Trial Title: **P**latform **A**daptive trial of **NO**vel antivi**R**als for e**A**rly treat**M**ent of covid-19 **I**n the **C**ommunity

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No potential conflict of interest

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

The term '**central clinical team'** refers to a team of medically qualified clinicians and research nurses located at the PC-CTU and ORTU.

The term '**central trial team'** refers to the team responsible for the day-to-day conduct of the trial, which includes the central clinical team, as well as other non-clinical trial staff.

PC-CTU SOPs will be used for all aspects of PANORAMIC.

See *supplementary material B* for **Key Trial Contacts**.

Platform Adaptive trial of NOvel antiviRals for eArly treatMent of covid-19 In the Community (PANORAMIC): Overview

Background: Despite high uptake of vaccination against COVID-19, the disease remains prevalent in the UK and in many countries around the world, with many patients continuing to experience considerable morbidity and require treatment in hospital. There is therefore an urgent need to identify treatments for COVID-19 for use in the community early on in the illness that speeds recovery and prevents the need for hospital admission.

Aims and objectives: This protocol describes a platform randomised trial of antiviral therapeutic agents for use by clinically vulnerable people in the community with confirmed acute symptomatic SARS-CoV-2 infection.

Platform trial: A "platform trial" is a trial in which multiple treatments for the same disease can be tested simultaneously, and in which new interventions can be added or replace existing ones during the course of the trial in accordance with pre-specified criteria.

Interventions: Participants will be randomised to receive either Usual Care (see Usual Care Intervention Specific Appendix), or an antiviral agent in addition to Usual Care (see Intervention Specific Appendices for each antiviral agent under study). Potential participants can be included if they are eligible to be randomised to at least one novel antiviral agent, as well as the Usual Care arm.

Eligibility: Participants who meet the following inclusion criteria may be eligible to take part in the main trial:

- Participant or their legal representative is able and willing to provide informed consent
- Symptoms attributable to COVID-19 starting within the past 5 days and ongoing
- A positive PCR SARS-CoV-2 test
- Aged ≥50 years OR aged 18-49 years with any known underlying chronic health condition considered to make them clinically vulnerable:

Adaptive randomisation: Participants in the main trial will be randomised to one study arm using equal allocation ratios corresponding to the number of eligible arms in the trial. Pre-specified decision criteria allow for dropping an antiviral agent for futility, declaring an antiviral superior, or adding a new antiviral to be tested. If at any point an antiviral agent is deemed superior to the Usual Care, the superior antiviral may become part of Usual Care arm as the new standard of care according to recommended treatment guidelines, and changing effects of Usual Care will be taken into account in the analysis.

Outcomes: The primary outcome will be all-cause, non-elective hospitalisation and/or death within 28 days of randomisation. Secondary outcomes will include time to self-reported recovery defined as the first instance that a participant reports feeling fully recovered from the illness; duration of symptoms; symptom recurrence; daily rating of feeling well reported by participants; healthcare service use; participant reported household infection rate; safety outcomes and cost-effectiveness outcomes; symptoms and well-being at three and six months (with determination

of proportion with Long Covid) from randomisation. See *supplementary material C* for details of objectives and outcome measures.

Efficient study design: Depending on the drug licensing status and available safety data, all enrolment (screening, informed consent, eligibility review and baseline data) can be done either by PANORAMIC Hubs or by the central trial team, with follow-up procedures (daily diary, data capture of hospitalisations and deaths) conducted remotely with participants using the trial website or a telephone call with the trial team. Randomisation will be online and automatic, following eligibility confirmation.

PANORAMIC Hubs: These will include GP Sites, Community Trusts and other NHS service providers who will actively identify potential participants and invite them to take part. Potential participants may be referred to Hubs by other NHS facilities for possible inclusion in the trial. A GP, Research Nurse or other healthcare professional from the Hub will complete all recruitment procedures, screening, baseline, informed consent and eligibility review. Participants will be provided with a participant pack (containing the antiviral agent, if randomised to this arm), either issued by the Hub or sent directly to participants homes. Hubs will be able to store and issue study antiviral agents. The Hubs will also allow additional safety monitoring visits where required and as defined in the Intervention Specific Appendix (ISA). A Principal Investigator at each hub will provide trial oversight for participants recruited via the hub.

Central recruitment: A central trial team will also be able to recruit and randomise participants. And a participant pack containing an antiviral agent (if randomised to this arm) will be sent directly to participants homes.

Data to be recorded: Demographic features including ethnicity will be captured at baseline. In the online daily diary (completed each day for 28 days) and during telephone calls, participants or their Study Partners will rate the severity of symptoms including how well they are feeling, record contacts with the health services (including hospital admission), record study medication use, resource use, and new infections in the household. Follow-up beyond 28 days after randomisation will be by accessing electronic medical records and by participant questionnaire for information relevant to the longer-term consequences of COVID-19 at three and six months from randomisation. . To investigate the impact of trial interventions on the longer-term effects of COVID-19, we will also remotely follow-up participants, for up to 10 years.

Numbers to be randomised: An estimated maximum of approximately 5300 participants per arm will be required to provide approximately 90% power for detecting a 33% relative reduction in the hospitalisation/death in an experimental arm relative to Usual Care, based on the assumption of an underlying 3% combined hospitalisation/death rate in the Usual Care arm, and an intervention lowering the hospitalisation/death rate to 2%.

To enquire about the trial, contact the PANORAMIC Trial Team:

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1. BACKGROUND and RATIONALE

Despite high uptake of vaccination against COVID-19, the disease remains prevalent in the UK and in many countries around the world, with many patients continuing to require hospital admission. COVID-19 causes considerable suffering, including loss of ability to perform activities of daily living, loss of educational and work opportunities, and inability to perform caring duties, with far reaching personal and societal consequences. Many go on to experience persisting and/or relapsing symptoms. People with underlying health conditions, unvaccinated people, and those in whom the vaccine is not effective are at increased risk of more severe disease.(1) New 'vaccine escaping' variants may yet emerge, and the impact of early antiviral treatment on long COVID syndromes is as yet unknown. Early treatment with antiviral agents may prevent progression to the later phase of COVID-19. Therefore, there is an urgent need to identify treatments for COVID-19 for use in the community early on in the illness that prevent the need for hospital admission and improves time to recovery.(2, 3)

Antiviral agents may reduce viral shedding, and use of antiviral agents may lead to the emergence of resistance to novel antiviral agents, but the impact of novel antiviral agents on shedding and resistance is not yet known.(4)

1.1 Aims and Objectives

Main Trial: The primary aim is to determine the effectiveness of selected antiviral agents in preventing hospitalisation and/or death in higher-risk patients with a confirmed positive SARS-CoV-2 PCR test result (see Inclusion/Exclusion Criteria, below).

2. TRIAL DESIGN AND PROCEDURES

PANORAMIC is an open label, prospective, individually randomised, platform, adaptive, controlled clinical trial in community care. Trial arms will include:

Intervention arms: Novel antiviral agents (or combinations) targeting SARS-CoV-2, specified by The Antivirals Taskforce (ATF) and with capacity for sequential introduction of each treatment regimen into the trial plus Usual Care.

Comparator arm: Usual Care, defined as the currently recommended treatment delivered by responsible clinicians. Usual Care will not be mandated by the trial, as recommended treatments may change and be tailored to individual characteristics, and self-care will vary. Use over the counter medication as well as key medications such as inhaled steroids and monoclonal antibodies will be captured, and changing outcomes and treatment modalities over time in the Usual Care arm will be accounted for in the analysis: see Usual Care Intervention Specific Appendix.

2.1 Participant Identification

2.1.1 Trial Participants

The trial includes participants who test positive for SARS-CoV-2 infection and with ongoing symptoms consistent with COVID-19, not hospitalised, and who are aged 50 years and over, or 18-49 years and considered clinically vulnerable (see Inclusion Criteria below).

2.1.2 Inclusion Criteria

- Participant is able and willing to provide informed consent, or their legal representative is willing to provide informed consent
- Symptoms attributable to COVID-19 started within the past 5 days and ongoing
- A positive PCR SARS-CoV-2 test * Aged ≥50 years OR aged 18-49 years with one of the following known underlying chronic health condition considered to make them clinically vulnerable:
    - chronic respiratory disease (including chronic obstructive pulmonary disease (COPD), cystic fibrosis and asthma requiring at least daily use of preventative and/or reliever medication)
    - chronic heart or vascular disease
    - chronic kidney disease
    - chronic liver disease
    - chronic neurological disease (including dementia, stroke, epilepsy)
    - severe and profound learning disability
    - Down's syndrome
    - Diabetes mellitus (Type or Type II)
    - immunosuppression: primary (e.g., inherited immune disorders resulting from genetic mutations, usually present at birth and diagnosed in childhood) or secondary due to disease or treatment (e.g., sickle cell, HIV, cancer, chemotherapy)
    - solid organ, bone marrow and stem cell transplant recipients
    - morbid obesity (BMI >35)
    - severe mental illness
    - care home resident
    - judged by recruiting clinician or research nurse (registered medical practitioner or trained study nurse) to be clinically vulnerable

* Any positive PCR test taken between two days before symptom onset and randomisation qualifies. A positive lateral flow test in a symptomatic person qualifies for randomisation and inclusion in the main analysis will be dependent on the positive PCR test.

2.1.3 Exclusion Criteria

- Patient currently admitted to hospital (inpatient)
- Previous randomisation in the PANORAMIC trial
- Currently participating in a clinical trial of a therapeutic agent for acute COVID-19
- Additional exclusions specific to each intervention arm, if any, as listed in the Intervention Specific Appendices (ISA's) of currently open trial arms

2.2 Trial procedures

Informing potential participants about the trial

I. All Health, health related, and Social Care professionals (including NHS 111 and Test and Trace clinicians, care home staff, pharmacy staff, etc) will be able to provide information about participation and direct potential participants to the online trial information and the trial website.

II. The ZOE COVID-19 Application, Health Wise Wales, Join Dementia Research (JDR) and other COVID-19 research studies e.g., REACT, VIRUS WATCH) will sign-post to the trial.

III. National media campaigns will use television, radio and social media platforms to generate awareness of the trial and to sign-post to the trial.
IV. Targeted campaigns for vulnerable groups will be by media campaigns, via national charities, social media groups and relevant secondary care clinicians.
V. All NHS facilities including testing centres including NHS walk in/ drive through centres will be able to inform potentially eligible participants about the trial, and refer them to the trial website and/or trial team.
VI. Clinicians are able to reach out to potentially eligible participants identified by receiving SARS-Cov-2 test results from Test and Trace and laboratories, and by regular searches for patients with a positive SARS-Cov-2 test result in their clinical database. Contact can be made with potential participants verbally or by text, email, and telephone.
VII. NHS Digital (and analogous services in devolved administrations) will provide a daily list of contact details from Pillar 2 testing data of people with a positive SARS-Co-V2 test. The trial team and the hubs will be able to contact these people within 24-48hrs of test result to discuss participation.
VIII. EMIS Anywhere, a data extraction service for primary care data, and analogous general practice clinical record facilities, will be able to reach out to potentially eligible participants and signpost them to the PANORAMIC website to explore their participation.

2.2.1 Recruitment

Face-to-face as well as remote (trial website or telephone call) screening, eligibility and consent procedures will be used. All participants (apart from those who lack capacity to do this) will have a two-way discussion, either face-to-face or by a telephone/video call from a medically qualified clinician or research nurse prior to randomisation.

For participants who are too unwell or unable to respond to surveys for themselves, a Study Partner they identify will be able to assist their participant in completing screening, baseline, consent and follow up online forms and/or calls and provide information to them on their behalf where necessary. A letter will be issued to Study Partners, informing them of the study, notifying them that they have been nominated for this role by the participant.

2.2.1.1 Recruitment at PANORAMIC Hubs

PANORAMIC Hubs will include GP sites (either single practices or a federation of practices that are able to operate under a single site agreement and Principle Investigator to undertake study procedures as detailed in the protocol), community trusts, and other healthcare providers. Potential participants can be referred to Hubs by other health care facilities for possible inclusion. As well as recruiting patients through routine consultations, Hubs will search their databases and test results they receive for patients defined as clinically vulnerable (see inclusion criteria for definition) with a positive test for COVID-19, and telephone or text them to invite them to take part in the trial. Either face-to-face or by telephone, an appropriately qualified clinician at the Hub will explain the trial to the potentially eligible participant; collect screening, baseline and contact information; take informed consent; and confirm eligibility (see details below for each trial procedure). If the participant is eligible, they will automatically be randomised to one of the trial arms, and provided with a participant pack (see section 3.1 Medication Distribution).

A Principal Investigator at each Hub will provide trial oversight, for participants recruited via the Hub and inform the central trial team of any Serious Adverse Events (SAE).

2.2.1.2 Central Recruitment

Potential participants are able to present directly to the central trial team via the trial website or free-phone telephone number, in additional to via a PANORAMIC hub. Screening, baseline, contact information and informed consent can be self-completed by the potential participant, or completed during a telephone call with a member of the central trial team. A medically qualified clinician or appropriately trained research nurse will then confirm eligibility. If eligible, the participant will be randomised and provided with a participant pack (see section 3.1 Medication Distribution). All trial procedures are described below in detail.

2.3 Screening

Screening can be completed face-to-face as well as remotely via the trial website, or a free-phone telephone service that enables participants to have a two-way discussion with the central trial team or Hub staff who are trained in trial procedures.

Participants of child-bearing potential are required to confirm a negative pregnancy test prior to starting any antiviral agent in the trial that may be teratogenic, and as specified in its intervention specific appendix. Thus, they should indicate willingness to take such a pregnancy test at screening. For those recruited at face-to-face visits at PANORAMIC Hubs, undertaking a pregnancy test will be part of the initial screening visit. For participants recruited remotely, the pregnancy test will be supplied in the participant pack with the antiviral agent. The pregnancy test must be completed prior to starting an antiviral agent that requires confirmation of a negative pregnancy test before staring the agent. This will be clearly explained prior to randomisation (see section 2.8 Follow-up Procedures for details regarding confirmation of a negative test result). Those who are ineligible because they are asymptomatic will be alerted to possible trial participation should they develop symptoms.

2.4 Informed Consent

There are separate procedures for recruiting eligible participants with capacity to give informed consent and residents of care homes who lack capacity to consent. All consent forms will be completed online and paperless.

Eligible participants capable of giving informed consent will be asked to provide informed consent after a two-way discussion between a medically qualified clinician or research nurse and the participant, either face-to-face or by telephone, prior to randomisation, where the risks and benefits of taking part and follow-up procedures will be explained.

In addition to taking consent face-to-face, consent may also be taken remotely, using online paperless consent forms and via telephone/Video discussion, because of the pandemic circumstances and the need to maximise the pragmatic nature of the trial. Participants will be able to download their consent form after completion, and it can be printed by the central study team and delivered to participants. Electronic consent forms will be held securely on the trial database. For those recruited in Hubs, a copy will be filed in patients' medical notes and a copy will be printed and given to patients.

Prior to consent, written and summary versions of the Patient 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. It will be clear that the participant is free to withdraw from the study at any time. A pictorial and/or video and a summary PIS will be available which can be more easily read by those feeling very unwell, or those with low reading comprehension skills. Adequate time will be given to the participant to consider the information and to ask any questions about the trial before deciding whether to participate. After consent, participants will enter online baseline information, including their address, contact details and those of a Study Partner. Identifying a Study Partner is not a requirement of study participation.

People who lack capacity to consent for themselves will only be recruited from care homes: adults who lack capacity to consent living elsewhere will not be recruited. If the recruiting health and social care professional deems that a patient in a care home lacks capacity to provide consent for themselves, then a personal or professional legal representative (England and Wales only) will be asked to provide consent. A personal legal representative is defined as a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the adult. A professional legal representative may be a doctor responsible for the medical treatment of the adult if they are independent of the study, or a person nominated by the healthcare provider. In all instances, a personal legal representative will be sought first and a professional legal representative sought only if a personal legal representative cannot be identified. Legal representative and recruiting clinicians will not endeavour to obtain consent for or recruit people into the trial people who, in addition to their lack of capacity, have a quality of life which can reasonably be considered as not acceptable to the potential participant in order to avoid potentially life lengthening intervention in those who would not wish to have such an intervention. Legal representative consent (relative/family member/independent treating physician) can be taken face to face or remotely.

The legal representative will be provided with information about the trial and made aware of the following: they are being asked to give consent on behalf of the incapacitated adult, they are free to decide whether they wish to make this decision or not, and they are being asked to consider what the adult would want, and to set aside their own personal views when making this decision.

2.5 Eligibility Assessment

For participants who have provided consent, eligibility will be assessed by a medically qualified clinician or a research nurse, who is suitably trained and experienced and has been delegated this responsibility, at a PANORAMIC Hub, other NHS healthcare provider or by the central clinical team. PANORAMIC Hubs can contact the central clinical team for guidance regarding eligibility queries. Depending on the exclusion criteria outlined in ISAs, eligibility can be assessed by eliciting medical history and relevant information directly from the participant, and the participant can be randomised if there is no contraindication to the study drugs currently in the trial. Where specified in the ISA, eligibility checking will be assessed additionally through direct access to the participant's Summary Care Record (or similar medical record summary), or by reference to relevant medical information obtained from the participant's primary care medical practice.

If an additional IMP is introduced into the trial, which requires extensive clinical interpretation of the eligibility criteria, the eligibility assessment process will be reviewed and amended accordingly

and outlined fully in the intervention specific appendix (ISA) with screening and eligibility CRFs and associated processes updated accordingly.

2.6 Randomisation

Participants will be randomised using a secure, fully validated and compliant web-based randomisation system. Once deemed eligible, the medically qualified clinician or research nurse from the central clinical team or Hub (as documented on the delegation log) will randomise the participant. Participants will be randomised to one study arm using equal allocation ratios corresponding to the number of eligible arms in the trial. For instance, if there are two active interventions (A & B), the allocation ratio will be 1:1:1 for Usual Care, active A, active B (respectively), such that 33% of participants are randomised to Usual Care. If there are 3 active interventions, the allocation ratio will be 1:1:1:1, such that 25% of participants are randomised to Usual Care. Patients must be eligible for at least two arms (Usual Care and at least one novel antiviral intervention). Stratification will be by age and vaccination status.

The randomisation database will automatically alert the relevant IMP distributor and the participant, trial team and legal representative if applicable will be notified electronically of the treatment allocation. If the participant does not have an email address, they will be notified by telephone.

2.7 Blinding and code-breaking

PANORAMIC is an open-label trial. The participant, legal representative if applicable, and the recruiting clinician will know the participant's allocation. Therefore, no unblinding or code breaking is required. However, those managing the data will be blind to participant allocation.

The trial team and recruiting clinicians will be blinded to emerging results of interim analyses. During the course of the trial, only the unblinding statisticians and the independent members of the Data and Safety Monitoring Committee (DSMC) will have access to the unblinded interim results.

2.8 Follow-up Procedures

Following randomisation, participants in the intervention arm will be sent a participant pack (see section 3.1 Medication Distribution). The participant pack will contain: the antiviral agent, an information booklet; medication card detailing how the medication should be administered, precautions and safety guidance; medication appendix providing further information about the treatment (available prior to randomisation as part of the PIS); emergency contact card; antiviral agent; pregnancy test (only for participants of child-bearing potential). Those randomised to Usual Care, will receive an information booklet via email or post.

Patients might be asked to attend a face to face visit or to donate a microbiological or blood sample, depending on the requirements for the evaluation of each specific antiviral agent. This will depend on the antiviral agents' licensing status, available safety data and their approval status. Thus, for antiviral agents with an established safety profile, follow-up will be via self-completed questionnaires online or through telephone calls, and primary care and/or hospital record searches. For other antiviral agents, the trial will have capability for face-to-face assessment, sampling and safety checks initially, after which a drug may progress to 'remote evaluation', which will only be implemented following approval of a substantial amendment.

A safety call will be made on Day 1 (day after randomisation) with participants of child-bearing potential who have been allocated to an antiviral agent with teratogenic potential (as specified in the relevant ISA) by a member of the central trial team, to confirm receipt of the participant pack (containing a urine pregnancy test). During this Day 1 call, a member of the study team will confirm with participants of child bearing potential, that a pregnancy test has been done and that the result is negative before starting an antiviral agent with teratogenic potential. In the event of a positive test result, the participant will be asked not to take any of the antiviral agent, return it, and will be withdrawn from the trial. Results will be documented in the Day 1 Call CRF. The pregnancy test must be completed prior to taking the antiviral agent in question and this will be clearly explained prior to randomisation. Participants of child-bearing potential will also be asked to confirm a negative pregnancy test result in their day 1-3 of daily diaries.

All participants, irrespective of group allocation, will be contacted on Day 2 (2 days after randomisation) to confirm receipt of study materials, confirm follow-up procedures and answer queries. At this day 2 call, Participants allocated to any antiviral agent arm of the trial, will be also asked if they have received their pack, experiencing any potential side-effects. This call will be made by clinicians or research nurses from the central PC-CTU team (for those recruited centrally or from a Hub) or PANORAMIC Hub (for those recruited via one of the Hubs).

If we are unable to reach the participant or their Study Partner at this stage, we will contact the patient's GP to request information on any healthcare contacts that the participant may have had since they were enrolled into the trial, in order to capture any potential safety events.

Participants on all arms of the trial will complete a daily diary each day for 28 days and be contacted at 3 and 6 months from randomisation, where they will rate the severity of symptoms, record contacts with the health services (including hospital admissions, hospital outpatient visits, accident and emergency attendances, use of specialist services and primary care encounters), impact of symptoms on work/study, record medication use and new infections in the household. We will collect the *EuroQoL EQ-5D-5L* (baseline, days 14 and 28, and 3 and 6 months). The central trial team will call participants/study partners with no internet access or those who have not completed their diary for at least two consecutive days before days 7, 14 and 28. No more than six contact attempts will be made at each of these follow-up points. All participants will be telephoned within one day, and 24-hour access to the safety phone line and emergency procedures will be emphasised to those randomised to an antiviral agent. Participants will be contacted at three and six months to ascertain wellbeing and longer-term consequences of their illness, including proportion meeting criteria for 'long Covid'. Vaccination status, including number of vaccinations received will be recorded.

Adherence to study medication will be assessed by self-report.

Participants' medical records will be accessed up to twelve months following enrolment to ascertain follow up data from enrolment to 6 months. Data will be collected as close to real time as possible; RCGP RSC, EMIS and NHS Digital and other sources of routinely collected data will be utilised if required. To investigate the impact of trial interventions on the longer-term effects of COVID-19, we will use these data collection methods to follow-up participants, for up to 10 years.

2.11 Economic evaluation

A prospective economic evaluation will be embedded within the trial design to assess the cost effectiveness of each antiviral from an NHS perspective. We will estimate the resource inputs associated with embedding each trial antiviral treatment into routine clinical practice, and estimate societal costs. Broader resource use will be drawn from General Practice Data for Planning and Research (GPDPR) data and linked Hospital Episode Statistics – encompassing primary care encounters, hospital inpatient/day case admissions, outpatient visits, and accident and emergency attendances. Unit costs will be valued using national reference tariffs and attached to resource inputs to generate a compound total health care cost per trial participant over the trial time horizon. EQ-5D-5L data will be converted using standard algorithms into utility scores for quality-adjusted life year (QALY) estimation, and cost-effectiveness expressed as incremental cost per QALY gained (5). Secondary expressions of cost-effectiveness will include incremental cost per hospitalisation and/or death prevented over 28 days.

Bivariate regression of costs and measures of health consequence, with multiple imputation of missing data, will be conducted to generate within-trial estimates of incremental cost-effectiveness. Sensitivity analyses will assess the impact of areas of uncertainty surrounding components of the economic evaluation. Cost-effectiveness acceptability curves will show the probability of cost-effectiveness of each treatment evaluated at alternative cost-effectiveness thresholds. Cost-effectiveness threshold values will be informed by guidance from UK government departments on the value placed by decision-makers on an additional QALY (6) and on a statistical life (7).

A decision-analytic modelling-based economic evaluation will also be conducted. The baseline decision-analytic model will be developed during the early stages of the study, and aim to provide a framework for extrapolating the cost-effectiveness of each antiviral beyond the parameters of PANORAMIC trial. Accepted guidelines for good practice in decision-analytic modelling will be followed. The model will consider the progression of symptomatic COVID-19 status over time, and the model structure will capture disease progression using health states that represent the important natural history and clinical- and event-related activity for symptomatic COVID-19 symptomatic status, the appropriate model type (e.g. Markov or discrete-event simulation approach) and the appropriate analytical framework (e.g. cohort analysis versus individual-level simulation). Parameter inputs into the model will be informed by data extracted from PANORAMIC trial, supplemented by data identified from external sources following targeted literature searches. As with the within-trial economic evaluation, cost-effectiveness will be expressed in terms of incremental cost per QALY gained. Multi-parameter uncertainty in the model will be addressed using probabilistic sensitivity analysis. Cost-effectiveness acceptability curves will be used to show the probability of cost-effectiveness of each anti-viral strategy at alternative cost-effectiveness thresholds held by decision-makers. Long-term costs and health consequences will be discounted using nationally recommended discount rates. Specific plans for the economic evaluation will be outlined in a pre-specified health economics analysis plan.

2.13 Early Discontinuation/Withdrawal of Participants

Each participant, or their legal representative on the participant's behalf, has the right to withdraw from the study at any time. For those that lack capacity, expression of dissent in any form will be taken as an indication they do not wish to be included and they will be withdrawn.

In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively)
- Withdrawal of consent

The reason for withdrawal will be recorded on the CRF. Data that has already been collected about the participant will be kept and used.

2.14 Definition of End of Trial

The end of the trial will be the last data capture of last participant.

3 TRIAL INTERVENTIONS

Antiviral agent information can be found in the relevant ISAs.

3.1 Medication Distribution

In general, the distribution of antivirals can be implemented by: the PANORAMIC Hubs; an accredited licensed central facility; an online, community or hospital pharmacy, and; the PC-CTU. if approved by MHRA. Distribution of trial packs to participants will be tracked via courier or call/text message. Clinicians may be able to prescribe trial antivirals that can be issued in the community, and pharmacies can issue antivirals to the patient by community pharmacy services or 'on-line pharmacy' services, or it can be collected from the pharmacy by the participant or someone on their behalf (with appropriate infection control measures).

The arrangements for the distribution of each antiviral agent are detailed in the ISA.

3.2 Medication adherence

Medication adherence will be captured in daily diaries and phone or video calls from the trial team.

Accountability logs will be kept by the distributor (as specified in the ISA) and central monitoring of the logs will allow oversight by the PC-CTU.

A member of the central clinical team will telephone all participants to confirm receipt of the antiviral agent, and that the participant has read the instructions on the medication card. Receipt will be documented in the Day 1/2 telephone calls (see section 2.8 Follow-up procedures). If we are unable to contact participants or their study partner, we will confirm and log receipt of antiviral agent by checking the patient's daily diary, where they are asked on a daily basis whether they have taken their trial treatment and the number of tablets/capsules taken. We can also check via the courier portal, whether the medication has been received by the participant, for additional confirmation.

If a participant decides that they no longer wish to take their medication, we will provide a pre-paid envelope so that they can return the medication to the trial team via courier and the trial team will ensure all drug accountability logs are updated accordingly.

4 SAFETY REPORTING

Symptoms, potential medication side-effects and Serious Adverse Events (SAE) will be collected from participant daily diaries, calls to participants/Study Partners, face-to-face visits with Hub clinicians, medical records, notes reviews, NHS Digital data extracts and RCGP data downloads.

We will adopt a risk assessed and proportionate approach to safety monitoring. In line with the SmPC or Investigator Brochure, we will assess the risks and the safety profile for each antiviral agent, and detail the mitigation and monitoring procedures in the ISA. All safety procedures will be according to PC-CTU pharmacovigilance SOP.

4.1 Procedures for Reporting Adverse Events and Serious Adverse Events

The participant will be asked to rate the severity of a number key COVID-19 symptoms which are also possible common medication side effects in their daily diary. The severity of individual events and symptoms will be assessed over time by participants on the following scale: no problem/mild problem/moderate problem/major problem.

	Participant reported symptom rating
No problem	Individual symptom not currently experienced
Mild problem	Symptom is short-lived or mild; medication may be required. No limitation to usual activity
Moderate problem	Symptom causes moderate limitation in usual activity. Medication may be required.
Major problem	Symptom causes considerable limitation in activity. Medication or medical attention required.

Symptoms of COVID-19 and medication adverse event symptoms may overlap and can be difficult to disentangle. Trends in the prevalence in the severity of symptoms between Usual Care and antiviral agent arms will be compared, for evidence of increased severity of measured symptoms in those randomised to receive study antiviral agents.

i. AE reporting

For each antiviral agent, we will collect the AEs if and when specified in the relevant ISA. AEs will be monitored from the start of treatment for the 28-day trial duration, unless otherwise specified in the ISA, and assessed by a clinician (independent from the Sponsor) for causality and severity (definitions below).

Participants will be free to withdraw from taking the antiviral if they perceive they have an intolerable AE. Participants will also be provided with a Trial Wallet Emergency Card detailing potential side-effects and a 24-hour contact telephone line, answered by a clinical team, enabling them to report AEs they experience 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, trial participants will be instructed to show this card to the clinician they see. Based on clinical judgement, the clinician may contact the participant directly within 24 hrs of becoming aware of an AE reported in their daily diary or on the Freephone number, to advise the participant on the appropriate clinical care.

ii. AE Severity Assessment (for assessing clinician)

	Clinical assessment of severity
GRADE 1 (Mild)	Short-lived or mild symptoms; medication may be required. No limitation to usual activity
GRADE 2 (Moderate)	Moderate limitation in usual activity. Medication may be required.
GRADE 3 (Severe)	Considerable limitation in activity. Medication or medical attention required.

iii. SAEs

All-cause hospitalisation and/or death is the primary outcome, and this data will be captured in CRFs. SAEs other than hospitalisation or death due to COVID-19 must be reported for all antiviral agents.

SAEs must be reported to PC-CTU by the person who has discovered the SAE or nominated delegate within 24 hours of becoming aware of the event. Some SAEs occurring within the 28-day follow-up period, may be identified retrospectively from data extracts which will be received monthly from NHS Digital and not in real-time. These will be reported within 24 hours of becoming aware of the event. The sponsor or delegate will ensure it is reviewed by the CI or other delegated personnel for relatedness and expectedness as soon as possible taking into account the reporting time for a potential SUSAR according to the relevant competent authority. If the event has not resolved, at the 28-day time point the SAE will be reviewed again by the central clinical team, to see if resolution has occurred. If the event is considered 'resolved' no further follow up is required. If not, the event must be followed up until such a time point.

All SAEs that have not resolved by the end of the study or those that are identified retrospectively, or that have not resolved upon discontinuation of the participant's participation in the study, 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 health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

See Appendix D. Supplementary Material for definitions of adverse events

4.2.1. Other events exempt from immediate reporting as SAEs

Hospitalisations will be defined as at least a one night admission to hospital, or at least one night in a 'Hospital at Home' program after hospital assessment. Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not contribute to our primary outcome and does not constitute an SAE.

4.2.2. Procedure for immediate reporting of Serious Adverse Events

- Trial team/responsible clinician/CI will complete an SAE report form, directly into the database, for all reportable SAEs.
- GP practice/trial team/RCGP will provide additional, missing or follow up information in a timely fashion.
- If necessary, the participant may be contacted to provide additional, missing or follow up information as required.

An investigator, who is independent to the Sponsor but part of the study team, will review the SAE once reported, collect as much information and report to the Sponsor delegate within the timeframe according to the PC-CTU SOPs.

4.2.3 Expectedness

For SAEs that require reporting, expectedness of SAEs will be assessed and determined by delegated members of the central trial team, according to the relevant Reference Safety Information (RSI) section of the Summary of Product Characteristics/Investigator's Brochure. The RSI will be the current Sponsor and MHRA approved version at the time of the event occurrence.

4.2.4 Assessment of Causality

The relationship of each serious adverse event to the antiviral agent 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 antiviral agent
- **Possibly** – although a relationship to the antiviral agent 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 antiviral agent.
- **Definitely** – the known effects of the antiviral agent, its therapeutic class or based on challenge testing suggest that the antiviral agent is the most likely cause.

For anyone recruited centrally, an investigator, independent of the Sponsoring Organisation, but part of the study team, will make the assessment of causality.

For anyone recruited through hubs, the site PI will make the assessment of causality.

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

4.3 SUSAR Reporting

All SUSARs will be reported by the sponsor delegate to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than seven calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within eight calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant antiviral agent for all studies with the same Sponsor, whether or not the event occurred in the current trial.

4.4 Development Safety Update Reports

The DSUR will be developed and submitted annually on the anniversary date that the trial receives Clinical Trial Authorisation +60 days. Due to the nature of this trial and the importance of sharing the science of COVID-19 and the drug, internationally, we expect to produce reports to the UK Government and regulatory agency more frequently upon request.

5 STATISTICS

5.1 Master Statistical Analysis Plan (M-SAP)

Details of the statistical design and methods for both the main trial and will be described in a Master Statistical Analysis Plan (M-SAP).

PANORAMIC will begin as a two arm, 1:1 randomised trial but will have the capability to add additional interventions over time. The evaluation of any new interventions will be governed by this master protocol and M-SAP (including adaptive algorithm and decision criteria), with any planned deviations from the master protocol and M-SAP to be specified in arm-specific appendices. The inclusion of any new interventions will require additional arm-specific appendices to the master protocol and M-SAP and will be implemented as a substantial amendment to regulatory bodies.

5.2 Open Platform Trial

5.2.1 Primary Efficacy Endpoints and Analyses

The primary efficacy endpoint is all-cause, non-elective hospitalisation and/or death within 28 days of randomisation ascertained through patient/study partner report, and/or patient medical records.

5.2.2 Primary Efficacy Hypothesis & Analysis

Let p_j denote the probability of hospitalisation/death for persons in treatment group j, where $j = 0$ denotes the Usual Care arm. A Bayesian posterior distribution will be derived for the estimated difference in probability of hospitalisation/death between treatment groups. Let θ_j denote the log odds ratio of hospitalisation/death comparing intervention j to Usual Care. The primary analysis for intervention j will test the following hypothesis:

$$H_0 : \theta_j \geq 0$$
$$H_1 : \theta_j < 0$$

If the Bayesian posterior probability of beneficial treatment effect (alternative hypothesis) is greater than or equal to a pre-specified threshold (e.g., 0.98), the null hypothesis will be rejected and the intervention will be deemed superior to Usual Care with respect to Hospitalisation/Death

in the primary analysis population. The exact threshold will be pre-specified and calibrated via simulation in the Adaptive Design Report to demonstrate control of Type I error at the traditional 0.05 two-sided level for each intervention, accounting for multiple interim analyses. Outcomes for those participants who were eligible on the basis of being symptomatic and with a positive lateral flow test but then did not have confirmation of SARS-CoV-2 infection on PCR test will be reported separately and not included in the main analysis.

The analysis of primary and some secondary outcome data analysis will be performed by Berry Consultancy with support from statisticians at the University of Oxford. The company is based in the USA, however no identifiable data will be given to them during this process.

5.2.3 Adaptive Design

The pre-specified design will allow 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 removal of treatment arms based on pre-specified decision criteria. The adaptive algorithm will be documented in the Adaptive Design Report, including pre-specified criteria for decisions regarding futility or effectiveness of interventions and/or replacing interventions in the trial. The Adaptive Design Report (ADR) will contain extensive simulations to explore the performance of the adaptive design, including power and Type I error. Due to the urgent nature of the pandemic situation, this comprehensive ADR will be developed and finalised prior to the first scheduled interim analysis by a blinded statistician.

5.2.4 Interim Analyses

Precise timing of the first interim analysis and frequency of subsequent interim analyses will be pre-specified in the Adaptive Design Report and DSMC Charter, based on both simulations and logistical considerations.

5.2.5 Allocation & Adaptive Randomisation

Participants will be randomised to one study arm using fixed equal allocation ratios corresponding to the number of eligible arms in the trial. For instance, if there are two active interventions (A & B), the allocation ratio will be 1:1:1 for Usual Care, active A, active B (respectively), such that 33% of participants are randomised to Usual Care. If there are 3 active interventions, the allocation ratio will be 1:1:1:1, such that 25% of participants are randomised to Usual Care. As this is a nationwide, individually randomised study that aims to include large numbers of participants, individual participant characteristics and infecting strain types of the infecting agent should be equally distributed between study arms.

5.2.6 Sample Size Justification

Main Study

The primary analysis will incorporate Bayesian logistic regression to estimate the odds ratio for hospitalisation/death for a treatment arm versus control, adjusting for age, vaccination status, and comorbidity status. An experimental treatment will be considered superior to the control if the Bayesian posterior probability of benefit is greater than a pre-specified threshold (e.g. 0.98) as detailed in the Adaptive Design Report. The trial design will incorporate multiple interim

analyses that allow each intervention to stop early for futility, stop early for superiority, or continue to randomise participants. Additional interventions may be added as appendices to the master protocol throughout the duration of the trial. Extensive simulations will be conducted to evaluate and understand the operating characteristics and performance of the adaptive algorithm, such as control of Type I error and stopping guidance for efficacy and futility. Type I error will be controlled at the traditional 0.05 two-sided level for each intervention. A statistical analysis plan will be prepared and finalised before the first scheduled interim analysis.

The primary analysis will include those allocated to a particular antiviral agent and to the control condition (Usual Care) only during the period that that antiviral agent was in the trial (concurrently randomised population). A sensitivity analysis of the effect of subsequently introduced agents will include relevant control participants recruited prior to the introduction of that agent. To account for changes in the standard treatment in the Usual Care arm in this sensitivity analysis, and in changing patterns of recovery due to possible new variants, immunisations, behavioural interventions and other factors, this analytic model will include parameters to adjust for this temporal drift in the trial population, by estimating the primary endpoint in the usual care group across time via Bayesian hierarchical modelling.

Should an intervention demonstrate superiority versus Usual Care, the superior intervention may become included in Usual Care and so become part of the control arm for subsequent interventions. Additionally, the Bayesian secondary analysis model will provide “bridging” across overlapping treatment groups through the temporal parameters, which will enable comparisons of subsequent interventions to the original Usual Care, even if there are no concurrent randomisations to the original Usual Care.

If there are important changes in Usual Care due to the introduction of new and superior interventions, the Trial Management Group will assess whether any design feature (such as futility and superiority criteria) need to be re-considered.
We estimated that the hospitalisation/date rate will be reduced to 3% in the Usual Care arm. Based on the unblinded data from the PRINCIPLE Trial that the overall estimated hospitalisation/death was 8.8% in the Usual Care arm for the period that Budesonide was open for recruitment. However, the percentage of fully vaccinated participants was lower than the current percentage. Subsequent blinded data from PRINCIPLE has observed the overall COVID-19 related hospitalisation/death was 3.8% between 27 May 2021 and 25 July 2021. So, we believe our estimated based rate is not overly overestimated for the primary outcome defined as all-cause hospitalisation/death. Although vaccine has been efficacious on preventing hospitalisation, there is still a sub-population of unvaccinated cohort that is at higher risk of hospital admission/death. The adaptive nature of the platform trial means that the recruitment will continue until a pre-specified probability of superiority or futility thresholds is met.

An estimated maximum of approximately 5300 participants per arm will be required to provide approximately 90% power for detecting a 33% relative reduction in the hospitalisation/death in an experimental arm relative to Usual Care, based on the assumption of an underlying 3% combined hospitalisation/death rate in the Usual Care arm, and an intervention lowering the hospitalisation/death rate to 2%. We expect fewer participants will be needed to detect the same relative reduction if the event rate is larger than 3% in the Usual Care arm (Table 1), or if there is a greater reduction in the relative risk of hospitalisation/death for a given intervention.

(8, 9)

Table 1: Power and sample size estimates for PANORAMIC

90% power			80% power		
Usual Care	**Treatment**	**Sample size**	**Usual Care**	**Treatment**	**Sample size**
3.0%	2.0%	5319	3.0%	2.0%	4023
4.0%	2.7%	4177	4.0%	2.7%	3159
5.0%	3.4%	3425	5.0%	3.4%	2590

Simulations are used to further quantify the statistical power for each experimental arm in the context of an adaptive design, as well as general performance characteristics, as detailed in the Adaptive Design Report.

(10) (11) 5.2.7 Virtual Trial Simulations

Virtual trial simulations are used to demonstrate good performance and adequate control of Type I error for the adaptive design. Simulations will be provided in the Adaptive Design Report.

5.2.8 Procedure for Accounting for Missing, Unused, and Spurious Data.

Full details of handling missing data will be specified in the M-SAP.

5.3 Primary Analysis Population

The primary analysis population is defined as randomised participants with confirmed SARS-CoV-2 infection during the same timeframe when the intervention was actively being randomised and according to the groups they were randomly allocated to as specified in the M-SAP. All other analysis populations will be defined in the M-SAP.

Complier Average Causal Effect (CACE) modelling will be undertaken to account for adherence.

5.4 Procedures for Reporting Unplanned Deviation(s) from the Master Statistical Analysis Plan

Analyses will be carried out in accordance with the M-SAP and corresponding appendices. Any additional analysis that is not specified in the M-SAP/appendices or any unplanned deviation(s) from the M-SAP/appendices will be specified in the Statistical Analysis Report. Reasons for these changes will be documented and authorised by the Chief Investigator.

6 DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

6.1 Source Data

Source documents are where data are first recorded. These include, but are not limited to, hospital/medical records (from which medical history and previous and concurrent medication may be summarised into the CRF), NHS Digital data, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

If a participant fails to complete data online and after six attempts at contacting the participant/Study Partner, any sources of routinely collected data may be utilised to obtain missing data. Data collected will include participant identifiable information and will be accessed at the University of Oxford according to PC-CTU Information Governance policies and UK GDPR. Data will only be held for the duration it is required; this will be reviewed annually.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

6.2 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution, centres in other UK Devolved Administrations and the regulatory authorities to permit trial-related monitoring, audits and inspections.

6.3 Data Recording and Record Keeping

The Investigators will maintain appropriate medical and research records for this trial, in compliance with the requirements of the Medicines for Human Use (Clinical Trial) Regulations 2004, ICH E6 GCP and regulatory and institutional requirements for the protection of confidentiality of volunteers. The Chief Investigator, Principal Investigator, Co-Investigators, clinical team, including Clinical Research Nurses, and other authorised members of the trial team will have access to records. The Investigators will permit authorised representatives of the sponsor, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

The data will be entered into CRFs in an electronic format by the participant, trial Partner, Hub team member or trial team using an FDA part 11B compliant database. Data is stored on a secure cloud hosted server physically located in London, UK. Data will be entered in a web browser and then transferred to the database by encrypted (Https) transfer. This includes safety data, laboratory data and outcome data. Safety data will be collected through electronic diaries. Risks are mitigated using the ISO97001 framework.

An online secure data entry system designed to collect sensitive data, such as participant and Study Partner contact details, will be used. All identifiable participant data is encrypted using the Advanced Encryption Standard. The participant portal will also manage online eligibility, eConsent and ePRO. Participant and Trial Partner data will be kept and stored securely for as long as it's required by the study and reviewed on annual basis.

7 QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and PC-CTU Standard Operating Procedures. All PIs, coordinating centre staff and site staff will receive training in trial procedures according to GCP where required. Regular monitoring will be performed according to GCP using a risk-based approach. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents where possible.

The PC-CTU Trial Management Group will be responsible for the monitoring of all aspects of the trial's conduct and progress and will ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the trial itself. The TMG will be comprised of individuals responsible for the trial's day to day management and will meet regularly throughout the course of the trial.

7.1 Risk assessment and Monitoring

A risk assessment and monitoring plan will be prepared before the study opens for each antiviral agent and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities. Monitoring will be performed by the PC-CTU Quality Assurance Manager or delegate. The level of monitoring required will be informed by the risk assessment.

7.2 Trial committees

The responsibilities of each group are as follows:

- Data and Safety Monitoring Committee (DSMC) will review the data received from the SAC at each interim analysis as described in the Statistical Analysis section, in order to ensure that the process is working correctly and to review and monitor the accruing data to ensure the rights, safety and wellbeing of the trial participants. Composition, and roles and responsibilities of the DSMC are detailed in the DSMC charter. The DSMC reviews data from interim analyses and makes recommendations to the TSC about antiviral agent s that have reached pre-specified thresholds for futility, success, or for which safety concerns have emerged.
- Trial Steering Committee (TSC) will ensure the rights, safety and wellbeing of the trial participants. They will make recommendations about how the study is operating, any ethical or safety issues and any data being produced from other relevant studies that might impact the trial. Composition, and roles and responsibilities of the TSC are detailed in the TSC charter. The TSC advises the TMG about the conduct of the study and stopping randomisation to study arms (based on recommendations received from the DSMC and/or relevant information external to the trial), and the addition of new study arms
- The Statistical Analysis Committee (SAC) will perform interim analysis and report these to the DSMC. The TMG will remain blind to these interim analyses until a recommendation is received form the TSC about stopping randomisation or safety concerns.
- Trial Management Group (TMG) – will be responsible for the day-to-day running of the trial, including monitoring all aspects of the trial and ensuring that the protocol is being adhered to. It will include Co-Investigators and will meet weekly in the first instance. Composition, and roles and responsibilities of the TMG are detailed in the TMG charter.
- A core project team (PT) from within the TMG will meet weekly or as required for operational decision making (meet daily at the start of the trial).
- Antivirals Task Force will advise on the antiviral agents to be included in the PANORAMIC trial.

8 PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good

Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

A PC-CTU SOP is in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

9 SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or
(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within one working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Declaration of Helsinki

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

10.2 Guidelines for Good Clinical Practice

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

10.3 Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheets and any proposed informing material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities, and host institution(s) for written approval. The PI and coordinating centres for each country will ensure and confirm correct regulatory approvals are gained prior to recruitment.

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

10.4 Other Ethical Considerations

If a particular arm is deemed futile and dropped, no further participants will be randomised to this arm and anyone who is currently on this arm will be informed it has been dropped.
Once a particular intervention has been declared superior and effective, that may become the comparator arm (i.e. standard care).

Participants who lack capacity to consent for themselves will only be recruited after consultation with their legal representative. Any sign of dissent in any form from the participant who lacks capacity to consent for themselves will be taken as an indication they do not wish to be involved and they will be withdrawn. Only residents of care homes who lack capacity to consent will be recruited, adults who lack capacity to consent will not be recruited from the wider community.

10.5 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

10.6 Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on the ISRCTN Database. Results will be uploaded to this register within 12 months of the end of trial declaration by the CI or their delegate. Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

10.7 Participant Confidentiality

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

10.8 Expenses and Benefits

All participants will be reimbursed with a £10 voucher as a token of recognition of giving their time and contribution to the study. There will be no prescription charges for trial antiviral agents incurred by trial participants.

11 FINANCE AND INSURANCE

11.1 Funding

The study is funded by the Department of Health and Social Care and the NIHR.
The Department of Health & Social Care will provide the antiviral agents to be evaluated in the trial without cost to the trial budget for trial use.

11.2 Insurance

The University has a specialist insurance policy in place, which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

11.3 Contractual arrangements

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

12 PUBLICATION POLICY

The Investigators (those listed on the protocol and others to be decided at publication) will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge the study funders. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

14 ARCHIVING

Archiving will be done according to the UOXF PC-CTU SOP and study specific working instructions. Research documents with personal information, such as consent forms, will be held securely at the University of Oxford's archiving facility according to the PC-CTU Archiving SOP.

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16 APPENDIX A: SCHEDULE OF PROCEDURES

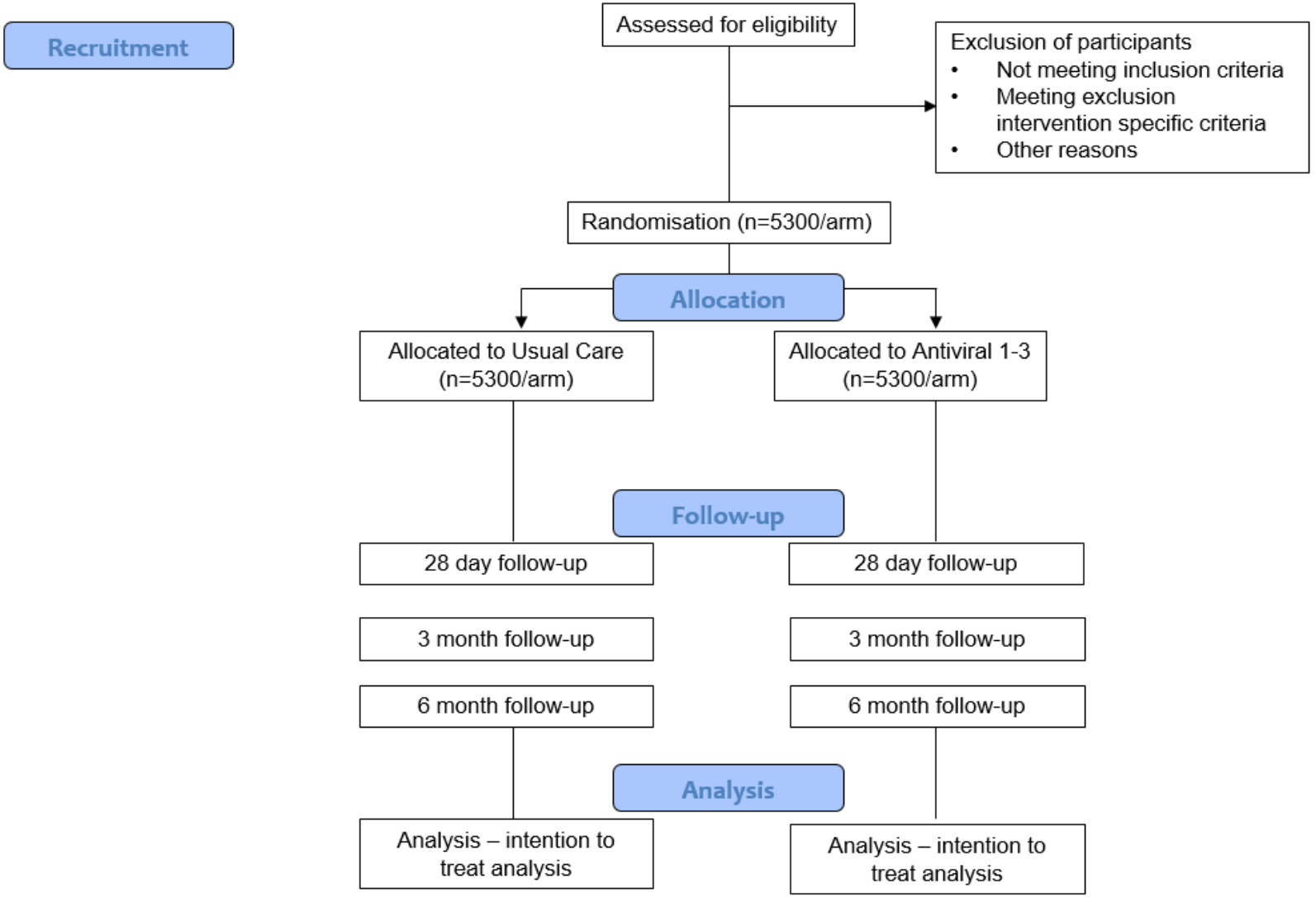
Main Trial

Procedures	Day 0	Day 0	Day 0	Day 1	Day 2	Day 0	Day 5	Daily Diary 1-28 and 3 and 6 months	Day 0 - 12mths	Up to 10 years
	Screening completed by participant online/ phone	Baseline completed by participant online/ phone	Re-affirm consent and Eligibility completed by Clinician online/ phone	Telephone call: confirm receipt of participant pack	Telephone call to all participants	Antivirals requiring face-to-face recruitment (as defined in its ISA)		Symptom Diaries completed by participant online/ phone	Retrospective data collection by study team	Data extraction from routine clinical records
						Screening/Baseline by Clinician face to face	Safety Review by Clinician face to face			
Informed consent	X	X	X			X	X	X		
Questionnaire	X	X						X		
Pregnancy test confirmation				X	X			X*		
Demographics	X	X				X			X	
Medical history	X	X	X			X			X	
Physical examination						X	X			

Concomitant medications		X	X			X			X	
Vital signs measurements (if specified in ISA)						X				
Eligibility assessment	X		X			X				
Randomisation			X			X				
Dispensing of trial drugs			X			X				
Administer drug in clinic						X				
Post drug observation (for high-risk antivirals)						X				
Compliance								X		
Primary endpoint and secondary outcomes								X	X	X
Adverse event assessments					X	X	X	X		
Safety bloods						X	X			
Evidence of sequalae and health care utilisation										X

* Days 1-3 only

17 APPENDIX B: Participant Flow Diagram



18 APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

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

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, HRA (where required) and/or MHRA.

19 APPENDIX D: SUPPLEMENTARY MATERIAL

A. Abbreviations

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
DHSC	Department of Health and Social Care
DSMC	Data Monitoring Committee / Data and Safety Monitoring Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GPDPR	General Practice Data for planning and research
GP	General Practitioner
HRA	Health Research Authority
HCP	Healthcare professional
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISA	Intervention Specific Appendix
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NIHR	National Institute of Health Research
RES	Research Ethics Service
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
R&D	NHS Trust Research and Development Department
RCGP RSC	Royal College of General Practitioners Research Surveillance Centre
REC	Research Ethics Committee
RGEA	Research Governance, Ethics and Assurance
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SmPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

B. Key Trial Contacts

Chief Investigator	Professor Chris Butler Nuffield Department of Primary Care Health Sciences Gibson Building Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG christopher.butler@phc.ox.ac.uk
Sponsor	Research Governance, Ethics and Assurance (RGEA) Joint Research Office 1st floor, Boundary Brook House Churchill Drive, Headington Oxford OX3 7GB ctrg@admin.ox.ac.uk Tel: +44 (0)1865616480
Funder(s)	UKRI/NIHR
Clinical Trials Unit	Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG panoramic@phc.ox.ac.uk Tel: TBC
Statistician	Dr Ben Saville, Berry Consultants, Austin, Texas, USA, And Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA Dr Ly-Mee Yu Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG
Committees	**DSMC Chair:** TBC **DSMC Members:**

	TBC
	TSC Chair **TBC** **TSC Members** TBC *PPI representatives* **TBC**

C. Objectives and Outcome Measures

	Objectives	Outcome Measures	Timepoint (s)
Main Study			
Primary	To determine whether antiviral treatment in the community safely reduces non-elective hospitalisations/ deaths in higher risk, symptomatic patients with confirmed COVID-19	All cause, non-elective hospitalisation and/or death, within 28 days of randomisation	Within 28 days of randomisation Patient report, Study Partner report, HES/ONS/medical record data linkage
Secondary	To explore whether antiviral treatment affects 1) Time to recovery (defined as the first instance that a participant report of feeling recovered from the illness) 2) Participant reported illness severity, reported by daily rating of how well participant feels, enabling identification of sustained recovery. 3) Duration of severe symptoms and symptom recurrence	1-3 Participant reports symptoms daily for 28 days and at 3 and 6 months.	1-3 Daily online symptom scores. Telephone call or text on days 7, 14 and 28 if data is not obtained through the online diary. Also, at 3 and 6 months.

	4) Contacts with the health services	4) Contacts with health services reported by patients and/or captured by reports of patients' medical records	4) GP notes review if available through Oxford RCGP RSC network; otherwise, other sources of routinely collected data after 28 days. Medical notes review for up to 10 years.
	5) New infections in household	5) Reports of new infections in the household from daily diary	5) Daily online symptom scores or telephone call or text on days 7, 14 and 28
	6) To investigate the safety of antiviral agents	6) Evaluation of overall safety of drugs by the monitoring of adverse events (AEs as defined in the ISAs)	6) For the duration of the antiviral course and a defined period after the antiviral finishes (see ISAs)
	7) Longer term effects	7) Well-being, symptoms and heath care utilisation	7) Patient contact at three and six months, electronic medical record search for up to one year
	8) Cost effectiveness	8) Resource use and cost data and EQ-5D-5L	8) Baseline and Day 28

D. Adverse Events

Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect*. Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. *NOTE: Pregnancy is not, in itself an SAE. In the event that a participant or their partner becomes pregnant whilst taking part in a clinical trial or during a stage where the foetus could have been exposed to the medicinal product (in the case of the active substance or one of its metabolites having a long half-life) the pregnancy should be followed up by the investigator until delivery for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".

Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial antiviral agents, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.

NB: To avoid confusion or misunderstanding the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness"

INTERVENTION SPECIFIC APPENDICES

1. USUAL CARE ARM

1. **Background and rationale**

This Usual Care arm will follow current NHS care provision, and provides a control against which the effect of new interventions that are added to usual care can be assessed. If a new trial intervention plus Usual Care is found to be superior to Usual Care alone, then the Usual Care will evolve to include interventions that are recommended as part of standard care in the NHS. Usual Care in the trial will not be specified or mandated, and it will vary over time according to emerging evidence and evolving national recommendations and will be tailored by responsible clinicians to patient characteristics, clinical picture, and individual need. In addition, individual patients will vary in the self-care they choose to use, including use of over the counter medication. Use of key treatments such as monoclonal antibodies will be captured and considered in analyses.

2. Detail of intervention

Participants randomised to the usual care arm will receive usual clinical care as per NHS care delivery practice.

a. Investigational Medicinal Product (IMP) description

Not applicable

b. Storage of IMP

Not applicable

3. Safety reporting

Mechanisms for safety reporting are outlined in the trial protocol.

2. USUAL CARE PLUS MOLNUPIRAVIR

1. Background

a. Potential mechanism of efficacy

Molnupiravir is an oral antiviral that was initially developed for treatment of influenza, but has now been developed for treatment and prevention of COVID-19.(12-14) It is a prodrug of the ribonucleoside analogue NHC that is incorporated into viral RNA by RNA-dependent RNA polymerase and inhibits viral replication by inducing *viral error catastrophe* (i.e. causing the build-up of viral mutations with each replication cycle that impair viral fitness).(14, 15)

b. Evidence for potential benefits of molnupiravir in COVID-19 illness

Pre-clinical data

Molnupiravir has been shown *in vitro* to have a high barrier to resistance and to inhibit pathogenic coronaviruses (e.g., MERS-CoV, SARS-CoV-1, and SARS-CoV-2)(8). Data from mouse,(9) ferret(10) and Syrian hamster models(11) shows that molnupiravir inhibits SARS-CoV-2 replication in vivo.

Phase 1 studies

A phase 1 study among 130 healthy adults found that molnupiravir was well tolerated with no signals of clinical concern.(12)

Phase 2/3 studies

As of 17-JUL-2020, 122 participants have received placebo or MK-4482 in single doses of 50 to 1600 mg or in multiple doses of 50 to 600 mg Q12H for 5.5 days. Molnupiravir was generally well tolerated in hospitalised and non-hospitalised participants. The proportion of participants with AEs, drug related AEs (per investigator), SAEs, and AEs leading to study intervention discontinuation during the protocol-specified AE safety follow-up period were comparable across the intervention groups, with no apparent dose effect observed. One participant was discontinued from study treatment because of a rash of moderate intensity, appearing following 3 days of dosing (6 doses) with 800 mg Q12H MK-4482 or placebo (blinded study). No clinically meaningful trends were observed for changes in clinical laboratory values as a function of dose or treatment. In study MK-4482-001 among hospitalised patients, there was a numerical imbalance in AEs resulting in death in participants treated with molnupiravir (14/218, 6.4%) compared with placebo (2/75, 2.7%). However, molnupiravir was well tolerated in both hospitalised (MK-4482-001) and non-hospitalised (MK-4482-002) participants with COVID-19, and there were no clinically meaningful differences in the incidence of AEs, SAEs, drug-related AEs, discontinuations due to AEs, and deaths observed when comparing molnupiravir to placebo, and no evidence of a dose response relationship with molnupiravir (see below). There was no apparent dose effect based on the incidence of death in each of the molnupiravir groups. None of the deaths were considered related to study intervention by the investigator, and most were associated with complications of COVID-19 or to secondary bacterial infections.

Virology data from the completed Phase 2 study (MK-4482-006) in 204 non-hospitalised participants with COVID-19 have shown that treatment with molnupiravir results in an antiviral effect, including reduction in viral load and in infectious virus as well as a higher percentage of random mutations in viral RNA posttreatment consistent with the mechanism of action (ie, viral error catastrophe).(13)

Regarding disease progression, in the ongoing Phase 2/3 randomised, placebo-controlled, double-blind MK-4482-002 study in non-hospitalised patients with COVID-19 (n=302), there was a consistent trend toward potential benefit from treatment with molnupiravir early in the course of disease as well as in individuals with risk factors for severe illness from COVID-19. Interim analyses showed the following:

- Fewer participants in the combined molnupiravir treatment groups (7/225, 3.1%) were hospitalised or died through Day 29 compared with participants in the placebo group (4/74, 5.4%).**
- While none of the comparisons reached statistical significance, the difference in the rate of death or hospitalisation favours molnupiravir in all comparisons.
- Most participants achieved sustained symptom improvement/resolution by Day 29, regardless of treatment received. However, confidence intervals were wide and did not provide clear evidence of treatment effect for time to progression or sustained improvement/resolution of COVID-19 signs and symptoms.

*** A post-hoc analysis of the primary endpoint in the subgroup of participants who were randomised within 5 days of initial COVID-19 symptom onset and who had at least 1 risk factor for severe illness was also performed: 4/107 (3.7%) participants were hospitalised in the combined molnupiravir groups compared with 4/34 (11.8%) participants in the placebo group representing an observed reduction in the relative risk for hospitalisation of 68%.*

A systematic review of early studies suggest benefit in terms of reduced hospital admissions.(16)

2. Detail of intervention

Participants randomised to the Usual Care plus molnupiravir arm will receive Usual Care as per NHS guidelines, plus molnupiravir for five days.

a. ***Precautions***

No adverse drug reactions have been defined for molnupiravir based on current data safety data from a Phase 1 study (MK-4482-004) in 130 healthy participants who received single doses up to 1600 mg (including the food effect panel) and multiple doses up to 800 mg Q12H for 5.5 days indicate that molnupiravir was generally well tolerated.(12) One participant discontinued from study treatment because of a rash, appearing following 3 days of dosing with 800 mg Q12H molnupiravir. This AE was rated as mild in intensity and considered by the investigator to be related to study drug.

Safety data from Phase 2 studies show that all evaluated molnupiravir doses were generally well tolerated in both hospitalised (MK-4482-001) and non-hospitalised (MK-4482-002) participants with COVID-19. No clinically meaningful differences in the incidence of AEs, SAEs, drug-related AEs, discontinuations due to AEs, and deaths were observed when comparing molnupiravir to placebo, and no evidence of a dose response relationship with molnupiravir.

There were no clinically meaningful trends for changes in liver enzymes or amylase and lipase as a function of either dose or treatment. Additionally, there were no meaningful abnormalities in haematological parameters as a function of either dose or treatment, and no evidence of changes relative to baseline in any haematological parameters over time in those treated with molnupiravir compared with placebo through Day 29. Preliminary unblinded safety data from MK-

4482-006 in non-hospitalised participants and blinded safety data from hospitalised participants in MK-4482-007 support the above safety conclusions. In MK-4482-001, there was a numerical imbalance in AEs resulting in death in hospitalised participants treated with Molnupiravir (14/218, 6.4%) compared with placebo (2/75, 2.7%). There was no apparent dose effect based on the incidence of death in each of the molnupiravir groups. None of the deaths were considered related to study intervention by the investigator, and most were associated with complications of COVID-19 or to secondary bacterial infections.

A dose-escalating, open-label, randomised-controlled (standard-of-care) Bayesian adaptive Phase I trial of adult outpatients with PCR-confirmed SARS-CoV-2 infection within 5 days of symptom onset randomised participants in 2:1 in groups of 6 participants to 300, 600 and 800mg doses of molnupiravir orally, twice daily for 5 days or control. A dose was judged unsafe if the probability of 30% or greater dose-limiting toxicity (the primary outcome) over controls was 25% or greater. Secondary outcomes included safety, clinical progression, pharmacokinetics and virological responses. Of 103 participants screened, 18 participants were enrolled between 17 July and 30 October 2020. Molnupiravir was well tolerated at 300, 600 and 800mg doses with no serious or severe adverse events. Overall, 4 of 4 (100%), 4 of 4 (100%) and 1 of 4 (25%) of the participants receiving 300, 600 and 800mg molnupiravir, respectively, and 5 of 6 (83%) controls, had at least one adverse event, all of which were mild (grade 2). The probability of 30% excess toxicity over controls at 800mg was estimated at 0.9%. They concluded that molnupiravir was safe and well tolerated at a dose of 800mg twice daily for 5 days.(17)

b. Pregnancy and lactation

In the reproductive and developmental toxicity studies, there were no molnupiravir-related effects on female or male fertility or early embryonic development up to the highest dose tested, 500 mg/kg/day (2.1/6.1-fold (female/male) the clinical NHC exposure at 800 mg Q12H). In pregnant rats dosed with molnupiravir during the organogenesis period, developmental toxicity including embryolethality (postimplantation losses) and teratogenicity was observed at 1000 mg/kg/day (7.5-fold the clinical NHC exposure at 800 mg Q12H), and reduced fetal growth was noted at ≥500 mg/kg/day (2.9-fold the clinical NHC exposure at 800 mg Q12H).
There was no developmental toxicity at doses up to 250 mg/kg/day (0.8-fold the clinical NHC exposure at 800 mg Q12H). In pregnant rabbits, developmental toxicity was limited to reduced mean fetal body weights at 750 mg/kg/day (18-fold the clinical NHC exposure at 800 mg Q12H). There was no developmental toxicity in rabbits at up to 400 mg/kg/day (6.5-fold the clinical NHC exposure at 800 mg Q12H).

There are no human studies of its use among pregnant or lactating women.

Pregnancy (known or suspected) and breast-feeding are exclusions for the molnupiravir arm of the trial based on the currently available data:

- Limited information on animal reproductive toxicity studies is provided in the SmPC.
- There is evidence for the potential teratogenicity of molnupiravir.
- The effects of molnupiravir on pregnant people are unknown.

To mitigate the risk of pregnancy in the trial, all participants of child-bearing potential will be required to take a urine pregnancy test prior to commencing trial treatment. We will confirm a negative test result during the Day 1 or Day 2 telephone call with a member of the trial team (see

section 2.8 of the master protocol for further information). Before starting the trial treatment the clinician/research nurse will explain to the participant that pregnancy is an exclusion criterion, and explain the contraception requirements during the trial. If the participant confirms that there is a possibility that they may be pregnant during this call, they will be excluded from taking part.

As per 'PC-CTU SOP TM119 Pharmacovigilance', any pregnancy that occurs during molnupiravir (antiviral agent) administration requires monitoring and follow-up until the outcome of the pregnancy is known. The CI, PI or delegated individual will report any pregnancy occurring whilst in the trial to the PC-CTU.

Participants themselves will be asked in their daily diaries or during the day 7, 14 and 28 phone calls, whether they have become pregnant since enrolling into the trial. These responses will be monitored daily and if a participant does become pregnant during the trial, the clinical team will inform them to immediately stop the medication. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be obtained. The CI or delegated individual will liaise with the relevant Obstetrician or equivalent healthcare professional throughout the pregnancy until delivery to monitor for congenital abnormality or birth defect, at which the pregnancy would fall under the definition of serious and require reporting as an SAE.

The DMSC will be informed of any pregnancies in this treatment group, in weekly safety reports. Pregnancies and outcomes will be included in annual safety reports.

3. Trial Visits

As per Master Protocol

4. Outcome Measures

As per Master Protocol

5. Eligibility criteria (in addition to master protocol)

Inclusion criteria:

- Willingness to take a pregnancy test prior to starting molnupiravir treatment (Participants of childbearing potential)

Exclusion criteria:

- Known or suspected pregnancy*
- Breastfeeding
- Participants of childbearing potential (participants who are anatomically and physiologically capable of becoming pregnant), or have a partner of childbearing potential, not willing to use highly effective contraceptive** for 28-day duration of the trial, and who do not confirm a negative pregnancy test prior to starting the drug.
- Known allergy to molnupiravir
- Currently taking molnupiravir

* As recorded by the participant on the screening form and confirmed by interaction between clinician and participant, and the pregnancy test supplied by the trial.

** Highly effective methods have typical-use failure rates of less than 1% and include sterilisation and long-acting reversible contraceptive (LARC) methods (intrauterine devices and implants) OR if a couple are using another method of contraception, such as a combined hormonal method, progestogen only pill or injection, they are only eligible if they are willing to use an additional barrier method (e.g. male condom) for the 28-day duration of follow-up in the trial.
Note: a barrier method on its own is not sufficient.

To confirm that the participant meets the criteria defined above, information will be elicited through a direct discussion between the clinician/research nurse and the participant, and can be randomised to molnupiravir if the recruiting clinician considers the potential participant is eligible.

6. Antiviral Agent: Molnupiravir

Dose
Molnupiravir 200 milligram (mg) capsules. The capsules are for oral administration. Four 200mg capsules (800mg) molnupiravir to be taken every 12 hours (twice a day), for five days. This regimen was identified and found to be safe in a dose finding study,(17) and has been used in a clinical trial in which early reports indicate was safe and efficacious.(18)

Common side effects
Common side effects, according to the SmPC, include dizziness, headache, diarrhoea and nausea. These symptoms will be collected in daily diaries and calls on 7, 14 and 28 and will be monitored weekly by DSMC committee.

Concomitant medications
Molnupiravir has been found to lack inhibitory or inductive activity towards xenobiotic metabolic enzymes and transporters tested in vitro, suggesting that the potential for DDIs between molnupiravir/NHC and co-medications is low.

Licensing Status
At the time of writing, the MHRA has approved the IMP for a Conditional Marketing Authorisation.

Manufacturer
Merck Sharp & Dohme (UK) Limited, Marketing Authorisation Number: PLGB 53095/0089.

Labelling and QP release
Vertical Pharma Resources Ltd (trading as IPS Pharma), 41 Central Avenue, West Molesey, KT8 2QZ, UK Authorisation number: WDA (H) 32879, will label and QP release the medication for trial purposes in accordance with Annex 13.

Storage
All study medication is to be kept in a dry area, stored at 1° to 30°C (59° to 86°F). We will ask participants to store the medication at room temperature.

The medication will be stored at Vertical Pharma Resources Ltd in locked cupboards in restricted access rooms. It may also be stored securely with restricted access in: the Nuffield Department of Primary Care Health Sciences; in GP Practices; in Pharmacies.

Distribution

Molnupiravir will be labelled and QP released by an accredited licensed central facility: Vertical Pharma Resources Ltd. Vertical Pharma Resources Ltd will prepare and dispatch the participant pack containing IMP, directly to the participant at home, in accordance with their SOPs. The labelled and QP released Molnupiravir can also be held by the PC-CTU and study Hubs, from where it may also be issued to participants.

Drug Accountability

No additional mechanisms for drug accountability are required beyond those outlined in the master protocol.

Drug Destruction/Returns

Participants will be asked to return unused molnupiravir to the PC-CTU via pre-paid courier, which will be documented in accountability logs. After a final reconciliation of drug accountability records and authorisation by the sponsor or delegate, unused study medication at the PC-CTU and Vertical Pharma Resources Ltd will be disposed of in line with local SOPs. Unused study medication may be destroyed by an authorised third party.

Overdose

There is no human experience of overdosage with Lagevrio. Treatment of overdose with Lagevrio should consist of general supportive measures including the monitoring of the clinical status of the patient. Haemodialysis is not expected to result in effective elimination of NHC. (SmPC, section 4.9). In line with the SmPC we will monitor potential overdoses by asking in the daily diary and Day 7,14 and 28 call CRF whether the participant has taken more than the specified dose. A safety alert will be triggered if the participant records that they have exceeded the dose. A Doctor from the central clinical team will contact the participant immediately and follow-up accordingly, with a minimum of daily telephone calls for 7 days to monitor any potential AEs caused by the overdose.

7. Safety reporting

a. Adverse-effects

Pregnancy will be recorded as an AE of Special Interest.
Reporting period: Occurring within 28-day following first administration of the IMP as requested by the MHRA. Such events discovered after 28-day time point, will also be reported.

b. Reference Safety Information (RSI)

See section 4.8 of the SmPC, Merck Sharp and Dohme (UK) Limited, 04 Nov 2021.

c. **Risk/Benefit Assessment**

The UK Antivirals Task Force established by the Department of Health and Social Care recommends including molnupiravir into the PANORAMIC platform with an 800mg twice a day, for five days**,** based on a review of efficacy and safety data.

i. Risks

In the available six clinical studies in participants with COVID-19 (n=922 with COVID-19 receiving placebo or molnupiravir as multiple doses up to 800 mg for 5 days), molnupiravir was well-tolerated, with no clinically meaningful trends were observed for changes in clinical laboratory values as a function of dose or treatment.

In one phase 1 randomised, double-blind, placebo-controlled SAD/MAD study (single ascending dose/multiple ascending dose) in 130 healthy adult male and female participants, receiving placebo or molnupiravir in single doses of 50 to 1600 mg or in multiple doses of 50 to 800 mg twice daily for 5.5 days, overall, found no clinically meaningful trends for changes in clinical laboratory values, vital signs, or ECGs as a function of dose or treatment.(12) No clinically meaningful haematological laboratory test result abnormalities were observed. Transient elevations in serum lipase of ≥3-times the ULN were observed ≥3 days after the last dose of study drug in a low and similar proportion of molnupiravir and placebo recipients and were not associated with clinical symptoms of pancreatitis.

In a Phase 2 study randomised, placebo-controlled, double-blind study in hospitalised patients with COVID-19, there was an imbalance in mortality rates in patients treated with molnupiravir (14/218, 6.4%) compared with placebo (2/75, 2.7%). None of the deaths were considered related to study intervention by the investigators, and most were associated with complications of COVID-19 or to secondary bacterial infections.

Taking this evidence into account, participation requires participants to agree to use adequate contraception for the duration of the treatment and 28 days of follow-up.

ii. Benefits

Molnupiravir may reduce SARS-CoV-2 viral loads, COVID-19 symptoms, risk of onward transmission, and severity of disease.

Virology data from clinical studies (Part 1 of MK-4482-001 in hospitalised patients and MK-4482-002 in non-hospitalised patients) show that treatment with molnupiravir reduces the SARS-CoV-2 VL compared with placebo (based on change from baseline, slope of decline, and greater proportion of participants with a VL below the LOQ at early time points) in non-hospitalised participants enrolled in MK-4482-002 and participants who had COVID-19 symptom onset ≤5 days prior to randomisation in both MK-4482-001 and MK-4482-002. In addition, consistent with the proposed mechanism of action of molnupiravir of viral error catastrophe, the highest percentage of mutations in viral RNA post-treatment at Day 5 were observed in the 800 mg Q12H intervention group in MK-4482-001 and MK-4482-002.

In hospitalised participants (MK-4482-001), the observed rate of sustained recovery through 29 days was low for all studied doses of molnupiravir as compared with placebo. While no clear dose effect was observed across molnupiravir doses studied, there were a higher number of deaths through Day 29 in participants who received molnupiravir compared with placebo. None of the deaths were assessed as related to study intervention.

In non-hospitalised participants (MK-4482-002) evaluation of the primary clinical efficacy endpoint showed that 11 of 299 participants were hospitalised through Day 29 (; ~3% of

participants in the molnupiravir intervention groups were hospitalised or died through Day 29 (compared with ~5% in the placebo group). All hospitalised participants had at least 1 risk factor for severe illness from COVID. Protocol-specified subgroup analyses for the primary endpoint indicated potential clinical benefit from treatment with molnupiravir early in the course of disease (ie, symptom onset ≤5 days prior to the day of randomisation) as well as in individuals with risk factors for progression to severe illness from COVID-19, including age >60 years.

d. Risk Assessment: Oral Molnupiravir Four 200mg capsules (800mg) molnupiravir, twice a day, for five days.

Hazard	Likelihood (L,M,H)	Impact (L,M,H)	Mitigation	Monitoring
1. Pregnancy: i. Potential teratogenicity ii. There are no human studies of use among pregnant or lactating people.	H	H	Requirement for negative pregnancy test in participants of child-bearing potential, prior to starting medication. We will exclude known pregnancy, breastfeeding, and require participants to use adequate contraception for the duration of the treatment and 28 days of follow-up, including participants with a partner with child bearing potential. During the pre-randomisation call, the clinician/research nurse will confirm this exclusion criteria with the participant.	Confirmation of negative pregnancy test documented in the Day 1 and/or Day 2 Call CRFs and Daily Diary We will monitor daily responses to the question 'have you become pregnant since starting the trial?' and follow-up as required to immediately stop treatment, if applicable. Pregnancy occurring during the 28-day trial follow-up period will be reported as an AE of Special Interest. As per 'PC-CTU SOP TM119 Pharmacovigilance', any pregnancy that occurs during IMP administration requires monitoring and follow-up until the outcome of the pregnancy is known. The CI or delegated individual will

				liaise with the relevant Obstetrician throughout the pregnancy. The DMSC will be informed of any pregnancies in this treatment group, in weekly safety reports.
2. Unknown/other potential side-effects	M	M	All participants will receive a call on day 1 to make sure that they understand the possible risks associated with molnupiravir and how to report potential side-effects and seek medical care if required. Participants will be provided with a 24 hour contact telephone line to report any AEs that they experience and are concerned about, directly to a clinician. We will collect symptoms and side effects from symptom diaries and participant telephone calls.	The DMSC will review weekly reports of unblinded symptom data to identify potential side-effects of molnupiravir. Any safety signals will be communicated to the TSC and TMG. The TMG will monitor SAEs, AEs and calls to the 24hr safety phone line, for potential safety signals,
3. Compliance			Participants will be asked in their daily diaries about trial medication use	The trial team will monitor daily diary responses where the participant indicates that they have taken too much IMP, and

				escalate to the clinical team to follow-up with the participant.