

Trial Title: Platform Randomised trial of INterventions against COVID-19 In older peoPLE

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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.

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

Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE): Overview

Background: There is an urgent need to identify effective treatments for SARS-CoV-2 infection, that reduce the need for hospital admission and reduce the time to recovery. We have established an open, adaptive, platform trial to evaluate treatments suitable for use in the community for treating COVID-like-illness that might prevent hospitalisation and/or death and help people recover sooner.

Eligibility and randomisation: This protocol describes a randomised trial for people in the community aged 65 and over, or 50 and over with comorbidity, with possible (in accordance with the United Kingdom’s Chief Medical Officer’s syndromic case definition) or confirmed SARS-CoV-2 infection. Participants are randomised to receive either usual care or a trial treatment (see appendices for details of all trial arms). Participants can take part in the study if they are eligible to be randomised to at least one intervention arm as well as the Usual Care arm.

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

Response adaptive randomisation: The initial randomisation ratio is fixed 1:1 for a comparison between two trial arms, but the trial has the capability for these proportions to be altered according to participants’ responses to interventions. Pre-specified decision criteria allow for dropping a treatment for futility, declaring a treatment superior, or adding a new treatment to be tested. If at any point a treatment is deemed superior to the usual care arm, the superior treatment may replace the usual care arm as the new standard of care. In the context of the COVID-19 pandemic, the trial may continue as long as the pandemic persists.

Outcomes: The trial has co-primary endpoints: 1) Time taken to self-reported recovery; and 2) hospitalisation and/or death. The main objective of the trial is to assess the effectiveness of the interventions in reducing time to recovery and in reducing the incidence of hospitalisation and/or death.

Key secondary outcomes include: Hospital assessment without admission; Oxygen administration; Intensive Care Unit admission; Mechanical ventilation (components of the WHO Clinical Progression Ordinal Scale); Duration of hospital admission; Duration of severe symptoms; Sustained recovery; Contacts with the health services; Consumption of antibiotics; Effects in those with a positive test for COVID-19 infection; WHO Well-being Index.

See *supplementary material C* for details of objectives and outcome measures.

Efficient study design: All enrolment (screening, informed consent, eligibility review and baseline data) and follow-up procedures (daily diary, hospitalisations and deaths) can be performed and captured online on the trial website or by telephone with a member of the trial team. Randomisation is online and automatic following eligibility confirmation. Participant packs and medications are sent from the central study team directly to the participant.

Data to be recorded: We will capture demographic features including ethnicity and care home residency at baseline. In the online daily diary (completed for 28 days)/ during telephone calls, participants or their Study Partners will rate the severity of symptoms, record contacts with the health services (including hospital admission), record medication use, and new infections in the household. The WHO-5 Wellbeing Index, a five-question instrument, will assess wellbeing at baseline and on days 14 and 28. Follow-up beyond 28 days after randomisation will be accessing electronic medical records and by participant questionnaire for information relevant to the longer term consequences of COVID-19.

Numbers to be randomised: The trial will continue until either superiority or futility is claimed for each intervention. We estimate that approximately 400 participants per arm (800 participants total if only a single intervention vs. Usual Care) will be required to provide 90% power for detecting an approximate difference of 2 days in median recovery time. We estimate that approximately 1500 participants per arm (3000 participants total if only a single intervention vs. usual care) will be required to provide 90% power for detecting a 50% reduction in the relative risk of hospitalisation and/or death.

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1. BACKGROUND and RATIONALE

We urgently need to know whether potential interventions for COVID-19-like-illness that are suitable for use in the community might help affected individuals recover more quickly and reduce the risk of hospitalisation and/or death. PRINCIPLE is a platform trial designed to efficiently evaluate potential treatments for people with COVID-19-like-illness, and who may be at higher risk of poorer outcomes. Eligible participants are those who meet the UK Chief Medical Officer's definition of COVID-19 illness, who are being managed in the community, and who are aged 50 and over with certain comorbidities, and those aged 65 and over (1-4).

The platform trial has the flexibility to allow additional interventions to be added in, or to replace existing interventions according to pre-specified criteria. If at any point a treatment is deemed superior to the usual care arm, the superior treatment may replace the usual care arm as the new standard of care. All approved intervention arms are outlined in Intervention Specific Appendices (ISAs).

The trial has co-primary endpoints: 1) Time taken to self-reported recovery; and 2) Hospitalisation and/or death. The main objective of the trial is to assess the effectiveness of the respective interventions in reducing time to recovery and in reducing the incidence of hospitalisation and/or death.

The primary analysis will be by "intention to treat", with secondary "intention to treat infected" analyses based on identified aetiology. Clinical data, and information from swab and blood tests, where available, will be used to classify participants according to aetiology.

2. TRIAL DESIGN AND PROCEDURES

PRINCIPLE is an open, prospective, individually randomised, platform, response adaptive, controlled clinical trial in community care.

2.1 Participant Identification

2.1.1 Trial Participants

The trial aims to include participants aged 50 and over with certain comorbidities, and those aged 65 and over with confirmed or possible COVID-19 who meet the case definition for COVID-19, and who are well enough to remain in the community. This definition can be found here: <https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases/investigation-and-initial-clinical-management-of-possible-cases-of-wuhan-novel-coronavirus-wn-cov-infection>

The study is for people who have ongoing symptoms.

2.1.2 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study;
- Participant is willing to comply with all trial procedures;
 - SARS-CoV-2 infection (suspected due to symptoms or laboratory confirmed). Onset of symptoms or a **positive test** for SARS-CoV-2 infection with symptoms of COVID-19 must be within the last 14 days.

- Age criteria: Patients aged ≥ 65 , or Patients aged $\geq 50-64$ years and meeting at least one of the following criteria:
- Known weakened immune system due to a serious illness or medication (e.g. chemotherapy);
- Known heart disease and/or a diagnosis of high blood pressure;
- Known asthma or lung disease;
- Known diabetes;
- Known mild hepatic impairment;
- Known stroke or neurological problem;
- Self-report obesity or body mass index ≥ 35 kg/m²

2.1.3 Exclusion Criteria

- Patient currently admitted in hospital
- Almost recovered (generally much improved and symptoms now mild or almost absent)
- Judgement of the recruiting clinician deems ineligible.
- Patient already taking an intervention arm medication
- Previous randomisation to an arm of the PRINCIPLE trial

Additional exclusions specific to each intervention arm are listed in the ISAs. For participation, participants must be eligible to be randomised to at least one intervention arm as well as the Usual Care arm.

2.2 Trial procedures

2.2.1 Recruitment

Recruitment is possible through a variety of mechanisms:

2.2.2 Face to face

Attending clinicians, including research nurses or other health care professionals, at general medical practices, paramedic services, hospital emergency departments, clinical care hubs, Hospital at Home facilities, care of the elderly services, pharmacies, social care services, residential and nursing homes, or any health and social care facility, can facilitate recruitment into the trial. They can do this by discussing the study with potentially eligible participants, guiding them through informed consent procedures, collection of baseline data, completion of screening questions, collecting information for eligibility assessment, and randomising the participant. If required and appropriate, licensed prescribers may prescribe the medication appropriate to the group to which the participant is randomised. Alternatively, health care professionals may revert to the PC-CTU to complete the activity, including eligibility confirmation and issue of study medication and materials.

2.2.3 Remote recruitment

i) All Health, health related, and Social Care professionals will be able to give information verbally or via a trial text, email, poster, social media post, adverts, media release, leaflet or letter, to

potential study participants and their study partners. They may also direct patients to the online study information and the study website.

ii) Potential participants may present directly to the study team via the website or by the study telephone contact. The study team can provide information about joining the trial and guide them through the consent and enrolment process.

iii) A General Practice may be contacted by a potential participant or the practice may contact patients, by text (or by letter), who may match the trial eligibility criteria, through running searches of their database. They will then direct patients to the trial enrolment website or seek verbal consent to be contacted by the trial team.

iv) NHS Digital will provide the PRINCIPLE trial with a daily list of contact details from the COVID-19 testing Pillar 2 data, for patients receiving a positive test result for SARS-Co-V2 infection, via a secure transfer system. NHS digital will apply an age filter to ensure only the details of those within the age range of the trial are passed on to PRINCIPLE. The trial team will make a limited number (maximum of 3) of attempts to telephone, text or email these patients to provide them with information about the trial, to invite them to consider taking part, and to enrol them if they provide full informed consent and are deemed eligible at screening.

Patient details will be provided in accordance with section 251 under the General Notice under the Health Service Control of Patient Information Regulations 2002, which applies only in England and Wales, providing patient information without consent for COVID-19 public health, surveillance and research purposes. The notice provides a temporary legal basis to avoid a breach of confidentiality for COVID-19 purposes.

For all recruitment models:

- Study Partner: at screening the potential participant will be asked to provide contact details for a Study Partner, to assist in completing trial procedures and to provide information on their behalf where necessary, but this is not a requirement for trial participation.
- Participants may be asked if they wish to enrol in additional studies that do not conflict with the main PRINCIPLE trial. Those who do not screen as eligible for PRINCIPLE may be alerted to the possibility of participating in other approved trials.

2.3 Screening

An online screening, eligibility and consent procedure is used. If online access is not possible, a member of the trial team collects this information during a telephone call. A trial free-phone number enables participants to contact the trial team for further information and study participation support. Participants are screened after they have read the PIS by completing an online eligibility questionnaire.

2.4 Informed Consent

If participants meet the screening criteria, they will be asked to provide informed consent and a screening trial ID number will be assigned to them. Remote, paperless online/telephone consent

is required, and appropriate during the pandemic. Participants will be able to download their consent form, or it may be printed by the central study team and delivered to participants with their study materials if they so prefer.

Written and verbal versions of the PIS and ICF will be presented to participants detailing no less than: the exact nature of the trial; 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 summary, pictorial PIS is available. 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, the participant will enter online baseline information, including their address, contact details and those of a Study Partner.

2.5 Eligibility Assessment

Eligibility of those who have provided appropriate consent can be checked at study sites or centrally by a medically qualified clinician or a research nurse, who is suitably trained and experienced and has been delegated this responsibility, and who has appropriate access to the participant's summary care record or relevant medical information. If a participant's summary care record cannot be accessed centrally, the clinician/delegate will contact the participant's primary care medical practice for information relevant to confirming eligibility. Participants will not be randomised to an arm if an exclusion criterion to that arm applies to them, but will need to have no exclusions relevant to at least one intervention and the usual care arm.

2.6 Randomisation

Participants will be randomised using a fully validated and compliant web-based randomisation system called Sortition. Once deemed eligible, the clinician or a member of the trial team will randomise the participant, to one of the arms they are eligible for (at least two arms), automatically by Sortition. Full details of response adaptive randomisation are described in section 5.2.

The participant, trial team and participant's GP will be notified electronically of the treatment allocation. If the participant does not have an email address, they will be notified by telephone. The research team may also send the GP or Care Home an email or letter via secure systems, containing personally identifiable data and treatment allocation.

2.7 Blinding and code-breaking

PRINCIPLE is an open-label trial. The participant 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. During the course of the trial, only those on the Data Safety and Monitoring Committee will have access to the unblinded interim results.

2.8 Baseline Assessments

Once randomised, study medication (if so randomised), and a participant pack will be sent to participants, from their general practice, study team, Public Health England (PHE) or other approved central service (or collected from a general practice or pharmacy). Participants may be offered a swab test as part of standard care. Where possible, and availability of sampling kits allows, one sample will be taken as close to study entry as possible to assess COVID-19 status and other viral aetiologies. While the aim is to have a swab result for all patients, where swabs are unavailable, patients may still participate and be included in the primary intention to treat analysis only.

2.9 Subsequent Visits

There is no requirement for participants to have a face-to-face visit as part of trial participation. All subsequent measurements consist of self-completed questionnaires online or through telephone calls, and primary care and/or hospital record searches. We will ascertain relevant data from primary care and/or hospital medical records about length of hospital stay, oxygen therapy, and ICU admission and ventilation, if applicable.

Participants will be sent a link to their online diary, which they will be asked to complete for 28 days. They will be asked to rate the severity of symptoms, record contacts with the health services (including hospital admission), record medication use and new infections in the household. It is becoming increasingly apparent the COVID-19 infection may have a considerable negative impact on well-being (14) and so the five questions of WHO-5, validated for measuring wellbeing over time, will be presented at baseline and on days 14 and 28. We will capture ethnicity and care home residency at baseline and day 28 (if missed at baseline).

All participants receive a call from the trial team on day 2/3 to confirm that they have received a participant pack, and trial medication (if randomised to a trial medication), and to explain that they should complete the daily diary for 28 days even if they feel better or their swab result is negative. The trial team calls participants/study partners on days 7, 14 and 28 if they do not have internet access or have *not* completed their diary for at least 2 consecutive days prior to the call. No more than six contact attempts will be made at each of these follow-up points.

We will seek consent from participants to contact them on a monthly basis for up to 12 months after enrolment (via email, text message or phone call) to collect information about any ongoing symptoms, hospitalisations and well-being. We will re-consent those already enrolled in the trial.

In addition to the swab being undertaken as part of the national RCGP RSC surveillance programme with PHE, trial participants will also be asked to consent to the trial team accessing a blood sample result.. The study team will obtain the result from RCGP RSC/PHE.

The RCGP RSC will report to the central trial office at regular intervals about healthcare contacts in the participant's clinical records, as they are able to download this information centrally. This will be used as confirmation and a back-up for information obtained directly from study participants and other data sources outlined above. If obtaining data is not possible using this

route, the GP surgery will be contacted to request a limited notes review. Participant records will be accessed up to twelve months following enrolment to ascertain follow up data from enrolment to day 28. 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.

2.10 Qualitative Sub-study

A qualitative sub-study will be nested within the trial, to capture data to understand how patients conceptualise their illness and how they respond to taking medication(s) as part of the trial. Once participants have completed the trial, we will interview their respective clinicians to explore their views of taking part in trials during a pandemic. Healthcare professionals will also be asked about their experiences of taking part in the trial. See *supplementary material E* for further details.

2.11 Early Discontinuation/Withdrawal of Participants

Each participant has the right to withdraw from the study at any time. 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 having been overlooked at screening)
- 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.

2.12 Definition of End of Trial

Last data capture of last participant, when: no further suitable interventions are available and/or COVID-19 is no longer prevalent. March 2022 has been decided as the formal end date at this stage, but this date may need to be amended depending on circumstances prevailing at the time.

3 TRIAL INTERVENTIONS

IMP information can be found in the relevant ISAs.

In general, re-packaging and issuing of medication can be completed by: the patient's registered GP surgery or treatment and assessment facility; an accredited licensed central facility; an online, community or hospital pharmacy, and The Primary Care Clinical Trials Unit (as approved by the MHRA). Distribution of trial packs to participants will be tracked via courier or call/text message. Clinicians can prescribe trial medications that can be issued in the community and pharmacies can issue medication to the patient by community pharmacy services 'on-line pharmacy' services, NHS volunteers, or it can be collected from the pharmacy by the participant or someone on their behalf.

To record presence of symptoms and severity, as well as adherence to trial treatment, participants will receive a daily email asking them to complete an online diary where they will record their symptoms and medicines use. If incomplete, the trial team will contact the participant and/or their Study Partner to obtain the data. A risk-adapted approach will be used for drug accountability. Accountability logs will be kept by PC-CTU when they ship drug.

4 SAFETY REPORTING

All symptoms, medication side-effects and SAEs will be collected from participant daily diaries, calls to participants/Study Partners, medical records, notes reviews and RCGP data downloads. SAE information will be analysed as part of the interim and whole trial analysis and will be reviewed at each Data Safety & Monitoring Committee meeting.

4.1 Procedures for Reporting Adverse Events and Serious Adverse Events

The severity of events will be assessed by participants in daily diaries on the following scale: minor problem/moderate problem/major problem. Serious Adverse Events (SAE), but not Adverse events (AE), will be assessed for causality and expectedness in the trial. A participant may voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE.

Hospitalisation and/or death due to confirmed or possible SARS-Cov-2 infection is a primary outcome, we will collect this data using a risk-adapted approach and will not report such SAEs. SAEs other than hospitalisation or death due to COVID-19 must be reported by the person who has discovered the SAE or nominated delegate 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 to see if resolution has occurred. If the event is considered 'resolved' or 'resolving' no further follow up is required. If not, the event must be followed up until such a time point.

See Appendix C for definitions of adverse events

4.1.1. Other events exempt from immediate reporting as SAEs

Hospitalisations will be defined as at least a one night admission to hospital. Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute an SAE, and standard supportive care for the disease under study are not SAEs and do not require SAE reporting.

4.1.2. Procedure for immediate reporting of Serious Adverse Events

- Trial team will complete an SAE report form for all reportable SAEs.
- GP practice/trial team/RCGP will provide additional, missing or follow up information in a timely fashion.

The CI or delegate will review the SAE once reported, collect as much information and report to the Sponsor within the timeframe according to the PC-CTU SOPs.

4.1.3 Expectedness and Causality

For SAEs that require reporting, expectedness of SARs will be determined according to the relevant RSI section of the Summary of Product Characteristics/IB. The RSI will be the current Sponsor and MHRA approved version at the time of the event occurrence.

Assessment of Causality

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

All SAEs labelled possibly, probably or definitely will be considered as related to the IMP.

4.2 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 IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

4.3 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 will be described in a Master Statistical Analysis Plan (M-SAP), in which an appendix to the M-SAP titled “Adaptive Design Report” (ADR) provides complete specifications for the primary analysis and pre-specified adaptive algorithm. In addition, the M-SAP will be accompanied by arm-specific appendices to describe any planned deviations from the M-SAP. A broad overview of the design and primary analyses is provided below.

5.2 Open Adaptive Platform Trial

PRINCIPLE is an open, adaptive, platform trial to evaluate emerging treatments for symptomatic COVID-19-like illness. A “platform trial” is a trial in which multiple treatments for the same disease are tested simultaneously. The backbone of the trial is an adaptive clinical trial design. Pre-specified decision criteria allow for dropping a treatment for futility, declaring a treatment superior, or adding a new treatment to be tested. If at any point a treatment is deemed superior to the Usual Care arm, the superior treatment may replace the Usual Care arm as the new standard of care. Because the process of dropping and adding treatments may be on-going for an indefinite period of time, platform trials may be better conceived of as a process rather than a singular clinical trial. In the context of the COVID-19 pandemic, the trial may continue as long as the pandemic persists.

The PRINCIPLE trial 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.

5.2.1 Co-Primary Endpoints & Analyses

There are two co-primary endpoints. The first co-primary endpoint is time to recovery from possible COVID-19 infection within 28 days from randomization, where time to recovery is defined as the first instance that a participant reports feeling recovered. The second co-primary endpoint is hospital admission or death related to possible or confirmed COVID-19 within 28 days from randomization. Unless otherwise specified in the ISAs, the co-primary outcomes will be evaluated using a “gate-keeping” strategy. For a given treatment, the hypothesis for the time to recovery endpoint will be evaluated first, and if the recovery null hypothesis is rejected, the hypothesis for the second co-primary endpoint of hospitalization/death will be evaluated. This gate-keeping strategy preserves the overall Type I error of the primary endpoints without additional adjustments for multiple hypotheses. In addition, the gate-keeping structure reflects the clinical belief that an intervention is unlikely to demonstrate benefit on the hospitalization/death endpoint without first demonstrating benefit on the time to recovery endpoint.

The primary outcome of time to recovery is defined as the first instance that a participant reports feeling recovered. The corresponding primary analysis for this outcome is a Bayesian piecewise exponential model, with time to recovery regressed on treatment and stratification covariates (age, comorbidity). Let θ_j denote the log hazards ratio comparing the hazards of recovery for participants in treatment group j versus participants in the Usual Care arm. A corresponding

Bayesian posterior distribution will be derived for the estimated log hazards ratio. The first co-primary analysis for intervention j will test the following hypothesis:

$$H_{10}: \theta_j \leq 0$$

$$H_{11}: \theta_j > 0$$

If the Bayesian posterior probability of superiority (a log hazards ratio greater than 0 corresponding to quicker recovery) for a treatment versus Usual Care is sufficiently large (e.g. ≥ 0.99), the null hypothesis will be rejected and the intervention will be deemed superior to Usual Care with respect to time to recovery. The exact threshold of the superiority decision criterion (e.g. 0.99) will be determined *a priori* via simulation to control the one-sided Type I error of the study at approximately 0.025, and will be specified in the Adaptive Design Report (Appendix to the M-SAP). The Adaptive Design Report will also specify appropriate methodology for the primary analysis when the Usual Care arm is replaced by a superior treatment, and for when the comparison of a treatment versus Usual Care includes non-concurrent randomisations.

The second co-primary endpoint is hospital admission or death due to possible SARS-CoV-2 infection. The corresponding analysis will be a Bayesian generalised linear model of hospitalisation/death regressed on treatment and stratification covariates (age, comorbidity). Let δ_j denote the log odds ratio comparing the odds of hospitalisation/death for persons in treatment group j versus persons in the Usual Care arm. A corresponding Bayesian posterior distribution will be derived for the estimated log odds ratio. If the first co-primary endpoint hypothesis (for time to recovery) is rejected for intervention j , the second co-primary hypothesis for intervention j be tested:

$$H_{20}: \delta_j \leq 0$$

$$H_{21}: \delta_j > 0$$

If the Bayesian posterior probability of superiority on hospitalization/death for a treatment versus Usual Care is sufficiently large (e.g. ≥ 0.99), the null hypothesis will be rejected and the intervention will be deemed superior to Usual Care with respect to hospitalization/death. The exact threshold of the superiority decision criterion (e.g. 0.99) will be determined *a priori* via simulation to control the one-sided Type I error of the study at approximately 0.025, and will be specified in the M-SAP.

5.2.2 Adaptive Design

The pre-specified design will allow adaptations to the trial based on the observed co-primary endpoint data. These adaptations include the declaration of success or futility of an intervention at an interim analysis, the addition or removal of treatment arms, and changes in the randomisation probabilities. Adaptations will occur at a given interim analysis if pre-specified conditions are satisfied. 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.

5.2.3 Interim Analyses

Precise timing of the first interim analysis and frequency of subsequent interim analyses will be specified in the Adaptive Design Report, based on both simulations and logistical considerations. At each interim analysis, all enrolled intervention arms will be evaluated for success and futility on both co-primary endpoints using the Bayesian primary analyses. These interim analyses will maintain the gate-keeping sequential order by first evaluating the hypothesis for time to recovery, and if the recovery endpoint null hypothesis is rejected, subsequently evaluating the hypothesis for hospitalisation and/or death. If the Bayesian posterior probability of superiority of a given intervention versus Usual Care is sufficiently large for a given endpoint (e.g. ≥ 0.99) within the gate-keeping structure, superiority will be declared versus Usual Care with respect to that endpoint.

If the Bayesian posterior probability of a clinically meaningful treatment effect is sufficiently small (e.g. < 0.01) for the first co-primary endpoint (time to recovery), the intervention arm may be dropped from the study for futility. If there are no other intervention arms available, the trial may be suspended; otherwise accrual continues to the remaining treatment arms. The exact futility thresholds will be pre-specified in the Adaptive Design Report and determined via simulation.

5.2.4 Allocation & Response Adaptive Randomisation

Initially, randomisation will be fixed 1:1 for a comparison between two trial arms, with stratification by age (less than 65, greater than or equal to 65), and comorbidity (yes/no). If a second experimental intervention arm is added to the study, randomisation allocation will be modified and the additional intervention will be included in the interim analyses (with evaluation for success and futility) as detailed in the Adaptive Design Report. If there are at least 3 arms (2 intervention arms plus Usual Care) in the study, each interim analysis may incorporate modified randomisation probabilities via response adaptive randomisation (RAR). Full details for implementing RAR will be provided in the Adaptive Design Report; the general idea is to allocate more participants to the intervention arms that have the best observed outcomes.

5.2.5 Sample Size Justification

Given the open perpetual trial structure, the trial does not have a finite ending based on sample size. Rather, the trial will continue until either superiority or futility is claimed for each intervention, or until the pandemic expires in the population. We estimate that approximately 400 participants per arm (800 participants total if only a single intervention vs. Usual Care) will be required to provide 90% power for detecting a hazard ratio of 1.3 (approximate difference of 2 days in median recovery time). This calculation is based on the assumption of an exponential distribution for time to recovery with a median of 9 days in the Usual Care arm, with some adjustments for missing data and multiple interim analyses. On average, we expect fewer participants to be required when there is a large treatment benefit or complete lack of benefit. For example, if the true hazard ratio is 1.5 (3 day benefit in median time to recovery), on average only 150 subjects per arm are required to provide sufficient power. The primary advantage of the adaptive design is the ability to adapt the sample size to the observed data, thus addressing the primary hypothesis as quickly and as efficiently as possible.

We estimate that approximately 1500 participants per arm (3000 participants total if only a single intervention vs. usual care) will be required to provide 90% power for detecting a 50% reduction in the relative risk of hospitalisation and/or death. This calculation is based on the assumption of

an underlying 5% combined hospitalisation and/or death rate in the Usual Care arm, with an intervention lowering the hospitalisation and/or death rate to 2.5%, with some adjustments for the multiple interim analyses. We expect fewer participants to be required to detect a 50% reduction if the event rate in the Usual Care arm is greater than 5%.

5.2.6 Virtual Trial Simulations

Because of the adaptive platform trial structure, there exists no simple formula(s) to calculate power and Type I error (false positive rate). Hence, virtual trial simulations will be used to fully characterize and quantify the power and Type I error of the design. These simulations will be conducted prior to the first interim analysis (with results described in the Adaptive Design Report), and will be used to optimize the adaptive decision criterion and RAR parameters. The simulations will include a comprehensive evaluation of trial performance across a wide range of assumptions (e.g. underlying distribution of outcome in Usual Care arm, treatment effect, accrual rates, etc.). This will include summaries regarding the number of subjects required to make a success or futility conclusions for each intervention. Complete details of the simulations will be provided in the Adaptive Design Report.

5.2.7 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 all randomised participants according to the groups they were randomly allocated to, regardless of deviation from protocol and irrespective of their COVID-19 status. Secondary analyses will conduct the primary analysis on the subset of participants with confirmed COVID-19.

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 Report. Reasons for these changes will be documented and authorised by the Chief Investigator.

5.5 Qualitative sub-study analysis

Audio-recordings of interviews will be transcribed verbatim and transcripts analysed using thematic analysis. Patient and HCP interviews transcripts will be analysed separately but findings will be compared and triangulated if deemed appropriate. Thematic analysis allows the research team to take a pragmatic approach to data collection, remaining grounded in the data but ensuring that the analysis answers the research objectives. NVivo software will be used to assist with the organisation and coding of data. Codes will be compared with one another to create categories, grouping similar codes together. A thematic framework will be developed to code all data and represent key themes for both sets of interviews.

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 records (from which medical history and previous and concurrent medication may be summarised into the CRF), 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/Trial Partner, the RCGP RSC 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 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 and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

6.3 Data Recording and Record Keeping

A CTU data manager will oversee the receiving, entering, cleaning, querying, analysing and storing all data that accrues from the study by designated persons. 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 software used for the trial is described in *supplementary material D*.

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 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 Monitoring and Safety Committee (DMSC) - to review the data at each interim analysis as described in the Statistical Analysis section, as the updates to the randomisation scheme occur 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.
- Trial Steering Committee (TSC) - the Trial Steering Committee 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.
- Trial Management Group (TMG) - is 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.
- A core project team (PT) from within the TMG will meet daily as required for daily operational decision making.

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 Investigator 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 Investigator 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 will become the comparator arm (i.e. standard care).

The vast majority of participant’s, due to their co-morbidities, will be exempt from prescription charges. All participants will receive a £20 voucher to cover any prescriptions and other expenses they may incur as a consequence of study participation.

We do not intend to recruit people who do not have capacity to provide consent for themselves to participate into this study.

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

10.8 Expenses and Benefits

All participants will be reimbursed with a £20 voucher, to cover the payment of a prescription, should they incur this as a result of study participation, and a token of recognition of giving their time and contribution to the study. The vast majority of participants will not have to pay a prescription charge, should a prescription be issued as a result of trial participation. Most people with the co-morbidities outlines and in the age-range required for eligibility, are not required to pay for prescriptions. Participants who complete a telephone interview as part of the qualitative sub-study will be reimbursed with a (second) £20 voucher for their time to participate.

11 FINANCE AND INSURANCE

11.1 Funding

The study is funded by the UKRI/NIHR via an MRC call.

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.

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22 APPENDIX A: SCHEDULE OF PROCEDURES

Procedures	Participant contacts								
	Visit timing Day 0	Day 0	Day 0	Day 0	Daily Day 1- 28 incl	Day 28-12 months (monthly contact)	Day 29- 12mths	Up to 10 years	
	Screening completed by participant online/phone	Eligibility completed by participant online/phone	Baseline completed by participant online/phone	Eligibility completed by Clinician online/phone	Symptom Diaries completed by participant online/phone	Contacted by study team if consent provided	Retrospective data collection by study team	By data extraction from clinical records	
Informed consent	X	X	X	X	X				
Demographics	X	X	X				X		
Medical history	X	X	X	X			X		
Swab as part of the RCGP RSC/PHE national surveillance programme	When available, preferably by self-swabbing at study entry								
Concomitant medications		X					X		
Eligibility assessment	X	X							

Randomisation				X				
Dispensing of trial drugs				X	X			
Questionnaire					X	X		
WHO 5 Well Being Index	X				Day 14 and day 28	X		
Telephone interview (for subset of patient participants)					X			
Compliance					X			
Adverse event assessments					X*		X	
Optional SARS-CoV-2 blood test as part of the RCGP RSC/PHE national surveillance programme							X	
Evidence of sequelae and health care utilisation						X		X

* Patient reported AEs will not be assessed by a clinician. The only exception is AEs collected from the hydroxychloroquine group. Participants in this group, will receive a telephone call on day 7 from the trial team to collect any information about cardiovascular Adverse Events (please see hydroxychloroquine appendix). Such events will be assessed by a clinician.

23 APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1		Emma Ogburn; Chris Butler; Gail Hayward	Inclusion criteria: change 'known heart disease' to 'Known heart disease and/or hypertension'; Exclusion criteria: exclude patients taking the following drugs: penicillamine, amiodarone, ciclosporin, chloroquine. Update section 9.6 to include vision changes and lowering of blood sugar. Update change in Funder and update Investigator list to reflect UKRI funder bid.
2	2.0		Emma Ogburn; Chris Butler; Gail Hayward, Hannah Swayze	Inclusion of TSC; central facility to distribute patient packs; addition of third arm; update of secondary outcomes to include WHO wellbeing questions; qualitative sub study; sign posting to other RCGP RSC study; eligibility confirmation by research nurse.
3	2.1		Hannah Swayze; Chris Butler; Emma Ogburn; Gail Hayward	Trial rationale; secondary outcomes to include blood test; 14 days of covid-19 symptoms; call to participant at day 2; poster
4	2.1		<i>No changes to the protocol</i>	
5	3.0		Hannah Swayze; Chris Butler; Emma Ogburn; Gail Hayward	Updated Azithromycin information; broadening of inclusion criteria; first interim analysis; primary analysis details; care home materials; administrative and typographical updates; study partner letter; recruitment via social media, care homes and pharmacies; GPs prescribe trial medication; eligibility to at least one intervention arm as well as the

				Usual Care arm; ICF may be sent to participants.
6	4.0		Chris Butler; Emma Ogburn; Gail Hayward; Ben Saville; Ly-Mee Yu; Hannah Swayze	Updating inclusion criteria; updating the rationale and evidence for safety of hydroxychloroquine; inclusion of a new arm, doxycycline; AE reporting for hydroxychloroquine arm; typographical clarifications.
7	5.0		Chris Butler; Emma Ogburn; Ben Saville; Ly-Mee Yu; Hannah Swayze	Including a second primary outcome, time to recovery, change to sample size estimation, new eligibility criteria: obesity, formatting changes, blood test process.
8	5.0		<i>No changes to the protocol</i>	
9	5.0		<i>No changes to the protocol</i>	
10	6.0		Chris Butler; Emma Ogburn; Hannah Swayze	Addition of inhaled corticosteroid treatment arm, enrolment to additional trials, long-term follow-up, access to NHS Digital Pillar 2 test data, removal of investigators, additional trial contact with participants for up to 12 months, changes to objectives/outcomes/ timepoints, removal of sampling from study

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) or MHRA.

24 APPENDIX C: USUAL CARE ARM

1. Background and rationale

COVID-19 disproportionately affects people over 50 years old with comorbidities and those over 65 years old. The disease causes considerable morbidity and mortality in this population group in particular, and is having a devastating effect on people's health, and society in the UK and internationally.(1-3, 9) So far, there are no specific treatments for COVID-19 that have been proven in rigorous clinical trials to be effective and that can be used in the community. Clinicians managing possible COVID-19 in the community will make clinical judgements about best treatment based on the clinical situation, but care is usually supportive to begin with, unless patients deteriorate and require hospital admission (<https://www.nice.org.uk/guidance/ng163>). The National Institute for Health and Care Excellence does not recommend the immediate use of antibiotics unless there are signs of pneumonia (<https://www.nice.org.uk/guidance/ng163>).

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 alone arm will be dropped, and the intervention that is found to be most effective will become the standard of care within the trial.

2. Changes to outcome measures

None

3. 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

4. Safety reporting

Mechanisms for safety reporting are outlined in the trial protocol.

25 APPENDIX D: USUAL CARE PLUS HYDROXYCHLOROQUINE ARM (DISCONTINUED)

1. Background and rationale

a. Evidence for potential Hydroxychloroquine benefits in COVID-19

A candidate intervention for COVID-19, a drug called hydroxychloroquine, has become available following early evaluation in some studies in China.(15, 16) Hydroxychloroquine is a hydroxylated version of the drug chloroquine.(16, 17) Both agents are commonly in use as anti-malarials, and are used in a variety of auto-immune diseases. They have received significant recent interest as potential modifiers of disease activity in COVID-19. (16, 18, 19) Hydroxychloroquine is already available within the NHS on prescription for other indications, and has a generally benign safety profile.(20) Chloroquine is available to buy in the UK over the counter in some formulations and is used as antimalarial prophylaxis and treatment.

Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.(5) Besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect *in vivo*.(17) Chloroquine is widely distributed in the whole body, including lungs, after oral administration.(16) The EC₉₀ value of chloroquine against the 2019-nCoV in Vero E6 cells was 6.90 µM in one study (15) which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration.(20)

Hydroxychloroquine has been found to be effective against intracellular micro-organisms including malaria and intracellular bacteria *Coxiella burnetii* and *Tropheryma Whipplei*.(17) Both chloroquine and hydroxychloroquine have been shown to have *in vitro* antiviral activity against SARS coronavirus in a number of studies.(17) Most recently activity against SARSCOV2 was shown to be greater for hydroxychloroquine than chloroquine (21).

Key publications that have relevance to the safety and rationale for use of hydroxychloroquine in the PRINCIPLE Trial:

1. **The Mahévas study** was an observational study that assessed whether hydroxychloroquine reduced the need for transfer to ICU in patients already sick enough to be hospitalised.(22) It focussed on sicker patients with hypoxic pneumonia, some requiring ITU care. It did not find a difference in transfers to ICU. So the question and population in the Mahevas study are very different compared to PRINCIPLE. Most importantly, unlike PRINCIPLE, the Mahevas study is **not a randomised clinical trial**. Numbers were relatively small (n=181), and it is at high risk of bias due to the observational design.

Regarding safety, those receiving hydroxychloroquine were prescribed 600mg per day, whereas the dose in the PRINCIPLE trial is 400mg per day; 18% of those who received hydroxychloroquine in the Mahévas study were also on azithromycin (which can be arrhythmogenic), and this combination is not possible in PRINCIPLE because of the additive risk. Moreover, PRINCIPLE excludes several other drug combinations that could be arrhythmogenic. In the Mahevas study, eight patients (10%) who were taking hydroxychloroquine experienced electrocardiographic changes that required discontinuation of hydroxychloroquine. Critically, those in the control

group did not have ECGs done, so we don't know if there was indeed a difference between groups, and we cannot therefore attribute the ECG changes to hydroxychloroquine. COVID-19 itself, or drug interactions, may well have been underlying reasons. The authors state, "Although hydroxychloroquine is considered safe in the context of systemic lupus erythematosus, these adverse events might be explained by the use of high dose hydroxychloroquine in patients older than 75 years with renal impairment and frequent drug interactions. We cannot rule out the possibility that these cardiac effects attributed to hydroxychloroquine were caused by COVID-19, especially given electrocardiograms were unavailable during follow-up in the control group."

2. The Tang study was a hospital-based, randomised study and included 150 patients; randomisation was done using sealed envelopes.(23) The trial found no difference in the proportion of patients with two sequential negative swab results.

Regarding safety, 75 participants received hydroxychloroquine 1200 mg daily for 3 days and then 800 mg for either 2 or 3 weeks. Again, the dose used in this study was much higher than the dose being used in PRINCIPLE (initially three times, and subsequently twice as high as PRINCIPLE). However, 63% and 64% of patients in the hydroxychloroquine and control groups respectively also received other antiviral agents. In PRINCIPLE, we are not evaluating the combination of antiviral agents and hydroxychloroquine. Importantly, this study did not find evidence of cardiac arrhythmias associated with hydroxychloroquine use. The authors state, "Events of cardiac arrhythmia, such as prolonged QT interval were not observed in our trial, possibly because of the relatively mild to moderate disease of patients investigated or the short term period of follow-up."

3. The Mehra study published in the Lancet on 22.05.2020 reported an association between hydroxychloroquine use and cardiac events and mortality amongst patients hospitalised with COVID-19.(24) The *observational* study design is inherently susceptible to bias, the study data integrity has been queried given the homogeneity of the baseline characteristics, the adequacy of the adjustment for confounders cannot be assessed from the published methods, and the registries used are in a different patient population compared to PRINCIPLE. Patients were much sicker and more advanced in the illness than in PRINCIPLE. The authors themselves state that "*Randomised clinical trials will be required before any conclusion can be reached regarding benefit or harm of these agents (hydroxychloroquine and chloroquine) in COVID-19 patients.*" The authors also state "These data do not apply to the use of any treatment regimen used in the ambulatory, out-of-hospital setting." This study has proved hugely controversial on social media, with a number of methodological and data integrity concerns already raised, for example:

1. There were inadequate adjustments for known and measured confounders (disease severity, temporal effects, site effects, dose used).
2. The authors have not adhered to standard practices in the machine learning and statistics community. They have not released their code or data. There is no data/code sharing and availability statement in the paper. The Lancet was among the many signatories on the Wellcome statement on data sharing for COVID 19 studies.
3. There was no ethics review.
4. There was no mention of the countries or hospitals that contributed to the data source, no acknowledgments to their contributions. A request to the authors for information on the contributing centres was denied.
5. Data from Australia are not compatible with government reports (too many cases for

just five hospitals, more in-hospital deaths than had occurred in the entire country during the study period). Surgisphere (the data company) have since claimed this was an error of classification.

6. Data from Africa indicate over 40% of all COVID-19 cases and deaths in the continent occurred in *Surgisphere*-associated hospitals which had sophisticated electronic patient data recording, and patient monitoring able to detect and record “non-sustained [at least 6 secs] or sustained ventricular tachycardia or ventricular fibrillation”. This seems unlikely.
7. Unusually small reported variances in baseline variables, interventions and outcomes between continents
8. Mean daily doses of hydroxychloroquine that are 100 mg higher than FDA recommendations, whilst 66% of the data are from North American hospitals.
9. Implausible ratios of chloroquine to hydroxychloroquine use in some continents.
10. The tight 95% confidence intervals reported for the hazard ratios are unlikely. For instance, for the Australian data this would need about double the numbers of recorded deaths that were reported in the paper.

This paper has now been retracted, and the data cannot be verified.

4. The Geleris study was an observational study of 1,376 consecutive COVID-19 patients at a New York hospital to determine whether hydroxychloroquine use was associated with intubation or death, as a primary composite outcome.⁽²⁵⁾ 811 (58.9%) of these patients received hydroxychloroquine. The authors excluded patients who were intubated, died, or who were transferred to another facility within 24 hours after presentation to the emergency department from the analyses. A propensity score matching model (C-statistic of 0.81) was used to ensure that groups were similar at baseline.

Regarding safety, multivariable adjusted analyses with inverse probability weighting revealed no significant association between treatment with hydroxychloroquine and intubation or death (HR 1.04 (95% CI 0.82 – 1.32)). Whilst the patient population in this study is different to that of PRINCIPLE, it is interesting that the findings contrast with those of a recent Lancet study published by Mehra *et al*. One possible reason for the difference is that patients receiving interventions like hydroxychloroquine in the study by Mehra *et al* were sicker than those in the study’s control group. This may have arisen through use of crude measures to account for baseline disease severity (qSOFA score and SpO₂ < 94%) in their propensity score matching model, and may also explain the big differences seen in patients requiring mechanical ventilation between controls (7.7%) and those in intervention groups (20-21.6%).

5. Boulware and colleagues conducted a Covid-19 postexposure prophylaxis, placebo controlled randomised trial of hydroxychloroquine in 821 asymptomatic patients; 11.8% of those taking hydroxychloroquine vs 14.3 of those taking placebo experienced a new illness compatible with COVID-19 (absolute difference -2.4%) but this difference was not statistically significant, indicating no evidence of benefit from the hydroxychloroquine. (26)

Regarding safety, while side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), no serious adverse reactions were reported.

Earlier studies of hydroxychloroquine for COVID-19

1. **Chen** and colleagues conducted a *randomised* controlled trial to test the effectiveness of hydroxychloroquine in 30 adult patients who tested positive for COVID-19 in China.(27) Patients in the treatment group received 400mg of hydroxychloroquine for 5 days, while the control group received usual care. The result of a nasopharyngeal swab on Day 7 was used as the primary outcome. The intention-to-treat analysis revealed that the treatment group did not differ from the control group in the number of patients testing negative for COVID-19 on Day 7 (13 versus 14 patients), nor the duration of illness (all $P > 0.05$).

Regarding safety, the authors report three adverse events in the control group (one patient with abnormal liver function and anaemia, and one patient with abnormal renal function), and four adverse events in the treatment group (two patients with diarrhoea, one with lethargy, and one patient with abnormal liver function tests), which the authors argue were not linked to treatment with HCQ. One patient in the treatment group deteriorated significantly and thus HCQ was stopped on Day 4 of the treatment. This study was under-powered according to their own calculations.

2. **Gautret** and colleagues presented the results of an open-label, non-randomised trial with 36 patients diagnosed with COVID-19 in French hospitals.(28) Six participants were asymptomatic, 22 had upper respiratory tract infection symptoms, and eight had lower respiratory tract infection symptoms. The twenty patients in the treatment group received HCQ 200mg three times a day for 10 days. Patients declining to take part in the study and not meeting the inclusion criteria were assigned to the control group and received usual care. Six of the patients in the treatment group additionally received azithromycin to prevent bacterial superinfection. The primary outcome was SARS-CoV-2 carriage at Day 6 on nasopharyngeal swabs. Patients treated with hydroxychloroquine were significantly more likely to test negative for SARS-CoV-2 on Day 6 compared with controls (70% versus 12.5% virologically cured, $p < 0.001$). All patients treated with hydroxychloroquine and azithromycin tested negative on Day 6.

Regarding safety, the authors did not report any safety data, stating that this would follow in a subsequent publication. Aside from a lack of adverse event reporting, there are many problems with the study methodology including the non-randomized design, under-powered sample size, lack of intention-to-treat analysis, and absence of medium to long-term follow-up data.

3. **Chen** and colleagues conducted a *randomised* clinical trial of adult patients admitted to hospital with confirmed COVID-19.(7) Sixty two patients were randomly assigned to usual care ($n=31$) or hydroxychloroquine (200 mg BD) for five days in addition to usual care ($n=31$). The authors report that there were 'significant differences' in time to clinical recovery (TTCR) between the two groups, with TTCR defined as the return of body temperature and cough relief, maintained for more than 72 hours. They also report that all four patients who 'progressed to severe disease' were in the control group. The reporting of empirical data by the authors is limited and unclear. They did not include a power calculation, but presumably this study was under-powered to detect differences between groups. No medium to long-term follow-up data is presented.

Regarding safety, the authors report that two mild adverse events occurred (a rash and a headache), both of which were in patients receiving hydroxychloroquine. No patients receiving usual care experienced adverse events.

In summary

The large scale hospital based Recovery trial has recently announced that they found no benefit from hydroxychloroquine (as yet unpublished). No safety concerns have been reported by the Principle Trial. A post exposure prophylaxis study found no benefit from hydroxychloroquine, but also found no safety concerns. These studies address a different research question and focus on different patient populations in comparison to the Principle Trial. Evidence about early treatment of COPVID-19 in the community is urgently needed: the potential application of the findings of the PRINCIPLE Trial of community treatment is considerable, and the 'reach' of the study is now nation-wide. Our study population are patients in the community and our trial question is about early treatment. Outcome data from studies with sicker hospitalised patients may not apply to our study population

A key, controversial observational study (Mehra et al) reported that those taking hydroxychloroquine had worse outcomes and suffered more cardiac events than those not taking hydroxychloroquine. However, major doubts have been expressed about the data integrity of this study and insufficient detail in the paper to judge the adequacy of the methods employed to adjust for the inevitable confounders in an observational study. Hydroxychloroquine is not a licensed drug for treating COVID-19. Patients doing well are therefore less likely to be prescribed this drug. When a patient is causing their clinical team more concern or their condition is deteriorating, the chances of them being prescribed hydroxychloroquine will be greater. Adjustment for potential confounders has been inadequate in the observational studies. Critically, these studies cannot adjust for the clinician's sense of how the patient is faring over time. The Mehra study has been retracted and can't be relied upon.

The deficiencies and differences in all of these studies highlight the need for well-conducted, adequately powered randomised clinical trials, to provide definitive evidence of the safety and effectiveness of hydroxychloroquine for the early community treatment COVID-19 illness. PRINCIPLE will assess whether hydroxychloroquine is safe and effective if given earlier in the course of illness and in patients with milder symptoms not requiring hospital admission.

2. Eligibility criteria specifically related to hydroxychloroquine

Inclusion criteria:

Exclusion criteria:

- Pregnancy;
- Breastfeeding;
- Known severe hepatic impairment;
- Known severe renal impairment;
- Known porphyria;
- Type 1 diabetes or insulin dependent Type 2 Diabetes mellitus ;
- Known G6PD deficiency;
- Known myasthenia gravis;
- Known severe psoriasis;
- Known severe neurological disorders (especially those with a history of epilepsy—may lower seizure threshold)
- Previous adverse reaction to, or currently taking, hydroxychloroquine or chloroquine

Patients currently taking the following drugs: penicillamine, amiodarone, ciclosporin, digoxin: the following antimicrobials; azithromycin, clarithromycin, erythromycin, ciprofloxacin, levofloxacin, moxifloxacin, ketoconazole, itraconazole, or mefloquine: the following antidepressants; amitriptyline, citalopram, desipramine, escitalopram, imipramine, doxepin, fluoxetine, wellbutrin, venlafaxine; the following antipsychotics or mood stabilizers; haloperidol, droperidol, lithium, quetiapine, thioridazine, ziprasidone: methadone: sumatriptan, zolmitriptan

- Known congenital or documented QT prolongation
- Known retinal disease

3. Outcome measures related to hydroxychloroquine

There are no outcome measures related specifically to this usual care plus hydroxychloroquine arm

4. Detail of intervention

Participants randomised to the usual care plus hydroxychloroquine arm will receive usual clinical care as per NHS guidelines, plus a course of oral hydroxychloroquine 200mg twice daily for seven days.

a. Investigational Medicinal Product (IMP) description

Hydroxychloroquine sulphate 200 milligram (mg) tablets. The tablets are for oral administration. One tablet (200mg) hydroxychloroquine to be taken twice daily for 7 days by mouth (14 tablets in total).

Special instructions: Each dose should be taken with a meal or glass of milk. Antacids may reduce absorption of hydroxychloroquine so it is advised that a 4-hour interval be observed between taking hydroxychloroquine and an antacid.

This is the standard therapeutic dose for its normal indication in adults which is for the treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight.

The Marketing Authorisation holder is Zentiva Pharma UK Limited Guildford Surrey GU1 4YS United Kingdom. Marketing authorisation number is PL 17780/0748.

b. Storage of IMP

: Stored at room temperature in locked cupboards in restricted access rooms in the Nuffield Department of Primary Care Health Sciences; in locked cupboards in restricted access rooms in GP Practices; in Pharmacies.

For hydroxychloroquine, GP practices can order a supply of trial medication from Public Health England using the existing ImmForm process. GPs will be provided with an envelope by the trial team which will be labelled appropriately for trial medication, and they will add the patient's details to this label. This pack, containing instructions on using the medication will be provided to the patient or their representative.

c. SmPC precautions and concomitant medication

Hydroxychloroquine: Hydroxychloroquine will be used for short-term use (7 days) in this trial. The SmPC and precautions listed below focus on longer term chronic use.

i. Precautions

Hydroxychloroquine might lower blood sugar levels in some people. If participants develop these symptoms, they will be advised in the Patient Information documents to eat something sweet and seek clinical advice if the symptoms continue.

Hydroxychloroquine occasionally causes blurred vision, which typically resolves once the medication is stopped. Participants will be advised via the Participant Information documents that if they develop any problems with vision, they should stop taking the medication immediately, seek clinical advice, and not drive or operate any heavy machinery.

ii. Concomitant medication

Hydroxychloroquine sulfate has been reported to increase plasma digoxin levels. Serum digoxin levels should be closely monitored in participants receiving concomitant treatment.

Hydroxychloroquine sulfate may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared. These include: potentiation of its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics; inhibition of its metabolism by cimetidine which may increase plasma concentration of the antimalarial; antagonism of effect of neostigmine and pyridostigmine; reduction of the antibody response to primary immunisation with intradermal human diploid-cell rabies vaccine.

As with chloroquine, antacids may reduce absorption of hydroxychloroquine so it is advised that a four hour interval be observed between hydroxychloroquine and antacid dosaging.

As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.

Halofantrine prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias, including hydroxychloroquine. Also, there may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin.

An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered.

Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions. Also, the activity of anti-epileptic drugs might be impaired if co-administered with hydroxychloroquine. In a single-dose interaction study, chloroquine has been reported to reduce the bioavailability of praziquantel. It is not known if there is a similar effect when hydroxychloroquine and praziquantel are co-administered. Per extrapolation, due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for hydroxychloroquine.

There is a theoretical risk of inhibition of intra-cellular α -galactosidase activity when hydroxychloroquine is co-administered with agalsidase.

iii. Pregnancy and Breastfeeding

A moderate amount of data on pregnant women (between 300 – 1000 pregnancy outcomes), including prospective studies in long-term use with large exposure, have not observed a significant increased risk of congenital malformations or poor pregnancy outcomes. Hydroxychloroquine crosses the placenta. Only limited non-clinical data are available for hydroxychloroquine, data on chloroquine have shown developmental toxicity at high supratherapeutic doses and a potential risk of genotoxicity in some test systems. Therefore, hydroxychloroquine sulfate should be avoided in pregnancy except when, in the judgement of the physician, the individual potential benefits outweigh the potential hazards. Careful consideration should be given to using hydroxychloroquine during lactation, since it has been shown to be excreted in small amounts in human breast milk, and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines.

Pregnancy and breastfeeding are exclusion criteria for the hydroxychloroquine arm of the PRINCIPLE trial.

5. Safety reporting

Hydroxychloroquine: has a well-documented safety profile and is a commonly used medication in a primary care setting (see above).

Common symptoms of hydroxychloroquine include abdominal pain; appetite decreased; diarrhoea; emotional lability; headache; nausea; skin reactions; vision disorders; and vomiting. Mechanisms for safety reporting are outlined in the trial protocol.

We will call all participants randomised to hydroxychloroquine on day 7 to ask about cardiovascular AEs. Our team of clinicians will review any AEs relating to cardiovascular symptoms from the day 7 call, and assess whether these may be related to hydroxychloroquine. If AEs are thought to be related and it's deemed necessary by the assessing clinician, the participant's GP will be contacted to arrange a face-to-face visit for further clinical evaluation.

26 APPENDIX E: USUAL CARE PLUS AZITHROMYCIN ARM

1. Background and rationale

a. Evidence for potential Azithromycin benefits in COVID-19

Atypical macrolides, especially Azithromycin, have activities that may be beneficial in the treatment of COVID-19 patients, and especially those in the at-risk or age range of the PRINCIPLE trial.

Firstly, Azithromycin appears to have some anti-viral mechanisms. In COVID-19, Azithromycin appears to inhibit viral replication and therefore reduces shedding. In the small open observational trial of Gautret *et al* the addition of azithromycin to hydroxychloroquine (HCQ) (at 200 tds for 10 days) in 6 of the 14 HCQ subjects of the total 36 COVID-19 patients in the study significantly reduced viral shedding at 3 days to 15% (one subject) versus 70% in the HCQ arm and 95% in the indirect control arm, with no shedding at 6 days in the combination arm versus 50% and 90% respectively.(28) Azithromycin was also used in some Chinese observational and interventional studies.

Azithromycin has also been shown to be active *in vitro* against Zika and Ebola viruses,(29-31) and to prevent severe respiratory tract infections when administrated to patients suffering viral infection.(32) Inhibition of viral infections by azithromycin may be linked to its suppressive effect on the production of viral interferon.(33) Longer term administration of low dose azithromycin in COPD has been shown to suppress proinflammatory cytokine production, potentiate macrophage phagocytosis and anti-inflammatory cytokine expression.(34-36) Azithromycin use is also associated with a decrease in the expression of human HLA (human leukocyte antigen) complex molecules in the respiratory tract, including HLA-A, HLA-B, HLA-DPA1, HLA-DRA, HLA-DRB4.(37)

b. Importance of treating CAP or CAP risk in the elderly or immuno-compromised

An important secondary pathway to severe illness and death with COVID-19 may be secondary infection and sepsis in the immune-compromised state, especially secondary community or hospital acquired pneumonia. Older people are more susceptible to pneumonia because of comorbidities, a weakened immune system and are therefore more likely to die.(38) The onset of pneumonia in the elderly can often be rapid, and for severe pneumonia, the prognosis is poor: as many as one in five will die.(38) Severe pneumonia is more prevalent the older you are and in those with more serious underlying diseases.(39) The leading cause of death is respiratory insufficiency. Death has been shown to increase in those not responding to initial antimicrobials, and consequently, the initial selection of the agent is important.

Common causative organisms in the elderly admitted to the hospital with pneumonia include *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Mycoplasma pneumoniae*. In severe pneumonia, *S. aureus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* have been identified as common causative organisms. Older patients often have polymicrobial infections, which may be a factor in non-responders. Assessment of 12,945 US

Medicare inpatients over 65 with pneumonia found that initial treatment with a second-generation cephalosporin plus macrolide ([HR, 0.71; 95% CI, 0.52-0.96), a non-pseudomonas third-generation cephalosporin plus a macrolide (HR, 0.74; 0.60-0.92), or a fluoroquinolone alone (HR, 0.64; 0.43-0.94) was associated with lower 30-day mortality.(40)

For CAP management NICE guidance currently recommends Amoxicillin 500mg tds combined with Clarithromycin 500mg bd for 5 days or, in penicillin sensitive, Clarithromycin 500mg bd for 5 days or Doxycycline 200mg stat then 100mg daily for the next 4 days. They also recommend starting therapy within 4 hours. The identification of the early stages of pneumonia in older patients can prove challenging since traditional symptoms and signs, including fever, may be lacking.

Azithromycin will have at least as broad a spectrum of action as clarithromycin in terms of bacterial infections and the additional potential anti-viral activity which has not been observed for other macrolides like Clarithromycin. It will also cover atypical organisms.

2 Changes to outcome measures

The addition of this usual care plus azithromycin arm will not require any changes to outcome measures

3 Eligibility criteria specifically related to azithromycin

Inclusion criteria: No changes

Exclusion criteria:

- Pregnancy
- Breastfeeding
- Known severe hepatic impairment;
- Known severe renal impairment;
- Known myasthenia gravis;
- Previous adverse reaction to, or currently taking, azithromycin or other macrolides or ketolides
- Patients taking the following drugs: hydroxychloroquine or chloroquine, sotalol, amiodarone, ciclosporin, digoxin, bromocriptine, cabergoline, ergotamine, ergometrine, methysergide or any ergot derivatives.
- Already taking antibiotics for an acute condition
- Known congenital or documented QT prolongation
- Known allergy to soya or peanut due to the risk of hypersensitivity reactions

4 Detail of intervention

Participants randomised to the usual care plus azithromycin arm will receive usual clinical care as per NHS guidelines, plus a course of oral azithromycin 500mg daily for three days. We will use the IMP distribution methods described in the protocol to deliver IMP to participants.

a. Investigational Medicinal Product (IMP) description

Azithromycin 250mg capsules. Participants in this arm will take 500 mg (two capsules) once daily for 3 days. The capsules are for oral administration.

Special instructions:

Azithromycin must be taken at least 1 hour before or 2 hours after antacids as this affects overall bioavailability. Azithromycin must be taken at least 1 hour before or 2 hours after food.

The marketing authorisation holder is: Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK.

Marketing authorisation number: PL 00289/1570

b. Storage of IMP

Azithromycin: Stored at room temperature in locked cupboards in restricted access rooms in the Nuffield Department of Primary Care Health Sciences; in locked cupboards in restricted access rooms in GP Practices; in Pharmacies.

c. SmPC precautions and concomitant medication

i. Precautions

Azithromycin is a commonly prescribed antibiotic with an established safety profile. The SmPC advises caution using azithromycin in the following conditions:

Elderly people with proarrhythmic conditions due to the risk of developing cardiac arrhythmia and torsades de pointes including patients with congenital or documented QT prolongation; receiving treatment with other active substances known to prolong QT interval such as anti-arrhythmics (e.g. amiodarone and sotalol), cisapride, and fluoroquinolones such as moxifloxacin and levofloxacin; known hypokalaemia and hypomagnesaemia; significant hepatic or renal impairment; patients with neurological or psychiatric disorders; myasthenia gravis. Azithromycin as other with the use of nearly all antibacterial agents, alters the normal flora of the colon leading to overgrowth of *Clostridium difficile* which can lead to *Clostridium difficile* associated diarrhoea.

ii. Concomitant medications

Effects of other medicinal products on azithromycin:

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of antacids and azithromycin, no effect on overall bioavailability was seen, although the peak serum concentrations were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the medicinal products should not be taken simultaneously. Azithromycin must be taken at least 1 hour before or 2 hours after the antacids.

Co-administration of azithromycin prolonged-release granules for oral suspension with a single 20 ml dose of co-magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.

Co-administration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole

Co-administration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Nelfinavir

Co-administration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment is required.

Rifabutin

Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either medicinal product.

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established.

Terfenadine

Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however, there was no specific evidence that such an interaction had occurred.

Cimetidine

In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Effect of azithromycin on other medicinal products:

Ergotamine derivatives

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.

Digoxin and colchicine (P-gp substrates)

Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

Coumarin-Type Oral Anticoagulants

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15-mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of

monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Cyclosporin

In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Theophylline

There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers. As interactions of other macrolides with theophylline have been reported, alertness to signs that indicate a rise in theophylline levels is advised.

Trimethoprim/sulfamethoxazole

Coadministration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1200 mg on Day 7 had no significant effect on peak concentrations total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

Zidovudine

Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Astemizole, alfentanil

There are no known data on interactions with astemizole or alfentanil. Caution is advised in the co-administration of these medicines with azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolid antibiotic erythromycin.

Atorvastatin

Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay).

However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

Carbamazepine

In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cisapride

Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.

Cetirizine

In healthy volunteers, coadministration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosins (Dideoxyinosine)

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Efavirenz

Coadministration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Indinavir

Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Methylprednisolone

In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam

In healthy volunteers, coadministration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

Sildenafil

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and C_{max} of sildenafil or its major circulating metabolite.

Triazolam

In 14 healthy volunteers, coadministration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

iii. **Fertility, pregnancy and lactation**

Pregnancy

There are no adequate data from the use of azithromycin in pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed. The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore azithromycin should only be used during pregnancy if the benefit outweighs the risk.

5 Safety reporting

Mechanisms for safety reporting are outlined in the protocol. In brief, we will collect symptoms and side effects of azithromycin from symptom diaries and participant telephone calls.

Common symptoms of azithromycin include diarrhoea, abdominal pain, nausea and flatulence. It may also cause headache, dizziness, insomnia, altered taste, pins and needles, changes in vision or hearing, rash, itching, joint pains or fatigue.

26 APPENDIX F: USUAL CARE PLUS DOXYCYCLINE ARM

1. Background and rationale

a. Evidence for potential doxycycline benefits in COVID-19

Doxycycline may be beneficial in the treatment of COVID-19 patients, and especially those in the at-risk or age range of the PRINCIPLE trial.

The rationale for testing doxycycline is based on three reasons:

Firstly, doxycycline may have direct antiviral activity against SARS-CoV-2 based on computer modelling. Analysing all the proteins encoded by SARS-CoV-2 genes and then predicting potential targets by performing target-based virtual ligand screening, doxycycline ranked in the group of compounds with the highest binding affinity to 3CLpro (3-chymotrypsin-like protease). 3CLpro is the main protease in SARS-CoV-2 which is critical in the life-cycle of the virus (41).

Secondly, doxycycline has known anti-inflammatory effects in various human diseases by inhibiting mitogen-activated protein kinase (MAPK) and SMAD pathways (42), as well as potent antioxidant properties(43). Doxycycline reduces the hyperinflammation associated with severe COVID-19 by antagonising metalloproteinases such as MMP9 that are linked with lung injury, including SARS and ARDS(44).

Lastly, from extensive experience in other infectious diseases, doxycycline has broad antimicrobial activity and is efficacious against a broad spectrum of bacteria including atypical bacteria and other pathogens including intracellular plasmodia, chlamydia, rickettsia, and RNA viruses like Dengue fever and chikungunya.

b. Importance of treating CAP or CAP risk in the elderly or immuno-compromised

An important secondary pathway to severe illness and death with COVID-19 may be secondary infection and sepsis in the immune-compromised state, especially secondary community or hospital acquired pneumonia. Older people are more susceptible to pneumonia because of comorbidities, a weakened immune system and are therefore more likely to die.(38) The onset of pneumonia in the elderly can often be rapid, and for severe pneumonia, the prognosis is poor: as many as one in five will die.(38) Severe pneumonia is more prevalent the older you are and in those with more serious underlying diseases.(39) The leading cause of death is respiratory insufficiency. Death has been shown to increase in those not responding to initial antimicrobials, and consequently, the initial selection of the agent is important. Common causative organisms in the elderly admitted to the hospital with pneumonia include *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and less commonly, atypical organisms, such as *Mycoplasma pneumoniae* and *Klebsiella pneumoniae*. All these organisms fall under doxycycline's antimicrobial spectrum.

We are aware that currently NICE, in their COVID-19 rapid guideline, advocates that clinicians offer oral doxycycline for treatment of suspected pneumonia in people who can or wish to be

treated in the community if: the likely cause is bacterial or; it is unclear whether the cause is bacterial or viral and symptoms are more concerning or; they are at high risk of complications (older or frail patients, pre-existing comorbidity or have a history of severe illness following previous lung infection).(45) Doxycycline will have at least as broad a spectrum of action as azithromycin in terms of bacterial infections with the potential anti-viral and anti-inflammatory effects.

Doxycycline for acute cough and community acquired pneumonia is recommended in the British National Formulary at a dose of Doxycycline 200mg stat then 100mg daily for the next 4 days. However, its use in COVID-19 is not proven and therefore important to address in this trial. Given the potential anti-inflammatory properties of doxycycline, we will use a slightly extended 7 day course.

2. Changes to outcome measures

The addition of this usual care plus doxycycline arm will not require any changes to outcome measures

3. Eligibility criteria specifically related to doxycycline

Inclusion criteria: No changes

Exclusion criteria:

- Pregnancy
- Breastfeeding
- Myasthenia gravis
- Systemic lupus erythematosus
- Previous adverse reaction to, or currently taking, doxycycline or other tetracyclines
- Sucrose intolerance (i.e. rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrose-isomaltase insufficiency)
- Already taking antibiotics for an acute condition
- Patients taking the following drugs: ciclosporin, retinoids (acitretin, alitretinoin, isotretinoin, tretinoin), methotrexate, ergotamine, methoxyflurane, lithium.

4. Detail of intervention

Participants randomised to the usual care plus doxycycline arm will receive usual clinical care as per NHS guidelines, plus a course of oral doxycycline for 7 days. We will use the IMP distribution methods described in the protocol to deliver IMP to participants.

a. Investigational Medicinal Product (IMP) description

Doxycycline 100mg capsules. Participants in this arm will take 200mg on the first day (as a single dose or in divided doses with a twelve hour interval) followed by 100mg a day for 6 days (7 day course in total). The capsules are for oral administration.

Special instructions:

Capsules should be swallowed whole with plenty of fluid, while sitting or standing. Capsules should be taken during meals, well before going to bed. Due to the risk of photosensitivity, patients should be advised to avoid exposure to sunlight or sun lamps.

The marketing authorisation holder is:

Accord-UK Ltd (Trading style: Accord), Whiddon Valley, Barnstaple, Devon, EX32 8NS
Marketing authorisation number: PL 0142/0407

b. Storage of IMP

Doxycycline: Stored at room temperature in locked cupboards in restricted access rooms in the Nuffield Department of Primary Care Health Sciences; in locked cupboards in restricted access rooms in GP Practices; in Pharmacies.

c. SmPC precautions and concomitant medication

i. Precautions

Doxycycline is a commonly prescribed antibiotic with an established safety profile. The SmPC states that in elderly patients “doxycycline may be prescribed in the usual dose with no special precautions. No dosage adjustment is necessary in the presence of renal impairment”.

ii. Concomitant medications

Warfarin

There have been reports of prolonged prothrombin time in patients taking warfarin and doxycycline. Tetracyclines depress plasma prothrombin activity and reduced dosage of concomitant anti-coagulants may be necessary

5. Safety reporting

Mechanisms for safety reporting are outlined in the protocol. In brief, we will collect symptoms and side effects from symptom diaries and participant telephone calls.

Common side effects of doxycycline include: Angioedema; diarrhoea; headache; Henoch-Schönlein purpura; hypersensitivity; nausea/vomiting; pericarditis; skin and photosensitivity reaction; dyspnoea; hypotension; peripheral oedema; tachycardia.

26 APPENDIX G: USUAL CARE PLUS INHALED CORTICOSTEROID (ICS) ARM

1. Background and rationale

a. Evidence for potential benefits of inhaled corticosteroids in COVID-19 illness

Inhaled corticosteroids (ICS) are a commonly prescribed class of medication throughout the world. They are reasonably cheap and have been used widely for the last 60 years. The inhaled action and type 2 pneumocyte target of COVID make ICS a potential therapeutic agent in COVID-19¹. They have been shown to be very effective in improving asthma and COPD care over the long term, where the recommendation is that most, if not all, patients with asthma should be prescribed an inhaled corticosteroid^{2,3} and up to 90% of patients with COPD in the UK are prescribed ICS⁴. The rationale of ICS is to reduce the inflammatory process that underlies exacerbations, which can be triggered by viruses in asthma and COPD. Systemic corticosteroids have been found to be effective at reducing mortality amongst hospitalised patients with COVID-19 [46, 47], but it is not known whether pre-hospital treatment with ICS is also beneficial.

Further evidence is as described below:

Evidence from the ARDS literature

ICS in patients at risk of acute respiratory distress syndrome (ARDS) have been shown to improve physiology and reduce inflammatory markers⁵. In patients admitted to hospital at risk of ARDS or acute lung injury, there was an almost 50% reduction of ARDS in patients that were using ICS pre-admission, even controlling for covariates such as age, gender and chronic respiratory disease⁶. Moreover, this ICS effect can also be seen to improve pulmonary physiology⁷.

Potential mechanism of efficacy

Recently published *in vitro* data suggest a role for ICS inhibition of coronavirus replication in infected epithelial cells⁸, whilst there is an indication that there is accelerated hyperinflammation at the onset of SARS-CoV-2 infection⁹, which potentially can be modified by anti-inflammatory therapy. This suggests a plausible mechanism for ICS efficacy against COVID-19 in which ICS has a dual role: firstly, toning down the inflammatory “runaway train” (ARDS-like) response affecting a minority of COVID-19 patients; and secondly, inhibiting viral replication. It has long been known that the ICS effect on epithelial cells is as a direct consequence of gene transcription¹⁰, and investigation of gene expression of ACE2 and TMPRSS2 in the sputum of asthmatic patients has very recently demonstrated lower expression of these key receptors in the presence of ICS¹¹. Furthermore, ICS attenuates expression of the ACE2 receptor in human and murine *in vitro* and *in vivo* models¹². This is of relevance as the SARS-CoV-2 mechanism of action is upon direct action of the ACE2 receptor, a receptor highly expressed on epithelial cells in the oral mucosa and type 2 alveolar cells and the serine protease TMPRSS2 for SARS-CoV-2 spike protein priming^{13,14}. Furthermore, there is experimental evidence that inhaled corticosteroids inhibit coronavirus replication *in vitro*^{15,16}. SARS-CoV-2 binds to cells via the angiotensin converting enzyme 2 (ACE2) receptor. ACE2 is highly expressed on epithelial cells in the oral mucosa and type 2 alveolar epithelial cells. The use of inhaled corticosteroids as a therapy suggests it would target the cells of interest. Furthermore, the primary action of the inhaled steroids is on the type 2 pneumocytes where viral replication is going to be at its most, where we know that ACE2 receptor expression is high.

2. Changes to outcome measures

The addition of this arm will not require any changes to outcome measures.

3. Eligibility criteria specifically related to ICS

Inclusion criteria: No changes

Exclusion criteria:

- A known allergy to inhaled corticosteroids
- Any known contraindication to inhaled corticosteroids (as per SmPC, *patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Lactose, the excipient in the product, contains small amounts of milk proteins and can therefore cause allergic reactions*).
- Patient currently prescribed inhaled or systemic corticosteroids

4. Detail of intervention

Participants randomised to the usual care plus ICS arm will receive usual clinical care as per NHS guidelines, plus inhaled corticosteroids for 14 days. We will use the IMP distribution methods described in the protocol to deliver IMP to participants.

a. Investigational Medicinal Product (IMP) description

The IMP is the inhaled corticosteroid budesonide (dose 400mcg, Pulmicort turbohaler®). Inhaled budesonide comes in a polyethylene container consisting of a white cover screwed onto a brown bottom plate. Inside this is the inhaler with its main parts: a mouthpiece, a dosing mechanism and a substance store. The device will have 50 actuations of 400mcg/actuation. This product has marketing authorisation in the UK (PL 17901/0164) and is manufactured by AstraZeneca UK Ltd, 600 Capability Green, Luton, LU1 3LU, UK. This IMP will be taken as 2 puffs twice a day for 14 days.

b. Storage of IMP

Stored at room temperature in locked cupboards in restricted access rooms in the Nuffield Department of Primary Care Health Sciences; in locked cupboards in restricted access rooms in GP practices; in Pharmacies

c. SmPC precautions and concomitant medication

iii. Precautions

Budesonide is a commonly prescribed inhaled steroid with an established safety profile.

iv. Concomitant medications

Largely, there is no restriction to concomitant medications using inhaled budesonide. The SmPC states that concomitant treatment with ketoconazole, HIV protease inhibitors or other potent CYP3A inhibitors may increase systemic budesonide levels, but that this is of little

clinical significance for a short term treatment of 2 weeks, which is the duration of IMP use in the trial.

5. Safety reporting

Mechanisms for safety reporting are outlined in the protocol. In brief, we will collect symptoms and side effects from symptom diaries and participant telephone calls.

Common and/or potential side effects from IMP include:

- Cough immediately after inhaling
- Mouth and throat pain
- Hoarse voice
- Oral candidiasis (thrush)

These are all reversible upon ceasing IMP

27. Supplementary Material

A. Abbreviations

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
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
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NIHR	National Institute of Health Research
RES	Research Ethics Service
PHE	Public Health England
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust Research and Development Department
RCGP RSC	Royal College of General Practitioners Research Surveillance Centre
REC	Research Ethics Committee
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	Joint Research Office 1st floor, Boundary Brook House Churchill Drive, Headington Oxford OX3 7GB ctrg@admin.ox.ac.uk Tel: +44 (0)1865572224 Fax: +44 (0)1865572228
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 principle@phc.ox.ac.uk 01865 289296
Statistician	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	DMSC Chair: Prof. Deborah Ashby Chair in Medical Statistics and Clinical Trials Director of the School of Public Health Imperial College London Faculty of Medicine, School of Public Health, 153 Medical School St Mary's Campus Imperial College London deborah.ashby@imperial.ac.uk

	<p>(0)20 7594 8704</p> <p>DMSC Members: Prof Simon Gates Cancer Research Clinical Trials Unit (CRCTU) Institute of Cancer and Genomic Sciences University of Birmingham Edgbaston Birmingham B15 2TT S.Gates@bham.ac.uk</p> <p>Prof Gordon Taylor College House, University of Exeter, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU, UK g.j.taylor@exeter.ac.uk</p> <p>Prof Nick Francis Primary Care and Population Science, University of Southampton, Southampton, UK. Nick.Francis@soton.ac.uk</p>
	<p>TSC Chair Prof Paul Little, Primary Care and Population Science, University of Southampton, Southampton, UK. P.Little@soton.ac.uk</p> <p>TSC Members Prof Philip Hannaford, NHS Professor of Primary Care University of Aberdeen, Aberdeen, UK p.hannaford@abdn.ac.uk</p> <p>Prof Matt Sydes, Professor of Clinical Trials & Methodology, MRC Clinical Trials Unit, University College of London, London, UK m.sydes@ucl.ac.uk</p> <p><i>PPI representatives</i> Ms Carol Green Mr Tim Mustill</p>

C. Objectives and Outcome Measures

	Objectives	Outcome Measures	Timepoint (s)
Primary	To assess the effectiveness of trial treatments in reducing 1) Time to recovery, for patients aged ≥ 50 years with comorbidity, and aged ≥ 65 with or without comorbidity and possible COVID-19 during a time of prevalent COVID-19 disease, and 2) Hospitalisation and/or death.	1) Time to recovery, defined as the first instance that a participant reports feeling recovered from possible COVID-19, and 2) Hospitalisation and/or death	Within 28 days of randomisation Patient report, Study Partner report, medical records, Daily online symptom scores
Secondary	To explore whether trial treatment reduces 1) Patient-reported illness severity 2) Duration of severe symptoms and symptom recurrence 3) Contacts with the health services 4) Consumption of antibiotics 5) Hospital assessment without admission 6) Oxygen administration 7) Intensive Care Unit admission 8) Mechanical ventilation 9) Duration of hospital admission 10) Negative effects on well being 11) New infections in household 12) To determine if effects are specific	1-2. Patient reports daily and monthly (after 28 days) symptoms. 3. Contacts with health services reported by patients and/or captured by reports of patients' medical records if the practice is a member of the RCGP RSC network 4. Bi-weekly reports from participants' primary care medical records 5-10. Patient report/carer report/medical record in primary and secondary care 9.. 10. WHO-5 Well Being Index 11. Reports of new infections in the household (from daily questionnaire)	Daily online symptom scores. Telephone call or text on days 2, 7, 14 and 28 and once a month for 12 months if data is not obtained through the online diary. 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. HES/ONS/EMIS/Medical record data linkage after 28 days if patients have been assessed in hospital Swab result from medical records, the supporting laboratory

	to those with a positive test for SARS-CoV-2	12. Swab test results will indicate an “Intention to Treat Infected” group within the overall cohort for sub analysis. Blood test results on recovery (optional) for evidence of historic COVID-19	and/or convalescent blood test result for evidence of historic COVID-19 WHO 5 Well Being Index at baseline, day 14, and day 28 and monthly for up to 12 months, either via online diary or telephone
Qualitative sub-study	<p>1. To explore patients’ experiences of consulting, being tested and taking (trial) medication for possible COVID-19.</p> <p>2. To explore healthcare professionals’ views of taking part in research during pandemics.</p>	<p>1. Telephone interviews with patients.</p> <p>2. Telephone interviews with healthcare professionals.</p>	<p>1. After 28 days.</p> <p>2. Once practice has completed recruitment.</p>
Intervention(s)	All trial interventions are detailed in the Appendices. Further interventions may be added or replaced during the course of the trial, subject to suitable interventions becoming available and all necessary approvals being obtained.		
Comparator	In the first instance, this will be a two-arm trial, with the intervention arm being usual care plus a trial drug and the comparator being usual care. There will be no placebo control in this study. Additional arms may be added as the trial progresses. These will be detailed in the Appendices. If an intervention arm is shown to be superior, then this will become the new standard of care. However, the primary analysis of subsequent interventions will correspond to the comparison versus the original Usual Care arm.		

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)	<p>An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.</p> <p>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.</p> <p>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.</p>
Serious Adverse Event (SAE)	<p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> • 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*. <p>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.</p> <p>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.</p> <p>*NOTE: Pregnancy is not, in itself an SAE. In the event that a participant or his/her 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".</p>

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 treatments, 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: <ul style="list-style-type: none"> • 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”

E. Data Recording and Record Keeping

The data will be entered into the CRFs in an electronic format by the participant, Trial Partner or trial team (using OpenClinica™ database via Sentry). OpenClinica™ is stored on a secure server – data will be entered in a web browser and then transferred to the OpenClinica Database by encrypted (Https) transfer. OpenClinica™ meets FDA part 11B standards. This includes safety data, laboratory data and outcome data. Safety data will also be collected through electronic diaries which are stored on a secure server.

Sentry is an online secure data entry system developed in-house at PC-CTU and hosted at Oxford. It is designed to collect sensitive data, such as participant and Trial Partner contact details, and securely retain them separate from a trial's clinical data. Sentry can also act as a central participant portal to manage online eligibility, eConsent and ePRO - acting as an intermediary between the participant and the clinical databases. Sentry is accessed via a secure HTTPS connection and all stored sensitive data is encrypted at rest to AES-256 standards. 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.

F. Qualitative Sub-study

With consent, participants will be contacted for a telephone interview within three months after they complete their day 28 follow up. The researcher will provide study information over the telephone and the Interview Patient PIS, and ICF will be available on the study website and emailed to participants if requested.

Once a practice has completed patient recruitment and one of their patients has been interviewed, we may ask 1-2 healthcare professionals who would be willing to share their experiences of taking part in the trial. Healthcare professionals will include clinicians and non-clinicians with the main criteria for inclusion in interviews being that HCP participants should have carried out trial activities in their practice. Potential HCP participants will be contacted in person or by email by the practice contact. They will be provided with the Interview HCP Invitation Email, Interview HCP PIS and Interview HCP ICF by email.

Patients recruited to both the intervention and usual care arms will be purposively sampled across the recruiting period with approximately 15-20 patients in each arm (30-40 interviews in total). We will seek to obtain maximum variation in age and symptom severity (as reported in daily diary at baseline). When the research team receives responses from HCPs, they will collect basic demographics to purposively select participants based on practice location, practice size, practice patient recruitment and job role. We aim to complete 20-25 interviews with HCPs.

All participants will only be required to take part in a single interview. Patient participant interviews will follow a semi-structured topic guide (Interview Patient Topic Guide) and ask about reasons for consulting and illness perceptions prior to the consultation, experiences of the consultation, the COVID-19 testing process (if applicable, and result if the participant has been notified) and medication adherence. The topic guide will be informed by the Common Sense Model which describes how people perceive and cope with symptoms of illness.

HCP interviews will follow the Interview HCP Topic Guide and will ask about experiences of carrying out trial activities, recruiting patients and the work required to set up a clinical trial during a pandemic.

Interviews with patient participants are expected to last approximately 30-45 minutes and interviews with HCPs are expected to last 15-30 minutes.

Data Collection:

Each interview will be audio-recorded with the participant's permission. Recordings will allow verbatim transcription of interviews. Transcription will be completed by an independent transcription company. Once transcribed and transcripts are checked, audio-recordings will be deleted. Transcripts will be labelled with a unique participant number and will omit any identifiable data either identifying the participant or their general practice.

Platform Randomised trial of INTERventions against COVID-19 In older people - PRINCIPLE

REC Number: 20/SC/058

IRAS Number: 281958

EudraCT Number:

2020-001209-22

Chief Investigator: Professor Christopher Butler

Participant ID:

CONSENT FORM

Thank you for completing the screening questionnaire, you have passed the screening stage for the trial.

Please read the [Participant Information Sheet](#) if you haven't already done so, and if you are willing to participate please select 'Yes', TYPE your FIRST and LAST names below and then click Submit
If you agree, please select 'Yes' to confirm that you have read and understood the following:

		YES	NO
1	I confirm I have read and understood the information sheet version number ____ - _____ dated ____ / ____ / _____ for the above study. I have had the opportunity to ask questions and had these answered satisfactorily.		
2	I understand my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.		
3	I understand that if I chose to withdraw data already collected will continue to be used.		
4	I understand that I will be randomised to receive either: standard care plus a trial treatment or standard care, and that I will not be able to choose which I will receive.		
5	I understand that relevant sections of my GP and Hospital medical notes and data collected during the study may be looked at by members of the research team and individuals from University of Oxford, both during and for up to 10 years after the scheduled follow-up period. It may also be reviewed by relevant people from regulatory authorities and from the NHS Trust(s). I give permission for these individuals to have access to my records		
6	I understand that my Summary Care Record may be looked at by members of the research team. I give permission for these individuals to have access to my records		
7	I consent to being contacted by the research team for the purposes of trial follow up (up to 12 months) and I understand that this will require me to provide my contact details to the research team.		
8	I consent to my GP and/or Care Home being informed of my participation within the study.		
9	I agree to take part in the study		
	ADDITIONAL (optional, not required for study participation)	YES	NO

1	<i>I agree to provide the research team with the contact details of my Trial Partner. I confirm my Trial partner is aware of their role and willing to answer questions.</i>		
2	<i>I am happy to be contacted by the research team to be invited to a telephone interview at the end of the study. (Taking part in the interview is optional and will not affect your study participation. If you agree to be contacted, the research team will contact you with details of the interview in approximately 28 days. You can then decide whether you want to take part or not.)</i>		
3	I consent to allow the study team to access my sample results which are part of the RCGP RSC and PHE surveillance programme, the trial team to inform my GP of the results if required		

If you are the participant completing the consent form, please provide your signature below

Participant Signature:

First Name: _____ Last Name: _____

Date: __ / __ / _____

If the participant has provided verbal consent, but they are unable to complete the consent form due to lack of online access, too unwell, too frail or consent is completed via the telephone (the participant must have capacity), please provide:

1. Name of the participant

First Name: _____ Last Name: _____

Date: __ / __ / _____

2. Signature of person completing the form

First Name: _____ Last Name: _____

Role: Study Partner/Trial Team Member/Health Care Professional

Date: __ / __ / _____

You will have the opportunity to print a copy of the consent form after submission. Please contact the study team if you would like a copy sent to you

By submitting, I confirm that I am the person whose name is stated above.

If you have any questions about this or any other part of the study please contact the study team:

Tel: 0800 138 0880

Email principle@phc.ox.ac.uk

Appendix 1— Azithromycin

Drug Information

Azithromycin is a widely used antibiotic, but is not currently used to treat infections like COVID-19.

Side-effects

The common side effects are:

- * abdominal pain;
- * headache;
- * nausea;
- * vomiting

Appendix 2— Doxycycline

Drug Information

Doxycycline is a widely used antibiotic, but is not currently used to treat infections like COVID-19.

Side-effects

The common side effects are:

- * swelling
- * diarrhoea
- * headache
- * Henoch-Schönlein purpura
- * nausea/vomiting
- * hypersensitivity
- * chest pains
- * rash
- * difficulty breathing
- * low blood pressure
- * swelling of lower legs or hand
- * abnormally rapid heart rate

Appendix 3

Inhaled Corticosteroid - Budesonide

Drug Information

Budesonide is a widely used inhaled corticosteroid used to treat asthma symptoms, but is not currently used to treat infections like COVID-19.

Side-effects

The common side effects are:

- * cough immediately after inhaling
- * mouth and throat pain
- * hoarse voice
- * oral candidiasis (thrush).



Platform Randomised trial of INTERventions against COVID-19 In older people

PARTICIPANT INFORMATION LEAFLET

We are inviting people who are experiencing symptoms of Covid-19 to consent to join this study comparing possible treatments.

This leaflet has information about the trial, including aims, risks and benefits of taking part.

What is the purpose of the trial?

COVID-19

The risk of complications from COVID-19 is generally greater in people aged 50 years and older with underlying health conditions and in those aged 65 years and older. This new viral infection can lead to significant medical problems, hospitalisation, and sometimes death.

So far, there are no treatments that have been proven in clinical trials to be effective in treating COVID-19 infection. Most of the infections are being managed in the community and it is essential that we identify treatments that help to reduce the progression of the disease and therefore the need for hospital admission.

The Trial

Our trial aims to evaluate potential treatments for Covid-19 as they are identified. To be able to do this, we aim to test one or more suitable, potential treatments for COVID-19, as soon as they become available.

We aim to find out whether selected treatments given to those at higher risk of becoming more ill when they are infected with COVID-19 helps reduce the need for hospitalisation and the length of stay required, helps people recover quicker and get fewer complications.

We will evaluate drugs that are well known and have been used for many years around the world. Please see Appendices for drug specific information and the known side-effects.

Can I take part?

We intend to recruit at least 3000 people to the trial.

To take part, you need to be experiencing symptoms that are likely to be caused by a COVID-19 infection, for **fewer than 15 days**:

a new continuous cough

or a high temperature

or a loss of, or change in, normal sense of **taste or smell**

OR

- You have had a **positive test** for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND are unwell with symptoms of COVID-19. These symptoms may include, but are not limited to, shortness of breath, general feeling of being unwell, muscle pain, diarrhoea, vomiting, fever and cough, and you must have had them for **fewer than 15 days**.

You **also** need to be **aged 65 and over**

OR aged 50 to 64, where one of the following applies:

- weakened immune system due to a serious illness or medication (e.g. chemotherapy)
- heart disease or high blood pressure
- asthma or lung disease
- known diabetes
- liver disease
- stroke or neurological problem
- self-reported obesity or recorded body mass index ≥ 35 kg/m²

Do I have to take part?

Participation is entirely voluntary. It is up to you to decide whether to take part in the trial or not. A decision not to take part will not affect the standard of care you receive from the NHS in any way, now or in the future.

We are contacting people who have recently tested positive for COVID-19 and your information has been provided to us by NHS Digital in these unique pandemic circumstances. You have the right to opt out of any future communications from PRINCIPLE should you wish to do so. If you do not wish to receive further communication from the trial team, please let us know next time we contact you. PRINCIPLE will not retain your data should you choose not to take part. Please see the General Notice under the Health Service Control of Patient Information Regulations 2002 for more information (LINK). [We will make a maximum of three attempts to contact you about the trial.](#)

What will happen to me if I take part?

If you are interested in taking part, we will ask you to complete a short online form to see if you are eligible. If you do not have internet access or would like to call us instead, then you can contact us using the contact details at the end of the document.

Informed Consent

You will be asked to complete a consent form online or by telephone. Instructions on how to fill out the form will be provided, so you will know what to do. You will be able to download and keep a copy of your informed consent form.

Initial Questionnaire

You will then complete a short questionnaire giving some details about you and the symptoms you have been experiencing. We will also collect some contact details such as your name, email address and telephone number. We will also ask you to provide details of a Trial Partner. This could be a relative, spouse, friend or carer, if such a person is available, who we will contact for information about you if we are unable to get hold of you for whatever reason.

Randomisation

The final part of the process will tell you whether you will receive standard care or standard care plus a trial treatment. You will be randomly allocated (like rolling a dice) by our computer system to one of these groups and neither you, your GP or the trial team can decide which group you will be in.

You will receive an email or phone call to let you know which group you have been allocated to; your GP and the trial team will also receive this email. If we find that you cannot participate, we will let you know by email or phone.

Trial Treatment

If you are randomised to the standard care plus trial treatment group, arrangements will be made for the drug to be delivered to you. You will also receive instructions on how to take it and for how long and you will be asked to confirm receipt of the medication via text or telephone call. Should your condition worsen at any time during the trial, you should not contact the study team but contact your GP or other usual services that are open to you.

Follow-Up

You will receive a text message from us to ask you to complete online questions relating to your symptoms and how well you feel every day for up to 28 days after you start the trial. If the trial team don't receive your daily diary answers online, they will text or telephone you on day 2, 7, day 14 and day 28 of the follow up period and ask you a brief set of questions over the phone. We may contact you (email, text message or telephone call) once a month for up to 12 months after you enrol into the trial to collect information about ongoing symptoms, hospital visits and your well-being. Samples you have given or go on to give for COVID-19 in your standard care may also be used for national surveillance, if this is the case we would like to access the results from any samples (including testing swabs and convalescent blood samples) held in your GP record or by PHE. In addition, we will collect information from your GP records and data held by central NHS bodies (such as NHS Digital) for long-term follow-up for up to 10 years, to help us better understand the long-term effects of COVID-19 and the trial treatments.

Supporting other COVID-19 trials

Our main aim is to find effective treatments for COVID-19 in the community and we are working in collaboration with other academic organisations to achieve this. You may receive information about other treatment trials from the PRINCIPLE trial platform.

What happens if I am admitted to Hospital?

It is important that we know if you are admitted to hospital at any point during the 28 day follow up period. We need to know this whether or not you are taking the trial medication. We will give you a card that you can carry to let other healthcare professionals know that you are taking part in this trial. It is also really important that someone close to you knows that you are taking part

in the trial, so that if you are admitted to hospital, they can use the details on the card to let us know.

We may also access your medical records and data held about you in central NHS registries and databases (including NHS Digital, Public Health England, other equivalent bodies, and genetic or other research databases if you have provided samples to them) to collect information on any hospital admission that you may have during the follow up period.

Optional Follow-up

We are planning to interview a group of participants after the main trial. This is optional and you will be able to confirm on the consent form whether you are happy to be contacted by the research team. If you agree to be contacted, the research team will contact you with details of the interview in approximately 28 days. You can then decide whether you want to take part or not.

What are the possible disadvantages or side effects of taking part?

With any medicine, including ones that are already used within the NHS, there is a risk of side effects. Please see Appendices for details of the side-effects common to each drug. You will be able to tell us if you are experiencing any of these symptoms in your daily diary.

Some people find having their blood taken causes slight discomfort and occasionally bruising.

What are the possible benefits of taking part?

We do not know if the treatments being tested will have additional benefits. Your study treatment may or may not help you personally, but this study should help future patients.

What will happen if I do not want to continue with the trial?

If you decide to take part, you can still withdraw at any time without giving a reason. Information collected up to that point will still be used.

If you wish to withdraw from the trial, please contact the trial team using the contact details on page 12. The decision to withdraw will not affect the standard of care you receive from the NHS in any way, now or in the future.

Expenses and Payments

You will be reimbursed for your participation through gift vouchers worth a total of £20. You will receive the voucher at the end of your follow up period, once we have received your completed symptom diary.

What if there are any problems?

If you have any questions about this trial, please contact the Trial Team (See Page 12 for contact details).

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this trial.

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this trial, you should contact the trial team on principle@phc.ox.ac.uk or **0800 138 0880** or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, or the head of CTRG, email ctrig@admin.ox.ac.uk.

What will happen to my data?

All information about you and your health will be kept private. The only people allowed to look at the information will be the doctors running the trial, the trial team and the regulatory authorities who check that the study is being carried out correctly. A privacy notice is on the study website www.principletrial.org.

As part of the trial enrolment process we may need to view your Summary Care Records (SCR) to check medication, allergies, adverse reactions and additional information to make sure that it is safe for you to take trial medication. A SCR is an electronic record of important patient information, created from GP medical records and includes information about your significant illnesses and health problems, operations and vaccinations you have had in the past, how you would like to be treated (such as where you would prefer to receive care), what support you

might need and who should be contacted for more information about you. They can be seen and used by authorised staff in other areas of the health and care system involved in the patient's direct care.

We will ask for your consent to view your SCR. The SCR will not be retained by the trial team. If your SCR is unavailable or you do not consent for us to access it, you can still take part in the trial as we will obtain this information from your GP.

What if relevant new information becomes available during the trial?

Sometimes during the course of a research project, new information becomes available about the treatment that is studied.

If this happens, the trial team will tell you about it and discuss with you whether you want to continue in the trial or not.

If you decide to continue you may be asked to sign an updated consent form.

What will happen to the results of the trial?

Results will be published in scientific journals, presented at scientific conferences, and published on the Oxford University departmental website. It will not be possible to identify you in any report, publication or presentation. If you would like to receive copies of any publications arising from this trial, please contact the trial team (details are at the end of the document)

Who is organising and funding the research?

Funding has been provided by UK Research and Innovation/Medical Research Council. PRINCIPLE has been set up by the Primary Care Clinical Trials Unit at the University of Oxford.

Who has reviewed the trial?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee (REC). The REC is there to protect your safety, rights, wellbeing and dignity. This trial has been ethically reviewed and was approved by the South Berkshire Research Ethics Committee.

This trial has also received approval from the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA regulates the use of all medicines in the UK.



Trial Team:

Tel. 0800 138 0880

Trial Email Address:

principle@phc.ox.ac.uk



PRINCIPLE Privacy Notice

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the data controller and is responsible for looking after your information and using it properly.

Responsible members of the University of Oxford, Host Organisations, and the Medicines and Health Care Products Regulatory Authority, may be given access to the trial data for monitoring and/or audit of the trial to ensure that the research is complying with applicable regulations.

We will be using information from you and your medical records and data held about you in central NHS registries and databases (including NHS Digital, Public Health England, other equivalent bodies, and genetic or other research databases if you have provided samples to them) in order to undertake this trial and will use the minimum personally-identifiable information possible. These registries include the Royal College of General Practitioners and Public Health England. We will share your name and date of birth with NHS digital to obtain data from your medical records. We may need to send a secure email or letter to your GP or Care Home (if applicable) containing personal identifiable information with your recruitment allocation. We will keep identifiable information about you for up to six months after the trial has finished. This excludes any research documents with personal information, such as consent forms, which will be held securely at the University of Oxford for 20 years after the end of the study.

Your GP/NHS Trust/Care Home/NHS 111 or other healthcare provider involved in enrolling you into the study will use your name and contact details, to contact you about the research study. Your GP may also be involved in confirming your eligibility to be enrolled into the trial. They will keep identifiable information about you from this study for 6-12 months after the study has finished.

Berry Consultants may assist with the statistical analysis for this trial and we will have to share the trial data with them in order for them to do this. The company is based in the USA, however no identifiable data will be given to them during this process.

The Royal College of General Practitioners Research Surveillance Centre may be used in order to gather data you haven't completed in your daily diaries. Data collected will include participant identifiable information and will be accessed at the University of Oxford according to PC-CTU Information Governance policies and GDPR.

Data will only be held for the duration for which it is required, this will be reviewed annually.

Platform Randomised trial of INterventions against COVID-19 In older peoPLE

Principle Privacy Notice, **Version/Date: v1.1 07 November 2020, EudraCT number:2020-001209-22**

Professor Christopher Butler IRAS Project number: 281958 REC Reference number: 20/SC/058



If we use a courier or home delivery service to provide you with trial materials, we will provide them with your name and address. These companies will use and store your data in accordance with GDPR.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate.

Further information about your rights with respect to your personal data is available at: <https://compliance.web.ox.ac.uk/individual-rights>

You can find out more about how we use your information by contacting principle@phc.ox.ac.uk



Instructions for participants

Thank you for taking part in the PRINCIPLE trial.

This information booklet will help guide you through what will happen during your time in the trial.

Please read on for more details about the trial medication and other key details.

Contact us

If you have any questions, please contact us on:

E-mail: principle@phc.ox.ac.uk

Telephone: 0800 138 0880

Summary

If provided with a swab through usual care, please take the swab as early as possible, before trial treatment begins.

Please take your medication (unless in Usual Care Group) for the *required number* of days. There is more detail in this booklet about how and when to

During the trial period, we ask you to complete a short daily diary about your symptoms. If we do not receive your diary, we will call you and/or your trial partner to ask a few short questions.

Your participation will last for a total of 28 days.

Taking your trial medication (unless in Usual Care Group)

Please see the drug information card for guidance on how you should take your medication.

Completing the daily online diary

We ask you to complete a short daily symptoms diary for 28 days. This will take less than ten minutes of your time each day.

- You will receive a daily email with an internet link, which will take you to a secure online system to collect your diary entries confidentially.
- You will receive a text asking you to submit your answers on the same day; you may prefer to do this at a regular time for your own convenience and routine.
- You will be asked to record whether you are experiencing a few simple symptoms, and to rate the severity of these symptoms.
- Please ensure that you submit your diary to us at the end of the questions, so we receive all of your answers.
- If we do not receive your completed diary, or you are unable to access the online diary, we will contact you and/or your nominated trial partner on day 7, day 14 and day 28 of the follow up period to collect this information.
- Finally, we will also ask that you, or someone close to you notifies us if you are admitted to hospital.

URGENT: We are supporting a study to find treatments for COVID-19

Dear **[insert patient name]** OR TO PATIENTS AT THE **[insert practice name]** SURGERY

At the **[insert practice name]** we are taking part in a research study to help find treatments for COVID-19. We are writing with information on how you may be able to join this study.

The study is called PRINCIPLE. It is run by the University of Oxford, and is funded by the UK government as a national priority study. The study aims to find treatments that reduce hospital admission and speed recovery for people with symptoms of COVID-19. People included in the study must be **aged over 65, or aged 50-64 with underlying health conditions**. They will either receive usual care, or usual care plus a study drug. All study drugs are widely used to treat other conditions and have been assessed as being safe for use in this study. **You may be able to take part in this study if:**

- i) **You have symptoms of COVID-19 (a new continuous cough or a high temperature or a loss of, or change in, normal sense of taste or smell), and have had them for less than 15 days.**

OR

- ii) You have had a **positive test** for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND are unwell with symptoms of COVID-19. These symptoms may include, but are not limited to, shortness of breath, general feeling of being unwell, muscle pain, diarrhoea, vomiting, fever and cough, and you must have had them for **fewer than 15 days**.

For more information about the study and signing up, please visit the study website (XXX) If you have any questions, or do not have internet access, please call the PRINCIPLE study team on 0800 138 0880.

We are pleased to be supporting this important research, as we urgently need to find effective, early treatments for COVID-19 that can be used in the community.

So, please make contact if you have **symptoms of COVID-19 and are aged over 65, or aged 50-64 with underlying health conditions!**

Yours Sincerely

[insert practice name]

PRINCIPLE video infographic script

Introduction

COVID-19 can lead to significant medical problems, hospitalisation, and sometimes death. The risk of complications from COVID-19 is generally greater in people aged 50 years and older with existing health conditions and in those aged 65 years and older. So far, there are no treatments that have been proven in clinical trials to help people recover from COVID-19 while in the community.

We need to find treatments that help people recover quicker and reduce the need for them to go to hospital.

What the study involves

We are looking for people aged 50 years or over with symptoms including a cough OR temperature OR loss/change of smell/taste, starting within the past 14 days. OR you may have had a recent confirmed test for COVID-19 with any other symptoms.

Registering for the study can be completed online or over the phone and no face to face visits are required. You will be randomly assigned to receive usual care or medication. We will send everyone a participant pack directly to their home. If you have any questions at all you can contact the trial free phone number or your GP.

Summary

If you are unwell now with COVID-19 or **become unwell in the future**, please visit our website www.principletrial.org for more information or to register for the trial. You can also call the team on 0800 138 0880

Please help us fight COVID-19 and consider registering for the PRINCIPLE Trial.

Participant Pictorial Information Sheet

Platform Randomised trial of Interventions against Covid-19 In older people

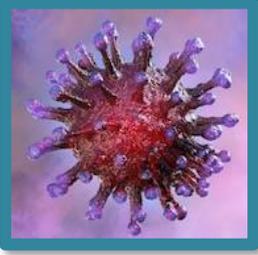
PRINCIPLE Trial

Platform Randomised trial of Interventions against COVID-19 In older peoPLE
Pictorial Participant Information Booklet v2.3, 09 November 2020,

EudraCT number:2020-001209-22

Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058

What is the trial about?

	1.	COVID-19 is caused by a new virus that is spreading quickly in many countries.
	2.	Being infected with the virus is more likely to cause more serious problems if you are older, or you have medical problems such as a diagnosis of high blood pressure or heart disease.

Platform Randomised trial of Interventions against COVID-19 In older people

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	<p>At the moment, we do not have treatments for COVID-19 that we know definitely work to help recovery and prevent hospitalisation.</p> <p>3.</p>
	<p>The aim of this trial is to test possible treatments for COVID-19 in older adults. We hope to find treatments that help people recover quicker.</p> <p>4.</p>

Platform Randomised trial of Interventions against COVID-19 In older people

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Who can take part?

	<p>Anybody aged 65 years or over.</p> <p>AND</p> <p>Anybody aged 50 to 64 years with:</p> <ul style="list-style-type: none">• Weakened immune system (e.g. taking chemotherapy)• Heart disease• Lung disease• Known diabetes• Liver disease• Stroke or neurological problem• Obesity <p>WITH</p>
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A new continuous cough or fever or a change in taste/smell
OR

You have had a **positive test** for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND are unwell with symptoms of COVID-19.

*These symptoms may include, but are not limited to, shortness of breath, general feeling of being unwell, muscle pain, diarrhoea, vomiting, fever and cough, and you must have had them for **fewer than 15 days**. If you are starting to feel better, this study isn't for you.*

Platform Randomised trial of INterventions against COVID-19 In older peOPLE

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What will happen if I take part?

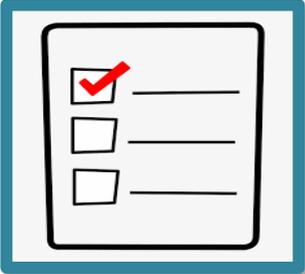
	<p>6. If you develop a fever or a new continuous cough or change in taste/smell, OR if you have a positive test for SARS-Co-V2 infection with symptoms in the past 14 days, please visit our trial website (see end of this leaflet).</p>
	<p>7. We will ask you to fill in a short form online, to check that you can take part</p>

Platform Randomised trial of Interventions against COVID-19 In older people

Pictorial Participant Information Booklet v2.3, 09 November 2020,

EudraCT number:2020-001209-22

Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058

	<p>8.</p>	<p>Your care will not be affected, whether or not you do take part in the trial.</p>
	<p>9.</p>	<p>If you are suitable to take part in the trial, you will be asked to fill in a consent form online, and to answer a few questions about yourself and your symptoms.</p>
	<p>10.</p>	<p>We will ask you to add details of a 'trial partner'. This is somebody that might be able help you with the study, and who we can also contact for information about</p>

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		<p>how you are getting on.</p>
	<p>11.</p>	<p>The information that you give us will be shared with your GP and the study team, so that we can double check that everything is in order for you to take part.</p>
	<p>12.</p>	<p>If you can take part, you will be randomly (like tossing a coin) entered into a group:-</p>
	<p>Or</p>	

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<p>a) Usual care for your symptoms</p>		<p>b) You will receive one of the treatments that we are testing, in addition to usual care for your symptoms.</p> <p>We will provide you with the trial medication and instructions on how to take it.</p>
	<p>13.</p>	<p>Whichever group you are in, we will ask you to answer a few questions each daily in an online diary for up to 28 days, so that</p>

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		<p>we know how you are feeling.</p>
	<p>14.</p>	<p>If you are unable to answer questions online, or forget to complete the questions, we might give you a phone call or send you a text message reminder.</p>
	<p>15.</p>	<p>If you are admitted to hospital, we would ask you, or someone close to you, to let us know.</p>

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16.

If you agree to join the study, we will contact you at 28 days to see whether you are happy for us to arrange to speak with you in more detail about your experience of taking part in the trial.

Samples you have given or go on to give for COVID-19 in your standard care may also be used for national surveillance, if this is the case we would like to access the results from any samples (including testing swabs and convalescent blood samples) held in

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		your GP record or by PHE.
--	--	---------------------------

What will happen to my information?

	17.	<p>We will use the information you give us to find out which treatments work. We may also look at your general practice and hospital medical records for further information about you and your illness.</p>
--	-----	--

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18.

Any information that we collect about you will be kept safe. Your name will not go on any reports, presentations or publications.

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What are the disadvantages of taking part?

	19.	There is a risk of side effects when taking any medicine. If you are taking a trial medication and have any symptoms, you can record them in the daily online diary.
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What are the benefits of taking part?

	20.	You will be contributing to important research to find effective treatments for COVID-19.
	21.	We have designed the trial so that whilst the trial is ongoing, if we find that one treatment is more effective, more people might receive this treatment. This means that more people in the trial have a chance of receiving the most effective trial treatment.

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Will I be reimbursed for taking part?

	22.	You will receive a gift voucher for £20 once we receive your completed online symptom diary, as a thank you for taking part.
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What if I do not want to carry on being part of the trial?

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	23.	You can decide to stop taking part at any time without needing to give a reason. This will not affect the care you receive now or in the future.
	24.	If you decide to withdraw from the trial, we will use the information collected up to that point.

What if there is a problem?



25.

If you have a concern about any aspect of this trial at any time, you can contact the trial team or the University of Oxford Clinical Trials and Research Governance (CTRG) office (Contact details below).

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Trial contact details

	26. Trial team: principle@phc.ox.ac.uk 0800 138 0880 Trial Website: www.principletrial.org CTRG: ctr@admin.ox.ac.uk 01865 616480
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	27. Thank you for taking the time to think about taking part in this trial.
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Thank you!

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How you can support someone to take part in a study to find treatments for coronavirus/COVID-19

Date:

Hello,

I'm writing to let you know how you can support someone taking part in a research study to help find treatments for coronavirus / COVID-19.

The study is called PRINCIPLE and it is run by the University of Oxford. It aims to find treatments for people with symptoms of COVID-19, and who are aged 65 years and over, or aged 50-64 with underlying health conditions. PRINCIPLE is supported by the UK government's Chief Medical Officer as a national priority study to find possible treatments for COVID-19.

People can get more information and sign up by telephoning 0800 138 0880 or at www.principletrial.org. There, they can also download a detailed patient information leaflet and a shorter summary that explains the study. All participants should understand the study before agreeing to take part. They will be able to nominate a 'Study Partner' (family, friend or carer e.g. care home staff) to help them with some of the things that will happen in the study. If you have any questions, please call/email the trial team, 0800 138 0880/principle@phc.ox.ac.uk.

Someone you know, who has already joined the PRINCIPLE study, may have asked you to be their Study Partner. Or you may know someone who is interested in joining and is thinking about asking you to be their Study Partner. The person joining the study has provided your contact details. Please see the Patient Information Sheet (<https://www.phctrials.ox.ac.uk/principle-trial/how-to-join>) for details about what will happen to personal data collected in the trial. The things that you could help with by being a Study Partner are described below:

What will happen in the study	How the Study Partner can help
People interested in joining the study will need to answer some questions on the telephone or online to check whether they are suitable, and provide consent.	Help with accessing information about the study and calling the study team on 0800 138 0880, or completing the online form at www.principletrial.org . Provide your email and/or telephone number for the

	PRINCIPLE team to contact you as the Study Partner
Their GP, or a study nurse or doctor, will also check their medical notes to make sure it is safe for them to be in the study.	
Once signed up, the participant will either receive usual care, or usual care and a study medication which will be delivered from their GP, or directly from the study team. All study medications are already widely used in the NHS and have been approved as safe for use in this study.	Help the participant to take the medication according to instructions in the medication pack.
If they can access the internet, for the next 28 days we would like them to complete an online diary of their symptoms and medical care they have received. The trial team may also phone them or their study partner after 2, 7, 14 and 28 days to get this information, especially if accessing the internet is difficult.	Help the participant with completing the online diary and/or by receiving telephone calls after 2, 7, 14 and 28 days (these can be timetabled with the study team). The Study Partner can also complete the diary or take the telephone calls themselves if the participant is unable to do this (for example if they feel too unwell).

Many thanks for thinking about supporting this study to find treatments for COVID-19, your help is much appreciated.

Yours Sincerely,

The PRINCIPLE Trial Team



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PRIMARY CARE
HEALTH SCIENCES

Primary Care | ●●●●
Clinical Trials Unit



Thank you for taking part in the PRINCIPLE Trial. Here is some information about the trial treatment you have been given.

The medication you have been given is called an **Inhaled Corticosteroid**. You need to take your trial medication for **14 days**. You have been given a corticosteroid called budesonide (400mcg, Pulmicort turbohaler®) and should take 2 puffs twice a day.

The common side effects of this medication include: **cough immediately after inhaling, mouth and throat pain, hoarse voice, oral candidiasis (thrush)**. These typically stop once you stop using the medication.

You will be able to tell us if you are experiencing any of these symptoms in your daily diary.



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HEALTH SCIENCES

Primary Care | ●●●●
Clinical Trials Unit



This medication can cause rare allergic reactions. **If you develop any problems please stop taking the medication immediately and seek clinical advice.**

Please remember that you should not be taking any other medications other than your usual prescribed medication and the medication you have been given for the trial.

Please store the medication at room temperature.

Should your condition worsen at any time during the trial, you should not contact the study team but contact your GP or other usual services that are open to you.

Study Title	Principle
EudraCT No	2020-001209-22
Version Number, Date	1.0, 07.11.20

Description of information needed	Label Text
Name, address and telephone number of the sponsor (the main contact for information on the product, clinical trial and emergency unblinding)	University of Oxford Joint Research Office 1st floor, Boundary Brook House Churchill Drive, Headington Oxford OX3 7GB Tel: +44 (0)1865572224 Fax: +44 (0)1865572228
Pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;	Budesonide (400mcg, Pulmicort turbohaler®) should take 2 puffs twice a day
Batch and/or code number to identify the contents and packaging operation;	
Trial reference code allowing identification of the <u>trial, site, investigator and sponsor</u> if not given elsewhere;	PRINCIPLE trial. University of Oxford Chief Investigator: Prof. Chris Butler
Trial subject identification number /treatment number and where relevant, the visit number;	
Kit/Pack number	
Investigator (if not included previously)	
Directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product)	Take two take 2 puffs twice a day, for 14 days. Special instructions: To breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs.
“For clinical trial use only” or similar wording;	For clinical trial use only
Storage conditions	Do not store above 30°C
Period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity	14 days Expiry date: month/year Shelf life: 24 months.
“keep out of reach of children” except when the product is for use in trials	Keep out of reach of children



where the product is not taken home by subjects	
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Pulmicort Turbohaler 400

Summary of Product Characteristics Updated 15-Jun-2017 | AstraZeneca UK Limited

1. Name of the medicinal product

Pulmicort[®] Turbohaler[®] 400.

2. Qualitative and quantitative composition

Budesonide 400 micrograms/actuation.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Breath-actuated metered dose powder inhaler.

4. Clinical particulars

4.1 Therapeutic indications

Pulmicort is recommended in patients with bronchial asthma.

4.2 Posology and method of administration

Posology.

When transferring patients to Turbohaler from other devices, treatment should be individualised, whether once or twice daily dosing is being used. The drug and method of delivery should be considered.

Divided doses (twice daily):

The dosage should be individualised.

The dose should always be reduced to the minimum needed to maintain good asthma control.

Adults (including the elderly) and children over 12 years of age: When starting treatment, during periods of severe asthma and while reducing or discontinuing oral glucocorticosteroids, the dosage in adults should be 200 - 1600 micrograms daily, in divided doses.

In less severe cases and children over 12 years of age, 200 - 800 micrograms daily, in divided doses, may be used. During periods of severe asthma, the daily dosage can be increased to up to 1600 micrograms, in divided doses.

Children 5 - 12 years of age: 200 - 800 micrograms daily, in divided doses. During periods of severe asthma, the daily dose can be increased up to 800 micrograms.

Once daily dosage:

The dosage should be individualised.

The dose should always be reduced to the minimum needed to maintain good asthma control.

Adults (including the elderly) and children over 12 years of age: 200 micrograms to 400 micrograms may be used in patients with mild to moderate asthma who have not previously received inhaled glucocorticosteroids.

Up to 800 micrograms may be used by patients with mild to moderate asthma already controlled on inhaled steroids (e.g. budesonide or beclomethasone dipropionate), administered twice daily.

Children 5 - 12 years of age: 200 micrograms to 400 micrograms may be used in children with mild to moderate asthma who have not previously received inhaled glucocorticosteroids, or who are already controlled on inhaled steroids (e.g. budesonide or beclomethasone dipropionate), administered twice daily.

The patient should be transferred to once daily dosing at the same equivalent total daily dose; the drug and method of delivery should be considered. The dose should subsequently be reduced to the minimum needed to maintain good asthma control.

Patients should be instructed to take the once daily dose in the evening. It is important that the dose is taken consistently and at a similar time each evening.

There are insufficient data to make recommendations for the transfer of patients from newer inhaled steroids to once daily Pulmicort Turbohaler.

Patients, in particular those receiving once daily treatment, should be advised that if their asthma deteriorates (e.g. increased frequency of bronchodilator use or persistent respiratory symptoms) they should double their steroid dose, by

administering it twice daily, and should contact their doctor as soon as possible.

In patients where an increased therapeutic effect is desired, an increased dose of Pulmicort is recommended because of the lower risk of systemic effects as compared with a combined treatment with oral glucocorticosteroids.

Patients maintained on oral glucocorticosteroids

Pulmicort Turbohaler may permit replacement or significant reduction in dosage of oral glucocorticosteroids while maintaining asthma control. When transferral from oral steroids to Pulmicort is started, the patient should be in a relatively stable phase. A high dose of Pulmicort is then given in combination with the previously used oral steroid dose for about 10 days. After that, the oral steroid dose should be gradually reduced (by for example 2.5 milligrams prednisolone or the equivalent each month) to the lowest possible level. In many cases, it is possible to completely substitute the oral steroid with Pulmicort. For further information on the withdrawal of oral corticosteroids, see section 4.4.

Patients should be reminded of the importance of taking prophylactic therapy regularly, even when they are asymptomatic. A short-acting inhaled bronchodilator should be made available for the relief of acute asthma symptoms.

Method of administration

Pulmicort Turbohaler is for oral inhalation.

Turbohaler is inspiratory flow-driven which means that, when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

Note: It is important to instruct the patient:

- To carefully read the instructions for use in the patient information leaflet, which is packed with each Turbohaler
- To breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs
- Never to breathe out through the mouthpiece
- To minimise the risk of oropharyngeal candida infection, the patient should rinse their mouth out with water after inhaling.

The patient may not taste or feel any medication when using Turbohaler due to the small amount of drug dispensed.

4.3 Contraindications

Hypersensitivity to the active substance.

4.4 Special warnings and precautions for use

Special caution is necessary in patients with active or quiescent pulmonary tuberculosis, and in patients with fungal or viral infections in the airways.

Non steroid-dependent patients: A therapeutic effect is usually reached within 10 days. In patients with excessive mucus secretion in the bronchi, a short (about 2 weeks) additional oral corticosteroid regimen can be given initially.

Steroid-dependent patients: When transferral from oral steroids to Pulmicort Turbohaler is started, the patient should be in a relatively stable phase. A high dose of Pulmicort Turbohaler is then given in combination with the previously used oral steroid dose for about 10 days.

After that, the oral steroid dose should be gradually reduced (by for example 2.5 milligrams prednisolone or the equivalent each month) to the lowest possible level. In many cases, it is possible to completely substitute Pulmicort for the oral steroid.

During transfer from oral therapy to Pulmicort, a generally lower systemic steroid action will be experienced which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain. Specific treatment should be initiated for these conditions. During the withdrawal of oral steroids, patients may feel unwell in a non-specific way, even though respiratory function is maintained or improved. Patients should be encouraged to continue with Pulmicort therapy whilst withdrawing the oral steroid, unless there are clinical signs to indicate the contrary. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary.

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. If this occurs, treatment with inhaled budesonide should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Patients who have previously been dependent on oral steroids may, as a result of prolonged systemic steroid therapy, experience the effects of impaired adrenal function. Recovery may take a considerable amount of time after cessation of oral steroid therapy, hence oral steroid-dependent patients transferred to budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances, HPA axis functions should be monitored regularly.

Acute exacerbations of asthma may need an increase in the dose of Pulmicort or additional treatment with a short course of oral corticosteroid and/or an antibiotic, if there is an infection. The patient should be advised to use a short-acting inhaled bronchodilator as rescue medication to relieve acute asthma symptoms.

Pulmicort is not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required.

If patients find short-acting bronchodilator treatment ineffective or they need more inhalations than usual, medical attention must be sought. In this situation consideration should be given to the need for or an increase in their regular therapy, e.g. higher doses of inhaled budesonide or the addition of a long-acting beta agonist, or for a course of oral glucocorticosteroid.

Patients, who have required high dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids, may also be at risk of impaired adrenal function. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid treatment should be considered during periods of stress or elective surgery. These patients should be instructed to carry a steroid warning card indicating their needs. Treatment with supplementary systemic steroids or Pulmicort should not be stopped abruptly.

Systemic effects may occur with any inhaled corticosteroids, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

Reduced liver function affects the elimination of corticosteroids causing lower elimination rate and higher systemic exposure. Be aware of possible systemic side effects.

The plasma clearance following an intravenous dose of budesonide however was similar in cirrhotic patients and in healthy subjects. After oral ingestion systemic availability of budesonide was increased by compromised liver function due to decreased first pass metabolism. The clinical relevance of this to treatment with Pulmicort is unknown as no data exist for inhaled budesonide, but increases in plasma levels and hence an increased risk of systemic adverse effects could be expected.

Co-treatment with CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products is expected to increase the risk of systemic corticosteroid side effects. Therefore, the combination should be avoided unless the benefit outweighs this increased risk, in which case patients should be monitored for systemic corticosteroid side effects. This is of limited clinical importance for short-term (1-2 weeks) treatment with itraconazole or ketoconazole or other potent CYP3A inhibitors, but should be taken into consideration during long-term treatment. A reduction in the dose of budesonide should also be considered (see section 4.5).

Oral candidiasis may occur during the therapy with inhaled corticosteroids. This infection may require treatment with appropriate antifungal therapy and in some patients discontinuation of treatment may be necessary (see section 4.2).

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Paediatric population

Influence on growth

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. The benefit of the corticosteroid therapy and the possible risk of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of budesonide is primarily mediated by CYP3A4. Co-treatment with CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products, are expected to increase the risk of systemic side effects (see section 4.4 and section 5.2).

The combination of Pulmicort with potent CYP3A inhibitors should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects. If Pulmicort is co-administered with anti-fungals (such as itraconazole and ketoconazole), the period between treatment should be as long as possible. A reduction of the budesonide dose could be considered.

Limited data about this interaction for high-dose inhaled budesonide indicate that marked increases in plasma levels (on average four- fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 µg).

Raised plasma concentrations of and enhanced effects of corticosteroids have been observed in women also treated with oestrogens and contraceptive steroids, but no effect has been observed with budesonide and concomitant intake of low dose combination oral contraceptives.

Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Most results from prospective epidemiological studies and world-wide post-marketing data have not been able to detect an increased risk for adverse effects for the foetus and newborn child from the use of inhaled budesonide during pregnancy. In animal studies, glucocorticosteroids have been shown to induce malformations (see Section 5.3). This is not likely to be relevant for humans given recommended doses, but therapy with inhaled budesonide should be regularly reviewed and maintained at the lowest effective dose. It is important for both foetus and mother to maintain an adequate asthma treatment during pregnancy. As with other drugs administered during pregnancy, the benefit of the administration of budesonide for the mother should be weighed against the risks to the foetus.

Inhaled glucocorticosteroids should be considered in preference to oral glucocorticosteroids because of the lower systemic effects at the doses required to achieve similar pulmonary responses.

Breast-feeding

Budesonide is excreted in breast milk. However, at therapeutic doses of Pulmicort Turbohaler no effects on the suckling child are anticipated. Pulmicort Turbohaler can be used during breast feeding.

Maintenance treatment with inhaled budesonide (200 or 400 micrograms twice daily) in asthmatic nursing women results in negligible systemic exposure to budesonide in breast-fed infants.

In a pharmacokinetic study, the estimated daily infant dose was 0.3% of the daily maternal dose for both dose levels, and the average plasma concentration in infants was estimated to be 1/600th of the concentrations observed in maternal plasma, assuming complete infant oral bioavailability. Budesonide concentrations in infant plasma samples were all less than the limit of quantification.

Based on data from inhaled budesonide and the fact that budesonide exhibits linear PK properties within the therapeutic dosage intervals after nasal, inhaled, oral and rectal administrations, at therapeutic doses of budesonide, exposure to the breast-fed child is anticipated to be low.

4.7 Effects on ability to drive and use machines

Pulmicort Turbohaler has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions

The following definitions apply to the incidence of undesirable effects: Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

Table 1 Adverse Drug Reactions (ADR) by System Organ Class (SOC) and Frequency

SOC	Frequency	Adverse Drug Reaction
Infections and infestations	Common	Oropharyngeal candidiasis
		Pneumonia (in COPD patients)
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and anaphylactic reaction
Endocrine disorders	Rare	Signs and symptoms of systemic corticosteroid effects, including adrenal suppression and growth retardation*
Psychiatric disorders	Uncommon	Anxiety
		Depression
	Rare	Psychomotor hyperactivity
		Sleep disorders
		Aggression
		Behavioural changes (predominantly in children)
Nervous System Disorders	Uncommon	Tremor**

Eye disorders	Uncommon	Cataract
		Vision, blurred (see also section 4.4)
Respiratory, thoracic and mediastinal disorders	Common	Glaucoma
		Cough
		Hoarseness
	Rare	Throat irritation
		Bronchospasm
		Dysphonia
Skin and subcutaneous tissue disorders	Rare	Hoarseness***
		Bruising
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasm

* refer to Paediatric population below

** based on the frequency reported in clinical trials

*** rare in children

Occasionally, signs or symptoms of systemic glucocorticosteroid-side effects may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous corticosteroid exposure, and individual sensitivity (see section 4.4).

Description of selected adverse reactions

The candida infection in the oropharynx is due to drug deposition. Advising the patient to rinse the mouth out with water after each dosing will minimise the risk.

As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases (see Section 4.4).

In placebo-controlled studies, cataract was also uncommonly reported in the placebo group.

Clinical trials with 13119 patients on inhaled budesonide and 7278 patients on placebo have been pooled. The frequency of anxiety was 0.52% on inhaled budesonide and 0.63% on placebo; that of depression was 0.67% on inhaled budesonide and 1.15% on placebo.

Paediatric population

Due to the risk of growth retardation in the paediatric population, growth should be monitored as described in section 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms

Acute overdosage with Pulmicort Turbohaler, even in excessive doses, is not expected to be a clinical problem. The only harmful effect that follows inhalation of large amounts of the drug over a short period is suppression of hypothalamic-pituitary-adrenal (HPA) function.

Management

No special emergency action needs to be taken. Treatment with Pulmicort Turbohaler should be continued at the recommended dose to control the asthma.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Budesonide is a glucocorticosteroid which possesses a high local anti-inflammatory action, with a lower incidence and severity of adverse effects than those seen with oral corticosteroids.

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, glucocorticoids. ATC Code: R03BA02.

Topical anti-inflammatory effect

The exact mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory actions, such as inhibition of inflammatory mediator release and inhibition of cytokine-mediated immune response are probably important.

A clinical study in asthmatics comparing inhaled and oral budesonide at doses calculated to achieve similar systemic bioavailability demonstrated statistically significant evidence of efficacy with inhaled but not oral budesonide compared with placebo. Thus, the therapeutic effect of conventional doses of inhaled budesonide may be largely explained by its direct action on the respiratory tract.

In a provocation study pre-treatment with budesonide for four weeks has shown decreased bronchial constriction in immediate as well as late asthmatic reactions.

Onset of effect

After a single dose of orally inhaled budesonide, delivered via dry powder inhaler, improvement of the lung function is achieved within a few hours. After therapeutic use of orally inhaled budesonide delivered via dry powder inhaler, improvement in lung function has been shown to occur within 2 days of initiation of treatment, although maximum benefit may not be achieved for up to 4 weeks.

Airway reactivity

Budesonide has also been shown to decrease airway reactivity to histamine and methacholine in hyper-reactive patients.

Exercise-induced asthma

Therapy with inhaled budesonide has effectively been used for prevention of exercise-induced asthma.

Growth

In short term studies a small and generally transient reduction in growth has been observed, which usually occurs within the first year of treatment. Long-term observational studies suggest that children and adolescents treated with inhaled corticosteroids on average achieve their adult target height. However, in one study children who had been treated with high dose inhaled budesonide (400 micrograms daily) for up to 6 years without titration to the lowest effective dose were found on average to be 1.2 cm shorter as adults than those treated with placebo over the same period. See section 4.4 about titration to the lowest effective dose and about monitoring the growth in children.

Paediatric Population

Slit lamp examinations were performed in 157 children (5-16 years old), treated with an average daily dose of 504 µg for 3-6 years. Findings were compared with 111 age-matched asthmatic children. Inhaled budesonide was not associated with an increased occurrence of posterior subcapsular cataract.

Influence on plasma cortisol concentration

Studies in healthy volunteers with Pulmicort Turbohaler have shown dose-related effects on plasma and urinary cortisol. At recommended doses, Pulmicort Turbohaler, causes less effect on the adrenal function than prednisolone 10mg, as shown by ACTH tests.

5.2 Pharmacokinetic properties

Absorption

Following oral inhalation via Pulmicort Turbohaler, peak plasma concentrations of budesonide (4.0 nmol/L after a dose of 800 µg) occur within 30 minutes. Maximum plasma concentration and area under the plasma concentration time profile increase linearly with dose, but are slightly (20-30%) higher following repeated doses (3 weeks treatment) than after a single dose. Lung deposition in healthy subjects was estimated to 34% ±10% of the metered dose (arithmetic mean ± SD), while 22% was retained in the mouthpiece and the rest (approximately 45% of the metered dose) was swallowed.

The maximal plasma concentration after inhalation of 1 milligram budesonide is about 3.5 nmol/L and is reached after about 20 minutes.

Distribution

Budesonide has a volume of distribution of approximately 3 L/kg. Plasma protein binding averages 85-90%.

Biotransformation

Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6 β -hydroxybudesonide and 16 α -hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome p450.

Excretion

The metabolites of budesonide are excreted as such or in conjugated form mainly via the kidneys. No unchanged budesonide has been detected in the urine. Budesonide has high systemic clearance (approximately 1.2 L/min) in healthy adults, and the terminal half-life of budesonide after iv dosing averages 2-3 hours.

Linearity

The kinetics of budesonide are dose-proportional at clinically relevant doses.

In a study, 100 mg ketoconazole taken twice daily, increased plasma levels of concomitantly administered oral budesonide (single dose of 10 mg) on average, by 7.8-fold. Information about this interaction is lacking for inhaled budesonide, but marked increases in plasma levels could be expected.

Paediatric safety data

Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 years old asthmatic children. Per kg body weight children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. This is about the same as in healthy adults. In asthmatic children treated with Pulmicort Turbohaler (800 μ g single dose), plasma concentration reached C_{max} (4.85 nmol/L) at 13.8 minutes after inhalation, and then decreased rapidly; AUC was 10.3 nmol·h/L. The value for AUC is generally comparable to that observed in adults at the same dose, however, the C_{max} value tends to be higher in children. Lung deposition in children (31% of the nominal dose) is similar to that measured in healthy adults (34% of nominal dose).

5.3 Preclinical safety data

The acute toxicity of budesonide is low and of the same order of magnitude and type as that of the reference glucocorticosteroids studied (beclomethasone dipropionate, flucinolone acetonide).

Results from subacute and chronic toxicity studies show that the systemic effects of budesonide are less severe than, or similar to, those observed after administration of the other glucocorticosteroids, e.g. decreased body-weight gain and

atrophy of lymphoid tissues and adrenal cortex.

An increased incidence of brain gliomas in male rats, in a carcinogenicity study, could not be verified in a repeat study in which the incidence of gliomas did not differ between any of the groups on active treatment (budesonide, prednisolone, triamcinolone acetonide) and the control groups.

Liver changes (primary hepatocellular neoplasms) found in male rats in the original carcinogenicity study were noted again in the repeat study with budesonide, as well as with the reference glucocorticosteroids. These effects are most probably related to a receptor effect and thus represent a class effect.

Available clinical experience shows no indication that budesonide, or other glucocorticosteroids, induce brain gliomas or primary hepatocellular neoplasms in man.

In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not appear to be relevant in humans at the recommended doses.

Animal studies have also identified an involvement of excess prenatal glucocorticosteroids, in increased risk for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range.

6. Pharmaceutical particulars

6.1 List of excipients

Pulmicort Turbohaler contains only active drug, budesonide. There are no propellants, lubricants, preservatives, carrier substances or other additives.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Polyethylene container consisting of a cover screwed onto a bottom plate. Inside this is the inhaler with its main parts: a mouthpiece, a dosing mechanism and a substance store.

The device also contains a desiccant.

400 micrograms/actuation, 50 actuations.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

See section 4.2.

7. Marketing authorisation holder

AstraZeneca UK Ltd

600 Capability Green,

Luton, LU1 3LU, UK.

8. Marketing authorisation number(s)

PL 17901/0164

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 11th June 1990

Date of latest renewal: 4th May 2006

10. Date of revision of the text

06th June 2017

Company Contact Details

AstraZeneca UK Limited

Address

Horizon Place, 600 Capability Green, Luton,
Bedfordshire, LU1 3LU

Fax

+44 (0)1582 838 000

Medical Information e-mail

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Medical Information Direct Line

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Customer Care direct line

+44 (0)1582 837 837

Medical Information Website

<https://medicalinformation.astrazeneca.co.uk/>

IRAS Project ID 281958. HRA and HCRW Approval for the Amendment

berkshire.rec@hra.nhs.uk <noreply@harp.org.uk>

Tue 11/17/2020 12:16

To: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>

Cc: Christopher Butler <christopher.butler@phc.ox.ac.uk>; CTRG Sponsorship Correspondence <ctr@admin.ox.ac.uk>

Dear Hannah,

IRAS Project ID:	281958
Short Study Title:	PRINCIPLE [COVID-19] [UPH]
Amendment No./Sponsor Ref:	10
Amendment Date:	04 November 2020
Amendment Type:	Substantial CTIMP - for review

I am pleased to confirm **HRA and HCRW Approval** for the above referenced amendment.

You should implement this amendment at NHS organisations in England and Wales, in line with the guidance in the amendment tool.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>.

Please contact [amendments@hra.nhs.uk]amendments@hra.nhs.uk for any queries relating to the assessment of this amendment.

Kind regards

Nafeesa Khanam

REC Assistant

Health Research Authority

Ground Floor | Skipton House | 80 London Road | London | SE1 6LH

E. amendments@hra.nhs.uk

W. www.hra.nhs.uk

Sign up to receive our newsletter [HRA Latest](#).

IRAS 281958. Amendment

New IRAS Dev <no-reply-iras@hra.nhs.uk>

Mon 11/9/2020 22:21

To: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>

IRAS Project : 281958
Sponsor amendment reference: Substantial Amendment 10

Thank you for submitting a substantial amendment. Your amendment will be processed, and you will receive further communication in due course.

Do not reply to this email as this is an unmonitored address and replies to this email cannot be responded to or read.

This message may contain confidential information. If you are not the intended recipient please inform the sender that you have received the message in error before deleting it. Please do not disclose, copy or distribute information in this e-mail or take any action in relation to its contents. To do so is strictly prohibited and may be unlawful. Thank you for your co-operation..



MHRA

10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

gov.uk/mhra

Prof C Butler
UNIVERSITY OF OXFORD
NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES,
RADCLIFFE OBSERVATORY QUARTER, WOODSTOCK ROAD
OXFORD
OX2 6GG
UNITED KINGDOM

16/11/2020

Dear Prof C Butler,

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	CTA 21584/0426/001-0009
Eudract Number:	2020-001209-22
Product:	Plaquenil-Hydroxychloroquine, Azithromycin, Doxycycline, Pulmicort Turbohaler 400
Protocol number:	PRINCIPLE
Substantial Amendment Code Number:	Substantial Amendment 10, 07 November 2020

NOTICE OF ACCEPTANCE OF AMENDMENT

I am writing to inform you that the Licensing Authority accepts the proposed amendment to your clinical trial authorisation (CTA), received on 10/11/2020.

This amendment may therefore be made.

You are reminded that where it is appropriate, the Ethics Committee should also be notified of amendments.

Yours sincerely,

**Clinical Trials Unit
MHRA**

IRAS 281958. Substantial Amendment valid for REC review

berkshire.rec@hra.nhs.uk <noreply@harp.org.uk>

Tue 11/10/2020 12:54

To: Christopher Butler <christopher.butler@phc.ox.ac.uk>

Cc: CTRG Sponsorship Correspondence <ctr@admin.ox.ac.uk>; Hannah Swayze <hannah.swayze@phc.ox.ac.uk>

Dear Professor Butler,

Study title: Platform Randomised trial of INterventions against COVID-19 In older peoPLE**REC reference: 20/SC/0158****IRAS project ID: 281958****Amendment number: Substantial Amendment 10****Amendment date: 04 November 2020**

Thank you for submitting the above amendment, which was received on 10th November 2020. I can confirm that this is a valid notice of a substantial amendment and will be reviewed by the Sub Committee ASAP.

Documents received

The documents to be reviewed are as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Completed Amendment Tool [SA10 Locked Amendment Tool]	N/A	04 November 2020
Cover Letter [REC SA10 cover letter]	N/A	09 November 2020
Other [Inhaled Corticosteroid Participant Card]	1.0	07 November 2020
Other [IMP_Label form_ Inhaled corticosteroid]	1.0	07 November 2020
Other [Privacy Notice]	1.1	07 November 2020
Other [Privacy Notice (tracked)]	1.1	07 November 2020
Other [UPH Approval]	N/A	29 October 2020
Other [Information for participants]	1.1	09 November 2020
Other [Information for participants (tracked)]	1.1	09 November 2020
Other [Patient Recruitment Letter]	2.2	09 November 2020
Other [Patient Recruitment Letter (tracked)]	2.2	09 November 2020
Other [Video infographic script]	1.1	09 November 2020
Other [Video infographic script (tracked)]	1.1	09 November 2020
Other [Study Partner Letter]	1.1	09 November 2020
Other [Study Partner Letter (tracked)]	1.1	09 November 2020

Participant consent form [Consent Form]	2.1	07 November 2020
Participant consent form [Consent Form (tracked)]	2.1	07 November 2020
Participant information sheet (PIS) [PIS Appendices]	1.3	07 November 2020
Participant information sheet (PIS) [PIS Appendices (tracked)]	1.3	07 November 2020
Participant information sheet (PIS) [PIS]	3.3	07 November 2020
Participant information sheet (PIS) [PIS (tracked)]	3.3	07 November 2020
Participant information sheet (PIS) [Pictorial PIS]	2.3	09 November 2020
Participant information sheet (PIS) [Pictorial PIS (tracked)]	2.3	09 November 2020
Study Design [Protocol]	6.0	02 November 2020
Study Design [Protocol (tracked)]	6.0	02 November 2020
Summary of product characteristics (SmPC) [Pulmicort Turbohaler 400_SMPC]	N/A	14 April 2020

Notification of the Committee's decision

The Committee will issue an ethical opinion on the amendment within a maximum of 35 days from the date of receipt.

Kind regards

Alison Doherty

Approvals Administrator

Bristol REC Centre | Whitefriars | BS1 2NT

T. 020 7104 8049

E. berkshire.rec@hra.nhs.uk

W. www.hra.nhs.uk

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South Central - Berkshire Research Ethics Committee

Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

12 November 2020

Christopher Butler
University of Oxford
Radcliffe Observatory Quarter, Woodstock Road
Oxford
OX2 6GG

Dear Christopher Butler

Study title: Platform Randomised trial of INterventions against COVID-19 In older peOPLE
REC reference: 20/SC/0158
Protocol number: PRINCIPLE
EudraCT number: 2020-001209-22
Amendment number: SA10
Amendment date: 04 November 2020
IRAS project ID: 281958

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Completed Amendment Tool [SA10 Locked Amendment Tool]	N/A	04 November 2020
Cover Letter [REC SA10 cover letter]	N/A	09 November 2020
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Participant information sheet (PIS) [PIS]	3.3	07 November 2020
Participant information sheet (PIS) [PIS (tracked)]	3.3	07 November 2020
Participant information sheet (PIS) [Pictorial PIS]	2.3	09 November 2020
Participant information sheet (PIS) [Pictorial PIS (tracked)]	2.3	09 November 2020
Study Design [Protocol]	6.0	02 November 2020
Study Design [Protocol (tracked)]	6.0	02 November 2020
Summary of product characteristics (SmPC) [Pulmicort Turbohaler 400_SMPC]	N/A	14 April 2020

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Amendments related to COVID-19

We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

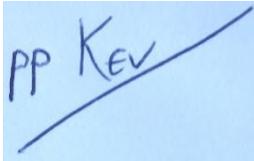
HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities— see details at: <https://www.hra.nhs.uk/planning-and-improving-research/learning/>

IRAS Project ID - 281958:

Please quote this number on all correspondence

Yours sincerely



**Mr David Carpenter
Chair**

E-mail: berkshire.rec@hra.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: CTRG

South Central - Berkshire Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 20 November 2020

Committee Members:

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
Mr David Carpenter	Retired Social Scientist	Yes	
Dr Mike Proven	University Research Governance Officer	Yes	

Also in attendance:

<i>Name</i>	<i>Position (or reason for attending)</i>
Miss Alison Doherty	Approvals Administrator