study-related staff will be trained in study procedures by the PI and core team. This will include training, delegation of responsibilities, and set-up to the local recruiting health clinics including procedures related to CRP testing.

9.3 Annual progress report

The PI will submit a summary of the progress of the study to the collaborating parties once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events, other problems, and amendments.

9.4 Temporary halt and (prematurely) end of study report

The collaborating parties must immediately be informed in case of a temporary halt of the study or prematurely end of study including the reason(s) of such an action.

The PI will notify the collaborating parties of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's follow-up phone call.
Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the collaborating parties and relevant sponsors.

9.5 Public disclosure and publication policy

The investigators will be involved in reviewing drafts of manuscripts, abstracts and press releases. Authors will acknowledge how the study was funded. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

10. STRUCTURED RISK ANALYSIS

Not applicable

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Appendix A: Screening form

Appendix B: Patient Information Sheets and Informed Consent Forms

Appendix C: CRF

Appendix D: Phone questionnaire for follow-up