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UMCU, UOXF, UA

Approved protocols for the observational study and the qualitative study with healthcare professionals and patients in primary care

Deliverable 2.1

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101003589.

Introduction

We are doing an observational study in primary care and additionally we are doing a qualitative study in 8 European countries exploring the views of primary health care professionals and patients to capture their views of their experiences of delivering and receiving health in primary care during the pandemic. The objectives for the observational study are different from the objectives of the qualitative research, and different European countries are involved in each study, therefore we have opted to write two different protocols for the separate studies.

SARS-CoV-2 Observational Study of community acquired acute respiratory tract infection during a time of widespread suspected COVID-19 in European primary care

PROTOCOL TITLE SARS-CoV-2 Observational Study of community acquired acute respiratory tract infection during a time of widespread suspected COVID-19 in European primary care

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Subsidising party	**The European Commission under H2020 call SC1-PHE-CORONAVIRUS-2020**

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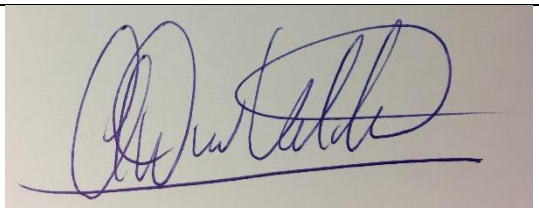
PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Manager Research Julius Center UMCU: Prof K.G.M. Moons	Bij deze mijn 'digitale goedkeuring en handtekening'. Met groet, Carl	**02-04-2020 (19:06)**
Coordinating Investigator/Project leader/Principal Investigator: Alike van der Velden Assistant Professor Julius Center UMCU		**02-04-2020**

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

BMI	Body Mass Index
CA-ARTI	Community Acquired Acute Respiratory Tract Infection
CI	Chief Investigator
CRF	Case Report Form
COVID-19	Coronavirus disease 2019
eCRF	Electronic Case Report Form
GP	General Practitioner
IC	Informed Consent
ICU	Intensive Care Unit
ICF	Informed Consent Form
ID	Identification
JC	Julius Centre
OS	Observational Study
PIS	Participant/Patient Information Sheet
PPAS	Point Prevalence Audit Survey
REC	Research Ethics Committee
RO	Research Online
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
UMCU	University Medical Centre Utrecht
UOXF	University of Oxford
VALUE-Dx	The value of diagnostics to combat antimicrobial resistance by optimising antibiotic use

SUMMARY

Rationale: When a new infection emerges, most detailed information about presentation, management and clinical course is obtained from severe and/or hospitalized cases. This is currently also the case for the COVID-19 pandemic. As a consequence, little information is available from patients with mild and/or undiagnosed SARS-CoV-2 infection. These patients often contact primary care providers, either at the practice or by telephone. There is still much uncertainty about who will develop mild or more severe symptoms upon acquiring the infection and who is at risk of severe complications. We will therefore perform a study in primary care with patients presenting with acute respiratory tract infection in 4-8 European countries.
Objective: To generate information on the presentation and management of patients with community-acquired acute respiratory tract infection in primary care during the COVID-19 pandemic, to determine the proportion of these patients infected with SARS-CoV-2 and risk factors for a complicated course of disease.
Study design: Observational study with patient follow-up.
Study population: Patients aged one year and older, presenting in primary care (either in person, or phone/video), with symptoms of community-acquired acute respiratory tract infection (CA-ARTI) during the COVID-19 pandemic.
Main study parameters/endpoints: The proportion of patients with SARS-CoV-2 infection in patients presenting with CA-ARTI in primary care settings in various European countries, with description of their course of disease (illness days, non-productive days, complications and death).
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 negligible. As part of the inclusion the throat and nose of patients will be swabbed for determining aetiology of disease, or patients will self-swab. Collecting swabs may cause transient discomfort. Discomfort and risk will be minimized by providing detailed instructions (written and video). Follow-up will be two short phone calls, 7 and 28 days after inclusion. There is no direct benefit to participants, apart that after study termination they can inquire the microbiological results of their swab. Children will be included in this observational study too, as course and burden of disease could be different in children and needs to be investigated too. If children don't visit their general practitioner, their parent will take the swab from their throat and nose, again with clear instructions.

- INTRODUCTION AND RATIONALE

COVID-19 represents a threat to the people of Europe and worldwide. Effective management of this pandemic requires estimation of the incidence, clinical presentation, severity, illness spectrum and outcomes of the infection, not only in hospitals, but also in primary care, where most cases are likely to present and be managed. Currently most published literature on COVID-19 represents severe cases admitted to hospital [Ref 1, 2, 3]. Reasonable estimates of the incidences over the illness spectrum are difficult to establish as mild and unsuspected cases need to be included in the 'denominator', and are currently largely unknown. There is an urgent need to understand the clinical presentation, severity, proportion with confirmed COVID-19 among symptomatic patients, and outcome of COVID-19 in primary care. In addition, it is important to capture the associations between this proportion and outcomes comparing European countries, as health service provision and preventive COVID-19 measures differ markedly between countries.

Furthermore, information and the inevitable "infodemic" of misinformation creates anxiety among the general public and health care professionals, which is likely to further stretch community-based health services. Identifying strategies to divert patients by anticipating their needs and direct them to appropriate services will be key to managing patient demand. To develop effective clinical continuity plans, public health and clinical service managers need information about patients' help-seeking behavior in order to identify and anticipate patient health needs and develop effective communication strategies that would encourage patients to self-triage.

This project builds on a point-prevalence audit survey (PPAS) that was implemented between January to March 2020 as part of the EU-funded VALUE-Dx project. Anonymized consultations of patients with community-acquired acute respiratory tract infection (CA-ARTI) were registered by their general practitioner (GP). This was a highly efficient approach to capture presentation, illness severity, illness characteristics, and management (diagnostic testing, prescribed and advised treatments, other provided advice), of nearly 5000 patients in 18 European countries.
Enhancing this already operative PPAS with microbiological analyses and outcomes within our primary care network would enable the rapid initiation of research into:

1) the proportion of patients presenting in primary care with symptoms of CA-ARTI that have confirmed SARS-CoV-2 infection;
2) a description of the typical clinical presentation of SARS-CoV-2 infection in primary care, and outcomes of COVID-19 in the community;
3) a description of GP- and self-management of patients with suspected COVID-19 in primary care during the pandemic;
4) risk-factors for acquiring COVID-19 and for an adverse outcome of COVID-19;
5) differences between European countries in the above mentioned aspects.

SOS COVID will build on an already highly effective pan-European Primary Care Research Network, that has demonstrated the capacity to deliver well-powered observational studies and randomised controlled trials of infectious diseases diagnostics in the primary care setting across Europe (FP6 GRACE and sustained in the European Science Foundation Research Networking Programme TRACE, and is currently active in the EU FP7 funded PREPARE project and the IMI funded VALUE-Dx project).

In SOS COVID we will maintain the same project organisation. UMCU and UOXF will coordinate and train the national network facilitators, who will cascade information and training down to their primary care practices (about 5 to 10 per country). The same countries, network facilitators and practices will contribute as in the VALUE-Dx PPAS, which will facilitate implementation.

The simple web-based VALUE-Dx PPAS data-capture tool will be adapted by implementing additional COVID-19 specific questions, removing non-relevant questions, adding whether informed consent (IC) and a swab were taken and will include follow-up responses. All participating practices have experience with the system, their log-ins and the system has been shown to produce nearly real-time data visualisation. Data can also be gathered on paper and subsequently entered into the data-capture tool.

- **OBJECTIVES**

Primary objective: To estimate the proportion of COVID-19 in patients presenting with CA-ARTI in primary care

Key-secondary objectives: To generate information on the clinical presentation and management of patients with CA-ARTI by their GP in primary care during the COVID-19 pandemic and to generate insight in differences in these aspects between European countries

Secondary objective 1: To determine risk factors* for acquiring COVID-19
* demographic variables, precautionary measures, work/school/day care environment, social life

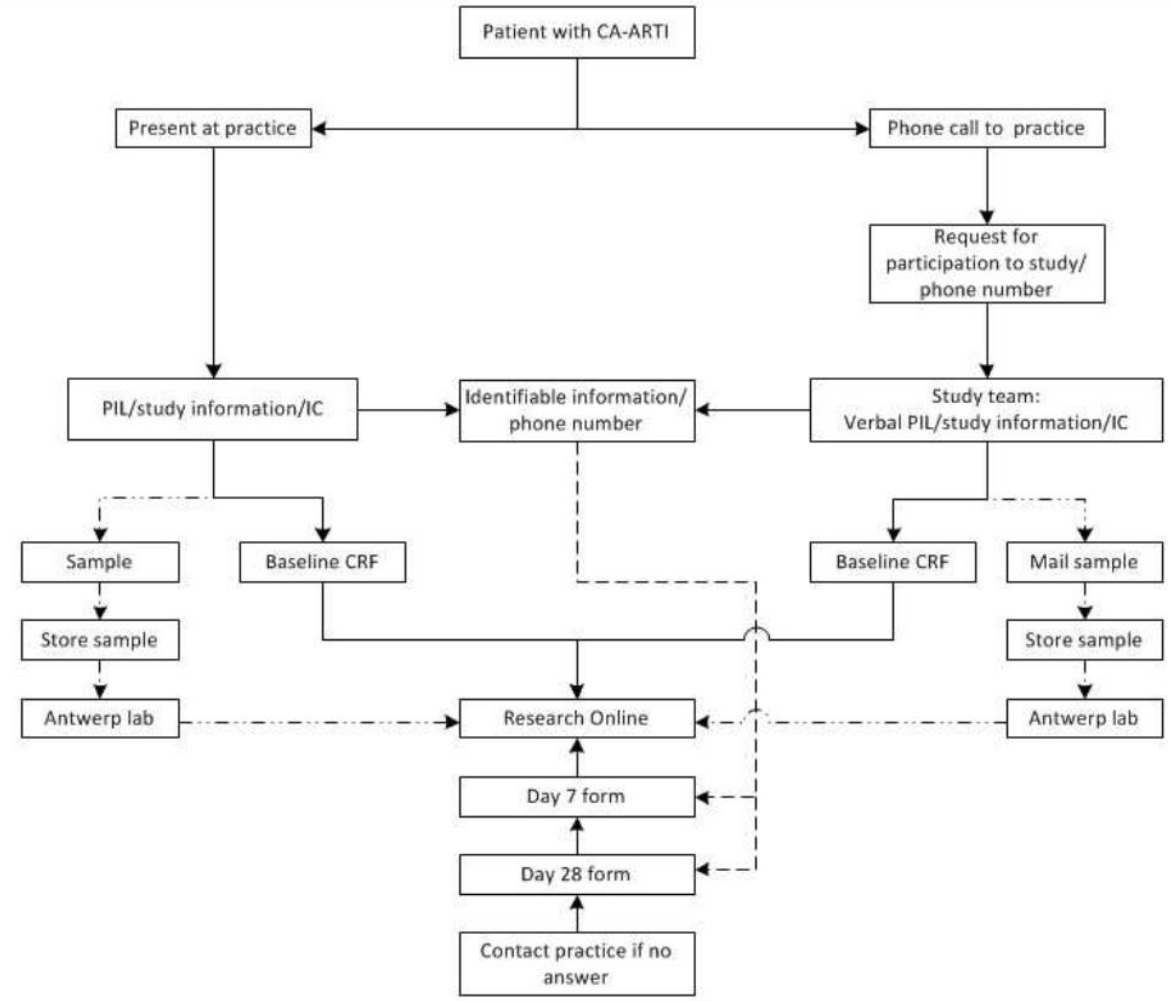
Secondary objective 2: To study risk factors of an adverse outcome# in patients with COVID-19 in primary care
death and/or hospitalisation

Secondary objective 3: To observe self-management of patients with CA-ARTI during COVID-19 pandemic and to generate insight in differences in these aspects between European countries

- **STUDY DESIGN**

This is an observational study of the presentation, management, aetiology and outcomes of CA-ARTI in primary care during the COVID-19 pandemic. This study will be performed in approximately 4-8 EU Member States and H2020 Associated Countries, and will capture the case-mix and care of patients consulting at, or telephoning/videoing their primary care practice with CA-ARTI during the COVID-19 pandemic, and test for the aetiology and record the outcomes of their illness, captured from phone calls at 7 and 28 days after their contact with primary care.

SOS COVID will run during the current COVID-19 pandemic until the inclusion target is reached, or until the pandemic is over, and could start again in a second COVID-19 wave. Primary care practices should aim to include all sequentially consulting (in person or remotely) eligible patients in this observational study.



- **STUDY POPULATION**

  - **Population (base)**

Subject will be drawn from the primary care population.
All patients aged one year and older consulting or calling the primary care practice during the COVID-19 pandemic with symptoms of CA-ARTI will be included, if:

a) an acute respiratory tract infection (upper and/or lower) is suspected, with symptoms of cough, sore throat, and/or rhinitis, or
b) the GP has another reason to suspect COVID-19

Given the pandemic situation, the high incidence of RTI, and streamlining patients with RTI to specific centres (hubs), planned number of patients should be feasible.
Patients of both sexes and all ethnic background can be included.

  - **Inclusion criteria**

A potential subject who meets the following criteria can be included in this study:

- Male or female aged one year or older;
- Consulting face-to-face, online, or telephoning with symptoms of CA-ARTI (upper and or lower), with symptoms of cough, sore throat and/or rhinitis, or when the GP has another reason to suspect COVID-19;
- Is able and willing to comply with all study requirements;
- Participant or legal guardian(s) of a child is able and willing to give informed consent;
- Availability of a freezer at the practice, patient's home, or a laboratory location to be reached within 1 hour.

  - **Exclusion criteria**

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

- Patients with symptoms of earache only;
- Patients who do not master the national language or are otherwise not able to participate in follow-up procedures;
- Patients who are terminally ill;
- Patients tested positive for SARS-CoV-2 prior to recruitment.

  - **Sample size calculation**

We do not intend to plan this study with a limit on sample size, as the required sample to achieve a useful description of this condition in primary will vary as the pandemic evolves, and so the extent and duration of this study will be assessed on a week to week basis. Sample size will also vary according to the variation in presentation, management and outcomes not only at the individual, but also at country level. Although each country will include 5-10 primary care practices, there will be power in pooling these observations and investigate influences of variation in care and health systems on incidence rates and outcomes across Europe.
With the current availability of swab material, we intend to include 50-100 patients per country in this observational study, which can be increased when more swab material becomes available.

- **TREATMENT OF SUBJECTS**

Not applicable

- **INVESTIGATIONAL PRODUCT**

Not applicable

- **NON-INVESTIGATIONAL PRODUCT**

Not applicable

- **METHODS**
    - **Study parameters/endpoints**

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure**
To estimate the proportion of COVID-19 in patients presenting with CA-ARTI in primary care To generate information on the presentation and management of patients with CA-ARTI in primary care during the COVID-19 pandemic To generate insight in differences between European countries in presentation and management of patients with CA-ARTI in primary care during the COVID-19 pandemic	GPs will be asked to fill out a brief Case Report Form (CRF) for patients 1 year and older who consult or telephone with symptoms of CA-ARTI during the COVID-19 pandemic. Information recorded includes: • Demographic details including: sex, age, co-morbidities, smoking, BMI; • COVID-19 specific questions and suspicion, precaution; • Duration of CA-ARTI symptoms prior to consulting; • Presence of signs and symptoms (RTI and general)and overall severity rating; • Additional measurements: oxygen saturation, respiratory rate, blood pressure, heart rate, temperature; • All routine diagnostic tests performed or ordered; • Prescribed medication (antivirals, antibiotics); • Suspected aetiology; • Working diagnosis (subcategory of CA-ARTI, e.g., pharyngitis, tonsillitis, exacerbation of chronic obstructive pulmonary disease, bronchitis, pneumonia, COVID-19; • Additional advice about treatments, precautions, home isolation, self-management, advice for family members; • Referral to hospital, or public health authority; • Phone number for follow-up.	April 2020 until the end of pandemic, or until target reached, whichever is first
To determine risk factors for acquiring COVID-19	A swab (preferably throat and nose combined) will be taken from all patients to be analysed for presence of SARS-CoV-2 virus and other	At inclusion

To study risk factors of an adverse outcome in patients with COVID-19 in primary care To observe self-management of patients with CA-ARTI during COVID-19 pandemic To generate insight in differences between European countries in self-management of patients with CA-ARTI during COVID-19 pandemic	pathogens; where this is not possible face-to-face, self-swabbing or parent/child swabbing will be employed at home. Patients will receive a phone call at day 7 and 28 to collect information on: • Duration of CA-ARTI episode and their symptoms; • Return to school/work/normal activities; • Additional contacts with healthcare professionals/facilities; • Complications such as pneumonia or hospitalisation; • CA-ARTI infection in other family members (if applicable); • General well-being; • Self-management, preventive measures. If no contact can be made after 3 phone calls, the practice will be informed and health records will be checked for additional information (i.e. hospitalisation and death).	At day 7 and day 28 a representative from the practice or the national coordination team will call the patient and ask for set of outcome data Only in case participants can't be reached by phone participating practices will be asked to provide a minimal set of outcome data.

- **Randomisation, blinding and treatment allocation**

Not applicable

- **Study procedures**

Recruitment:
See 11.2

Screening and Eligibility Assessment
See 11.2

Informed Consent
See 11.2

Study Visit - Inclusion
Patients will be included when they visit, phone, or video-consult the practice. During this consultation the baseline CRF data will be gathered (see appendix A, for the exact information that will be recorded):

- COVID-19-specific questions;
- Demographic details including: sex, age, co-morbidities, smoking, BMI category;
- Duration of CA-ARTI symptoms prior to consulting;
- Presence of specific RTI and general symptoms;
- Overall severity rating (GP's perception);
- Clinical assessments taken (oxygen saturation, respiratory rate, blood pressure, heart rate, body temperature);
- All diagnostic tests performed or ordered;
- Suspected aetiology, working diagnosis and COVID-19 suspicion;
- 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, or the swabbing material will be delivered at the patient's home, see below.

Follow-up with Phone Calls

Patients will be treated according to usual care during the COVID-19 pandemic. There is no study intervention. There will be no scheduled follow-up visit at the practice required by the study. Patients will be phoned 7 and 28 days after the index consultation to record outcomes. Phone calls will be performed by practice personnel, or the national coordination team (see appendix B for the exact information that will be recorded):

- Number of symptomatic days after the consultation;
- Duration of specific symptoms;
- Return to school/work and usual activities;
- Additional contacts with health care providers;
- 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;
- Experience with care during the pandemic.

Sample Taking and Handling

All included patients will have a flocked swab taken at baseline. Where this cannot be done face-to face by the GP, practice assistant or medical student, a self-swabbing procedure will be made available, with clear instructions (pictures with text and/or video) available in the PIS. For children, the parent will be properly informed about how to take the swab. The child will be informed about the tickly feeling in the throat, that won't hurt. Swabbing the nose is not expected to be uncomfortable.

This will be a combined swab from the throat (around the pharynx) and then into the nose (both nostrils). The swab (COPAN) will be placed in the provided tube with universal transport media. The patient's date of recruitment and study ID number will be used to link the sample to the outcome information. Materials will be provided by the University of Antwerp, the central laboratory. After having taken the swab, the sample will be stored in a freezer. Depending on countries' preferences, set-up and possibilities this can either be in the practice where the patient was

recruited, the coordinating centre, a laboratory to be reached within one hour, or at the patient's home. There is no maximum time period of storage under these conditions. At appropriate time points, the samples will be collected, under cooled conditions, from aforementioned locations and stored at one central location; this can either be one of the practices, a laboratory, or the coordinating centre. From this central location, samples will be regularly transported, under cooled conditions, to the University of Antwerp. The export of all samples to Belgium will be performed in accordance to country and Europe specific regulations. In Antwerp, samples will be analysed for the presence of viral and bacterial pathogens (Polymerase Chain Reaction-based routine analyses), including: SARS-CoV-2, influenza A and B, Respiratory Syncytial Viruses A and B, para influenzaviruses1-4, human rhinovirus, human coronaviruses (229E, NL63, HKU1, OC43), human bocavirus, human metapneumovirus A&B, parechovirus, enterovirus, adenovirus, Mycoplasma pneumonia, Chlamydia pneumonia, Haemophilus influenzae B, and Streptococcus pneumoniae.

Sample analyses will become available weeks after the samples were taken, and thereby don't and can't influence patient care or management. The laboratory and study team will have access to results for the purposes of sample tracking and linkage. Upon request, the national coordinators can be supplied with the sample results of their countries' participants after full data analysis, and forward to the practices that participated. Patients can request their outcomes at their primary care practice.

- **Withdrawal of individual subjects**

Subjects 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.

- **Replacement of individual subjects after withdrawal**

New participants can be added after withdrawal if swabbing material allows.

- **Follow-up of subjects withdrawn from treatment**

Not applicable, no treatment

- **Premature termination of the study**

This observational study will run during the COVID-19 pandemic period. If the pandemic is declared over by regulatory authorities (in the Netherlands: the RIVM), patient inclusion in the study will be (temporarily) terminated. Included patients will still receive phone calls as part of follow-up. In the situation where a new 'wave of COVID-19' should begin, the study can be re-opened.

- **SAFETY REPORTING**

  - **Temporary halt for reasons of subject safety**

In accordance to section 10, subsection 4 of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

  - **AEs, SAEs and SUSARs**

    - **Adverse events (AEs)**

This observational study only involves throat/nose swabbing. Due to the negligible risk of this procedure, no adverse events will be reported.

    - **Serious adverse events (SAEs)**

This observational study only involves throat/nose swabbing. Due to the negligible risk of this procedure, no serious adverse events will be reported.

As part of the study, we will collect the following outcomes at day 7 and 28:

- Death
- Inpatient hospitalisation

These will, however, not be reported as SAEs, since they will be unrelated to participation in this observational study.

  - **Data Safety Monitoring Board (DSMB) / Safety Committee**

Given the negligible risk of this observational study, no Data Safety Monitoring Board or Steering/Safety Committee will be appointed.

- **STATISTICAL ANALYSIS**

An outline of the statistical analysis of the study is provided below. Details on the statistical analysis and methods will be described in the Statistical Analysis Plan (SAP) prior to database lock. The SAP will include a description on the handling of missing data.

All patients enrolled into the study will be analysed.

- **Primary study parameter**

The primary study parameter is the proportion of COVID-19 in patients presenting with CA-ARTI in primary care.

- **Secondary study parameters**

The key-secondary study parameters are the clinical presentation and management of patients with CA-ARTI by their GP in primary care during the COVID-19 pandemic, and differences in these aspects between European countries.

The secondary study parameters are:
1) risk factors for acquiring COVID-19 (demographic variables, precautionary measures, work/school/day care environment, social life)
2) risk factors of an adverse outcome in patients with COVID-19 in primary care (death and/or hospitalisation)
3) self-management of patients with CA-ARTI during COVID-19 pandemic, and differences in these aspects between European countries

Analyses:
Data will be described and summarized 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).

The proportion of COVID-19 in patients presenting with CA-ARTI in primary care will be presented with 95% confidence intervals, overall, per country, and -if applicable- by season, or pandemic wave.
Outcome parameters with a continuous distribution will be analysed using linear regression models. Outcome parameters with a discrete distribution (dichotomous variables, ordered categorical variables, and counts) will be analysed with generalized linear models, or non-parametric methods.

- **Other study parameters**

Not applicable

- **Interim analysis (if applicable)**

Not applicable

- **ETHICAL CONSIDERATIONS**

  - **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.

Each national team will ensure the correct regulatory approvals are gained for their country. The protocol, and attached documents (ICFs, PISs, CRF and phone questionnaire) will be submitted to an appropriate Research Ethics Committee (REC), and, if needed, regulatory authority. The national team will submit and, where necessary, obtain approvals for all substantial amendments to the original approved documents. Any substantial amendment to the protocol must be approved by the CI at UMCU 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.

  - **Recruitment and consent**

Recruitment

Patients will be included during the COVID-19 pandemic period, or when there is widespread COVID-19 transmission, which can differ per participating country and will be based on national and regional reports of the progression and resolution of the situation. In general, this study is to be conducted during a disease outbreak. This is a challenging research situation because this falls in the area between clinical care, public health and clinical research (World Health Organisation Ethical Review in Disease Outbreak Expert Meeting, 2009).

All patients presenting, telephoning, or video-conferencing/consulting the primary care practice for their symptoms described above can be included in the study (see chapter 3: study flow). Therefore, the GPs, as well as others who see (real life, or phone/video), answer and advise patients during this pandemic from a primary care clinic (nurses, practice assistants and medical students) will be involved in the inclusion procedures. Depending on the pandemic situation and the primary care practice organisation, (part of the) work load of including patients could be on the national coordinating team too.
In situations where patients are only consulted over the phone or video, the study will be briefly explained during this encounter, a verbal IC will be taken, CRF data will be entered and the patient will be asked for permission to be contacted by someone from the national coordination team. Upon approval, the national coordination team will contact the patient and start the study-related procedures. A paper IC form (ICF, appendix C) together with all other study-related materials will be delivered, or posted to the patient's home by personnel trained by the practice or national coordination team.

Screening and Eligibility Assessment

Any patient aged one year and older contacting the participating practices in participating countries, who meets the eligibility criteria during the COVID-19 pandemic will be included. Patients will be assessed against the inclusion criteria by the GP, nurse, student, or practice assistant, who will complete the CRF on paper or online.

Informed Consent
When the patient consults at the practice, explanation of the study, provision of study-related information, patient information sheet (PIS) and informed consent will be performed at the practice by the GP, or other personnel trained by the practice or national network facilitator, detailing no less than: the exact nature, implications and constraints of the study, and risks and benefits of participation. The study will provide an age-appropriate PIS (appendix D) that includes all necessary information. PIS and other participant-relevant study material will be available in the official national language. Half a day will be given to the participant or parent(s)/legal guardian(s) to consider the information given to them and to ask any questions they may have about the study to decide whether they/their child will participate in the study. If the participant has the legal age of consent for the jurisdiction in which they are being recruited, they must personally sign the ICF. However, if the participant is not of legal age of consent in their jurisdiction, consent will be provided by their parent/legal guardian (either one or both parents will be required to give consent in accordance with the permissions of the jurisdiction where recruitment is taking place). It will be clearly stated in the PIS 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.

In this study it is important to also capture data and samples from patients that are consulted and advised over the phone/video, and are recommended to stay at home. The majority of GP practices may no longer be conducting face-to-face appointments during the COVID-19 pandemic, and all potential COVID-19 sufferers are being informed by a national campaign to contact clinicians by telephone or online in many jurisdictions. These patients will be informed during the phone/video call about the study and when they agree to participate *verbal informed consent* will be sought. This means that *under these exceptional circumstances* the patient, or parent(s) sign the ICF on their own at home, and the person who took the verbal consent will sign later. After these steps the written ICF will contain the dated signatures of the participant and/or their parent(s)/legal guardian(s) and the person who verbally presented the IC (during the personal consultation, or phone/video). A copy of the signed ICF will be returned to the participants (directly or via regular mail).

As we will perform this study in multiple countries, the national teams can choose which of the following procedures they implement to obtain written IC from participants:
Someone trained by the practice will post, or personally deliver by hand, or via the mailbox all study-related material at the patient's home: ICF, patient information sheet, contact form, sample material. At a time agreed on the phone/video, materials will be collected, in a similar way.

- **Objection by minors or incapacitated subjects**

The 'Gedragscode verzet bij minderjarigen' is applicable for children included in the study.
No incapacitated adults will be enrolled.

- **Benefits and risks assessment, group relatedness**

This observational study is considered a negligible risk study as it does NOT interfere with, or influence participant's care. If as part of routine care during the COVID-19 pandemic the GP or public health authority decides to swab for COVID-19 diagnosis, this will be prioritised. The patient can still be included in this observational study and a second swab will be taken.
Inclusion procedures and the telephone calls are NOT burdensome. Taking a swab, or self-swabbing is also classified as a negligible risk procedure.

This observational study will enrol children. It is considered relevant to know the proportion of children infected with SARS-CoV-2, especially as it seems that children are generally developing mild symptoms from COVID-19. Furthermore, as for adults, it is important to gain insight in how parents handle a child with symptoms of RTI during the COVID pandemic.

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 coordinators can be supplied with the sample results of their countries' participants after full data analysis, inform the primary care practices, where patients can inquire their results.

- **Compensation for injury**

Given the negligible risk of the study-related procedure, the throat/nose swab, we ask for an exemption for arranging participant insurance.

- **Incentives**

Upon completion of follow-up of the study, having provided answers in the two telephone calls, the participants will receive a gift voucher (VVV bon in the Netherlands) of 10 euros.

- **ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION**

  - **Handling and storage of data and documents**

All study-specific documents and (laboratory) outcomes, other than the signed ICF, will be coded with the participant ID, a unique number incorporating the country (two letters), practice (one letter) 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: recruiters in the practices, the national network facilitator, and personnel specifically dedicated by the national network facilitator 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 primary care practice.

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 national network facilitator. The eCRF and electronic entries of the phone calls will be stored securely at the Research Online web servers maintained by the Julius Center, UMCU. The system meets all International Conference on Harmonisation on Good Clinical Practice requirements safeguarding data integrity and electronic data security regulations. Data traffic within RO 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 15 years. See Data Management Plan for further details.

Direct access to source, patient and RO data and the swab material will be granted to authorised representatives from the Sponsor, 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 CI at UMCU.

The study will comply with the General Data Protection Regulation and Data Protection Act 2018. With the procedures described the national network facilitator and 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 practices, all staff will safeguard the privacy of patients' personal data.

At the end of the study and after the database has been locked, all essential documents and study data will be archived for 15 years in accordance with UMCU Archiving Standard Operating Procedures. Storage of the ICFs, at the national coordinating center, and material isolated from the swab, at the Microbiology Laboratory of Antwerp, will also be for 15 years.
Specifically for children, their material isolated from the swab will be destroyed before they turn 16 years of age.

  - **Monitoring and Quality Assurance**

Monitoring

Central monitoring, using Research Online, will be implemented as soon as the study starts, checking IC procedures, swab taking and storage, patient inclusion and data entry. Central monitoring will be performed by a responsible delegate from the Julius Center, UMCU. 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 and travel constraints. If required, countries' networks or primary care practices will be monitored when travel is allowed at the end of the study, or afterwards by a responsible delegate from the Julius Center, UMCU, or a Clinical Research Organisation. More details are described in the Monitoring Plan.

Quality Assurance Procedures
The study will be conducted and executed in accordance with the approved protocol, and relevant regulations and Julius Center UMCU Standard Operating Procedures. Prior to starting the study, all network facilitators and their study-related staff will be trained in study procedures by the core team based at the UMCU and UOXF, and will cascade this training, delegation of responsibilities, and set-up to the local investigators and their study-related personnel of the recruiting primary care practices. The UMCU will take overall management of regulatory aspects, and will cover training, site set-up, initiations and logistics.

- **Amendments**

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

- **Annual progress report**

The investigator will submit a summary of the progress of the study to the accredited METC 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.

- **Temporary halt and (prematurely) end of study report**

The investigator will notify the accredited METC 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.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

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 accredited METC.

- **Public disclosure and publication policy**

The investigators, Alike van der Velden, Chris Butler, Theo Verheij, Emily Bongard, Akke Vellinga, and one investigator from each country network, to be decided at publication, 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.

- STRUCTURED RISK ANALYSIS

Not applicable

- REFERENCES

Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. D. Wang, B. Hu, C. Hu, et al. JAMA. 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585

Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. B.E. Young, S. W. Xiang Ong, S. Kalimuddin, et al. JAMA. Published online March 3, 2020. doi:10.1001/jama.2020.3204

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. F. Zhou, T. Yu, R. Du, et al. Lancet 2020 DOI:https://doi.org/10.1016/S0140-6736(20)30566-3

Appendix A: CRF

Appendix B: Phone questionnaire for follow-up

Appendix C: Informed Consent Forms

Appendix D: Age-appropriatie Patient Information Sheets

Rapid European SARS-COV-2 Emergency research Response (RECOVER): Qualitative interviews with patients and healthcare professionals.

1.1. RECOVER Qualitative interviews (RECOVER-QUAL)

Ethics Ref: 20/SC/0175

IRAS Project ID: 281980

Date and Version No: 25th March 2020, v1

Chief Investigator:	Dr Sarah Tonkin-Crine, Nuffield Department of Primary Care Health Sciences, University of Oxford
Lead EU Investigator	Prof Sibyl Anthierens, Department of Primary and Interdisciplinary Care, University of Antwerp, Belgium
Investigators:	Dr Marta Wanat, Dr Nina Gobat, Dr Emily Bongard and Prof Chris Butler; Nuffield Department of Primary Care Health Sciences, University of Oxford. Ms Melanie Hoste; Dr Annelies Colliers, Department of Primary and Interdisciplinary Care, University of Antwerp. Dr. Alike van der Velden and Prof Theo Verheij; Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht
Sponsor:	University of Oxford, Clinical Trials and Research Governance, Joint Research Office, 1st floor, Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB.
Funder:	European Commission Horizon 2020 (H2020) – Research and Innovation Framework Programme

Chief Investigator Signature: 

The research team have no conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, HRA (where required) unless authorised to do so.

TABLE OF CONTENTS

1. KEY STUDY CONTACTS

Chief Investigator	Dr Sarah Tonkin-Crine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG. Email: Sarah.Tonkin-Crine@phc.ox.ac.uk Tel: 01865 289316 / 07792794836.
Sponsor	University of Oxford, Clinical Trials and Research Governance, Joint Research Office, 1st floor, Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB. Email: ctrg@ox.ac.uk
Funder(s)	European Commission Horizon 2020 – Research and Innovation Framework Programme. https://ec.europa.eu/programmes/horizon2020/en

2. LAY SUMMARY

Over 20,000 people have been infected with COVID-19, a new illness caused by a type of virus called coronavirus. This situation, because of the number of people affected, called a pandemic, has created a number of challenges for both patients and healthcare professionals. We know from previous studies that healthcare professionals are able and willing to provide care to patients under such demanding circumstances despite personal risk; however, they also need to be supported to provide the best care possible whilst protecting themselves. Similarly, patients need to be provided with information about potential symptoms, when and how to seek help.

We have not found any studies looking at patient experiences of seeking medical advice during a pandemic. It is critical to listen to patient views to help ensure that they receive the best possible care and advice which meets their needs. Previous studies with healthcare professionals and patients looked at their experiences after a pandemic was over which does not allow us to gain an understanding of patients' and healthcare professionals' needs when a pandemic situation is active.

The main aim of the study is to find out patients' and healthcare professionals' views and experiences of seeking medical help and providing care during the COVID-19 pandemic. We will carry out interviews with patients and healthcare professionals across a number of European countries and rapidly feedback our findings to healthcare managers and policy makers to ensure that required changes can be implemented quickly.

3. SYNOPSIS

Study Title	Rapid European SARS-COV-2 Emergency research Response (RECOVER): Qualitative interviews with patients and healthcare professionals.
Internal ref. no. / short title	RECOVER Qualitative interviews (RECOVER-QUAL)
Sponsor	University of Oxford, Clinical Trials and Research Governance, Joint Research Office, 1st floor, Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB.
Funder	European Commission Horizon 2020 – Research and Innovation Framework Programme. https://ec.europa.eu/programmes/horizon2020/en
Study Design, including methodology	Interviews conducted during the COVID-19 pandemic across European countries. These semi-structured interviews will be conducted with patients and health care professionals.
Study Participants, including sampling strategy	Interviews will be conducted with: • Patients consulting for CA-ARTI symptoms (in person or remotely) in European primary care. Maximum variation sample based on age, gender, relevant comorbidities and whether patients have been tested for COVID-19, where possible. • Healthcare professionals (e.g. doctors, nurses and non-clinicians) who work in European primary care and deliver care to patients with CA-ARTI symptoms. Maximum variation sample, based on job role, any additional responsibilities as a result of the COVID-19 response in their organisation, years of experience and any specialty training in respiratory medicine and/or response to epidemics, where possible.
Sample Size	Up to 70 healthcare professionals; 8-15 per country in 3-7 countries. Up to 70 patients; 8-15 per country in 3-7 countries.
Planned Study Period	Length of project: 12 months Length of participant involvement: single interview for all participants.
Planned Recruitment period	April 2020 - March 2021
Aim/Research Questions/Objectives	
Primary	To explore health care professionals' views and experiences of delivering care, either in person or remotely, in European

	primary care to patients with CA-ARTI symptoms during the COVID-19 pandemic. To explore the views and experiences of patients who consult (in person or remotely) in European primary care services for CA-ARTI symptoms during the COVID-19 pandemic.

4. ABBREVIATIONS

A/H1N1	***Influenza A*** virus subtype ***H1N1***
CA-ARTI	Community acquired acute respiratory tract infection
CI	Chief Investigator
CTRG	Clinical Trials & Research Governance, University of Oxford
H2020	Horizon 2020 EU Framework Programme for Research
HCP	Health care professional
HRA	Health Research Authority
ICF	Informed Consent Form
NHS	National Health Service
RES	Research Ethics Service
PCP	Primary Care Professional
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee

5. BACKGROUND AND RATIONALE

Qualitative work has shown that primary care professionals (PCPs) are willing to provide clinical services in a pandemic, motivated by altruism in the context of high personal risk.[1,2] Previous research during the 2009 /A/H1N1 pandemic indicated that PCPs struggled with implementing new workflows in response to the pandemic, in particular juggling activities to provide care to patients and report suspected cases to health authorities.[2] PCPs also felt uncertain about using drugs with which they are not familiar.[2] Appropriate education, training and supply of equipment is reported as necessary to support PCPs outside of, and during, outbreak periods.[1-4]

PCPs see the management of 'worried-well' patients as one of their key roles and highlight media-induced anxiety as a factor which adds strain on healthcare resources.[2] PCPs report spending a significant amount of time giving advice and reassuring patients, even when national advice phonelines are available, highlighting the importance of their role in disseminating trusted advice.[2] Studies have also shown that PCPs report lack of cooperation from some patients who do not report relevant symptoms until they are with a doctor, indicating that patients need support in following health protection guidance.[1,4]

We have not identified any qualitative work exploring the patient experience of consulting healthcare treatment and advice during a pandemic. Experts have highlighted the need to "put the patient central during epidemics" and to ensure patient-centred research is carried out to improve patient outcomes.[5,6] Qualitative work has indicated that patients would be willing to participate in research during an epidemic.[6]

Qualitative work with PCPs on pandemics, for practical reasons, is often carried out retrospectively and capturing views of patients, in real time, is rare. Retrospective interviews, once an outbreak is over, will be clouded by knowledge of how the outbreak evolved: capturing perceptions during the outbreak, with any associated uncertainty, would be highly informative and critical to developing more effective risk communication strategies within a pandemic and to learn for future pandemics.

As a result of existing networks and access to clinicians and patients we have a unique opportunity to gather data on the social dynamics between Health Care Professionals (HCPs) and patients in the context of the COVID-19 pandemic. As part of our EU wide RECOVER research consortium, we plan to interview professionals and patients across a select number of European countries to understand experience about delivering and accessing care during the COVID-19 pandemic. Insights from this research will be rapidly shared with participating sites to inform improvements to primary care services being offered during the COVID-19 pandemic, and to anticipate additional health needs, for example, related to psychosocial support.

Our objectives are:

1. To explore health care professionals (clinicians' and non-clinicians') views and experiences of delivering care to patients with CA-ARTI symptoms during the COVID-19 pandemic in European primary care.
2. To explore the views and experiences of patients' who consult (in person or remotely) in European primary care services for CA-ARTI symptoms during the COVID-19 pandemic in European primary care.

Interviews are most likely to be carried out remotely by telephone or videoconference such as Skype (audio-recording only, not video recording). In person interviews may be carried out at primary care sites where researchers have access depending on the local situation. Primary care healthcare professionals include doctors, nurses, and any other clinician or non-clinician who can comment on how care is delivered to patients with CA-ARTI symptoms during the COVID-19 pandemic. Patients are anyone consulting primary care services, in person, by telephone or e-consultations, for CA-ARTI symptoms during the COVID-19 pandemic.

There is very minimal risk to participants, discussions will not include topics which are sensitive or embarrassing. We recognise that discussing the COVID-19 pandemic may be upsetting for some participants however participants will have volunteered to discuss this topic when agreeing to take part. Experience of conducting such research in China during early phases of the COVID-19 pandemic indicated patient and public willingness to be involved, particularly during periods of quarantine or self-isolation. It is unlikely criminal or other disclosures requiring action could occur during the study.

6. AIM / RESEARCH QUESTIONS / OBJECTIVES

2.

Research Question / Objectives
What are primary care healthcare professionals' and patients' views and experiences of primary care service delivery during the COVID-19 pandemic?
Objectives: 1. To explore health care professional experiences on delivering care during the COVID-19 pandemic, including adaptations to service delivery such as telemedicine. 2. To explore health care professional perceptions of personal risk of COVID-19 and prevention behaviours. 3. To explore patient reports of help-seeking during the COVID-19 outbreak and perceptions of care received. 4. To explore patient perceptions of personal/family risk of COVID-19 and reports of prevention behaviours before and after consultation in primary care, including home care. 5. To explore patient perceptions of research participation during a pandemic. 6. To explore differences in patient and healthcare professional views and experiences in different EU countries.

7. STUDY DESIGN

7.1 Methodology

We will conduct individual semi-structured interviews with primary care health care professionals and patients who consult for CA-ARTI symptoms in primary care. Only adults aged 18 years and older will be invited to participate. Participants may include parents/carers of who sought care on behalf of their child/dependent.

Interviews will explore the views and experiences of health care professionals on delivering care during the COVID-19 pandemic and their own perceptions of risk of being infected. Interviews with patients will explore experiences of consulting in primary care with CA-ARTI symptoms, perceptions of personal risk of COVID-19, self-care and prevention behaviours and views on research participation.

Interviews will allow us to identify the immediate and short-term needs of healthcare professionals and feedback findings to policy makers, healthcare managers and clinicians to support primary care practice. Interviews with patients will allow us to identify patient needs and understanding to feedback findings to health authorities and support optimal communication practices whilst avoiding undue anxiety and distress.

7.2 Sampling Strategy

Country selection

We will select 3-7 European and H2020 countries, from those in our existing clinical VALUE-Dx European primary care network, consisting of national networks in 17 countries, but will definitely include the UK and Belgium. We will purposively select countries, where possible, to get those which have some of the highest numbers of confirmed cases of COVID-19 which differ in health system organization and location in Europe. Each country has an existing primary care network and network coordinator who is already carrying out research for the wider RECOVER project. Each country will obtain its own necessary local approvals. Each network has a number of primary care sites which are already participating in other RECOVER research activities. Patients and professionals will be recruited from these existing sites in each country.

We will also respond to ad hoc requests from (clinical) colleagues within our RECOVER consortium who work with healthcare professionals willing to take part in this study. We have already had two requests along these lines, including at a primary care practice in Switzerland where clinical colleagues who are self isolating have requested to take part in research to share their unique experiences and challenges. As such we may include additional EU countries to those selected as described above and within countries interviews may only be carried out with HCPs.

Recruitment of healthcare professionals and patients

The research team will work with primary care practices to identify and recruit participants.

The practice contact in each practice will invite all eligible patients to the study. Patients will be told about the study at the time of their consultation or invited by telephone or email (**Patient invitation email**). All patients will be provided with a copy of the **Patient Information Leaflet (PIL)** and **Patient Informed Consent Form (ICF)** either in person or by email. The research team will ask the practice contact in each practice to invite all eligible HCPs to the study. HCPs will include all those helping to deliver care for patients presenting with respiratory symptoms. This will be done in person or by email (**HCP invitation email**) and potential participants will be provided with the **HCP PIL** and **HCP ICF**.

Patients and HCPs will be asked to contact the research team by email or telephone if they are interested in taking part. The research team will collect expressions of interest, some information on participant characteristics (described below) and will answer any questions about the study.

We will aim to recruit a sample that varies across important characteristics for both HCPs (e.g. job role, years of experience, additional responsibilities due to COVID-19 response) and patients (age, gender, whether tested/ suspected of COVID-19). We will prioritise recruitment of clinical staff but non-clinicians will also be included. Characteristics of potential participants will be gathered when HCPs and patients contact the research team.

Recruitment will be flexible to adapt to the local clinical situation and convenience sampling for both patients and professionals will be used where needed.

The research team will arrange a convenient time and date for an interview with those patients and professionals who are willing to participate and who have been selected for interview. Interviews with patients will be scheduled to take place within 2 weeks of their consultation where possible. Interviews may be carried out by a member of the research team who is in a different country from the participant when the researcher can speak the required language (e.g. a researcher in the UK interviewing a participant in Poland when the researcher can speak Polish).

We aim to conduct approximately 8-15 interviews with patients and 8-15 interviews with healthcare professionals in each country, in 3-7 countries, with a total of up to 70 interviews with patients and 70 interviews with healthcare professionals.

7.3 Methods of Data Collection

Interviews will be carried out by telephone, by Skype/Zoom tele-conferencing or in person where suitable and given the participant's preference. Interviews will be carried out with healthcare professionals only where workflows and delivery of care allows and with patients, only where patients are well enough to participate.

Interviews will follow semi-structured topic guides, one for professionals (**HCP Topic guide**) and one for patients (**Patient Topic guide**). Patient interviews will discuss help-seeking behavior, perceptions of risk from COVID-19, self-care behaviours, including experience of home care, protection, emotional burden and impact on of others living in the home and on other aspects of life, as well as of prevention behaviours. Healthcare professional interviews will discuss their experiences of delivering care during the outbreak and managing patients with suspected COVID-19, as well as their experience of local and national policy and practice changes, for example, the shift to telemedicine. Interviews with clinical and non-clinical professionals will discuss changes in patient demand and presentation, changes to practice as a result of responding to coronavirus policies and protocols and self-protection behaviours. Topic guides have been informed by existing literature, rapidly emerging anecdotal and empirical evidence on Covid-19, and theory to ensure that questions elicit likely key determinants of behaviour.

Interviews will be carried out in (one of) the primary language(s) in each country. Interviews will be audio-recorded and are expected to last between 15 and 30 minutes but may be longer if a participant wishes to provide more information and is happy to continue.

7.4 Methods of Data Analysis

2.1.

2.2. Audio recordings of interviews will be transcribed verbatim and translated into English where required. A member of the research team or an independent transcription/translation company will transcribe and translate interviews. If an external company is used they will have a contract with the University of Oxford or University of Antwerp to handle data securely. On occasion, for speed, analysis may be done directly from audio recording.

2.3.

2.4. Data from the two sets of interviews (professionals and patients) will be analysed separately following the same approach. Data will be analysed inductively using framework analysis.[7] Framework analysis allows rapid analysis of data using an a priori framework centred on questions most relevant to policy makers. This approach will be used flexibly to allow us to identify additional themes which are relevant to the research questions.

8. PARTICIPANT IDENTIFICATION

8.1 Study Participants

Primary care health care professionals (including general practitioners, nurse (practitioners), other non-medically qualified health care professionals) who carry out consultations with patients presenting with CA-ARTIs symptoms and health professionals (non-clinical) who support wider delivery of care to patients in primary care (e.g. practice managers). Up to 70 healthcare professionals will be recruited; 8-15 per country in 3-7 countries.

Patients who have consulted primary care services for CA-ARTI symptoms (lower and/or upper) either by telephone, e-consultation or in person. Up to 70 patients will be recruited; 8-15 per country in 3-7 countries.

Sampling for semi-structured interviews with HCPs and patients will not be able to be informed by data analysis as this process will take too long and we will need to collect interview data quickly given the changing situation of COVID-19 infection in clinical practice. Instead researchers in each country will aim to sample a selection of patients and professionals to get variation in characteristics and experiences.

8.2 Inclusion Criteria

All participants:

- Male or female, aged 18 years or above
- Participant is willing and able to give informed consent for participation in the study
- Participant is will enough to participate in an interview (this may include participant who have a current CA-ARTI or who have been diagnosed with COVID-19 where the participant is happy to participate).

For HCP participants:

- If a clinician: Has delivered care for patients presenting with CA-ARTI symptoms in primary care services in Europe
- If a non-clinician: Supports the delivery of primary care services to patients presenting with CA-ARTI symptoms in primary care services in Europe (e.g. general practice manager).

For patient participants:

- Has consulted in European primary care for CA-ARTI symptoms for themselves and/or their child/dependent.

8.3 Exclusion Criteria

No exclusion criteria applicable to either group beyond that specified by inclusion criteria.

9. STUDY ACTIVITIES

9.1 Recruitment

This is a multi-centre study involving professionals and patients from a number of primary care sites in Europe.

Primary care sites in our existing clinical network, part of the larger RECOVER study, will be contacted by the research team to discuss the study by telephone. The practice contact will be provided with the **HCP Invitation Email** and **HCP PIL** to provide to HCPs who are eligible to take part. The practice contact will also be provided with the **Patient invitation email** and **Patient PIL** to provide to eligible patients. Ad hoc request by primary care sites to join the study will also be considered.

Professionals and patients will be asked to contact the research team if they are interested in participating. The research team will collect expressions of interest and purposively select participants to get variation in characteristics and experiences. The research team will then contact participants by telephone or email to arrange a time and date for interviews.

9.2 Informed Consent

Informed consent will be taken from all participants prior to completing an interview. Given that the majority (if not all) of interviews will be conducted remotely, and the urgent need to conduct this research, verbal consent will be taken at the start of each interview using the relevant Informed Consent Form (Patient ICF or Professional ICF). Verbal consent will be audio-recorded and stored as data, and a copy of the completed form will be emailed to the participant. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief Investigator.

All participants will receive a copy of the PIL. The PILs will detail no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Participants invited for an interview will be allowed at least 24 hours to consider the information and the opportunity to question the Investigator, their GP (if a patient) or other independent parties to decide whether they will participate in the study. We will aim to conduct interviews with patients within 2 weeks of their consultation although this could be longer if required to fit with patients' needs.

9.3 Screening and eligibility

There will be no exceptions made regarding eligibility and each participant must satisfy all the approved inclusion and exclusion criteria. If found eligible and if selected based on maximum variation sampling where possible, the potential participant would be invited to participate and give informed consent.

9.4 Subsequent visits

All participants will take part in a single interview and there will be no follow-up activities.

9.5 Discontinuation/Withdrawal of Participants from Study

During the course of the study a participant may choose to withdraw their consent, meaning that they wish to withdraw from the study completely.

Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis. Any de-identified transcripts of interviews would be identified through the unique participant number.

In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)

Withdrawal from the study will result in exclusion of the data for that participant from analysis. The reason for withdrawal by researcher (and by participant, if this information is volunteered) will be recorded in a study file. Participants who withdraw will be replaced if recruitment is still active but will not be replaced once recruitment has ended.

9.6 Definition of End of Study

The end of study is the date of the last interview of the last participant.

10. ANALYSIS

10.1 Description of Analytical Methods

Data from the two sets of interviews (professionals and patients) will be analysed separately following the same approach. We will include interview transcripts, participant demographics and characteristics and field notes within our analysis. Interview transcripts and field notes will be analysed inductively using framework analysis.[7] Framework analysis allows rapid analysis of data using an a priori framework. This framework will be developed to allow researchers to search for key data in interviews which answer questions of most importance for healthcare managers and policy makers. NVivo software will be used to assist with the organisation and coding of data. To ensure confirmability of results we will follow a systematic approach to analysis where each stage of interpretation is recorded and provide rationales for decisions made to ensure that findings portray participants' responses. Transcripts will be coded using the existing framework and researchers will note any novel additional themes which are mentioned by participants, expanding the framework as necessary. The final framework will be used to chart and map data across all sets of interviews and will aid comparisons between HCP and patient experiences.[7] We will clearly describe our participant population based on the characteristics used in sampling participants to increase transferability of findings to other contexts and similar populations.

11. DATA MANAGEMENT

11.1 Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations. Members of the study team (as listed on p. 1) will have access to the data.

11.2 Data Recording and Record Keeping

Participants will be identified by a unique participant number in any data.

Interviews will be audio-recorded with participants' permission. Recordings will allow verbatim transcription using Microsoft Word. Transcription and translation (where required) will be completed by a member of the research team or an independent transcription and/or translation service approved by the University of Oxford or University of Antwerp to ensure data security. Transcription/translation companies will hold a contract with the University of Oxford or University of Antwerp and agree to keep participant data confidential and will delete their copy of recordings and any other identifiable data following the completion of work. Once transcribed, transcripts will be checked for accuracy, de-identified and labelled with a unique participant number. For any audio-recorded data that is not being transcribed, detailed field notes will be taken from the audio recording. Following this audio-recordings of interview data will be deleted. The written version of participants giving verbal consent for interviews will be stored securely on University of Oxford computers for 10 years after the end of the study. For analysis, interview transcripts will be managed using NVivo software. All data collected in networks outside the UK and Belgium will be sent to the research teams in University of Oxford and University of Antwerp. No copies of data will be stored outside of these institutions.

Participant characteristics will be entered on a separate Microsoft Excel spreadsheet with the unique participant numbers. This will be stored electronically until all data has been analysed and reported in publications and then deleted.

12. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Declaration of Helsinki

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

13.2 Approvals

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

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

13.3 Other Ethical Considerations

The study will not involve any vulnerable participants or participants who are unable to consent for themselves. There is minimal risk to participants, discussions are not likely to include topics which are sensitive or embarrassing. We recognise that discussing the COVID-19 pandemic may be upsetting for some participants however participants will have volunteered to discuss this topic when agreeing to take part. It is unlikely criminal or other disclosures requiring action could occur during the study however is this does occur, where the participant is a patient, we will contact their primary care practitioner and where the participant is a HCP we will contact their manager.

It is possible, although unlikely, that interviews will be carried out in person in practices. This will only happen when researchers are located in practices already and researchers will not visit practices, or anywhere else, other than their usual place of work (which may be home working) in order to carry out this study. This will reduce the risk of transmission of COVID-19 to either participants or researchers.

13.4 Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required), host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5 Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

13.6 Expenses and Benefits

Participation will be on a voluntary basis. Professionals will be reimbursed £40 or €40 in vouchers, and patients will be reimbursed £15 or €15 in vouchers for their time to complete an interview. We

will provide vouchers which can be used for online shopping suitable for all countries (e.g. Amazon) and these will be sent by email to all participants.

14. FINANCE AND INSURANCE

14.1 Funding

This study is funded as part of a European Commission Horizon 2020 grant. All study activities will be carried out within this funding.

14.2 Insurance

The University of Oxford maintains Public Liability and Professional Liability insurance which will operate in this respect.

14.3 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the European Commission Horizon 2020. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

16. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable.

17. ARCHIVING

Following the end of the study and the completion of all analysis and all reporting the study will be archived. Electronic documents which will include audio recordings of verbal consent, de-identified interview transcripts and study reports will be stored on University of Oxford computers for 10 years.

18. REFERENCES

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4. Raven, J., Wurie, H. & Witter, S. Health workers' experiences of coping with the Ebola epidemic in Sierra Leone's health system: a qualitative study. BMC Health Serv Res 2018;18: 251.
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7. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman A, Burgess R, eds. Analysing qualitative data. London: Routledge; 1993:173–94.


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