European Clinical Research Alliance on Infectious Diseases – Primary care adaptive platform trial for pandemics and epidemics (ECRAID-Prime)

UK-specific Master Protocol

A randomised, comparative trial to investigate the effect of Investigational Products and Usual Care in non-hospitalised patients with COVID-19 or COVID-like-illness

European Clinical Research Alliance on Infectious Diseases – primary care adaptive platform trial for pandemics and epidemics

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UK-specific Master protocol	25 SEP 2025 V1.0	Substantial amendment to specify the UK-only applicable procedures. Addition of the decentralised trial approach with recruitment by the central trial team. Removal of the individual interventions in the synopsis; a separate synopsis including the UK applicable interventions is now submitted.

CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the investigative team, regulatory authorities, and members of the Research Ethics Committee.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ADR	Adaptive Design Report
AE	Adverse Event
APT	Adaptive Platform Trial
ASR	Annual Safety Report
BMI	Body Mass Index
CA	Competent Authority
CRF	Case Report Form
CTA	Clinical Trial Agreement
CTIS	Clinical Trials Information System
CTR	EU Clinical Trial Regulation 536/2014
CTCC	Clinical Trial Centre Cologne
DMP	Data Management Plan
dPCR	Digital Polymerase Chain Reaction
DPIA	Data Protection Impact Assessment
DSMB	Data Safety Monitoring Board
(e)CRF	(electronic) Case Report Form
ECTR	Clinical Trial Regulation 536/2014/EU
EID	Emerging Infectious Diseases
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
FMP	File Management Plan
G6PD	glucose-6-phosphate-dehydrogenase
GCP	Good Clinical Practice
GDP	Good Documentation Practices
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
GxP	Collectively, cGCP, cGLP, cGDP, cGMP and other applicable, generally accepted industry best practice standards for the pharmaceutical or biotech industry.
HCP	Healthcare professional
IB	Investigator's Brochure
ECRAID-Prime	European Clinical Research Alliance on Infectious Diseases – Primary care adaptive platform trial for pandemics and epidemics
ICH-GCP	International Conference on Harmonisation guidelines for Good Clinical Practice
ID	Infectious Diseases
IEC	Independent Ethics Committee
IMD	Investigational Medical Device
IMP	Investigational Medicinal Product
IP	Investigational Product
ISA	Intervention Specific Appendix
MHRA	Medicines and Healthcare products Regulatory Agency
M-SAP	Master Statistical Analysis Plan
NONS	Nitric Oxide Nasal Spray
OTC	Over-the-counter
PC-CTU	Primary Care-Clinical Trials Unit

PCR	Polymerase Chain Reaction
PI	Principle Investigator
PIS	Participant Information Sheet
RdRp	RNA-dependent RNA polymerase
REC	Research Ethics Committee
RSI	Reference Safety Information
RSV	Respiratory Syncytial Virus
(S)AE	(Serious) Adverse Event
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TTR	Time to first self-report of feeling recovered
VOC	Variants of concern
WOCBP	Women of childbearing potential
WMA	World Medical Association
YR	YourResearch

The term **‘central clinical team’** refers to the team of medically qulified clinicians, prescribing pharmacists and research nurses at the Primary Care-Clinical Trials Unit (PC-CTU).

The term **‘central trial team’** refers to the team at the PC-CTU, responsible for the day-to-day conduct of the trial, which includes the central clinical team, as well as other non-clincal staff.

SYNOPSIS of the UK-specific Master Protocol

2022-501707-27
European Clinical Research Alliance on Infectious Diseases – primary care adaptive platform trial for pandemics and epidemics

Background
COVID-19 and COVID-like-illness cause significant ill-health. Given that the greatest burden of ill-health is in the community, it is in primary care and community settings where emerging antiviral and other early treatments for COVID-19 and COVID-like-illness will be of most overall benefit. Despite novel antiviral agents coming to market, it remains imperative that the search for better treatments continues, especially as many new drugs are expensive, require a diagnostic test before they are used, and may have numerous important drug interactions and exclusions. An adaptive platform trial (APT) is an efficient way to trial such potential agents as it allows for multiple interventions to be tested under a single master protocol.

Rationale
The rationale of the ECRAID-Prime trial is to test the safety and efficacy of agents for patients presenting to primary care with COVID-19 or COVID-like-illness in a phase II or phase III type evaluation. This helps determining whether agents should progress to a next phase of evaluation. Using qualitative research methods, we will additionally assess the platform trial process and procedures in order to optimize trial implementation, thereby enhancing and facilitating patient recruitment throughout the course of the trial and beyond.

Main trial
The UK-specific master protocol describes a platform randomised, multi-country, multi-centre, decentralised trial for the evaluation of new investigational products (IPs) for treatment of non-hospitalised patients with COVID-19 and COVID-like-illness.

Platform trial
A “platform trial” is a trial in which multiple IPs for the same illness can be tested simultaneously, and in which new interventions can be stopped or added during the course of the trial in accordance with pre-specified criteria. The UK-specific master protocol describes the overall structure and processes of the platform, while specific information regarding interventions and comparators under investigation are described in intervention specific appendices (ISAs).

Outcomes
The primary outcome will be phase dependent. For Phase IIb/III type evaluations the primary outcome will be time to first self-report of feeling recovered from symptoms of COVID-19 or COVID-like-illness. For Phase II(a) type evaluations the primary outcome parameter will be viral clearance or potentially impact on specific biomarkers.

Secondary outcomes might include: (early) sustained recovery; time to first self-report of return to usual daily activity; time to first self-report of feeling recovered from symptoms of COVID-19 or COVID-like-illness (for Phase II(a) type evaluation); viral clearance (for Phase IIb/III type evaluation); reduction in viral load, presence, duration and severity of individual respiratory infection symptoms; participant-reported overall wellbeing; safety of the IPs through monitoring of (serious) adverse events; tolerability of the IPs, IP intake adherence, use of additional antiviral medication, use of other prescribed and/or over-the-counter medication for the

respiratory infection; occurrence of complications, impact on usual daily activities; impact on health care utilization; long-term (up to 3 months) consequences of COVID-19 or COVID-like-illness (including long-COVID); and, the incidence of COVID-19 or COVID-like-illness in other members of the household.

Exploratory outcomes might include: the emergence of mutations in causative pathogens; the experiences of researchers and network coordinators of setting up a platform trial that requires modifications throughout the execution of the trial in multiple countries; and the views and experiences of healthcare professionals and patients taking part in such a trial (qualitative interview study).

Trial design

Trial activities (pre-/screening, eligibility check, informed consent, enrolment, IP supply, follow-up) will be either face-to-face or remote. After obtaining informed consent and confirmed eligibility, baseline information will be collected. Participants will be randomly allocated to receive usual care with either an IP, or the specified comparator, or -when appropriate- usual care alone. If recruitment is remote, screening/recruitment/randomisation can be the day before Day 0 (Day -1) to allow next day delivery of the IP. A swab will be (self-)taken on Day 0 (either during the inclusion visit, or in case of remote recruitment and IP arrival 1 day later, the day after inclusion) prior to the start of IP intake. This swab will be used to determine disease aetiology (retrospectively). Additional swabs will be (self-)taken on relevant days (as specified per ISA). Participants will be asked to report their symptoms each day in a daily diary (either paper or online) for 28 days starting at Day 0. All participants will receive an end-of-treatment telephone call assessment at day 14 (window +3 days) and an optional end-of-month telephone call assessment at day 28 (window +7 days), where appropriate (as specified in the ISA). These telephone calls will elicit additional safety data, and ascertain a minimal set of outcome data. Where relevant (as specified in ISA), longer-term follow-up can be at 3 months by an online questionnaire, or telephone call. The duration of the trial for each participant can be up to a maximum of 3 months.

Nested qualitative study

A qualitative study (interviews) will be nested within the trial to understand the experiences of researchers/network coordinators in delivering the APT, the experiences of healthcare professionals and patients in taking part, and their views on and acceptance of the IPs.

Trial population

Participants who meet the following *inclusion criteria* are eligible to take part in the trial:

- Aged ≥18 years on the day of inclusion.
- Presence of at least two symptoms suggestive of COVID-19 or COVID-like-illness: one respiratory (cough, sore throat, running or congested nose or sinuses, shortness of breath) and one systemic (fever, feeling feverish, sweats/chills or shivering, low energy or tiredness, headache, muscle, joint and/or body aches, loss of taste and/or smell).
- Judged by recruiting medically qualified clinician or delegate that the illness is due to a respiratory infection.
- Onset of symptoms less than x days (x will be specified per ISA) from the start of IP intake.
- Willing and able to give informed consent for participation in the trial.
- Willing and able to comply with all trial procedures.

Participants who meet any of the following exclusion criteria will be excluded from participation in the trial:

- Requiring admission to the hospital on the day of screening, or inclusion.
- Known allergies or hypersensitivities to any of the components used in the formulation of the IP, or the comparator.
- Any disease, condition, or disorder that precludes participation in the trial, in the opinion of the person checking eligibility and taking consent.
- Any planned major surgery in the next 28 days.
- Currently participating in a trial of a pharmacological treatment.
- Any personnel involved in the trial.

Any additional specific information, eligibility criteria relevant to women of child-bearing potential, including current pregnancy and/or breastfeeding, and specific inclusion and/or exclusion criteria for IPs will be specified in the ISAs.

Interventions

Each IP will have a comparator, which can be a placebo or comparator IP. Usual Care alone can be an additional control arm. Participants will be randomised to receive an IP, or the comparator in addition to Usual Care, or -when appropriate- to Usual Care alone. Potential participants can be included if they are eligible for at least one IP.

ECRAID-Prime started with arms A (Usual Care), B (Usual Care + Nitric Oxide Nasal Spray) and C (Usual Care + Saline Spray), where Usual Care is the control for Saline Nasal Spray and Saline Nasal Spray is the comparator of NONS. Specific information about each arm is detailed in their individual ISA.

1. INTRODUCTION, RATIONALE AND PROTOCOL STRUCTURE

1.1 Background

The World Health Organisation declared that COVID-19 (Coronavirus disease 2019) was a pandemic on 11th March 2020 [1]. Despite the successful rollout of vaccination programmes worldwide [2, 3], COVID-19 continues to rage [4] having caused over 6,000,000 deaths globally [5], and it is likely that COVID-19 will remain endemic. There is, therefore, a pressing need to identify and evaluate new therapeutics, including testing their efficacy against new variant strains of SARS-CoV-2. As lockdowns and social distancing measures have eased, there has been a resurgence of COVID-19 and COVID-like-illness, such as influenza and respiratory syncytial virus (RSV) [6], which cause significant ill-health and mortality, particularly in clinically vulnerable individuals [7, 8]. Influenza causes around 400,000 deaths globally annually [9]. Therapeutics should be evaluated in the context where they are intended to be deployed. Despite novel antiviral agents specific for SARS-CoV-2 and other viral infections such as influenza coming to market, it remains imperative that the search for better treatments continues, especially since many new drugs are expensive, require a diagnostic test before they are used, and may have many important drug interactions and exclusions. Cost-effective and safe treatments that can be used very early in in the illnesses in the community, where treatment is most likely to have maximum impact are still urgently needed. Given that the greatest burden of ill-health is in the community, with around 90% of all patient contacts take place in primary care [10], it is in primary care and community settings where emerging antiviral and other early treatments for COVID-19 and COVID-like-illness will be of most overall benefit.

Because respiratory tract infections can be caused by a variety of pathogens, a treatment that has broad-spectrum anti-viral and/or protective activity, and does not require a diagnostic test before use would be particularly attractive. Molnupiravir was originally developed as a treatment for influenza, but has been shown to have activity against coronaviruses, including SARS-CoV-2 [11], owing to its ability to induce viral error catastrophe through uptake into viral RNA by RNA-dependent RNA polymerase (RdRp) [12]. Targeting enzymes and structures that are common to many viruses, such as RdRp in RNA viruses, has the potential for broad anti-viral activity [13]. Inhaled budesonide, traditionally used as an asthma and COPD therapy, was found to speed up the time to feeling recovered by three days in community-dwelling COVID-19 patients in the UK who were older and had comorbidities, compared with those receiving usual care [14]. Antibiotics such as doxycycline and azithromycin were trialed as COVID-19 treatments due to their theoretical abilities to reduce inflammation [15, 16], which could in turn have reduced the pro-inflammatory state induced by viral infections. Treatment with antibiotics could also reduce the chance of developing a secondary bacterial infection, a potential complication that is common to respiratory tract infections, but these agents have been shown to be ineffective for this indication. There are a number of promising candidate interventions, including nose sprays that are considered to inactivate all viruses and prevent transmission into host cells. Identifying therapeutic agents with broad antiviral activity and deploying them to patients with early symptoms of COVID-19 and COVID-like-illness in the community on a syndromic basis has the potential to significantly reduce ill-health and illness duration, viral transmission, hospitalisations and deaths, and have a considerable favourable economic benefit. This is particularly important given that primary care physicians typically manage respiratory tract infection syndromic illness without knowing and/or identifying the causative pathogen. These agents should be safe and ideally inexpensive, to maximise scalability and impact.

An adaptive platform trial with nested process evaluation is an efficient way to test such potential agents as it allows for multiple interventions to be tested under a single master protocol [17]. Interventions can be added to the trial platform whilst the trial is in progress [17], negating the need to set up a new trial for each therapeutic that emerges. Through interim analyses, interventions can be dropped from the trial due to pre-specified success or futility criteria being met [17]. If appropriate, a shared control group can be used as a comparator for multiple interventions in the platform [18]. Furthermore, accumulating data can influence the course of the trial; for example, response adaptation can be used to allocate more participants to better performing interventions [19]. These features: increase trial efficiency and reduce the overall sample size; enable the trial to remain relevant to evolving circumstances, which is particularly important in the context of epidemic and pandemic illnesses; and, allow intervention findings to be disseminated in a timely fashion without having to wait for the overall conclusion of the trial.

Platform trials have been used successfully to evaluate therapeutics for COVID-19 [20-22] and influenza [23]. However, to date, there is no platform trial with Europe-wide reach to thoroughly evaluate early treatment of COVID-19 and COVID-19-like illness symptoms in patients treated in primary care. The SARS-CoV-2 pandemic has highlighted the critical importance of establishing rapid, adaptive platform trials to identify effective therapeutics for pandemic, epidemic and emerging infectious diseases. A Europe-wide, primary care adaptive trial platform would allow an evolving strategic focus on countries with higher prevalence of COVID-19 and COVID-like-illness, and would facilitate large-scale, rapid recruitment, thereby providing faster, more robust and meaningful results than would typically be possible through a single country approach. ECRAID-Prime will thus become a trial platform in perpetuity, ready to be leveraged in light of any emerging infectious disease threats.

1.2 Study rationale

The rationale of the ECRAID-Prime trial is to test safety and efficacy of treatments for patients presenting to primary care with COVID-19 and COVID-like-illness in a phase II/III type evaluation, with the aim of determining whether treatments should progress to a next phase of evaluation, and evaluate the trial process and procedures in order to optimize it and enhance recruitment. Under the master protocol, patients will be included on the basis of a syndromic clinical picture. Before medicine trial intervention is given, an initial test will be taken to establish the aetiology of the infection, to guide inclusion into appropriate trial arms guide inclusion into arms evaluating aetiology-specific treatments (as specified in the Intervention Specific Appendices (ISA) to the master protocol for such a treatment). Depending on the Investigational Product (IP) under investigation, this master protocol, therefore, allows for inclusion based on meeting syndromic inclusion criteria for some agents as well as a “test-and-treat-if-positive” approach, in case patients with a specific aetiology are expected to benefit from a specific IP only. In this way, the ECRAID-Prime trial and this master protocol retain focus on COVID-19, while also potentially giving answers to effectiveness of relevant trial interventions for any current, or future epidemic and pandemic respiratory infections. The platform will also evaluate the effect of treatments on longer-term participant outcomes captured at three months. It is possible that treatments given during acute illness could reduce the occurrence or severity of post-viral syndromes, such as long-COVID. Long-COVID, defined as symptoms persisting beyond four weeks after the index illness, can cause significant morbidity and economic burden through delayed return to work/usual activities [24].

1.3 Background/embedment of ECRAID-Prime in Ecraid

The European Clinical Research Alliance for Infectious Diseases (Ecraid) is an EU-funded research infrastructure with the purpose of reducing the impact of infectious diseases (ID) on individual and population health. ID pose a serious threat to European citizens and economies. Of particular concern are pathogens that have the potential to cause major epidemics or even pandemics and for which 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, increases in 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, prevention and treatment of infections and to better respond to ID threats. Within Ecraid, primary care research will focus initially on COVID-19 and COVID-like-illness by implementing ECRAID-Prime and a perpetual observational study.

ECRAID-Prime will fit in this structure by recruiting patients into a therapeutic trial to treat COVID-19 and COVID-like-illness with the ultimate aim to reduce illness duration, complications, and possibly transmission of SARS-CoV-2, influenza, RSV and other respiratory pathogens.

1.4 Protocol structure

The structure of this protocol differs from a traditional study protocol. The perpetual platform nature of ECRAID-Prime allows for multiple interventions to be tested simultaneously and in series. The ECRAID-Prime UK-specific master protocol will describe the overall structure and processes of the platform, while any specifics for the interventions and comparators under investigation will be fully described in separate appendices which detail all specifics to the controls, interventions and their evaluation, e.g. the IP-specific background and information, route of administration, dosage, known and potential risks and precautions, and if applicable, additional objectives, assessments and/or criteria. This will also include the stage of development of the IP and thereby the type of study evaluation that will be performed (e.g. study phase IIa, IIb, III). New interventions that enter the trial will be fully described in additional ISAs as appendix to this UK-specific Master Protocol, requiring full approvals in an amendment procedure.

2. OBJECTIVES

The generic platform study objectives are listed in this section. Potential additional objectives per IP will be detailed in each ISA.

2.1 Primary study objectives

The primary objective(s) of this platform trial will be phase dependent.
To assess the efficacy of the trial IP versus control (Usual Care) or versus a comparator (placebo, or comparator IP) on:

- Time to first self-report of feeling recovered from symptoms of COVID-19 or COVID-like-illness (for Phase IIb/III type evaluation, as specified in the relevant ISA).

- Viral clearance, and potentially viral load and/or impact on biomarkers, for example on illness severity or immunological response (for Phase IIa type evaluation as specified in the relevant ISA).

2.2 Secondary study objectives

The key secondary outcome will be early sustained recovery, which is defined recovery by day 14, sustained until day 28.
Other secondary objectives include assessment of the efficacy and safety of the IP versus control, or versus the comparator on:

- Sustained recovery (participants' reported recovery that was maintained until 28 days)
- Time to first self-report of feeling recovered from individual symptoms of COVID-19 or COVID-like-illness (for Phase IIa type evaluation)
- Viral clearance (for Phase IIb and III type evaluation)
- Reduction in viral load
- Tolerability of the IP
- IP intake adherence
- Time to first self-report of return to usual daily activity
- Presence, duration and severity of individual respiratory symptoms
- Participant reported overall wellbeing
- Evaluation of overall safety of the IP by monitoring of (serious) adverse events and (serious) adverse drug reactions
- The use of additional antiviral medication
- The use of other prescribed and/or over-the-counter (OTC) medication for the RTI
- The occurrence of complications (hospitalisation, death; all-cause, non-elective hospitalisation will be assessed)
- Impact on usual daily activities
- Health care utilisation (e.g. general practitioner (GP) and hospital visits)
- Long-term (up to 3 months) consequences of COVID-19 or COVID-like-illness
- The incidence of COVID-19 and COVID-like-illness in other members of the household

2.3 Exploratory objective

Exploratory objectives include:

- The emergence of mutations in causative pathogens in participants and potentially in household members (where specified in the relevant ISA).
- To assess the experiences of researchers/ network coordinators of setting up the trial in multiple countries, including views on optimising trial delivery, recruitment, and implementation (qualitative study).
- To assess healthcare professionals' views and experience of taking part in the trial (in the context of an epidemic or pandemic), the novel trial design, recruiting patients and views on the intervention(s) (qualitative study).
- To assess patient views and experiences of taking part in the trial and trial interventions, including intervention adherence (qualitative study).

3. STUDY DESIGN

3.1 Study Design

ECRAID-Prime is a randomised, multi-country, multi-centre platform trial with options for decentralised procedures -with early stopping for futility and superiority if prespecified criteria are met- for the evaluation of new IPs for treatment of non-hospitalised patients with COVID-19 and COVID-like-illness. When a novel IP is added to the platform, an additional ISA will be written as a substantial modification/amendment to this Master Protocol. All appropriate ethical and competent authority approvals will be gained for each ISA prior to its implementation in the platform. Evaluation of each additional IP will follow to the same core trial structure, trial processes and data collection as described in this master protocol, and only deviate where essential, and as described in the relevant ISA. Novel IPs can be evaluated simultaneously or sequentially.

3.2 Study description

Trial activities (pre-/screening, eligibility check, informed consent, enrolment and follow-up) will be either face-to-face or remote (see section 4.1). After having fully informed the potential participant the informed consent procedure will be executed. There will be a person-to-person discussion about the trial when taking consent with participants, and there will be an opportunity for asking questions and for full verbal explanations. This conversation may be face-to-face or video/phone call (see section 8.3.1). After obtaining IC, eligibility for trial participation will be assessed (general and specific in- and exclusion criteria) and confirmed by a medically qualified clinician or qualified delegate (e.g. research nurse or prescribing pharmacist). Baseline information will be collected (see section 8.3 Study Procedures). Participants will be randomly allocated to receive either an IP, a comparator, or -when appropriate- control (Usual Care). Each IP, control and comparator will have an ISA. The aim is for starting IP intake to occur within x days since onset of symptom; x will be specified in the ISA. Participants will receive study instructions, including how to administer the IP/comparator (if participant is allocated to a study arm with an IP/comparator). IP/comparator treatment duration will be described in the ISA. Use of diaries and questionnaires will be explained. These diaries and questionnaires can be online, paper-based, or completed by telephone, and the relevant and preferred approach will be explained, and access provided.

Participants will be asked, where appropriate, to report feeling recovered, individual symptoms, overall wellbeing, AEs, use of mediation, complications, reason for stopping treatment, impact on usual daily activity and health care utilisation in a daily diary (either paper or online) for 28 days starting at Day 0.

A swab will be (self-)taken on Day 0 (either during the inclusion visit, or in case of remote recruitment and IP arrival 1 day later, the day after inclusion) prior to the start of IP intake. This swab will be used to determine disease aetiology (retrospectively). Additional swabs will be (self-)taken on relevant days (as specified per ISA).

Blood samples or blood spot tests (self)-taken may be taken at inclusion and later, if specified in the ISA.

All participants will receive an end-of-treatment telephone call assessment at day 14 (window +3 days). During this call diary completion, questions related to feeling recovered and return

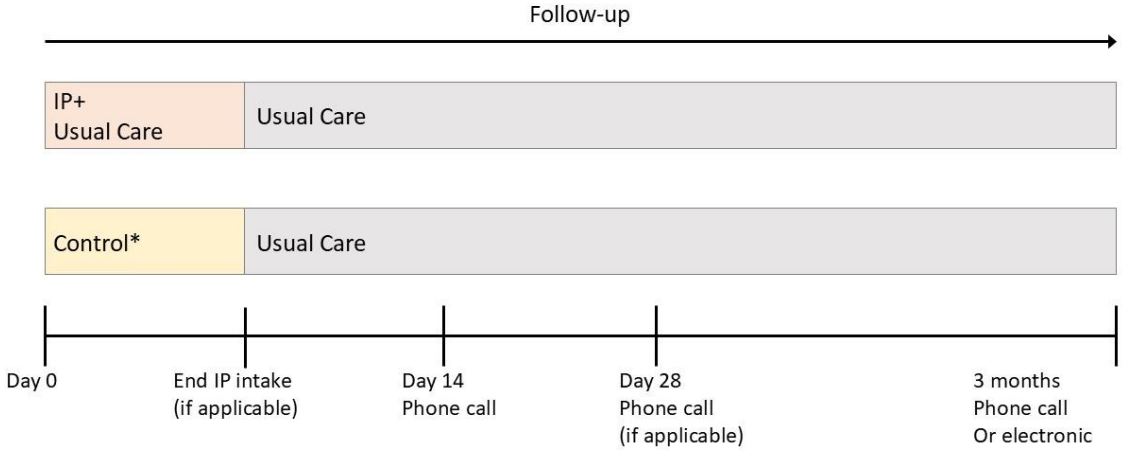
to usual activity, IP intake, reason for stopping medication, health care utilization, and (serious) adverse events ((S)AEs) not reported in the diary will be captured where appropriate.

In addition, participants can receive an end-of-month telephone call at day 28 (window +7 days) in case their diary is incomplete to capture a minimal outcome set, or if needed for end-of-study purposes. If specified in the ISA, longer-term follow-up will be at 3 months by an online questionnaire or telephone call. Specifically, these calls/questionnaires will capture data on whether the participant feels recovered from their index illness, participant's reported overall wellbeing, long-term consequences of the illness, healthcare utilization related to persisting symptoms, and impact of ongoing symptoms on activities.
For more details on trial procedures, see section 8.3 Study Procedures. More trial specific requirements will be described in the ISA.

3.3 Schematic diagram of study design

The core schematic diagram of the study design is presented below (see **Figure 1**). If the core diagram needs adaptation for a specific IP, this will be specified in the ISA.

Figure 1. Study Design
This figure provides the general set-up of the trial, specific moments of follow-up can be adjusted to the trial and described in the ISA.



* Control = Usual Care, IP can be placebo, or (comparator) IP.

3.4 Duration of the study per participant

The duration of the trial for each participant is maximum 3 months. Participants will be monitored daily for their acute symptoms for 28 days via a diary (paper, online). All participants will receive an end-of-treatment telephone call assessment at day 14 (window +3 days). In addition, participants can receive an end-of-month telephone call at day 28 (window +7 days) in case data capture is not complete, to enable capturing a minimal set of outcome data, or if needed for end-of-study purposes. If needed, longer-term follow-up will be at 3 months by an online questionnaire or telephone call.

3.5 Nested qualitative study

A qualitative study will be nested within the trial to understand the experiences of researchers/ network coordinators in delivering the trial, the experiences of healthcare professionals and

patients in taking part in the trial, and views on and acceptance of trial interventions. The qualitative work will aim to include researchers/ network coordinators from all countries and networks which take part in the trial. A sub-set of networks will be selected to undertake interviews with healthcare professionals and participants. These networks will be purposefully selected to give variation in factors such as healthcare system, geographic location in Europe and income. Interviews will be conducted with participants from these three stakeholder groups (researchers/network coordinators, healthcare professionals and participants) either remotely (by telephone or online (e.g. using Microsoft Teams)) or in person as appropriate.

Interviews with researchers/network coordinators will take place throughout the period of ECRAID-Prime prior to trial set up through to completion of recruitment and follow-up of participants. We will aim to include longitudinal interviews, interviewing the same participant at multiple and crucial timepoints of the trial, where possible, to gain insights into how researchers/network coordinators apply learning to improve trial processes throughout the study. Interviews will ask researchers/ network coordinators about how they deliver the trial and any advantages and issues of working within an existing platform to deliver trials efficiently. The number of interviews conducted will depend on the number of interventions trialled and the data collected but will be approximately 20-60 interviews in total.

Interviews with healthcare professionals will take place throughout the trial and will focus on key timepoints such as the introduction of a new intervention arm. Health care professionals will include clinicians who see patients when they first consult and who assess eligibility and/or randomise them in the trial. Network coordinators will identify eligible healthcare professionals at their sites. Interviews will ask about experiences of taking part in the trial (in the context of an endemic or pandemic situation), views of trial processes, the novel trial design and introduction of new interventions, experience of recruiting patients and views of interventions. The number of interviews will depend on data collected and the number of interventions being trialled over time but will include approximately 6 healthcare professionals per network, per trial intervention giving a total of 30-70 interviews.

Interviews with trial participants will take place at a suitable timepoint after their initial consultation (depending on their diagnosis, likely recovery time and the regimen of any trial intervention), likely around 2 weeks, to understand their experience of being recruited to the trial, trial processes, their views of the intervention and intervention adherence (where relevant). Trial participants in any intervention arm may be invited to take part in an interview. The number of interviews will depend on data collected and the number of interventions being trialled over time but will include approximately 10 trial participants per network, per trial intervention giving a total of 40-80 interviews. We will seek to obtain variation in factors such as age, symptom presentation, and intervention arm.

All individuals invited to an interview will be sent an invitation letter and participant information leaflet relevant to the stakeholder group they are in (researcher, healthcare professional, patient). We will obtain written or verbal consent prior to an interview.

Interviews with researchers/network coordinators will be analysed using methods specific for longitudinal qualitative studies to capture their evolving experiences in delivering a trial. Interviews with healthcare professionals and trial participants will be analysed using thematic

analysis and/or framework analysis to help answer questions about trial design, experiences of recruiting and being recruited into the trial, and views on interventions.

4. STUDY POPULATION

4.1 Participant identification and recruitment strategies

Potentially eligible participants can be identified and informed about the trial through different approaches, including:

- posters, leaflets, banners, website, TV screens at GP practices, local pharmacies, social media;
- text message or email to potentially eligible participants sent by participating GP practices to inform them about the trial;
- publicising via various healthcare service systems (e.g. Be Part of Research Registry, TrialeX, Optum and/or Patient.info);
- potentially eligible participants contact or present to their primary healthcare providers (e.g. GP practice, pharmacy, care home) with symptoms suggestive of COVID-19 or COVID-like illness according to the eligibility criteria.

Several recruitment strategies can be implemented in parallel if deemed suitable for the trial's circumstances and subject to regulation and full approval. If a specific IP requires a specific recruitment strategy, this will be specified in the ISA. Recruitment can be face-to-face as well as remote (telephone/video call).

4.1.1 Recruitment at primary healthcare facilities (face-to-face)

Participating primary healthcare facilities will be primarily GP practices (either single practices or a federation of practices that are able to operate under a single site agreement), but can include other healthcare facilities, like pharmacies and/or care homes. As well as recruiting through routine consultations, potentially eligible participants can contact their GP upon onset of symptoms suggestive of COVID-19 or COVID-like-illness (see section 4.2 and 4.3 for eligibility criteria) for a face-to-face recruitment visit. A medically qualified clinician or qualified delegate (e.g. research nurse or prescribing pharmacist) at the GP practice will explain the trial to the potentially eligible participant, perform the pre-screening, take consent (either paper or e-consent), assess eligibility, collect baseline CRF and contact information, take the baseline swab (can be self-taken by the participant), randomise, provide the participant pack and, if randomised to an IP arm, the investigational product pack (see section 8.3 Study Procedures).

4.1.2 Recruitment by the central trial team (remote via telephone or video call)

The central trial team based at the Primary Care Clinical Trials Unit (PC-CTU), University of Oxford, will be able to recruit and randomise participants remotely. Potentially eligible participants will be informed about the trial via the different approaches mentioned above, and instructed to contact the central trial team at the PC-CTU immediately upon onset of symptoms suggestive of COVID-19 or COVID-like illness. Once they expressed interest in trial participation, an appropriately trained member of the trial team (e.g. clinician, research nurse, trial manager, assistant trial manager or trial coordinator/administrator) will conduct initial pre-screening, explain the trial and obtain informed consent via phone/video call. Opportunity will be given for discussion and questions prior to consent and randomisation (see chapter 11).

Once a participant has provided informed consent, the eligibility assessment will be performed by a medically qualified clinician or qualified delegate (e.g. research nurse or prescribing pharmacist). Due to the low risk nature of the IPs being investigated, eligibility will be assessed by obtaining relevant information directly from the potential participant only. Depending on additional exclusion criteria outlined in specific ISAs, eligibility can be assessed by eliciting medical history and relevant information, including current and previous medication use, directly from the potential participant. Where specified in the ISA, eligibility checking will be assessed additionally through direct access to the participant's Summary Care Record in England or a medical record summary in use for clinical care in any UK Devolved Administration, and by reference to relevant medical information obtained from the participant's primary care or secondary care records (where the person confirming eligibility deems this necessary).

If an additional IP is introduced which requires extensive clinical interpretation of eligibility criteria, the eligibility assessment process will be reviewed and amended accordingly and outlined fully in the ISA, with updates to the associated processes in relevant documents.

After randomisation, a central trial team member will collect all information for the baseline Case Report Form (CRF), record contact information, and arrange for the participant pack and, if randomised to an IP arm, the investigational product pack, to be collected at the GP practice or delivered to the participant's home (see section 8.3 Study Procedures).

Both recruitment pathways, face-to-face and remote, are depicted in a recruitment flow chart (Appendix II).

4.2 Inclusion criteria

The generic platform inclusion criteria are listed in this section. Potential additional inclusion criteria for specific IPs will be detailed in the ISA.

In order to be eligible to participate in ECRAID-Prime, a participant must (at minimum) meet all the following criteria:

1. Participant is ≥18 years of age on the day of inclusion.
   If people aged <18 years are suitable for inclusion in the evaluation of an IP, then this will be described and justified in the relevant, approved ISA.
2. Presence of at least two symptoms suggestive of COVID-19 or COVID-like-illness, one respiratory (cough, sore throat, running or congested nose or sinuses, shortness of breath) and one systemic (fever, feeling feverish, sweats/chills or shivering, low energy or tiredness, headache, muscle, joint or body aches, loss of taste and/or smell).
3. Judged by recruiting medically qualified clinician or delegate that the illness is due to a respiratory infection.
4. Onset of symptoms less than x days (x will be specified in the ISA) from start of IP intake.
5. Willing and able to give informed consent for participation in the trial.
6. Willing and able to comply with all trial procedures (including self-collected, store and post swabs).

For each of the IPs being investigated, a risk-adapted approach will be carefully considered. Any additional eligibility criteria relevant to women of child-bearing potential (WOCBP), including current

pregnancy or breastfeeding will be specified in the ISA.

Participants of childbearing potential are defined as participants who are potentially fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy.
Highly effective contraception methods include sterilisation, combined oestrogen and progestogen containing hormonal contraception (oral, intravaginal, transdermal), progestogen-only hormonal contraception (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner (provided that partner is the sole sexual partner of the WOCBP trial participant, and that the vasectomised partner has received medical assessment of the surgical success).
If women have been abstinent of heterosexual sex for the 30 days before enrolling in the trial and will agree to continue to be abstinent of heterosexual sex for a further 30 days after the end of IP intake, where this is in line with their preferred and usual lifestyle, this would also count as effective contraception.

4.3 Exclusion criteria

The generic exclusion criteria are listed in this section. Potential additional exclusion criteria for individual IPs; for example, specific comorbidities or medication use, will be detailed in the ISA.

A potential participant who meets any of the following criteria will be excluded from participation in ECRAID-Prime:

1. Requiring admission to the hospital on the day of inclusion.
2. Known allergies or hypersensitivities to any of the components used in the formulation of the IP, placebo or comparator IP.
3. Any disease, condition, or disorder, or language barrier that precludes participation in the trial, in the opinion of the recruiting medically qualified clinician or delegate checking eligibility.
4. Any planned major surgery in the next 28 days.
5. Currently participating in a trial of a pharmacological treatment.
6. Any personnel involved in the trial.

4.4 Sample size calculation

Sample size requirements will be phase dependent and are detailed in the ISA.

5. STUDY TREATMENTS

The sections of this chapter e.g., name and description of the IP/comparator, status of development of the IP/comparator, description and justification of dosage and route of administration, preparation and labelling of the IP/comparator, will be described in the ISA.

6. OTHER TREATMENTS AND RESTRICTIONS

6.1 Concomitant therapy

6.1.1 *Permitted medication*

The ISA describes for each investigational product which co-medication will be permitted during the trial. Ongoing long-term medications should be continued for the management of underlying conditions (to be recorded in the CRF).

6.1.2 Prohibited medication

The ISA describes for each IP which co-medication is not permitted during the trial, which results in additional exclusion criteria.

6.1.3 Escape medication

Symptomatic therapy to manage symptoms related to COVID-19 or COVID-like-illness, such as antipyretics, analgesics, as well as other OTC medication is allowed. Use of OTC medication will be captured in the participant diary.

6.2 Lifestyle restrictions

6.2.1 Contraception measures

If there are any specific criteria for women of child-bearing potential, this will be specified in the ISA.

6.2.2 Other requirements

If there are any other requirements, then these will be described in the ISA.

7. TRACEABILITY, STORAGE, ACCOUNTABILITY AND COMPLIANCE

In ECRAID-Prime, IPs will be tested, which can be Investigational Medicinal Products (IMPs) or Investigational Medical Devices (IMDs). These will be prepared and supplied by different pharmaceutical companies. Certified vendors of these pharmaceutical companies will be responsible for overall management of IPs, until arrival of the IP in the UK (at a central location or directly at the site, according to the UK regulation), which will include procurement, receipt, storage and stock maintenance of the IP, labelling, packaging of the IP, and distribution of the IP. This will occur in accordance with International Conference on Harmonisation guidelines for Good Clinical Practice (ICH-GCP (R2)), good manufacturing practice (GMP), good documentation practices (GDP) and all other applicable (national) laws and regulations.

A unique IP number is printed on the trial IP label. IP labels will comply with the UK regulations.

IPs will be received by designated persons at the University of Oxford, Primary Care CTU's dispensary and GMP facility (a facility that has been awarded a pharmacy premises registration exemption from the MHRA and General Pharmaceutical Council (GPhC) in 2023 and a MIA(IMP) license for the GMP Facility), or directly at recruiting sites, handled and stored safely and properly, and kept in a secured location to which only designated personnel has

access. Upon receipt, all IPs must be stored according to the instructions specified in the IP handling and administration protocol. IPs are only to be dispensed in accordance with the protocol. Technical complaints are to be reported to the Sponsor's Quality Assurance.

The Central PC-CTU Pharmacist and/or Site Investigator or delegate must maintain an accurate record of receipt and dispensing of the IP using an IP accountability log. Monitoring of IP accountability will be performed by monitors during site visits, remotely, and at the completion of the trial.

At the end of the trial, and as appropriate during the course of the trial, IP accountability will be performed, and unused IPs will be destructed in the UK, by the vendor, or the Sponsor. A copy of the completed IP accountability log should be returned to the Sponsor as part of the final accountability filing.

Further detailed specification of vendor and IP handling will be described in the ISAs.

Compliance
Study product compliance will be assessed by using a study product intake diary on adherence to the prescribed dose of the study product per day enabling to determine:
- Days of study product intake
- Adherence to the prescribed dose per day

8. METHODS

8.1 Study parameters/ endpoints

8.1.1 Primary study endpoints (phase dependent) will be:
- Time to first self-report of feeling recovered from symptoms related to COVID-19 or COVID-like-illness (for Phase IIb/III type evaluation).
- Viral clearance and potentially reduction in viral load and/or impact on biomarkers of illness severity (for Phase IIa type evaluation), from baseline to ISA-specified days between day 1 and 14.

8.1.2 Secondary study parameters/endpoints include:
Key secondary outcome: early sustained recovery (recovery by day 14 sustained until day 28).
Other secondary endpoints might include:
- Sustained recovery (participants' reported recovery that was maintained until 28 days)
- Time to first self-report of feeling recovered from symptoms of COVID-19 or COVID-like-illness (for Phase IIa type evaluation).
- Viral clearance at ISA-specified days.
- Reduction in viral load from baseline to ISA-specified days.
- Time to first self-report of return to usual daily activity.
- Presence, duration, and severity of individual respiratory symptoms (runny/congested nose, sore throat, cough, fever shortness of breath, fatigue/tiredness, sweats/chills, headache, muscle, joint and/or body aches, loss of taste/smell, diarrhoea, nausea/vomiting, other) as: absent, mild, moderate, severe.

- Participant reported overall wellbeing, reported by rating of how well participant feels (scale 0-10).
- Overall safety of the IP by reporting (serious) adverse drug reactions.
- Tolerability of the IP, via reasons for stopping IP intake.
- The use of additional antiviral medication (yes/no, name of medication)
- The use of other prescribed and/or OTC medication for the respiratory infection (antibiotics, antiviral medication, ibuprofen, other pain/fever medication, inhaled medication, intranasal medication, other).
- Impact on usual daily activities (work/education and social life), as: no, slight, moderate, severe, not applicable.
- Complications (hospitalisation, death; all-cause, non-elective hospitalisation).
- Health care utilisation for COVID-19 or COVID-like-illness (GP and hospital visits).
- Long-term consequences of COVID-19 or COVID-like-illness (e.g. cough, shortness of breath and/or difficulty breathing, fast heart rate, fatigue, tiredness and/or loss of energy, sleep alterations, loss of smell and/or taste, emotional sensitivity, depression and/or anxiety, concentration problems and/or difficulty thinking, muscle aches and or generalised body pains, diarrhoea and/or stomach pain, other).
- The incidence of COVID-19 and COVID-like-illness in other members of the household (using participants diaries and/or swabbing the symptomatic household member(s)).

8.1.3 Exploratory parameters

- Emergence of mutations in causative pathogens in index cases.
- Experiences of researchers and network coordinators of setting up the trial in multiple countries, including views on optimising trial delivery, recruitment, and implementation (qualitative study).
- Healthcare professionals' views and experiences of taking part in the trial (in the context of a pandemic), the novel trial design, recruiting patients and views on the intervention(s) (qualitative study).
- Patient views and experiences of taking part in the trial and trial interventions, including how they conceptualise their illness and recovery (qualitative study).

8.1.4 Parameters to be recorded in the baseline CRF

Demographics

- Age (years)
- Sex at birth (male/female/not specified)
- Ethnicity
- Household (living with others (yes/no), how many people, living situation)
- Regular paid work (yes/no)

Relevant comorbidities and medication at baseline

- Relevant comorbidities ((e.g. cardiovascular disease, lung disease, asthma, diabetes, joint disease, neurological disease, severe mental illness, weakened immune system, other comorbidities) that started before inclusion in the trial

Vaccination history

- COVID-19, influenza, pneumococcal and RSV vaccination status

Signs and symptoms at presentation/inclusion

- Individual symptoms at presentation/inclusion (self-reported during remote inclusion)

- Overall illness severity (recruiting clinical assessor's impression)
- Days since onset of symptoms

BMI

- BMI known from records, otherwise:
  impression of the recruiting clinical assessor: underweight, normal weight, overweight, obese or self-reported (height and weight) during remote inclusion.

Lifestyle parameters

- Smoking (never, former, current, unknown)

Baseline vital signs

- Body temperature (°C) measured using available device (self-reported if central/remote inclusion, self-measured using TempaDOTs, or measured by recruiter)
- Peripheral oxygen saturation level as measured non-invasively by pulse oximetry, systolic/diastolic blood pressure, respiratory rate, heart rate (if inclusion is face-to-face)

Usual care

- Prescribed medication
- Advice given (if inclusion is face-to-face at GP)

8.2 Randomisation, blinding and treatment allocation

8.2.1 Randomisation

With each new IP entering the platform, the randomisation ratio will be adapted. For face-to-face recruitment, the day of randomisation will be the same day of inclusion (Day 0). For remote recruitment, the day of randomisation can be the day before Day 0 to allow next day delivery of the swab material and the IP for the participant to start the trial as defined Day 0. Treatment initiation will be within a defined number of days since onset of symptoms, and as close to randomisation as possible, using methods that may include directly dispensing IP to participants and taking the first dose during the recruitment visit, or couriering medications to participants who are recruited remotely and start IP intake one day after randomisation.

Participants will be allocated to either an IP arm, a comparator or -when appropriate- control arm. Each IP has a matching placebo or comparator IP. For specific IPs Usual Care can be a control arm (specified in ISA).
When there is more than one arm with matched placebos in the trial simultaneously, placebos will be pooled for the primary analysis. This means that allocation will be split equally between all active IP arms the participant is eligible for, and placebo. For example, if there are 2 IPs with matching placebo randomisation will be 1:1:1 (Active A):(Active B):(Placebo), and within Placebo allocation will be 1:1 (Placebo A):(Placebo B). Primary analysis for a particular IP will include all participants allocated to placebo who were eligible for the IP and randomised in the same time frame, i.e. concurrent and eligible placebo participants. Potential participants can be included if they are eligible to be randomised to at least one IP.

Participants will be randomised using a rapid, secure, web-based randomisation system using non-deterministic minimisation, with a random element. The minimisation factors will be age (<55/≥55 years), time since onset of symptoms to start of IP intake (≤x/>x days, as specified in the ISA), and country (Belgium/France/Germany/Ireland/Poland/Spain/UK/Georgia). The

randomisation sequence will be saved electronically in a working environment with restricted access.

Participants randomised to a treatment arm will be allocated to an IP pack number. This individual IP pack will be dispensed/delivered to participants once randomisation.

8.2.2 Implementation

Once deemed eligible, the recruiter, a medically qualified clinician or qualified delegate (e.g. research nurse or prescribing pharmacist) from the research site or the central clinical team will randomise the participant.

8.2.3 Blinding

This is a participant, investigator, and sponsor-blinded trial. Each IP has a comparator (placebo or comparator IP). Participants, investigators, and the Sponsor will remain blinded to the trial treatment (IP or comparator) throughout the trial, except for the person who is responsible for generating the randomisation sequence, and the person who needs to be unblinded in order to label the (comparator)IP/placebo. In case of a medical emergency that requires unblinding, the Site Investigator can unblind the participant in order to give optimal medical care.

8.3 Study procedures

*General procedures are listed in this section (see also **Table 1**). Potential additional procedures for specific IPs will be detailed in each ISA.*

8.3.1 Pre-screening, consenting, baseline visit, allocation, and IP supply

<u>Pre-screening (remote)</u>

Patients with symptoms suggestive of COVID-19 or COVID-like-illness can be pre-screened remotely via phone/video call for eligibility, and will be fully informed about the trial by the central trial team or participating site staff who are trained in the trial procedures.

<u>Informed consent (face-to-face or remote)</u>

Potentially eligible participants will be requested to give informed consent prior to start of eligibility assessment and trial procedures. In addition to taking consent face-to-face, consent may also be taken remotely, using online paperless forms (e-consent) and via telephone/video discussion. Participants will be able to download their electronic consent form after completion, or it can be provided to the participants by email/post. Electronic consent forms will be held securely on the trial database. For those recruited at the GP practice and opted in for paper consent form, a copy will be filed in patient's medical records and a copy will be printed and given to participants.

Prior to consent, written versions of the Participant Information Sheet (PIS) and Informed Consent Form (ICF) will be available to participants detailing no less than: the exact nature of the trial; and the known side-effects and risks involved in taking part. Electronic versions of the PIS may be sent to the patients through different approaches detailed in section 4.1 to consider participation before contacting the trial team. It will be clearly stated that the participant is free to withdraw from the trial at any time. Adequate time will be given to the participant to consider the information given to them and to ask any questions they may have about the trial before

deciding whether to participate. However, they must still be recruited and be able to start IP intake within the required number of days since the onset of their symptoms.

An optional consent question will be included on whether the participants would like to be contacted by the research team to be invited to an interview for the nested qualitative study (see section 3.5). Any potential participant approached to take part in the qualitative study will be provided with an additional PIS specific to their role (researcher, healthcare professional or patient). Verbal, written informed consent or e-consent will be taken prior to the start of an interview.

After consent, participants will be asked to provide baseline information, including their address and contact details, and the following procedures can be performed:

- Checking inclusion and exclusion criteria
- The following information will be collected in the baseline CRF:
    - Demographics
    - Lifestyle
    - Relevant comorbidities at presentation/inclusion
    - Vaccination history
    - Individual signs and symptoms at presentation/inclusion
    - BMI
    - Clinical assessments taken (if inclusion is face-to-face)
    - Usual Care provided
- Swab will be (self-)taken
- Participants will receive trial instructions
- Participants will be randomly allocated to IP/comparator, or control group
- If allocated to IP/comparator: product dispensing and instructions (in person at GP practice, or via post after remote recruitment)
- Diaries/questionnaires will be explained and in case of paper, handed over or posted to participants; in case of serious doubt about a participant's ability to complete the online diary, a paper diary should be recommended
- Collection of additional samples if the specific IP requires, and further specified in the ISA

Participant pack:
Participants will receive a participant pack, containing: the participant information sheet (PIS), the signed informed consent form (if requested a printed copy), swab kit(s), instructions for taking the combined throat-nose swab, and a paper diary (if applicable). If allocated to a trial arm with an IP, the participant will also receive an investigational product pack, a participant card, and instructions detailing how the IP should be administered and detailing precautions and possible adverse drug reactions or discomforts. Upon remote inclusion these materials are sent by post to the participant's home address.

Days of study product intake (if applicable):
IP intake, doses per day and for the number of days are indicated in the instructions. The duration of IP/comparator intake is dependent on the IP and will be described in the ISA.

8.3.2 Follow-up

For 28 days

- Daily diary (with questions asked on relevant days where appropriate):
  - Questions related to feeling recovered
  - Questions related to return to usual activity
  - Individual symptoms with severities
  - Serious adverse events
  - Adverse events; data collection period will be twice as long as the duration of IP intake, as specified in ISA, e.g. 1 week for IP administration of 3 days and 2 weeks for IP administration of 7 days
  - Participant reported overall wellbeing
  - IP intake
  - Other medication intake
  - Stopping IP intake and reason
  - Impact of symptoms on daily activities
  - New cases in households of participants
  - For women of childbearing potential: reporting of pregnancy on day 28
- Weekly diary:
  - Health care utilization
  - Complications
- Swab will be (self-)taken on ISA-specified days

Telephone call day at day 14 (+3) as end-of-treatment visit:

- Completion of diary
- Questions related to feeling recovered and return to usual daily activity
- IP intake
- Stopping IP intake and reason
- Health care utilization
- (Serious) adverse events

Telephone call day 28 (+7) to capture a minimal outcome dataset

- Questions related to feeling recovered and return to usual daily activity
- Health care utilization
- (Serious) adverse events
- For women of childbearing potential: reporting of pregnancy

If relevant: Follow-up 3 months

- Questions related to feeling recovered
- Questions related to return to usual activity
- Questions related to longer-term consequences of COVID-19 or COVID-like-illness
- Impact on daily activities
- Participant reported overall wellbeing
- Healthcare utilization

Unscheduled call:

In case a participant discontinues the trial due to the occurrence of a (S)AE, potentially related to the IP, the Site Investigator or delegate contacts the participant by telephone. In case of an SAE,

a SAE form will be completed.

Contact details will be collected from the participants at baseline, including mobile and/or home telephone numbers to enable the collection of follow-up data.

8.3.3 Sample collection for laboratory measurements

Virology sampling

For the analysis of aetiology, participants will have a combined pharyngeal/nasal swab taken at baseline. The swab will be placed in 1 ml universal transport media UTM. Samples can be transported using standard transfer systems to a local laboratory, ensuring adherence to country-specific requirements for transfer of samples and according to the ECRAID-Prime laboratory sampling and storage manual. Once at the local laboratory the samples will be stored at -70°C, before transportation to the central laboratory in Antwerp, Belgium. In case the local lab does not have immediate access to a -70°C freezer, samples can be stored at -20°C. In Antwerp, samples will be stored at -70°C.

The export of all samples to Belgium will be done in accordance with country-specific regulations. The participant's date of recruitment and participant ID number will be used as identifiers for the samples. Laboratory and trial 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 will not affect patient treatment and are only for research purposes. Analysis may be some time after swabs were taken. Each participant's swabs will be analysed to identify the causative pathogen, which will be done by a polymerase chain reaction (PCR)-based analysis with a multiplex test detecting COVID-19 or a COVID-like-illness. Upon identification of SARS-CoV-2, the sample will undergo next-gen sequencing (either short read Illumina based or long-read sequencing) to characterise the viral variants and identify variants of concern (VOCs), and also to identify viral mutations impacting the studied treatments. Following analysis, the remaining samples will be stored in a biobank being hosted by the Antwerp laboratory for Ecraid and for ECRAID-Prime. Samples will **only** be biobanked when specific consent was given for this procedure. Samples will be biobanked for further research into infectious diseases (as explained in the PIS).

Viral clearance, viral load and impact on biomarkers of illness severity

A semi-quantitative PCR will be applied to be able to conclude on lower test positivity. Viral clearance for a specific target (irrespective of SARS-CoV-2 or any other viral target) means that the PCR is negative on the day that Ct values are above a threshold of 35.

PCR currently most often used is known as real-time quantitative PCR (RT-qPCR). PCR-based detection technology is ultrasensitive, and the detection results can be obtained within 4–6 h and can detect the extremely low viral load of different microorganisms that are difficult to monitor routinely. However, the limitation of qPCR is that the quantification of results requires a standard curve analysis using the known standards of PCR amplicons, DNA fragments, genomic DNA, DNA constructs, cDNA, and nucleic acid from the samples. Variations in experiment conditions, data analysis and software used in the laboratories can result in unreliable results.

Digital polymerase chain reaction (dPCR) is a relatively new technique for the detection and quantification of DNA. In dPCR, a nucleic acid sample is partitioned into thousands of compartments or chambers with a volume as low as a few picolitres, each of which is examined separately after amplification. Similar to qPCR, dPCR technology also employes a Taq polymerase to amplify DNA fragments along with primer and probe complexes. Once the PCR

has been carried out simultaneously in all compartments, the number of positive and negative signals for each partition is counted by a fluorescence measurement. Without the need for calibration, the percentage of PCR-positive compartments is sufficient to estimate the concentration of the target sequence. With this technique, an absolute, accurate and reproducible quantification of DNA copy numbers can be performed because this quantification does not rely on the reference material [25].
The dPCR will be used if main secondary outcome is 'viral load'.

Potential outcomes, impact on biomarkers, for example illness severity or immunological response, will be specified in the ISA.

Viral mutations

Raw sequencing reads will undergo quality assessment using FastQC, followed by quality trimming with TrimGalore v. 0.6.7 (https://github.com/FelixKrueger/TrimGalore), and reference mapping against the SARS-CoV-2 genome (GenBank: NC_045512.2) using the CLC Genomics Workbench v.9.5.3 (Qiagen). Clade and lineage assignment will be performed for all SARS-CoV-2 consensus sequences using Nextclade v.2.2.0 (https://clades.nextstrain.org) and Pangolin v1.9 (4.0.6) (https://pangolin.cog-uk.io), respectively. SARS-CoV-2 genome sequencing will be considered successful if: i) the resulting genome sequence harbored < 15% ambiguous base calls (Ns) in the consensus sequence, and ii) was successfully classified by both Pangolin and NextClade. For detection of genetic variants, trimmed reads will be mapped against the SARS-CoV-2 genome (GenBank: NC_045512.2) using the CLC Genomics Workbench v.9.5.3 (Qiagen) with a length and a similarity fraction of 0.7 and 0.99, respectively.

Other sampling

Specific biological marker levels and immunological response are dependent on the IP, and will be specified in the ISA.

Table 1. Schedule of Assessments (example, specifics in ISA)

	Baseline and Start trial (remote recruitment only)		Baseline and Start trial (site/in person recruitment)	Follow-up			
	Day -1[1] Screening/Randomisation (remote)	Day 0[1] Screening/Randomisation (remote)	Day 0 Screening/Randomisation (face-to-face)	Days 1-28	Telephone call 14 (+3) days	Telephone call 28 (+7) days[5]	3 months
Informed consent	x		x				
Demographics	x		x				
Relevant comorbidities and medication	x		x				
Randomisation	x		x				
BMI, lifestyle parameters	x		x				
Baseline vital signs			x[2]				
Vaccination history	x		x				
Usual Care			x				
Virology sampling (swab)		x[3]	x[3]	x[3]			
Dispensing/sending study product	x		x				
Return to usual activity and recovered				Daily	x	x	x
Symptoms with severities		x	x	Daily			
Participant reported overall wellbeing		x	x	Daily			x
Impact on daily activities				Daily	x	x	x
Household transmission				Daily			
IP intake		x[4]	x[4]	Daily[4]	x	x	
Health care utilization				Weekly	x	x	
Blood sample				If required, see ISA			
Long-term infection consequences							x
Interview for qualitative study (if invited)				Approximately two weeks after the initial consultation			
(S)AEs, if required see ISA		x	x	Daily	x	x	
Pregnancy reporting				At day 28		x	

[1] For remote recruitment, screening/randomisation can be the day before Day 0 to allow next day delivery of IP
[2] If inclusion is face-to-face
[3] Virology sample will be (self-)taken prior to starting IP on Day 0; additional swabs will be specified in the ISA
[4] The duration of study product intake is dependent on the IP requirements and will start on Day 0
[5] In case diary is incomplete to capture a minimal outcome set

8.4 Withdrawal of individual participants

Participants are free to withdraw from the study at any time for any reason if they wish to do so without any consequences to their health care.

A Site Investigator or a central trial team clinician can decide to withdraw a participant from the trial at any time if the Site investigator or the central trial team clinician considers it necessary for any reason including:
- Ineligibility (either arising during the trial or retrospectively)
- If participation in the study will be perceived as a major burden for the patient

The reason for withdrawal will be recorded in the CRF. Whenever feasible, the following information should be documented on the End of Study form:
- Date of last contact
- Date of last intake study product
- Date of early termination
- Primary reason for early termination

Data up to the time of withdrawal will be included in the analyses.
For participants who withdraw from the study due to the occurrence of an SAE, appropriate follow-up will take place (if agreed by participant) until the SAE has abated, or until a stable situation has been reached, with findings being recorded in the SAE form. Medical care of the discontinued participant is to be arranged by and at discretion of the Site Investigator or delegate, if necessary. In case of recruitment by the central trial team, the central trial team clinician may advise the participant on the appropriate clinical care based on their clinical judgement, including visiting their own GP.

Participants without the primary endpoint reported can be replaced.
A participant will be considered "lost to follow-up" if the participant is no longer available, or cannot be contacted for follow-up data collection, and it is reasonably expected that the primary endpoint information cannot be obtained from the participant. For follow-up assessments via phone, email, or mail (on D14, D28 and Month 3), the maximum number of attempts allowed in a county will be respected. Participants who cannot be contacted around D14 and D28 are not automatically lost to follow-up as they still might provide primary endpoint information at Month 3.

8.5 Replacement of individual participants after withdrawal

Additional participants will be included to compensate for participants that withdraw (equal number); withdrawals due to adverse drug reactions or adverse events based on study procedures will not be replaced.

8.6 Discontinuation treatment of individual participants

A Site Investigator or a central trial team clinician can decide to discontinue a participant from treatment at any time for safety reasons if the Site investigator or the central trial team clinician considers further treatment is a health risk for the participant, at the supervising clinician’s discretion. IP/comparator specific guidance for discontinuation of treatment will be specified in the ISA.

Cessation of study IP/comparator is not considered withdrawal from the trial (see section 8.4 for description for participants who withdraw their consent).

For participants who discontinue treatment due to the occurrence of an SAE, appropriate follow-up will take place until the SAE has abated, or until a stable situation has been reached, with findings being recorded in the SAE form. Medical care of the participant is to be arranged by the Site Investigator or delegate, if necessary. In case of recruitment by the central trial team, the central trial team clinician may advise the participant on the appropriate clinical care based on their clinical judgement, including advising them to visit their GP.

8.7 Premature termination of the study or arm

The Sponsor has the right to terminate the trial or a specific arm prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer feasible. Premature termination of ECRAID-Prime may occur because of a Regulatory Authority decision or a change of the opinion of the Independent Ethics Committee (IEC). If such action is taken, the reasons for terminating the trial must be documented in detail and the Sponsor must inform the MHRA, the REC and other IECs and the Competent Authorities (CA) within 15 days or according to local regulations. All trial participants still in the treatment period at the time of termination shall undergo a final examination which must be documented. The Sponsor must be informed without delay if any Site Investigator or the central trial team clinician has ethical concerns about continuation of the trial. Premature termination of a specific IP/comparator will be considered if:

- The risk-benefit balance for the participant changes markedly
- It is no longer ethical to continue treatment with the IP/comparator
- The Sponsor considers that the trial must be discontinued for safety reasons (e.g. on the advice of the Data Safety Monitoring Board (DSMB))
- An interim analysis or results of other research show that one of the IPs is superior or inferior to another
- It is no longer feasible to complete the trial (e.g. it is unlikely that sufficient participants can be recruited in the trial within the agreed time frame etc.)

The Sponsor decides on whether to discontinue the specific IP/comparator in consultation with the trial statistician, as applicable. As directed by the Sponsor, all trial materials must be collected and all CRFs completed to the greatest extent possible. All essential documents necessary for the Trial Master File as defined in GCP will be filed.

9. SAFETY REPORTING

(S)AEs will be collected from participant's daily diaries, calls to participants, face-to-face visits, and medical records, and can be reported spontaneously by the participant, by the GP or the central clinical team (e.g. clinician or research nurse).

ECRAID-Prime will implement a risk-assessed and proportionate approach to safety monitoring. In line with the summary of product characteristic (SmPC) or IB, we will assess the risks and the safety profile for each IP/comparator, and detail the mitigation and monitoring

procedures in the ISA. All safety procedures will be according to Sponsor's Standard Operating Procedure (SOP).

9.1 Temporary halt for reasons of participant safety

The Sponsor will suspend the trial if there is sufficient ground that continuation of the trial will jeopardise participants' health or safety. The Sponsor will submit the notification as a substantial amendment to the MHRA and REC within 15 days of the date of the temporary halt. It shall clearly explain what has been stopped and the reasons for such action and specify follow-up measures. The study will be suspended pending a further positive decision by the MHRA and REC. The central trial team and investigators will take care that all participants are kept informed. To restart the trial, a subsequent request as a substantial amendment will be submitted providing the evidence that it is safe to restart the trial.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

The AE data collection duration period will be based on duration of IP intake as specified in ISA. The period of AE data collection will be twice as long as the duration of IP intake; e.g. 1 week for IP administration of 3 days and 2 weeks for IP administration of 7 days. AEs are defined as any undesirable experience, unrelated to the respiratory infection, occurring to a participant during the study, whether or not considered related to the IP. For each IP/comparator, all AEs reported by participants in a daily diary or during the end-of-treatment telephone call assessment at day 14 (+3 days) will be recorded. AEs will be assessed by a registered/delegated/central trial team clinician for causality and severity (definitions below).

The participant will be asked to rate the severity of symptoms related to the respiratory infection, which can also be adverse drug reactions (for example headache), in their daily diary. The severity of individual events and symptoms will be assessed over time by participants on the following scale: absent, mild, moderate, severe.
Respiratory symptoms and adverse drug reactions may overlap and can be difficult to disentangle. Trends in the prevalence in the severity of symptoms between control, IP and comparator arms will be compared, for evidence of increased severity of measured symptoms in those randomised to receive IPs.

Participants will be free to withdraw from taking the IP/comparator if they perceive an intolerable AE, unrelated to the respiratory infection. Participants will be provided with a participant card with a telephone number of the coordinating team, enabling them to report issues that are experienced whilst taking the drug. This card will also alert hospital clinicians about trial participation, should a participant be admitted to hospital. In the event of a medical emergency, participants will be instructed to show this card to the clinician they see. Based on clinical judgement, the medical monitor/study team may contact the participant to advise the participant on the appropriate clinical care.

9.2.2 Adverse drug reactions (ADRs)

All adverse events judged by either the investigator/delegate or the Sponsor as having a reasonable suspected causal relationship to the IP/comparator qualify as adverse drug

reactions (ADR). An unexpected ADR is an ADR of which the nature or severity, outcome or frequency is not consistent with the applicable reference safety information for the IP.

9.2.3 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- results in death
- is life threatening (at the time of the event)
- requires hospitalisation or prolongation of existing inpatients' hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the Site Investigator.

An elective hospital admission will not be considered as an SAE.

The Site Investigator, the central trial team clinician or delegate will report all SAEs to the Sponsor without undue delay after obtaining knowledge of the events. If they become aware of an SAE with a suspected causal relationship to the (comparator)IP that occurs after participants' study termination but within the period of the IP-specific evaluation (as specified in the ISA), the investigator shall, without undue delay report to the Sponsor. Hospitalisation will be defined as at least one overnight stay. Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute an SAE.
SAEs must be reported to the Sponsor by the person or nominated delegate who has discovered the SAE within 24 hours of becoming aware of the event. Some SAEs occurring within the 28-day follow-up period, may be identified retrospectively from diaries which will be received after 28 days. These will be reported within 24 hours of becoming aware of the event. The Sponsor or delegate will ensure SAEs being reviewed by the medical monitor for relatedness and expectedness as soon as possible, taking into account the reporting time for a potential suspected unexpected serious adverse reaction (SUSAR).

Procedure for immediate reporting of Serious Adverse Events

- The GP or central trial team will report all SAEs via the SAE form in the online data capture system 'Castor'. The study team at the Sponsor and the medical monitor will receive a notification about the SAE. GP and central trial team will provide additional, missing or follow-up information in a timely fashion.
- If necessary, the participant may be contacted by GP practice or central trial team to provide additional, missing or follow-up information as required.

A medical monitor will review the SAE once reported, collect information and report to the Sponsor within the SOP's timeframe. The Sponsor will submit an Annual Safety Report (ASR) including a list table of SAEs to all IECs and CAs of the participating countries (to all Member States concerned) through the CTIS once a year.

Expectedness

For SAEs that require reporting, expectedness of SAEs will be assessed and determined by the medical monitor, according to the relevant Reference Safety Information (RSI) section of

the SmPC/IB. The RSI will be the current Sponsor and IEC/CTA approved version at the time of the event occurrence.

Assessment of Causality

The Site Investigator or delegate will report a first assessment of causality. For participants recruited centrally, an investigator, independent of the Sponsor, will make the first assessment of causality. The relationship of each SAE to the IP/comparator must be determined by a medically qualified individual according to the following definitions:

- **Unrelated** – where an event is not considered to be related to the IP
- **Possibly** – although a relationship to the IP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible
- **Probably** – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IP
- **Definitely** – the known effects of the IP, its therapeutic class or based on challenge testing suggest that the IP is the most likely cause

AEs/SAEs judged possibly, probably or definitely related will be considered as related to the IP.

9.2.4 Pregnancy notification

The GP or the central clinical team has to notify to the Sponsor, immediately and no later than 48 hours after being made aware of a pregnancy, initiated during study participation, despite taken measures and precautions. Participants will be asked at Day 28, via their diary, whether they (WOCBP) have become pregnant. In situations where WOCBP have become pregnant within 28 days of study participation whilst being randomised to a (comparator)IP, unblinding will take place. If unblinding reveals that the participant did receive the IP with an unknown or unfavourable safety profile when used during pregnancy (as also outlined in the ISA), the participant will be asked to sign and date an informed consent form for following up the pregnancy until birth. The initial pregnancy report should be reported in a detailed, written report, using the "Pregnancy Initial Notification Form" (in ISF) and should specify estimated date of delivery, obstetrician contact and name of maternity hospital, only for (comparator)IP with unknown or unfavorable safety profile when used during pregnancy.

The investigator or the central clinical team has to follow-up the participant until the end of the pregnancy or its interruption and to notify the outcome to the Sponsor using the “Pregnancy Follow-Up Form” (in ISF).

Warning:

If the pregnancy outcome fulfilled a seriousness criterion (e.g.: anomaly or birth defect, fetal death, voluntary or therapeutic interruption of pregnancy, miscarriage needed a hospitalisation), the GP or the central clinical team has to notify it to the Sponsor as an SAE.

All pregnancies should be recorded in in the Pregnancy form located in the Investigator Site File and sent to the Safety Department of CTCC.

9.2.5 Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. The event must be serious (see chapter 9.2.2)
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the IP under investigation, regardless of the administered dose

3. The event must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
    - SmPC for an authorised medicinal product
    - IB for an unauthorised medicinal product

All SUSARs will be reported by the Sponsor or delegate to the relevant CAs and/or IECs as per national regulations.

The period for the reporting of SUSARs by the Sponsor, taking into account the seriousness of the reaction, will be as follows:

- In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than **7 days** after the Sponsor became aware of the reaction
- In the case of non-fatal or non-life-threatening SUSARs, not later than **15 days** after the Sponsor became aware of the reaction
- In the case of a SUSARs which was initially considered to be non-fatal or non-life-threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than **7 days** after the Sponsor became aware of the reaction being fatal or life-threatening

Where necessary to ensure timely reporting, the Sponsor may submit an initial incomplete report followed up by a complete report.

9.3 Unblinding procedures for safety reporting

The Site Investigator (GP) or the central clinician will only unblind the treatment allocation of a participant during the trial if unblinding is relevant to the safety of the participant and if knowledge of the treatment allocation could influence the immediate medical management of a participant, or in case a participant randomised to a IP/comparator reports a pregnancy within 28 days of study participation. Emergency unblinding will be performed by the Site Investigator or the central clinician by either 1) opening the emergency unblinding envelope for that participant stored at the site; or 2) digitally using the randomisation tool; or 3) using a central phone number. Sites and central trial team members will be trained on which method for emergency unblinding to follow.

When reporting a SUSAR, the Sponsor will only unblind the treatment allocation of the affected participant to whom the SUSAR relates.

Unblinded information will be accessible only to persons who need to be involved in the safety reporting to the CAs, to the DSMB, or to persons performing ongoing safety evaluations during the trial.

9.4 Annual safety report

In addition to SUSAR reporting, the Sponsor will submit the Development Safety Update Report (DSUR) to the Medicines and Healthcare products Regulatory Agency (MHRA) annually. The DSUR will include information on all IPs assessed in the trial.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported SAEs, ordered by organ system, per arm.
- a report concerning the safety of the participants, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the IP under investigation.

9.5 Follow-up of SAEs

All SAEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the GP or a medical specialist.
All SAEs that have not resolved by the end of the study, those that are identified retrospectively, or that have not resolved upon trial discontinuation of the participant, must be followed until any of the following occurs:

- The event resolves
- The event stabilises
- The event returns to “baseline”, if a “baseline” value/status is available
- The event can be attributed to agents other than the study intervention, or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or GP refusal to provide additional information, or lost to follow-up (defined at 8.4).
- In case of a pregnancy reported within 28 days in a participant randomised to IP with an unknown or unfavourable safety profile when used during pregnancy (as also outlined in the ISA), the pregnancy will be followed until the end of pregnancy if the participant is willing to sign the Pregnancy ICF.

9.6 Urgent safety measures and other relevant safety reporting

Where an unexpected event is likely to seriously affect the benefit-risk balance, the Sponsor and the Site Investigator(s) or the central trial team clinician will take appropriate urgent safety measures to protect the participants. In addition, the Sponsor will notify the MHRA, the REC and relevant Competent Authorities of the participating countries of the event and the measures taken. That notification will be made without undue delay but no later than **7 days** from the date the measures have been taken.
In case of data security breaches, the breach will be reported to the appropriate authority (e.g. Authoriteit Persoonsgegevens) as soon as possible, but at least within 72 hours after discovering the breach. If necessary, those affected by the breach will be informed. It will be agreed upon with participating NCTs and sites in the MSA/CTA that NCTs or sites will report data breaches concerning participant data to the Sponsor and inform applicable regulatory authorities.

9.7 Data Safety Monitoring Board

Given the adaptive nature of ECRAID-Prime, a DSMB will be set up that will review new ISAs and safety data. The DSMB is an independent committee; the chair will be selected based on clinical trial methodology, and experience with adaptive clinical trial design. Additional medical, statistical, and other experts will be selected to ensure all necessary expertise. Members have no conflict of interest with the Sponsor of the study and IPs tested in the study.

The charter document describes the roles and responsibilities of the DSMB, including the timing of meetings, methods of providing information to and from the DSMB, frequency and format of meetings, statistical issues, and relationships with other committees. The DSMB will be unblinded to ensure the highest quality oversight of the trial, in accordance with current recommendations of regulatory authorities.

Possible recommendations of the DSMB could include:

- No action needed, trial continues as planned
- Early stopping due to, for example, clear benefit, futility, harm of an IP, or external evidence
- Stopping recruitment within a specific subgroup
- Extending recruitment (based on actual control arm outcomes being different to predicted rather than on emerging differences) or extending follow-up
- Stopping a single arm of a multi-arm trial
- Sanctioning and/or proposing protocol changes

The advice(s) of the DSMB will only be sent to the Sponsor of the study. Should the Sponsor decide not to fully implement the advice of the DSMB, the Sponsor will send the advice to the reviewing IECs, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

10. STATISTICAL ANALYSIS

Full details of the statistical analysis will be described in the Master Statistical Analysis Plan (M-SAP). An appendix to the M-SAP titled “Simulation Report” provides simulation results that justify the sample size and design of the study. In addition, the M-SAP will be accompanied by arm-specific appendices to describe any planned deviations from the M-SAP. A broad overview of the design and primary analysis is provided below.

ECRAID-Prime is an adaptive platform trial with early stopping rules for futility or superiority. Comparisons will be based on concurrent and eligible control, the comparator or usual care. If there are 2 matched placebos with concurrent randomisation, the primary analysis will pool controls unless it is decided otherwise and specified in the ISA. We may carry out sensitivity analyses with placebos only included. Early stopping rules will be based on posterior probabilities with thresholds defined using simulations to ensure good trial performance with respect to power and type 1 error.

Each treatment will be analysed separately.

Baseline characteristics will be summarised by arm. Continuous variables will be presented as means and standard deviations (or medians and inter-quartile ranges for skewed data). Categorical and binary data will be presented as frequencies and percentages. AEs and SAEs will be summarised by treatment arm.

10.1 Primary study estimand and parameter(s)

10.1.1 Definition of the primary estimand

Participants aged ≥18 years with at least 2 symptoms suggestive of COVID-19 or COVID-like-illness (one respiratory and one systemic) and meeting the IP eligibility criteria, what is the between group difference, estimated by a hazards ratio, in time to first self-report of feeling recovered (TTR) after treatment with an IP compared with placebo or comparator, regardless of treatment discontinuation for any reason or feeling better before starting the medication, and in conjunction with concomitant medication (including anti-viral medication) as necessary. Participants who die within 28 days from randomisation will be censored at 28 days. TTR is measured by response to the daily diary question "do you feel recovered today from your respiratory infection?", and censored at 28 days after randomisation.

Attributes of estimand:

Population – people in the community aged ≥18 years with at least 2 symptoms suggestive of COVID-19 or COVID-like-illness (one respiratory and one systemic) and meeting the IP eligibility criteria.

Treatment conditions – IP compared to their comparator (placebo or comparator IP), regardless of treatment discontinuation for any reason or feeling better before starting the medication, and in conjunction with concomitant medication (including anti-viral medication) as necessary. Participants who die will be given a worst-case value and censored at 28 days.

Outcome variable – time to first self-report of feeling recovered, as measured by response to the daily diary question "do you feel recovered today from your respiratory infection?", censored at 28 days after randomisation.

Handling of intercurrent events – treatment policy strategy applied to study treatment discontinuation, feeling better before starting the medication and use of concomitant medication (including anti-viral medication). Composite strategy applied to death within 28 days of randomisation.

Population level summary measure – hazard ratio.

10.1.2 Estimator

Analysis will include all eligible randomised participants with at least one follow-up time point (any diary data or information from the 28-day follow-up call) in the group to which they were randomised, regardless of subsequent treatment received. A Bayesian piecewise exponential model with weakly informative priors will be used to estimate the hazard ratio for the time to first self-report of feeling recovered within 28 days of randomisation, adjusting for stratification variables and using all observed data (including data observed after treatment discontinuation and irrespective of use of concomitant medication or feeling better before starting the medication, except for participants who die within 28 days of randomisation who will be censored at day 28.

The endpoint 'time to recovery', is defined by the first instance that a participant reports this. The primary analysis will be a Bayesian piecewise exponential model with weakly informative priors (specified in the M-SAP), with endpoints regressed on treatment and stratification covariates. Let θ_j denote the log hazards ratio comparing the hazards of recovery for participants in treatment group *j* versus participants in the comparator arm. We will test the hypothesis that:

H_0: $\theta_j \leq 0$

H_1: $\theta_j > 0$

If the Bayesian posterior probability of superiority (a log hazards ratio greater than 0 corresponding to quicker return/recovery) for a treatment versus control is sufficiently large (e.g. >= 0.99), the null hypothesis will be rejected and the intervention will be deemed superior to control. The exact threshold of the superiority decision criterion will be determined a priori via simulation to control the one-sided type 1 error of the study at approximately 0.025, and will be specified in the M-SAP.

We will carry out sensitivity analyses to explore the robustness of inferences from the main estimator to deviations from its underlying modelling assumptions and limitations in the data. This may include fitting an adjusted Cox proportional hazards model. A supplementary analysis using an unadjusted log-rank test may also be performed. All sensitivity and supplementary analyses will be specified in the M-SAP.

The pattern of missingness will be reported, for instance if there is a difference by group in the proportion of participants lost to follow-up, with no post-baseline data, and withdrawals. We will also check for a pattern of missingness related to intercurrent events. If the pattern of missingness differs between groups, relevant imputation methods will be used to take account of this and an additional sensitivity analysis carried out using imputation.

If an IP is evaluated in a phase IIa-type evaluation, the first interim analysis will use viral clearance and possibly impact on biomarkers as the primary outcome, and will only progress to the next stage of the trial if the IP is looking promising enough. Precise definitions and rules will be specified in the M-SAP.

10.2 Secondary study parameter(s)

Details of secondary analyses will be given in the M-SAP.

10.3 Exploratory parameters

Qualitative data collection and analysis will be done concurrently. Interview data from the three stakeholder groups (researchers, healthcare professionals 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.

10.4 Interim analysis (if applicable)

The pre-specified design allows adaptations to the trial based on the observed primary endpoint data. These adaptations include the declaration of success or futility of an intervention at an interim analysis and the dropping of treatment arms based on pre-specified decision criteria. The adaptive algorithm will be documented in the M-SAP, including pre-specified criteria for decisions regarding futility or effectiveness of interventions and/or replacing interventions in the trial. The Simulation Report in the M-SAP will contain extensive simulations to explore the performance of the adaptive design, including power and type 1 error.

The timing of the first interim analysis and frequency of subsequent interim analyses will be pre-specified in in the M-SAP and DSMB charter and will be based on both simulations and logistical considerations.

10.5 Subgroup analysis

We will look at the effect of aetiology on treatment effect by fitting the primary outcome model with an interaction term between aetiology and treatment, where aetiology is split for the most prevalent circulating viruses (2 or 3, and rest) at the time of inclusion.
Additionally, subgroup analyses will be performed by age, comorbidity status and vaccination status.

10.6 Definition of population for analysis

For each intervention, the primary analysis population is defined as participants who were randomised to that intervention or the usual care arm and eligible for randomisation to that intervention, during the same time frame when the intervention was actively randomising (i.e. Concurrent Randomised and Eligible Analysis Population) and have at least one post-baseline measurement.

Primary Analysis Set:
For each IP, all participants randomised to either the IP, its comparator or usual care. Participants later found to be ineligible (randomised in error) will be excluded. Non-concurrent comparators will not be included.
Safety Analysis Set:
All participants who took at least one dose of IP.
Symptomatic Analysis Set:
Primary Analysis Set restricted to those participants who report having the symptom at baseline.
Symptom Free Analysis Set:
Primary Analysis Set restricted to those participants who report not having the symptom at baseline.
Virology Analysis Set:
To be defined.

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Declaration of Helsinki

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

11.2 Guidelines for Good Clinical Practice

The Investigators will ensure that this trial is conducted in accordance with relevant regulations and Good Clinical Practice.

11.3 Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheets and any proposed informing material will be submitted to an appropriate REC, HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval. For the UK, the PI and the central trial team at the PC-CTU will ensure and confirm

correct regulatory approvals are gained prior to recruitment. The central trial team at the PC-CTU will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents and the addition of new interventions.

11.4 Benefits and risks assessment, group relatedness

Participation in this trial poses a minimal risk of inconvenience through swab taking, follow-up (calls) and potential side-effects of the IP.

Discomfort of respiratory swabs
(Self-)collecting combined pharyngeal/nasal swabs may cause transient discomfort. Discomfort and risk will be minimized by using experienced clinical staff and proper guidance for self-swabbing. Since the pandemic, self-swabbing has become a routine procedure for most in the community.
Custody of data and samples is specified in section 12.

Blood sampling
Blood sampling will only be performed when required for a specific IP. If blood sampling will be required for an IP, then the procedures and risks will be specified in the ISA.

Adverse drug reactions of the IP
Potential adverse drug reactions and risks of the IP will be specified per IP in the ISA and PIS.

Overall benefit for participants in the intervention group are related to the expected treatment effects of the IP on their respiratory infection.

11.5 Compensation for injury

The participants taking part in the trial will be covered by the insurance taken out by the Sponsor for this study in accordance with national regulatory requirements. This insurance covers damage to research participants through injury or death caused by study participation.

The Sponsor certifies that it has taken out a liability insurance policy in accordance with national regulatory requirements. The liability insurance of the recruiting physician/ GP practice and their team is arranged according to their national requirements regarding liability insurance.

11.6 Expenses and benefits

Reimbursement of travel and parking costs to the participant will be considered if allowed by local regulations and deemed appropriate by central trial team. A voucher as a token of recognition of giving their time and contribution to the trial will be offered to the participants who participated in the trial and to any individuals who participated in an interview.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

eCRF

All data required by the protocol will be recorded in a secured electronic case report form (eCRF) specifically designed for this study. This data capturing software, Castor, meets all requirements according to ICH-GCP standards, applicable data protection laws and complies with provisions set forth by the General Data Protection Regulation (EU) 2016/679. The eCRF will be web-based and accessible by investigator site staff, national coordinating teams, Sponsor study team members and monitors and will be specific password protected. Persons will not be given access to the eCRF system until they have been trained on the eCRF, and will be granted access only to those participants and/or sections of the eCRF relevant to their task.

An eCRF will be completed for each study participant. All data generated during the study will be reported in the eCRF by the Investigator, the national coordinating team, or designated person. The Site Investigator or central team will ensure that all data are entered promptly, legibly, completely, accurately and conform to participants reports or source documents, in accordance with specific instructions accompanying the eCRF. Data not requiring a separate written record can be recorded directly in the eCRF. All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. Should a correction be necessary, the corrected information will be recorded in the eCRF by the authorized person. All (corrected) data will be tracked through an audit trail. The Site Investigator will oversee and coordinate data collection and protection. The Site Investigator must certify that the data entered are complete and accurate by signing off the data in the eCRF at completion of the trial, or completion of a specific intervention.

Source documents

Source data are all the information in original records and certified copies of original records of clinical findings, observations, or other activities in the study, which are necessary for the reconstruction and evaluation of the study. Source documents are printed or electronic documents containing source data. Sponsor provides an Investigator Site File to store study documents. Source documents include but are not limited to: ICFs; laboratory results; lists of adverse events; lists of concomitant medication; documentation of existing conditions. All source documents will be kept in a locked facility at the Study Site or at the PC-CTU.

YourResearch

In ECRAID-Prime, participants can be recruited centrally by the central trial team and in/via GP practices or primary health care service (e.g. pharmacy) whereas in the latter case the follow-up of participants can be performed by central trial team members. Therefore, contact details of participants (name, phone number and email address) need to be shared between GP practices and the central trial team. In order to do this in a GDPR compliant way, the Your Research system (YR) will be used. YR is a cloud-based, secure, GDPR compliant, ISO 27001 certified system. 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 the YR system. Two factor authentication is compulsory for all users.

GPs and the central trial team will enter contact details in YR during, or after the inclusion of a participant. GPs will only have access to participants of their own GP practice, whereas the central trial team member(s) will have access to contact details of participants of all participating GP practices. Data entered in YR will never be exported or linked to collected clinical data in the CASTOR EDC system. After the end of the trial, data will be deleted from the YR database. System administrators will not have access to any contact details of participants.

Data confidentiality

The study will comply with UK General Data Protection Regulation (UK GDPR) and Data Protection Act 2018. All source documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed ICF, the participant will be referred to by a unique trial-specific number in any database, not by name. The unique trial-specific number will not contain any identifiers that allow to identify the participant. Information linking the participant to trial-related and database materials will be maintained in a secure location at the Study Site. The key to code and recode participant identifiers will only be accessible to Study Site staff and national coordinating team (covered in ICF). Coded (pseudonymised) participant data and records will be held in strictest confidence by the Site Investigator, their healthcare staff, and by all central research staff, as permitted by law.

Besides the monitor, members of IECs/Review Boards, the Sponsor's clinical quality assurance group or any other Sponsor's representative may carry out source data checks and/or on-site audits or inspections. In compliance with GCP, direct access to source data will be required for these monitoring, audit and inspection visits. The Site Investigator will assure the monitor, Health authorities and the Sponsor or its representative of all necessary support at all times, providing direct access to source data and documents, according to all regulation. The confidentiality of the verified data, the identity and personal medical information of the participants should be respected during these monitoring visits, audits and inspections, being understood that monitors/auditors/inspectors are bound by professional secrecy.
The Sponsor will make sure that each participant gave a written consent about the collection of its private data, being strictly required for study quality control.

Retention of records and archiving

All data, collected in the eCRF, source documents and all other essential documents will be saved securely for at least 25 years. The Sponsor will be responsible for the retention of data in the eCRF. The Sponsor will setup a local data warehouse (DWH) that will be populated with collected data from the Castor eCRF. All data residing in the DWH will be directly accessible for reporting purposes. Data required for further analysis can directly be exported from the Castor database or can be exported from the DWH. The DWH resides within the UMCU. Role based authorization prevents unauthorized data access.
At the end of the study and after the database has been locked, all essential documents and study data will be archived for 25 years in accordance with the CTR and UMCU Archiving Standard Operating Procedures. The Study Site and central team will be responsible for the storage of source documents for 25 years according to article 58 of the EU Clinical Trial Regulation 536/2014.

Further details on handling and storage of data and will be provided in the Data Management Plans (DMP), the Data Protection Impact Assessment (DPIA) and the File Management Plan (FMP).

12.2 Monitoring and Quality Assurance

The trial will be conducted in accordance with the most recently approved protocol, the approved ISAs, Good Clinical Practice, relevant regulations and SOPs. The objective of the monitoring procedures is to ensure that the trial participant's safety and rights are respected, that accurate, valid and complete data is collected, and that the trial is conducted in accordance with the trial protocol and the ISAs.

To ensure the accuracy and reliability of trial results qualified Site Investigators, Study Sites and Central Trial Team will be participating. Appropriate guidance, review and training of trial procedures with the Site Investigators, site personnel and central trial team members will be offered by the Sponsor and the national coordinating team.
A teleconference or network initiation visit will be conducted before activation of the national network. The national team will cascade training down to their Study Sites. All trial activities mentioned in the protocol such as, IP handling, sampling, processing, responsibilities and data capture requirements with the Site Investigator and site staff will be reviewed during execution of the trial.

During the trial, the national networks and Study Sites will be regularly monitored to ensure the quality and completeness of the data and samples collected. The monitor regularly visits the NCT and/or Study Sites to assure that the Site Investigator will receive appropriate support in his/her activities. The Site Investigator will secure access for the monitor to all necessary documentation for trial-related monitoring. Visits will be performed as frequent as necessary depending on the recruitment frequency and on the risk assessment of each IP. A monitoring plan will define the monitoring frequency and procedures, where IP specific items might be added if deemed necessary.

The on-site visits will for example consist of checking consent procedures, access/storage of participant identifiers, trial supply and sample storage/handling, IP access/ storage/accountability and handling, data entry, source document verification, etc. Remote and/or centralized monitoring will for instance consist of automatic validation checks for data discrepancies in the eCRF, electronic rules in the eCRF to check for missing data, data queries, identifying unusual data patterns and following up on recruitment rates.

Any discrepancies will be resolved with the NCT, Site Investigator or designee, as appropriate.

Intervention-specific monitoring items issues are addressed in each ISA. In addition, further details of monitoring procedures are described in a separate monitoring plan.

12.3 Reporting

The Sponsor shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisations and funder (where

required). In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC and host organisations.

12.4 Temporary halt and (prematurely) end of study report

ECRAID-Prime is designed as a platform trial, allowing for continued research in participants with COVID-19 or COVID-like-illness in primary care. The platform allows for the trial to be perpetual.
It is anticipated that after inclusion of the initially planned sample size, the trial could continue to include additional participants and test additional interventions until one of the following occurs:

- The effectiveness and/or cost-effectiveness of all interventions are known and there are no new plausible interventions to test
- All the interventions have been tested

Should the trial be stopped, the end of trial is the date of the last scheduled follow-up for any participant. The Sponsor will notify the MHRA and the REC of the end of the trial within a period of 90 days.

Within one year after ending a specific intervention, the Sponsor will submit an intervention-specific trial final report with the results of that IP, including any publications regarding that IP, to the MHRA and the REC.

In accordance with article 38 of the CTR, the Sponsor will suspend the trial, or specific trial arms if there is sufficient ground that continuation of the trial will jeopardise participant health or safety. The temporary halt or early termination of a clinical trial (arm) for reasons of a change of the benefit-risk balance will be notified to the MHRA and the REC within 15 days of the date of the temporary halt or early termination. The notification will be made as a substantial amendment, clearly explaining what has been stopped and the reasons for such action and specify follow-up measures. To restart following a temporary halt, a subsequent request as a substantial amendment will be submitted providing the evidence that it is safe to restart.

12.5 Public disclosure and publication policy

The trial will be registered on a publicly accessible database such as clinicaltrials.gov, ISRCTN registry and European drug regulatory affairs Clinical Trials (EudraCT). Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial. Results will be uploaded to the register within 12 months of the end of trial date as given on the End of Trial Declaration.

Trial results will be disseminated in compliance with Ecraid's 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-Prime trial management board and Network PIs. All parties are committed to review within a period of 2 weeks and shall not unduly delay the submission of the trial results. Proposed publications shall not include either the Sponsor confidential information other than the trial results or personal data on any participants, such as name or initials.

Results will also be published in the European database: https://euclinicaltrials.eu, when the summaries become available. In addition, lay terms summary of trial results will be published on the Ecraid website.

13. STRUCTURED RISK ANALYSIS

All elements of this chapter, potential issues of concern and/or synthesis will be described in the ISA.

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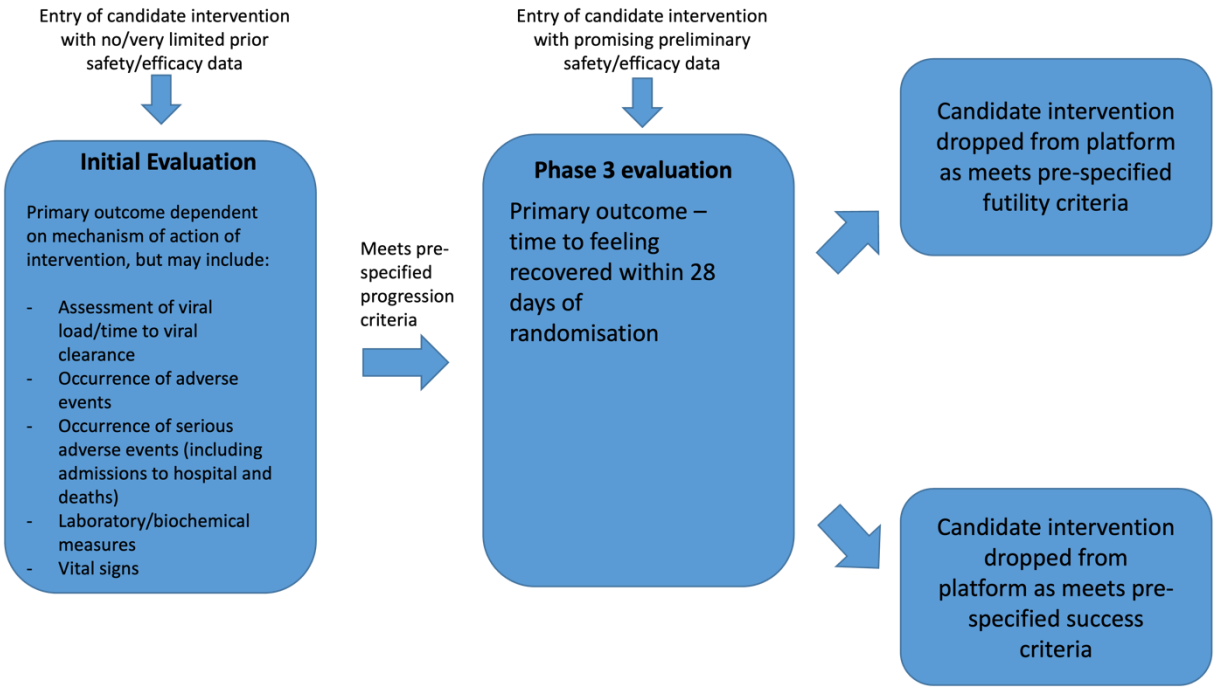
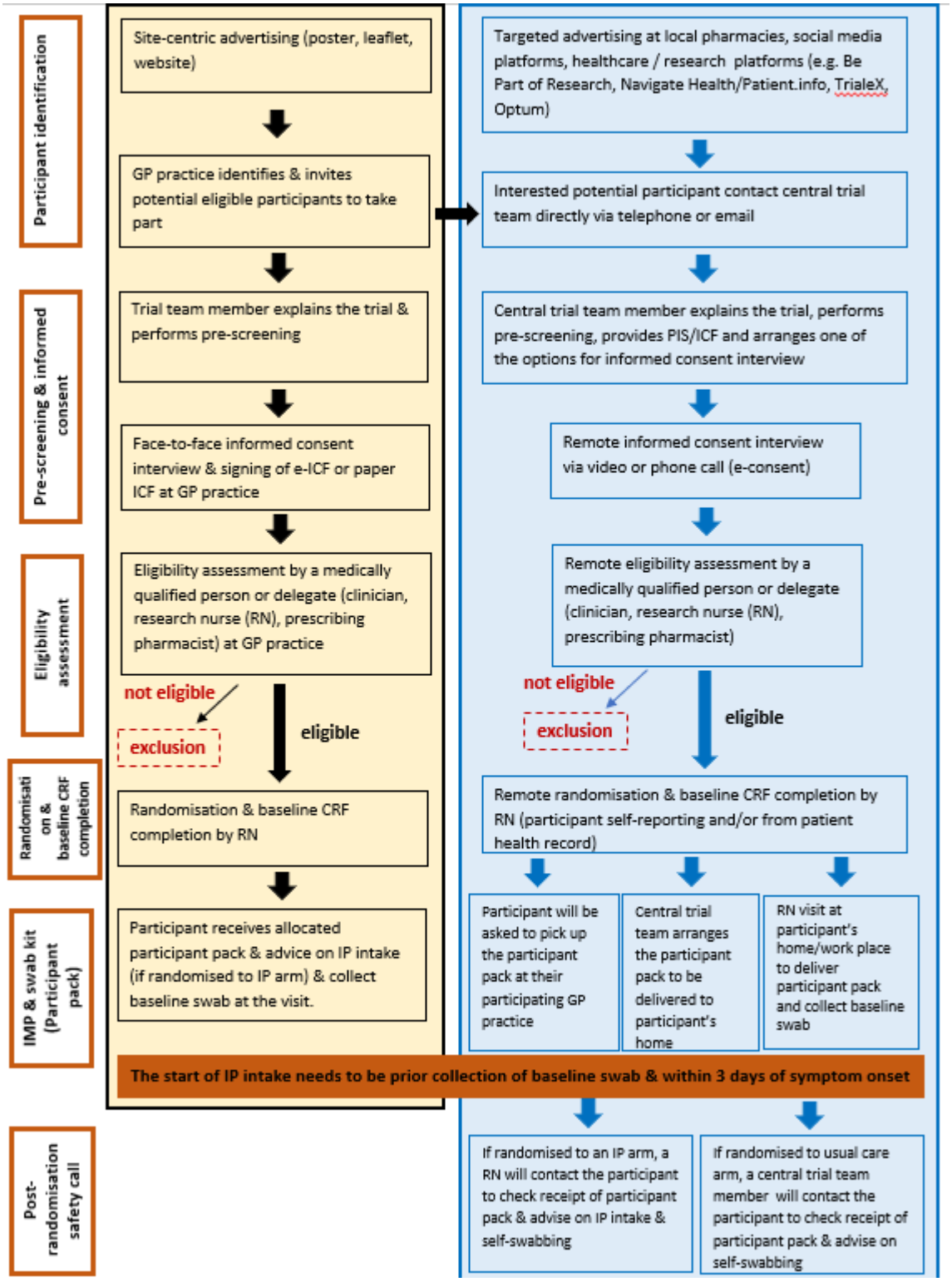
15. APPENDIX I STUDY FLOW CHART



16. APPENDIX II RECRUITMENT FLOW CHART



Conventional recruitment at participating site

Decentralised recruitment by central trial team

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