PROTOCOL TITLE: Perpetual Observational Study (POS) of Acute Respiratory Infections (ARI) in primary care settings (PC) across Europe

POS-ARI-PC Core

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1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AMR	Antimicrobial resistance
ARI	Acute Respiratory Infections
BMI	Body Mass Index
CA-ARTI	Community Acquired Acute Respiratory Tract Infection
CI	Chief Investigator
CRF	Case Report Form
COVID-19	Coronavirus disease 2019
DWH	Data Warehouse
ECRAID	European Clinical Research Alliance for Infectious Diseases
eCRF	Electronic Case Report Form
EID	Emerging infectious diseases
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HIPAA	Health Insurance Portability and Accountability Act
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
ID	Infectious Diseases
ISA	Intervention Specific Appendix
JC	Julius Centre
LRTI	Lower Respiratory tract Infection
OS	Observational Study
PC	Primary Care
PIS	Participant/Patient Information Sheet
POC	Point of Care
POS	Perpetual Observational Study
PPAS	Point Prevalence Audit Survey
REC	Research Ethics Committee
RTI	Respiratory Tract Infection
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2 (virus causing COVID-19 disease)
SD	Standard deviation
SMG	Study Management Group
SSA	Study Specific Appendix
UMCU	University Medical Centre Utrecht
UOXF	University of Oxford
URTI	Upper Respiratory Tract Infection
VALUE-Dx	The value of diagnostics to combat antimicrobial resistance by optimising antibiotic use
YR	Your Research

2. SUMMARY

Influenza pandemics, the current COVID-19 pandemic, and the more silent but ongoing pandemic of antibiotic resistant infections - driven partly by overuse of antibiotics for respiratory infections - all serve to emphasise that acute infections with a primary respiratory tract focus, and their treatment, continue to represent one of the greatest threats and challenges for humanity. The vast majority of acute respiratory infections (ARI) present to, and are diagnosed and managed in, primary care. Describing existing aetiology, presentation, management, and clinical outcomes, and time trends for ARI in the community will help optimise care, ensure preparedness, and act as a platform for the identification and the evaluation of new interventions.

This is a Core Protocol for a Perpetual Observational Study of community acquired acute respiratory infection (POS-ARI-PC). The perpetual, observational study (POS) has been designed to provide data for clinical characterisation of ARIs in adults and children presenting to primary care (PC) settings across Europe, and to serve as an overarching research infrastructure for rapid implementation of randomised clinical trials (RCTs) and other clinical studies related to diagnosis, treatment and possibly prevention of ARI. The overarching goal of this Core Protocol is to generate robust evidence for optimizing management of patients with community-acquired ARI in PC settings. There are two components of the POS-ARI-PC:

Component 1 (POS-ARI-PC Audit): An anonymous, multi-country, prospective audit-type registration to describe the presentation and management of patients presenting in primary care with ARI. Because this part of the study is purely descriptive, there are no samples taken, no interventions given nor interviews conducted, and no personally identifiable information will be collected, patients will not be asked to provide written informed consent. ECRAID-Base POS-ARI-PC Audit aims to describe current patient care, rather than provide information about specific individuals, and acts as a monitoring system to determine where to implement interventions. All eligible patients will be registered. Details of component 1 are provided in a separate ECRAID-Base POS-ARI-PC Audit Protocol.

Component 2 (POS-ARI-PC Core): Component 2 has the following three objectives detailed in this POS-ARI-PC Core Protocol:

Objective 1. A prospective, observational study of ARI patients in primary care to undergo study-specific sampling upon inclusion, and be followed up for 28 days to capture the aetiology of their ARI and describe clinical outcomes.

Objective 2. A qualitative study with research professionals, clinicians and patients to a) gain a deep understanding of the research process, meaning of results and to identify barriers and opportunities for implementation of changes in light of findings, and b) explore the views and experiences of patients who consult European primary care services for ARI symptoms.

Objectives 3. To use the infrastructure developed in the POS-ARI-PC including key case report forms, and capability in the research platform to achieve readiness for adding studies that cover additional observational research questions ('embedded' observational studies), and for efficient, rapid pivoting into randomising ARI participants to answer questions about effectiveness of diagnostic, behavioural or therapeutic management strategies for ARI in primary care. Such embedded studies will require formal amendments to this protocol, attached to this protocol in the form of Study Specific Appendices (SSA). These need full approvals in all participating countries. This current Core protocol has capacity

to embed additional studies (as outlined above), but does not describe these additional studies. Such studies can efficiently build on the research infrastructure, continual enrolment, and learnings from this POS-ARI-PC.

Therefore, this POS-ARI-PC Core Protocol describes Objectives 1 and 2, and signals that, subject to appropriate approvals, additional embedded studies may be added as SSAs (Objective 3). Certain key study procedures (e.g. inclusion criteria, data capture and management, follow-up procedures, CRFs), as described in this Core POS-ARI-PC Protocol, will be harmonised as far as possible across any future embedded studies. Each embedded study will be identified by a unique code (e.g. POS-ARI-PC-001) and name, and will be described within a SSA to the Core Protocol, detailing any additional study procedures and data collection relevant to the specific study. SSAs will be independent of each other and the embedded studies may run concurrently or sequentially. Recruitment to the Core POS-ARI-PC study will be continuous but might be scaled down dependent on recruitment activity in embedded studies.

The POS-ARI-PC Core Protocol covers data collection from patients who present with ARI in PC settings, including paediatric care, in Europe. Data will be collected using standardised case report forms (CRFs) that capture clinical, point of care (POC)/lab-based tests, and management information along with patient outcome data that will be collected via diaries (Objective 1). Objective 1 and 2 will run throughout the five years with qualitative data collection with different stakeholder groups, at appropriate timepoints.

(Country-specific) data captured within the delivery of the POS-ARI-PC Core Protocol will inform the design of future embedded studies e.g. informing prioritisation of research questions, assessing feasibility of planned studies, and providing data to support assumptions for clinical trial sample size calculations.

Setting up new research each time a new study question arises within a clinical area is highly wasteful, inefficient and means that time to result takes longer, and therefore impact on care is reduced. Therefore, the goal of the POS-ARI-PC is to eventually achieve sustainability beyond five years so that Europe has a lasting PC research infrastructure for delivering this research mission.

i) Nature and extent of the burden and risks associated with participation, benefit and group relatedness

Risks, inconvenience and burden associated with participating in the POS-ARI-PC (Objectives 1-2) are negligible, and any risks associated with future studies that are embedded in this Core Protocol will be outlined in the relevant SSA. There is no direct benefit to participants from participating, however, their contribution is essential to research that may lead to more effective and standardised approaches to managing ARI in PC across Europe.

ii) Background to Ecraid

The European Clinical Research Alliance for Infectious Diseases (Ecraid) is a European Commission funded research infrastructure with the purpose of reducing the impact of infectious diseases (ID), including COVID-19, influenza and RSV, on individual and population health. IDs pose a fundamental ongoing threat to European citizens and economies. Of particular concern are pathogens that have the potential to cause major epidemics or pandemics and for which few or no effective treatments and/or

vaccines are available. The frequency and impact of these (re-) emerging infectious diseases (EID) have been amplified by global trends such as population growth, increasing trade and travel, urbanisation, deforestation, and climate change. The COVID-19 pandemic has led to unprecedented public health measures across the globe. The vision of Ecraid is to efficiently generate rigorous evidence to improve the diagnosis, treatment and prevention of infections and to better respond to ID threats.

This is facilitated by a European multidisciplinary clinical research network and innovative research approaches. The Ecraid clinical research network includes primary care settings, hospital settings, paediatric care settings, and laboratories. These networks have been, or are currently functioning as, the clinical research base for the studies in PREPARE, COMBACTE, RECOVER and many others. The Ecraid clinical research network will need to acquire all eight "OPERATES" qualities of a true 'warm base' network (see figure 1). If even one of these essential OPERATES requirements represent a 'weak link', the entire 'warm base' function of the network is threatened and diminished.

Figure 1: The eight 'OPERATES' qualities of a 'warm base' clinical research network.

"Warm Base" is defined as a fully operational pan-European clinical research network that has the capacity and capability to:

- directly enrol patients with infectious diseases for generating evidence to support testing and development of new diagnostic, preventive and/or therapeutic strategies and therapies;
- conduct a broad range of clinical studies with nested qualitative evaluation efficiently, and rapidly;
- pivot rapidly into recruiting patients in randomised studies (diagnostic, treatment, behavioural);
- function as a platform for a rapid research response in the face of serious ID outbreaks.

The POS-ARI-PC study will contribute to this operational pan-European clinical research network by specifically enrolling patients presenting to primary care services with ARI to generate evidence for treatments, diagnostics, therapeutic and possibly preventive strategies and therapies.

iii) Study rationale

ARI are one of the most frequent reasons for patient presentation to primary care and for antibiotic prescription/consumption, and can be caused by a broad range of respiratory viruses and bacteria (1). In the context of the ongoing COVID-19 pandemic, the importance of ARI as a major health concern cannot be overstated and has raised new challenges in addition to antimicrobial resistance (AMR) (2).

The main aim of *Objective 1* in this POS-ARI-PC Core Protocol is to describe the aetiology and explore the effects of different diagnostic and therapeutic aspects of existing routine ARI care on patient

outcomes. Establishing the aetiological cause of ARI at the time of presentation is difficult with currently available diagnostic approaches and is hardly ever done in routine PC practice. Lack of an aetiological diagnosis (e.g., viral vs bacterial) contributes to unnecessary use of (broad-spectrum) antibiotics in many patients, exacerbating AMR (3). POC diagnostics in PC can provide clinicians with rapid results that are clinically actionable at the time of prescribing decisions. However, the implementation of these technologies into routine PC clinical practice has not been widely evaluated, though considerable variation in their use has been reported in primary care settings across Europe (4, 5). Most research in the field of diagnostic tests is limited to studies of accuracy with very few evaluations of the impact on patient outcomes or cost effectiveness/utility (18). Moreover, test results do not provide conclusive answers about the effectiveness of antibiotic treatment; prognostic studies are needed in addition to diagnostic studies. Improvements in diagnosis and strategies for use of targeted antibiotic and antiviral treatments are needed to improve patient outcomes, and to reduce selection of AMR and antiviral resistance. The assessment of outcomes in relation to routine practice provides a foundation on which to build improvements in patient care through currently available approaches, as well as informing the development of new strategies and management pathways.

Through ongoing recruitment (objective 1), aetiological causes for ARI and patient outcomes can be monitored over time across the European region. This will include successive winter seasons when incidence of common respiratory viruses, including influenza virus, RSV and coronaviruses, has historically been higher. Since the COVID-19 pandemic, epidemiological patterns of common respiratory pathogens have changed, likely as a result of non-pharmaceutical interventions and changes in human behaviour, leading to reduced exposures and transmission events (9, 10). The impact of the low incidence of common respiratory viruses during 2020-2021 is not known, but there is potential that reduced exposure may lead to increased population susceptibility, with consequent changes in patterns of transmission and/or more severe presentations. Continual clinical characterisation through the POS-ARI-PC will provide data on changes to the relative contribution of respiratory pathogens in adults and children presenting to PC and patterns of disease severity in the years following the emergence of SARS-CoV-2 and the acute pandemic phase in Europe.

The POS-ARI-PC Objective 1 will benchmark the case-mix of disease aetiology, patient management (including POC tests, laboratory or hospital investigations, treatments and advice) and patient outcomes (illness duration, complications, and hospitalisation). It will provide an estimate of overall incidence of illness, also of emerging diseases, and will be able to identify variation in management, care and outcomes between sites and countries. Benchmarking best practice and identifying clinically unwarranted variations in care will lead to sharing of best practice and provision of enhanced evidence-based clinical guidelines. Patient sampling will contribute to early warning capability of epidemic or pandemic outbreaks. It will also help to provide a description of the phenotype of early presentation of the illness spectrum, and clinical features, which may predict both mild and more severe outcomes of infections with existing and new pathogens.

Objective 2 will use robust qualitative research methods from the social sciences to: identify ways for improving the experiences of research professionals, clinicians and patients in contributing to this research; achieve a deep understanding of the meaning of key findings and identify barriers and opportunities for implementation of relevant findings; and identify wider lessons for improving communication about participation in studies and to optimise their delivery. Qualitative research that

builds on the perceptions of the people that really matter in delivering and receiving clinical care, namely research infrastructure managers, clinicians and patients, is essential to gaining overall holistic picture of the research implementation, understanding of the findings, and the barriers and facilitators to implementing changes into routine care, where appropriate. COVID-19 has presented unique challenges for patients with ARI with new prevention and management strategies put in place. A large body of evidence shows that patients' preferences differ substantially from those of professionals. Both perspectives are essential to improving the user experience and efficient design of trials, interventions and care to generate robust clinical findings and value for individuals and society. Patient-centricity requires that we tailor studies to patients' needs, unravel and understand the motivation for behaviour, and measure outcomes that matter to patients.

We aim to capture patients' experiences in relation to their own vulnerability and management of ARI in community care since the COVID-19 pandemic and capture their views how care could be improved.

Objective 3 builds in capacity for adding observational studies, or randomised controlled trials on diagnostics, therapeutics, and behavioural interventions to this POS-ARI-PC Core Protocol. Epidemic and pandemic ARI can emerge rapidly, and there is a strong pipeline of therapeutic agents and behavioural interventions that could be relevant to the management of ARI. Especially in pandemic and epidemic contexts, the ability to rapidly set up and integrate evaluations of new interventions is critical to ensuring a brief time to result so that evidence from research informs clinical care as quickly as possible. The goal is to ensure capability of opening RCTs within weeks of evidence of a new or emerging infection. Approval of this POS-ARI-PC Core Protocol in no way implies approval of subsequent embedded studies: any future embedded studies will be approved separately by an amendment (SSA) to this POS-ARI-PC Core Protocol. These studies will range from further observational studies, diagnostic accuracy studies, behavioural studies, randomised controlled trials, clinical trials of investigational medicinal products and potentially vaccine studies. Each additional study will follow the same structure, processes and data collection as the core POS-ARI-PC as far as is possible and only deviate where essential. These studies will not necessarily be run in all networks and/or practices taking part in the POS-ARI-PC, but in an agreed sub-set where appropriate. New studies can run sequentially or concurrently.

Studying patients presenting with ARI, including both common respiratory infections and those with proven epidemic potential e.g. respiratory viruses such as influenza viruses and coronaviruses, will also provide valuable data in the context of the ongoing COVID-19 pandemic, and emergence of new SARS-CoV-2 variants, and/or other emergent respiratory pathogens. Little is known about the significance of seasonal community-acquired ARIs occurring at the same time as SARS-CoV-2 infections ("co-infections"). Initial data suggest that influenza and SARS-CoV-2 co-infection is associated with worse outcomes compared with SARS-CoV-2 infection alone (6). Furthermore, there is evidence that RSV is associated with poor outcomes in older adults and ideally would be managed through isolation of patients in residential and hospital settings. The POS-ARI-PC study will be well placed to provide informative data on the interplay between SARS-CoV-2 and other commonly circulating respiratory pathogens, and also outcomes of co-infections for patients.

iv) Need for a perpetual, observational study platform

The COVID-19 pandemic has demonstrated the utility of research-preparedness, with informative characterisation studies and clinical trials that were successful, and provided timely evidence in the context of a health emergency, due to rapid activation and/or adaptation of existing platforms and core/master protocols (7, 8, 19). This international, multi-centre POS-ARI-PC aims to provide a platform for continuous data capture for patients with ARI presenting to primary care settings across Europe, covering cases caused by known and emerging respiratory pathogens with epidemic and pandemic potential, in order to generate observational evidence to inform care and maintain study-readiness for RCT evaluations. The POS-ARI-PC platform will thereby support the efficient set-up of new clinical studies and trials, which will be embedded into the platform. Under the POS-ARI-PC Core Protocol, with study approvals and patient recruitment already in place, implementation of new studies will be expedited through efficiencies in regulatory approvals processes and streamlined procedures for PC network team and site contracting, facilitating the rapid enrolment of patients into studies for evaluation of diagnostic, therapeutic, behavioural and possibly prevention strategies.

Qualitative work will be conducted to observe the set-up and establishment of the POS platform and how it supports delivery of clinical studies and trials. It will investigate key stakeholder perspectives about research processes, ethical considerations and participation, including upscaling of delivery of interventions that have been found to be effective during a public health emergency and will provide frequent feedback to the network to enable learning about efficient study delivery and recruitment. Qualitative research will also inform the implementation of findings in a way that is meaningful to patients and clinicians.

3. OBJECTIVES

The overarching goal of this POS-ARI-PC Core Protocol is to generate robust evidence for optimizing management of patients with community-acquired ARI in PC settings, using disease aetiology and patient outcomes. There are three objectives:

	Objectives	Key variables and outcome measures
Objective 1:	**A prospective observational study of ARI patients in primary care who undergo study-specific sampling upon inclusion, and are followed up for 28 days to:** • Describe disease aetiology • Determine clinical outcomes • Determine the incidence of subtypes of ARI and of new, emerging diseases • Determine risk factors for a complicated course of ARI • Identify best care in terms of patient recovery, complications and appropriate antimicrobial prescribing	• Age bands, the proportion with preliminary diagnosis of various sub-categories of ARI (e.g. LRTI, URTI), overall illness severity rating • Swab samples taken at the baseline visit and retrospective viral/microbiological infection analysis performed (multiplex PCR) • Proportion undergoing POC (with results) and lab-based investigations • Proportion given treatment and class of drug treatment for ARI • Details of prescriptions given on presentation of ARI • Details of tests ordered on presentation of ARI

	Objectives	Key variables and outcome measures
		• Return to usual daily activities, feeling recovered from RTI, use of prescription medication, complications, use of over the counter medications • Complications reported associated to ARI presentation • Variation in practice and advice from national guidelines, to be fed back to national teams Feedback of details of treatment practices and trends across networks linked to patient outcomes
Objective 2	Using qualitative research methods, conduct interviews with research professionals, clinicians and patients to gain a deep understanding of the research process, meaning of results and to identify barriers and opportunities for implementation of findings. Capturing patients' views on their vulnerability towards ARI in the community since the COVID19 pandemic.	• Recommendations on how to improve study processes, recruitment and study communication based on shared understanding and insights from researchers, clinicians, and patients. • An understanding of the meaning of study results for European primary care, from the perspectives of clinicians and patients, and recommendations regarding the implementation of findings. • An understanding of changing health seeking behaviour, management and expectations to inform clinical studies and trials.
Objective 3	To ensure research readiness for including embedded observational and randomised evaluations to answer questions about the effectiveness of diagnostic, behavioural or therapeutic management strategies for ARI in PC.	• Approval for a study specific appendix (SSA) or an intervention specific appendix (ISA) of an embedded (non) randomised study for ARI in primary care associated with this POS.

4. STUDY DESIGN

Objective 1 will be achieved through a prospective observational study of approximately 400 ARI patients in primary care annually who will consent to undergo study-specific sampling upon inclusion, and followed up for 28 days for clinical outcomes.

Objective 2 will be achieved by conducting qualitative research with research professionals, clinicians and patients to gain a deep understanding of research processes, meaning of results, to identify barriers and opportunities for implementation of findings, and to gain understanding in changing patients' views on their vulnerability towards ARI in the community.

Objective 3 will be achieved by the approval of amendments for SSAs or ISAs to this POS-ARI-PC Core Protocol of embedded studies or randomised evaluations of diagnostic, therapeutic or behavioural

strategies for managing ARI in primary care. These will be implemented in the networks and sites delivering this POS-ARI-PC and builds on capability developed by this POS-ARI-PC.

When a new embedded observational study or RCT is added to the POS-ARI-PC a SSA or an ISA will be developed which details the (changes in) study population, the research question, objectives, outcomes, study specific processes and analysis. This will be appended to the POS-ARI-PC Core Protocol and all appropriate approvals will be gained for each SSA or ISA.

i) Inclusion criteria

Eligible patients will be of any age consulting (telephone, video, face to face) with a participating primary health care facility and (if needed and feasible) primary care homes with:

- Symptoms suggestive of an acute lower respiratory infection with cough as the predominant symptom, with illness duration less than 28 days,
  AND/OR
  Symptoms suggestive of an acute upper respiratory infection with sore throat and/or coryza as the predominant symptom, with illness duration of less than 14 days
  AND/OR
  Other symptoms suggestive of COVID-19, Influenza, RSV
- Participant or legal guardian(s) willing and able to provide informed consent and comply with study procedures

ii) Exclusion criteria

Patients will not be eligible if:

- According to the judgement of the recruiting clinician, they will not be able comply with study procedures, for example because they do not understand the language in which the study is being conducted locally (and have no one to help and translate for them); have a serious psychiatric disorder; or are terminally ill
- Symptoms of presumed non-infective origin
- Participant requires admission to hospital on the day of inclusion

Additional in/exclusion criteria might apply to embedded studies and will be described in the SSA or ISA.

iii) Sample size estimation

POS-ARI-PC Objective 1 will recruit 400 participants with ARI in 5-15 European countries annually over a period of 5 years, totalling 2,000 patients. For Objective 2, approximately 20-30 participants will be interviewed.
For embedded studies (Objectives 3) sample size calculations will be described in the SSA or ISA.

5. STUDY PROCEDURES

i) Screening and Eligibility Assessment

Potential patients will be identified when they present to/contact their participating PC health care facility or at their primary care home with symptoms suggestive of an ARI (see eligibility criteria). The screening clinician can recruit the patient or refer to an appropriately trained delegate, where they will have the study presented to them. Where possible, eligibility assessment for any embedded

studies will be conducted at the same time as the initial eligibility assessment for the core POS-ARI-PC study.

ii) Informed Consent

Informed consent for recruitment into the POS-ARI-PC will be sought by an appropriately trained and qualified member of the local research team. No study specific procedures will be performed until consent has been obtained. Potential participants will be given a copy of the patient information sheet (PIS) and informed consent form (ICF), on paper or electronically. The latter could be done, if approved and circumstances demand, via a link to the study website presenting the PIS/ICF which will be sent to the potential participants by their GP via a text message or email. They will be given an explanation of the study, 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 that includes all necessary information. The PIS and other participant-relevant study material will be available in the official national language. Adequate time will be given to the participant or parent(s)/legal guardian(s) to consider the information given 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 (or their legal guardian) 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.

Written informed consent will be confirmed by the dated signatures of the participant or their legal guardian and by the person who presented and obtained the informed consent, or electronic equivalent. Verbal or electronic consent may be taken from participants under specific circumstances when written consent is not feasible and if country-specific regulation allows. The person taking consent will use a specific verbal consent form in which they can record that the patient has agreed each of the items on the consent form and verbally consented to participate in the study. The person obtaining consent must be suitably qualified and experienced, and be authorised to do so. A copy of the signed ICF will be provided to the participants. The original signed ICF will be retained at the study site in the patient notes. Where electronic forms are used an electronic copy will be filed in the participant notes and a copy emailed to the participant or guardian. Where possible, informed consent for any embedded study will be obtained allowing patients to take part in embedded studies and the POS-ARI-PC.

For those who are going to be recruited for the qualitative work in Objective 2, approaching potential participants will follow the same procedures as above. A separate PIS and ICF will be provided for each stakeholder group (research professionals, clinicians and patients). Verbal consent will be taken for those participating in the qualitative study, prior to the start of an interview, with a written or electronic record of consent signed by the researcher. The participant will be emailed a copy of the record of consent.

ICFs for embedded studies will contain all elements of the ICF for the POS-ARI-PC with the addition of necessary study/trial-specific elements for the embedded study or trial.

iii) Baseline visit

For Objectives 1 the following information will be gathered:

- Demographic details including: age, co-morbidities (cardiovascular disease, lung disease (COPD/asthma), diabetes, joint disease, neurological disease, severe mental illness, weakened immune system, other chronic conditions);
- Duration of ARI symptoms prior to consulting;
- Vaccinations for respiratory infections;
- Presence of selected symptoms;
- Overall illness severity rating;
- Clinical assessments only if captured routinely (temperature, blood pressure, oxygen saturation, respiratory rate, heart rate, with outcomes (if applicable));
- All diagnostic tests done or ordered (with outcome of POC testing);
- Antimicrobial prescription (class);
- Whether patient/parent/legal guardian requested antimicrobial prescription;
- Additional prescribed medicines for ARI;
- Working diagnosis (e.g., pharyngitis, tonsillitis, exacerbation of chronic obstructive pulmonary disease (COPD), bronchitis, pneumonia, bronchiolitis);
- Advice about symptomatic medicine use;
- Advice about taking time off work or school/out of home childcare;
- Referral to hospital.
- Category of employment

A combined throat/nose swab will be taken at baseline.

Any additional information required for embedded studies will be detailed in the SSA or ISA and added to the baseline CRF for those participants taking part in each embedded study.

iv) Follow-up with Participant Diaries and/or Phone Call

There is no requirement for recruited participants to have a research-specific face-to-face follow-up visit as part of their study participation, as all subsequent measurements consist of paper, online, or app-based self-completed questionnaires. Where a participant is unable or unwilling to complete online forms the recruiting site team can telephone them to complete the forms.

Participants (or their legal guardian or their carer) will be asked to complete a simple, user-friendly diary each day to gather the following information:

- Whether the participant has returned to their usual activities
- Whether the participant feels fully recovered
- Antimicrobial use
- Use of other prescription medication for ARI
- Presence of selected symptoms
- Use of over-the-counter and non-prescription medication or remedies for ARI

Participants who have not completed/returned/entered their diary information by day 14 will be telephoned on or after day 14 (+10 days) by the study team and asked a brief set of questions to establish a minimal data set including the day they returned to their usual activity and the day when they felt fully recovered. When no follow-up information is available, patient is considered lost-to-follow-up.

v) Follow-up with the recruiting site

The following information will be collected from the participants via the GP practice for a period of 28 days after inclusion:

- Results of diagnostic tests ordered
- Information on re-consultation for ARI
- Information on hospitalisations related to ARI
- (If relevant) date and cause of death

6. SAMPLING

Patients will have one combined oropharyngeal and nasal flocked swab taken at baseline by the responsible clinician or recruiter, or where this is not possible by the participant or their parent or guardian. The swab will be placed in one container with 3 ml universal transport media (UTM). All samples will be refrigerated or frozen and batched before being transported using standard systems to a local laboratory, ensuring adherence to country specific requirements for the shipment of samples. Once at the local laboratory the samples will be frozen and stored at -70°C, and then transported to the central laboratory in Antwerp, Belgium. For storage at sites and local laboratory, storage at -20°C will be acceptable if there is no deep-freezer available. The export of batches of samples to Belgium will be done in accordance with country specific regulations.

The participant's date of recruitment, sex and participant ID number (same number as used for online data capture) will be used as identifiers for these samples. Only the laboratory and local study team will have access to this information for the purposes of sample identification and tracking. The participant's responsible clinician will not be informed of the results of these swabs because the results are only for research information. Swabs will be batched before being transported to a central laboratory, and analysis may be some time after they are taken.

Each patient's swabs will be subjected to PCR-based analysis to identify potential causative pathogens.

Following analysis, the remaining samples will be stored in a biobank being developed by the Antwerp laboratory for the ECRAID-Base Consortium. The samples will be stored for the purpose of further research relevant to the understanding and management of infectious diseases. The participant will be asked to give consent for this pseudonymised storage of their sample and to share pseudonymised data within and outside the ECRAID-Base Consortium.

7. PARTICIPANT WITHDRAWAL

Participants can withdraw from the study (Objective 1), or part of the study at any time for any reason without any consequences. The investigator can decide to withdraw a participant from the study for urgent medical reasons. If a participant withdraws from the study, the data collected up to withdrawal will be kept and available for analyses, as mentioned in the ICF. The sample already obtained for the study will be processed according to the protocol, as mentioned in the ICF.

Participants taking part in the qualitative work under Objective 2 can withdraw from the study at any time for any reason if they wish to do so without any consequences. If a participant withdraws from the qualitative study, the data collected up to withdrawal will be kept and used in analysis, as mentioned in the ICF.

i) Replacement of individual participants after withdrawal

In the POS-ARI-PC Objectives 1 and 2 no new participants need to be added after withdrawal as no specific sample size calculation is in place. For embedded studies with a sample size calculation, new participants may be added after withdrawal.

8. PREMATURE TERMINATION OF THE STUDY

As this POS-ARI-PC is an observational study with the ambition of providing ongoing, longitudinal data, a premature termination of the study is not expected.

9. QUALITATIVE EVALUATION (Objective 2)

A qualitative evaluation will occur alongside the set up and running of the POS to explore the experiences of research professionals, clinicians and patients to provide feedback on optimal study delivery including participant experience, to achieve a deep understanding of the meaning of results, and to identify barriers and opportunities to implementation of findings from the POS.

The qualitative work will aim to include research professionals (including network coordinators) from all countries and networks which take part in the POS. All network coordinators will be invited to an interview and any additional researchers who played a significant part in setting up and/or delivering the study will also be invited. A sub-set of networks will be selected to undertake interviews with clinicians and patients, to give variation in experience of study delivery, patient recruitment and experience of the research. Interviews will be conducted with participants from these three stakeholder groups (research professionals, clinicians and patients) either remotely (by telephone or online (e.g. using Microsoft Teams)) or in person, as appropriate. Interviews will be audio recorded on a dictaphone or other recording device and audio files will be transferred as soon as possible after interview to secure computer files, accessible only to the research team. Audio files will then be permanently deleted from the dictaphone or other recording device.

Interviews with research professionals will take place throughout the 5year period of ECRAID-Base from the start of recruitment to POS, through delivery of embedded studies, to completion of recruitment and any follow-up. Interviews are likely to be longitudinal in design with the same research professional being interviewed at multiple timepoints, determined by key events in delivering the POS and initiating embedded studies/trials. Interviews will explore the perceptions of researchers and network coordinators regarding how they deliver the POS and potentially embedded studies and their experience of working within an existing platform to deliver studies efficiently, how to enhance participant experience of involvement in the studies, and of their perceptions of the meaning of results and barriers and opportunities for implementation of relevant findings.

Interviews with clinicians will take part once recruitment to the POS is established at each site. Clinicians will be sampled from a subset of countries/networks taking part in the POS with interviews being undertaken by members of the research team in each network. Additional interviews may be undertaken when sites set up embedded studies/trials. All clinicians recruiting patients to the POS and other clinical studies will be invited to take part in interviews. Network coordinators will identify eligible clinicians in their own network. Interviews will ask about experiences of study delivery, being part of the ECRAID network, recruiting patients, any interventions delivered in embedded studies, the meaning of study results for primary care practice and views on implementing findings in European

primary care. The number of interviews will depend on data sufficiency and the number of embedded studies.

Patients will be invited to take part in one-off interviews. Interviews will take place close to the initial consultation when the patient was recruited to the POS or at an appropriate timepoint in an embedded study to ask about patient experience of the key study processes and/or interventions experienced, their views on their vulnerability of ARI in the community since the COVID-19 pandemic (health seeking behaviour, management etc), and whether they feel care could be improved. Patients will be purposefully sampled from a sub-set of countries and networks taking part in the POS with interviews being conducted by members of the research team in each network. Network coordinators will identify eligible patients in their own network.

Individuals who are approached to take part in the qualitative evaluation will be provided with a participant information sheet (PIS) and informed consent form (ICF) specific to their role (researcher, clinician, or patient). Written or verbal informed consent will be taken prior to the start of an interview.

The number of interviews carried out across these stakeholder groups will be determined by data sufficiency and the number of embedded studies delivered. At least one qualitative study each with researchers, clinicians and patients will be conducted. The number of interviews conducted will depend on the number of networks involved and the data sufficiency, but will typically be approximately 20-50 per study.

10. SAFETY REPORTING

For (Objective 1) the following data will be collected up to and including day 28:

- Death
- Inpatient hospitalisation

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

Safety reporting requirements for any of the embedded studies will be assessed separately, and if any additional safety reporting is required this will be documented in the SSA or ISA. This will be in accordance with all relevant regulatory requirements and will be subject to formal review and approvals process in subsequent submissions.

i) Data Safety Monitoring Board (DSMB) / Safety Committee

A joint DSMB and Study/Trial Steering Committee (TSC) will be set up. While the POS-ARI-PC is running on its own, with no embedded studies open, and because of its negligible risk, this joint DSMB/S/TSC will not be required to meet for the purposes of overseeing the POS-ARI-PC alone. However, they will review any new SSA or ISA (amendment) to the POS-ARI-PC Core Protocol and if the risk for any embedded study is higher, they will review the associated safety data for that embedded study, and may decide to separate out DSMB and TSC functions, depending on the requirements of any approved embedded study.

11. STATISTICAL ANALYSIS

See below for an overall outline of the statistical analysis approach of the POS-ARI-PC. Details on the specific statistical analyses and methods for specific research questions in the POS-ARI-PC will be

described in a Statistical Analysis Plan (SAP) prior to database lock. The SAP(s) will include a description of the handling of missing data.

Additional to describing overall care provided, aetiology and patient outcomes, additional emerging questions will be answered using POS-ARI-PC data. Sample size and power calculations will not be performed for the POS-ARI-PC. However, we plan to recruit 400 patients from 5-15 European countries per year for Objective 1. All patients recruited into the study will be analysed. Descriptive analyses will be done by reporting percentages, means, SD and 95%CI.

A separate sample size calculation and statistical analysis plan (SAP) will be developed and approved for each additional embedded study and will be documented in the SSA or ISA.

i) Primary study parameter

- Patient recruitment and full data collection of approximately 400 patients with ARI per year
- Description of overall presentation and management, aetiology and outcomes for 400 patients presenting with ARI per year
- Performance of the national teams, primary care network per country, and individual practices. Endpoints of emerging questions and related analyses are fully described in a SAP.

ii) Interim analysis (if applicable)

When required and dependent on recruitment, interim analysis of the POS-ARI-PC data may be performed, which could be per full year of recruitment, after each winter season, or when emerging questions need to be answered. Additional triggers for analysis could be to determine best care (in terms of patient recovery and appropriate antibiotic prescribing); identify areas of change to remove unhelpful care and reduce unwarranted variation between countries/sites; to allow feedback to the countries/sites; and continually review changes in management and aetiology and how this relates to outcomes over the 5 years POS-ARI-PC.

iii) Qualitative analysis (Objective 2)

Qualitative data collection and analysis will be done concurrently with the POS and for any embedded study as required. Interview data from the three stakeholder groups (research professional, clinicians and patients) will initially be analysed separately from one another, using thematic and framework analysis taking an inductive approach. NVivo software will be used to assist with the organisation of data. A thematic framework will be used to chart data across all interviews within stakeholder groups and will aid comparisons between participants. Later stages of analysis will compare data across stakeholder groups.

12. ETHICAL CONSIDERATIONS

i) 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), Good Clinical Practice (GCP) and other applicable privacy laws, General Data Protection Regulation and Data Protection Act 2018, national/local guidelines, regulations and Acts.

Each national team will ensure the required, relevant regulatory approvals are gained for their country. The protocol, and all other required documents will be submitted to an appropriate Research Ethics Committee (REC) for each country. The national team will submit and, where necessary, obtain approvals for all amendments to the original approved documents. No patients will be recruited in participating countries until all approvals have been obtained for that country. Any amendment to the protocol must be approved by the CI and Sponsor before they are submitted for national REC and other required bodies.

Medical management of participants in this study will not be compromised by study procedures. At all times, priority will be given to providing standard of care patient management.

ii) Recruitment and consent

Prior to recruitment into the POS-ARI-PC (Objective 1), written, verbal or electronic -if approved- informed consent will be obtained from patients and/or their legal representatives.
Participants taking part in the qualitative evaluation (Objective 2) will be provided with a Participant Information Sheet and Informed Consent Form specific to their role (research professional, clinician or patients). Written or verbal informed consent will be taken prior to the start of an interview.

iii) Objection by minors or incapacitated participants

The 'Code of conduct resisting minors' (Gedragscode verzet bij minderjarigen) is applicable for children recruited in the POS-ARI-PC (Objective 1).
Consent to participate in the POS-ARI-PC that require individual informed consent from adults who lack capacity to provide informed consent for themselves will be not be requested.

iv) Benefits and risks assessment, group relatedness

The POS-ARI-PC is considered a negligible risk study as it does not interfere with, or influence patient's care. Taking swabs is classified as a negligible risk procedure.

For POS-ARI-PC Objective 1, children, pregnant women and elderly people will be recruited.

The results of the sample analyses will become available sometime after the samples are taken, and are not intended to influence patient care or management. Upon request, the national coordinators can be supplied with the sample results of their country's participants after full data analysis to inform the primary care practices where patients can inquire about their result.

v) Compensation for injury

Given the negligible risk of the study-related procedure, the combined throat/nose swab, an exemption for arranging participant insurance will be applied.

vi) Incentives

No incentives to patients for their participation are planned.

13. DATA MANAGEMENT

All study-specific documents of patients recruited into the study and (laboratory) outcomes, other than the signed ICF, will be coded with the participant ID, a unique number incorporating the country (two letters), practice (two digits) and sequential numbers. The CRF, swab, contact details and information

from diaries/phone calls will be identified with this ID. The participant code-list (name, birthdate and study ID) will be stored securely at recruiting sites.

All paper patient documents will be stored safely in a locked cabinet in a locked room in the practice, or office of the national network coordinator.

Follow-up of participants can be performed by the members of the national network study team, therefore, contact details of participants (name, phone number and email address) need to be shared between GP practices and the national network study team. The Your Research (YR) system, a cloud-based, secure, GDPR compliant, ISO 27001 certified system, will be used. Users will get role-based access and only have access to the contact details of participants that they are allowed to. No other data will be captured and stored in YR. Two-factor authentication is compulsory for all users. GPs will enter the participant's contact details in YR during or after the inclusion of a participant. GPs will only have access to contact details of participants of their own GP practice, whereas the member(s) of the national network study team will have access to contact details of participants of all GP practices in their network (country). Data entered in YR will never be exported or linked to collected clinical data in the CASTOR system. After the end of the study, data will be deleted from YR database. System administrators will not have access to any contact details of participants.

The POS-ARI-PC eCRF, including electronic diaries and telephone call forms will be implemented on the CASTOR Electronic Data Capture (EDC) system. CASTOR is compliant with 21 CFR Part 11, ICH E6 GCP, GDPR, and HIPAA. The cloud-based system is ISO27001 and ISO9001 certified. Data entered into CASTOR will be stored securely at the CASTOR web servers in Amsterdam, the Netherlands. The database is backed up daily.
Users will have unique log-ins and role-based access to CASTOR. 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 and transcripts of interviews will be stored for 25 years. See the separate ECRAID-Base Data Management Plan for further details.

UMCU Data Management will setup a POS-ARI-PC data warehouse (DWH) that will be populated with collected data from the CASTOR eCRF. All data residing in the POS-ARI-PC DWH will be directly accessible for reporting purposes. Data can also be exported from the DWH for further analysis. The POS-ARI-PC DWH resides within the UMCU.

Direct access to source, patient and CASTOR 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 is granted by the study CI.

The national network coordinator and the personnel dedicated for participant follow-up will ensure that participants' privacy is maintained. All documents will be stored securely and 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, study data and transcripts from interviews will be archived for 25 years in accordance with Ecraid's Archiving Standard Operating Procedures. Storage of the ICFs, at the national coordinating centre, and material isolated from the swab, at the Microbiology Laboratory of Antwerp, will also be for 25 years.

For the qualitative study, each interview will be audio-recorded with the participant's permission. Recordings will allow verbatim transcription of interviews in Microsoft Word. Transcription will be completed by an independent transcriptionist who holds a contract with a partner university. If any interview is conducted in a language other than English, recordings will be transcribed and translated by a member of the research team or by an independent transcriptionist and translator who holds a contract with a partner university. Once transcribed and transcripts are checked, recordings will be deleted. Transcripts will be labelled with a unique participant number and will omit any identifiable data either identifying the participant or their general practice. Interview transcripts will be stored at University of Oxford (UOXF) and University of Antwerp.

14. MONITORING AND QUALITY ASSURANCE

i) Monitoring

Central monitoring using Power BI will be implemented as soon as participant recruitment starts, to check whether consent and swab were taken, whether inclusion criteria were properly endorsed, and for missing/non-complete data. Central monitoring will be performed by the study teams following the instructions of the responsible delegate from Ecraid. 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.

If required, countries' networks or recruiting sites may be monitored during the study by a responsible delegate from Ecraid, UOXF or a Clinical Research Organisation. More details are described in the Monitoring Plan specific to the POS-ARI-PC.

ii) Quality Assurance Procedures

The study will be conducted and executed in accordance with the approved protocol, relevant regulations and Sponsor's Standard Operating Procedures. Prior to starting the study, all network coordinators and their study staff will be trained in study procedures by the core team based at the UMCU and UOXF. National network teams will cascade this training, delegation of responsibilities, and study set-up to the study-related personnel of the recruiting sites.

iii) Annual progress report

National Network Coordinators are able to submit a summary of the progress of the study to their accredited ethical committee annually, if required. Information will be provided on the date of inclusion of the first participant, numbers of participants included and numbers of participants that have completed the study, and amendments. The national network coordinators can also submit study reports, including any publications/abstracts of the POS-ARI-PC, to their ethical committees.

iv) Temporary halt and (prematurely) end of study report

The POS-ARI-PC is aimed to be a perpetual study. If there is a temporal halt or the study ends prematurely, the Sponsor will notify all relevant ethical committees within 15 days, including the reason for the pause/premature termination.

v) Public disclosure and publication policy

Study results will be disseminated in compliance with ECRAID-Base publication policy, via manuscripts in peer-reviewed open-access scientific journals, conference abstracts, posters and/or oral presentations, ensuring an accurate and balanced presentation of these data. Before submission, manuscripts or conference abstracts shall be reviewed by the ECRAID-Base Trial Management Board and PIs. All parties are committed to review within a period of 2 weeks and shall not unduly delay the submission of the study results. Proposed publications shall not include either the Sponsor's confidential information other than the study results, nor personal data on any participants, such as name or initials.

The investigators as listed in this protocol, together with one member 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.

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16. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	05 Apr 2023	Fiona Mowbray	- Added University of Antwerp logo to header. - Clarification about who will be invited to/eligible for researcher and clinician interviews and that network coordinators are responsible for identifying clinicians and patients in their own networks. - Details now included about the transfer of audio recordings from portable devices to secure files.
2	3.0	19 Nov 2023	Nguyen Tran, Sibyl Anthierens, Alike van der Velden	- Added Ecraid's (Sponsor's) logo to header. - Changed of Sponsor from UMCU to Ecraid. - Added statement of funding from the EU Horizon 2020 programme. - Removed Emily Bongard from 'Other investigators' list. - Changed to sharing pseudonymised data within and outside the ECRAID-Base Consortium. - Aligned the consent options in section 12ii) Recruitment and consent with what is describes in section 5ii) Informed Consent. - Added primary care homes as an option for including patients. - Added option for providing PIS and ICF electronically. - Clarified that number of interviews conducted will depend on the number of networks involved and the data sufficiency. - Added details for the management of qualitative data. - Minor wording corrections throughout the document.
3	4.0	17 Jan 2024	Alike van der Velden	- Added Your Research system for capturing and storing of participants' contact details for

				the purpose of follow-up procedure. - Updated List of Abbreviation with YR (Your Research)

List details of all protocol amendments here whenever a new version of the protocol is produced.

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