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Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE): protocol for a randomised, controlled, open-label, adaptive platform, trial of community treatment of COVID-19 syndromic illness in people at higher risk

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ABSTRACT

Introduction There is an urgent need to idenfy treatments for COVID-19 that reduce illness duration and hospital admission in those at higher risk of a longer illness course and complications.

Methods and analysis The Platform Randomised trial of INterventions against COVID-19 In older peoPLE trial is an open-label, multiarm, prospective, adaptive platform, randomised clinical trial to evaluate potential treatments for COVID-19 in the community. A master protocol governs the addition of new interventions as they become available, as well as the inclusion and cessation of existing intervention arms via frequent interim analyses. The first three interventions are hydroxychloroquine, azithromycin and doxycycline. Eligible participants must be symptomatic in the community with possible or confirmed COVID-19 that started in the preceding 14 days and either (1) aged 65 years and over or (2) aged 50–64 years with comorbidities. Recruitment is through general practice, health service helplines, COVID-19 'hot hubs' and directly through the trial website. Participants are randomised to receive either usual care or a study drug plus usual care, and outcomes are collected via daily online symptom diary for 28 days from randomisation. The research team contacts participants and/or their study partner following days 7, 14 and 28 if the online diary is not completed. The trial has two coprimary endpoints: time to first self-report of feeling recovered from possible COVID-19 and hospital admission or death from possible COVID-19 infection, both within 28 days from randomisation. Prespecified interim analyses assess efficacy or futility of interventions and to modify randomisation probabilities that allocate more participants to interventions with better outcomes.

Strengths and limitations of this study

► The adaptive platform design allows new interventions to be added as they become available and for futile interventions or those with safety concerns to be stopped.

► Response adaptive randomisation means that more participants may be randomly assigned to better performing interventions.

► Eligible participants are able to participate regardless of where they receive their healthcare.

► The trial is open label and so will not be able to quantify possible placebo effects, especially regarding patient-reported outcomes.

► The primary analysis will include those meeting syndromic criteria for COVID-19.

Ethics and dissemination Ethical approval Ref: 20/SC/0158 South Central - Berkshire Research Ethics Committee; IRAS Project ID: 281958; EudraCT Number: 2020-001209-22. Results will be presented to policymakers and at conferences and published in peer-reviewed journals.

Trial registration number ISRCTN86534580.

INTRODUCTION

The SARS-CoV-2, which causes COVID-19, has now infected over 98 million people globally, with over 2 million deaths.[1] As of 23 January 2021, 3 583 907 confirmed cases and

95 981 deaths had been reported in the UK.[23] There is an urgent need to identify interventions against COVID-19 suitable for wide use in the community that have been proven to be effective in reducing symptom duration or hospitalisation.[4] We urgently need to know whether potential COVID-19 treatments that are available for rapid pragmatic evaluation might modify the course of COVID-19 infections, particularly among those who are at higher risk of complications, such as those aged 50 years and over with comorbidity and those aged 65 years and over.[5–8]

The majority of reported trials have been conducted in hospital settings, and there is little evidence from community settings, where most people with COVID-19 receive care and where deployment of effective early treatment could speed time to recovery and reduce complications.[49]

We established a multiarm, adaptive platform, randomised controlled trial for community treatment of COVID-19 syndromic illness in people at higher risk of an adverse illness course.

Objectives
To assess the effectiveness of treatments in reducing time to feeling recovered and the need for hospital admission (or death) among patients with possible COVID-19 in the community and who are at higher risk of a complicated illness course.

METHODS AND ANALYSIS
Trial design
The Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE) study is an open-label, multiarm, prospective, adaptive platform, randomised clinical trial in community care. A 'platform trial' is an adaptive clinical trial in which multiple treatments for the same disease are tested simultaneously. The platform trial design allows further interventions to be added while the trial is in progress and for futile interventions to be dropped via frequent interim analyses.[10–12] In addition, response adaptive randomisation is used to allocate more participants to interventions resulting in better outcomes, potentially leading to more rapid and efficient discovery of beneficial interventions.

Participants are randomised to either usual care or usual care plus a study drug. Usual care is not specified or mandated in the protocol but refers to the care that participants receive, decided on by the responsible treating clinician. The first three interventions included are hydroxychloroquine, azithromycin and doxycycline. A master protocol[13] defines prospective decision criteria to allow for dropping a treatment for futility, declaring a treatment superior, or adding a new treatment to be tested. If at any point, usual care plus a study drug is deemed superior to usual care alone for both the recovery and hospitalisation coprimary endpoints (see further), the superior treatment will be incorporated into usual care as the new standard of care. Because the process of dropping and adding treatments may be ongoing for an indefinite period of time, platform trials may be better conceived of as a process rather than a single clinical trial.

Ethics and dissemination
All participants provide informed consent, online or by telephone, before participation. An independent Data Monitoring and Safety Committee (DMSC) reviews emerging data from the Statistical Analysis Commitee (SAC) and communicates key decisions to the Trial Steering Committee (TSC), who advises the Trial Management Group (TMG) and also provides oversight of the trial. Manuscripts with the results of the primary outcomes will be published in peer-reviewed journals.

Patient and public involvement
Five women and two men in our target recruitment age group with an interest in diagnosis and management of infections reviewed the patient-facing materials, including outcomes, and trial delivery plans. They were very supportive of including a nominated support person to help the recruited patients with trial participation. They suggested edits for clarity to the patient information sheet and daily diary. They were keen to document their strong support of work to evaluate possible treatments for COVID-19 in community settings. Two public contributors serve on the TSC and have reviewed patient-facing materials and commented on study design and dissemination.

Study setting
The trial is managed by the University of Oxford Primary Care and Vaccines Collaborative Clinical Trials Unit (PCV-CTU),[14] supported by the National Institute of Health Research Clinical Research Network and the National Institute of Health Research and is implemented in the UK through general practices (GPs), the Primary Care specialty of the Clinical Research Network, community-based COVID-19 services, including telehealth services such as the UK National Health Service (NHS) 111 and community clinics and testing centres that provide COVID-19 assessments to community-based patients. All mandated study procedures can be conducted remotely, in keeping with the current self-isolation guidance for patients with possible COVID-19 in the community.[15]

Eligibility criteria
To facilitate early intervention, and in keeping with the changing situations in primary care, the trial enrols participants with possible COVID-19 irrespective of whether they have had confirmatory SARS-CoV-2 testing. Possible COVID-19 is determined using the United Kingdom NHS definition of high temperature and/or a new, continuous cough and/or a change in sense of smell or taste. Patients with other symptoms consistent with COVID-19 and a positive SARS-CoV-2 PCR test are also eligible. Symptoms must have started within the previous 14 days and be ongoing at the time of enrolment. To target patients at high risk of morbidity and mortality from COVID-19, the

Table 1 Current inclusion and exclusion criteria for the PRINCIPLE trial

Inclusion criteria	Exclusion criteria*
► Willing and able to give informed consent for participation in the study. ► Willing to comply with all trial procedures. ► Symptoms of possible COVID-19 (any of fever, cough, change in taste/smell or other symptoms with a positive SARS-CoV-2 test). Onset of symptoms or a positive test for SARS-CoV-2 with symptoms of COVID-19 must be within the last 14 days. ► Patients aged ≥65 years. OR Patients aged ≥50–64 years with any of the following listed comorbidities: ► Known weakened immune system due to a serious illness or medication (eg, 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/m^2.	► 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.

*Exclusion criteria for specific intervention arms detailed in intervention specific appendices to the master protocol.
PRINCIPLE, Platform Randomised trial of INterventions against COVID-19 In older peoPLE.

trial enrols people aged 65 years and over or 50–64 years with comorbidities (table 1). Patients with contraindications to a trial drug are excluded from enrolment into that particular intervention arm but remain eligible for randomisation into other arms. Patients must be eligible for the usual care arm and at least one intervention arm in order to take part in the trial.

Study procedures
Recruitment
The trial is low burden for participants and those recruiting into the trial. All health and social care professionals and members of the public are able to refer potential participants to the study website, or suggest they contact the trial team directly by telephone or email. They may also send a text message or letter to patients who are potentially eligible to let them know that if they have, or should they develop, symptoms, they may be eligible for the trial, and are given a link to the trial website and freephone number. Participants may also hear about the trial through media and can self-refer via the study website and freephone number.

Screening, informed consent and enrolment
An online screening, eligibility and consent procedure is used. Patients without internet access or requiring help with the online procedures can be assisted by a clinician or the trial team by telephone. Interested patients can access the patient information leaflet on the trial website or by telephoning the trial team. The patient information leaflet is available in English and nine other commonly spoken languages in the UK. After reading the patient information leaflet, potential participants are screened through an eligibility questionnaire and asked to complete an online consent form. The trial team is then notified electronically and assess the participant's eligibility using information from the participant's medical records. If they are unable to access the participant's medical records, the participant's GP is contacted for further information. Healthcare providers can also choose to fully confirm eligibility before referring the patient to the trial team.

In addition, participants can be screened and enrolled by their GP at participating primary care practices. The participant and GP can use the online screening, consent and randomisation procedures, with the GP confirming eligibility using the patient's medical record.

Participants are asked to nominate and include contact details for a study partner (eg, family member) who may provide assistance in completing trial procedures and in providing follow up information. Nominating a study partner is not a requirement of participation.

Randomisation and blinding
After informed consent is obtained and eligibility has been confirmed, participants are randomised using a rapid, secure, web-based randomisation system called Sortition (Oxford University Innovation). The participant, specific members of the trial team and participant's GP are notified electronically regarding treatment allocation. The trial started by using randomisation proportions but subsequently uses response adaptive randomisation via interim analyses to allocate more subjects to the interventions with better outcomes (see Statistical methods).

This is an open-label trial. Participants and recruiting clinicians know the participant's allocation. Therefore, no unblinding or code breaking is required. However, those managing the data are blind to participant allocation, and the trial team and recruiters are blinded to emerging results. Only those on the DMSC and the unblinding statisticians have access to the unblinded interim analysis results. Any changes made in the allocation probability are blind to the trial team apart from the programmer who needs to implement this to the randomisation system.

Baseline assessments
During screening and enrolment, participants record baseline demographic and medical data, which may be supplemented by a clinician using data from the participant's summary medical care record (table 2). Participants are also asked to complete the WHO – Five Well-Being Index (WHO-5), a simple instrument that has been validated for measuring well-being over time.[16]

Table 2 Schedule of evaluation in the PRINCIPLE trial

	Study period			
	Screening	**Enrolment**	**Follow-up**	
Days in study	0	0	1–28 days	29 days–onwards
Participant completes screening, eligibility and baseline questionnaire	×	×		
Clinician completes eligibility*	×	×		
Informed consent*	×	×		
Demographics, medical history and test results*§	×	×		
Concomitant medication	×	×		×
Randomisation		×		
Self-swab for SARS-CoV-2 testing		×		
Dispensing of trial drugs†		×	×	
Usual clinical care§	×	×	×	
Daily questionnaire			×	
WHO-Five Well-Being Index		×	Days 14 and 28	
SARS-CoV-2 serology test if available and obtainable				×
Telephone interview: qualitative study				×‡
Adherence			×	
Adverse event assessments			×	×

*Online or by phone.
†In trial drug arms only.
‡For subset of patient participants.
§Retrospective data collection by study team.
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Participants are also asked to provide a self-swab for SARS-CoV-2 testing, when available, and report the result of any recent test results for the virus.

Interventions

Trial drugs tested in PRINCIPLE are considered to have the potential for widespread and generally safe use in primary care. GPs may be able to issue study medication directly to participants or prescribe it for collection at a pharmacy. Medication may also be delivered to patients directly from the trial team. Side effects are reported through the online diary, telephone calls to the trial team and through electronic medical care record review. More details regarding intervention treatments, including the rationale for testing them in the trial, contraindications and eligibility criteria, are detailed in Intervention Specific Appendices to the master protocol.

Due to the urgent need for rapid trial implementation in the ongoing pandemic, this is a pragmatic, open-label trial with no placebo control.[12 17–19] The current control arm in PRINCIPLE is usual care. Current UK guidelines for managing possible COVID-19 infections in the community do not currently recommend the routine use of any antiviral drugs nor antibiotics unless there are signs of pneumonia.[20] Clinicians make clinical judgements about best treatment on an individual basis, but care is usually supportive to begin with.[20] In all study arms, participants will receive the usual care that they would normally receive following UK NHS practice and guidelines but with the addition of a trial drug in intervention arms. The trial team is not involved in clinical care or treatment decisions.

Follow-up

All participants receive a call from the trial team 3 days after enrolment to confirm the receipt of study materials including swab and medication (if randomised to a study drug) and to address any questions. For the 28 days after enrolment, participants and/or their study partner are asked to use a daily online diary to record whether they feel recovered ('Do you feel recovered today? (ie, symptoms associated with illness are no longer a problem)'); how well they feel ('How well are you feeling today? Please rate how you are feeling now using a scale of 1–10, where 1 is the worst you can imagine, and 10 is feeling the best you can imagine'); trial medication adherence; presence of individual symptoms (fever, cough, shortness of breath, muscle ache, nausea/vomiting, diarrhoea, generally feeling unwell, all rated as 'no problem', 'mild problem', 'moderate problem' or 'severe problem'); use of other medicines to control symptoms, contacts with health services; and new infections in the household. In addition, at days 14 and 28, the WHO-5 questionnaire is administered for follow-up. Participants and/or their

study partner who have not entered data online are contacted by telephone on days 7, 14 and 28 to obtain information about hospital admission, recovery, presence and severity of symptoms, and healthcare utilisation.

We also obtain consent from participants to ascertain relevant outcome data from general practice and hospital records about hospital assessments, COVID-19 related admissions, oxygen use, intensive care and mechanical ventilation, and longer term outcomes relevant to COVID-19. Trial implementation began through the Oxford-Royal College of General Practitioners Research and Surveillance Network, which has the capacity to extract patient information from the clinical records and provide a trial observatory to report on trial progress and a dashboard to flag the number of potentially eligible patients in each practice (https://clininf.eu/index.php/principle).[21] GP surgeries outside this network may also be contacted separately by the trial team to request specific data from participants' primary care medical records.

Sample handling

We endeavour to provide participants with a self-sampling kits for evidence of SARS-Cov-2 through their practice, the trial team, Public Health England or other central service to be taken at baseline. However, this depends on swab availability. If swabbing kits are unavailable, patients may still participate in the trial and are included in the intention-to-treat analysis. We also seek optional consent from participants to be contacted about providing a sample for serological testing for SARS-CoV-2 infection during convalescence.

Study outcomes

There are two coprimary endpoints. The first is time to recovery from possible COVID-19 infection within 28 days from randomisation, with time to recovery defined as the first instance that a participant reports feeling recovered. Although a number of secondary outcomes also evaluate recovery, self-report of feeling recovered was chosen for the primary outcome as the most direct measure of patient experience. The second is hospital admission or death within 28 days of randomisation. Decision to hospitalise is made by clinicians independent of the trial. Secondary outcome measures are listed in table 3.

Data collection and management

Data are entered into the participant's electronic case report form by the participant, study partner or trial team using an OpenClinica database via Sentry. OpenClinica is stored on a secure server and meets FDA part 11B standards. This includes safety data, laboratory data and outcome data. Sentry is an online secure data entry system developed in-house at the PCV-CCTU and hosted at Oxford. It is designed to collect sensitive data, such as participant contact details, and securely retain them separately from a trial's clinical data. To protect confidentiality, all study-specific documents other than the signed consent form refer to the participant using their study participant number rather than their name.

Statistical methods

Coprimary outcomes analysis

Full statistical methods are detailed in a master statistical analysis plan. In brief, the first coprimary analysis is a Bayesian piecewise exponential of time to recovery regressed on treatment and stratification covariates (age, comorbidity or high risk). The second coprimary analysis is a Bayesian logistic regression model of hospitalisation/death regressed on treatment and stratification covariates. The coprimary outcomes are evaluated using a 'gate-keeping' strategy. For a given treatment, the hypothesis for the time to recovery endpoint is evaluated first, and if the recovery null hypothesis is rejected, the hypothesis for the second coprimary endpoint of hospitalisation/death is evaluated. This gate-keeping strategy preserves the overall type I error of the primary endpoints without additional adjustments for multiple hypotheses.

The prespecified design allows adaptations to the trial based on the observed 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. At each interim analysis, all enrolled intervention arms will be evaluated for success or futility using the Bayesian primary analysis. If the Bayesian posterior probability of superiority of a given intervention over usual care is greater than or equal to 0.99 for the recovery endpoint and greater than or equal to 0.975 for the hospitalisation endpoint, superiority versus usual care will be declared on both endpoints, in which case the superior arm will replace the usual care arm as the new standard of care. The superiority thresholds of 0.99 and 0.975 for the first and second coprimary hypotheses, respectively, were determined a priori via simulation in order to control the one-sided type I error of the study at approximately 0.025.

If the Bayesian posterior probability of a clinically meaningful treatment effect (≥ 1.5 days) on time to recovery is sufficiently small (<0.05), the intervention arm will be dropped from the study for futility. If there are no other intervention arms available, the trial will be suspended; otherwise accrual continues to the remaining treatment arms.

Response adaptive randomisation

Prior to the first interim analysis, allocation will be equal among all treatment arms, with randomisation stratified by age (<65 or ≥ 65) and comorbidity. Response adaptive randomisation is activated at the time of the first interim analysis if there are at least two active interventions in the trial. When response adaptive randomisation is activated, the usual care arm will continue to receive a fixed allocation of $1/Z$, where Z is the total number of treatment arms in the study. The remaining $(Z-1)/Z$ allocation probability will be divided among the intervention arms based on interim response adaptive randomisation

Table 3 Study outcomes in the PRINCIPLE trial

Primary outcome measures	Data source	Timepoint(s)
Time to recovery defined as the first instance that a participant reports feeling recovered from possible COVID-19	Patient or study partner report.	Within 28 days.
Hospital admission or death	Patient or study partner self-report and medical record review.	Within 28 days.
Secondary outcomes		
Duration of severe symptoms measured through daily diary Patient-reported illness severity	Self-report using online diary or telephone call/text.	Daily online diary or telephone/text at days 7, 14 and 28 if no online data received.
Number of contacts with the health services Additional antibiotic use Hospital assessment without admission Oxygen administration Intensive care unit admission Mechanical ventilation (5–8 allows for an estimation of a version of the WHO Clinical Progression Ordinal Scale) Duration of hospital admission	Participant of study partner report using online diary, or telephone call/text and medical record review in primary care and hospital care.	Daily online diary or telephone/text at days 7, 14 and 28 if no online data received primary care and hospital records.
WHO-Five Well-Being Index	WHO-Five Well-Being Index.	Baseline and days 14 and 28 either via online diary or telephone
To determine if effects are specific who test positive for SARS-CoV-2	Swab results and optional serology for SARS-CoV-2 to determine an 'Intention to Treat Infected' group within the overall cohort for sub analysis.	Swabs from enrolment and/or day 5. Convalescent serology.
Qualitative substudy		
Patient experiences of consulting, being tested and taking (trial) medication for possible COVID-19	Telephone interview with participant.	After 28 days.
To explore healthcare professionals' views of taking part in research during pandemics	Telephone interview with healthcare professional.	At least 2 months after practice started recruiting.

probabilities. This is done by fitting the primary analysis model for time to recovery at an interim analysis and defining new randomisation probabilities proportional to the probability that each intervention is optimal with respect to the first coprimary endpoint. The purpose of implementing response adaptive randomisation is to allocate more participants to the intervention arms with the better observed outcomes (relative to usual care).

Sample size
Given the open, 'perpetual' trial structure, the trial does not have a finite ending based on sample size. 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. A key feature 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.

Virtual trial simulations
Because of the adaptive platform trial structure, there exists no simple formula(e) to calculate power and type I error (false positive rate). Hence, virtual trial simulations are used to fully characterise and quantify the power and type I error of the design. These simulations include a comprehensive evaluation of trial performance across a wide range of assumptions (eg, underlying distribution of outcome in control arm, treatment effect, accrual rates, etc). This includes summaries regarding the number of subjects required to make a success or futility conclusion for each intervention. For example, we quantify the probability of claiming superiority at the first and each of the subsequent interim analyses. Details of the simulations are provided in an Adaptive Design Report.

Primary analysis population

The primary intention-to-treat analysis population is defined as all randomised participants according to the group they were randomly allocated to, regardless of deviation from protocol and irrespective of their COVID-19 status.

Secondary endpoints/analyses

Secondary outcomes include duration of severe symptoms, contacts with health services, antibiotic prescriptions, oxygen administration, intensive care admission, mechanical ventilation (allowing for an estimation of a version of the WHO Clinical Progression Ordinal Scale) and self-reported well-being (table 3). Participants recruited into the study are asked to indicate if they have already had a positive test and to provide a self-swab to confirm SARS-CoV-2 infection, allowing 'intention to treat infected' analyses to be performed among those with evidence of a positive test. Blood tests may also be taken for evidence of having had COVID-19 illness. Hence, the primary analyses and key secondary analyses can be replicated on this 'intention to treat infected' population.

Qualitative substudy

We will perform semistructured telephone interviews with a subset of participants after they have competed 28 days of follow-up to ask about illness perceptions, reasons for consulting (if applicable), experiences of the consultation, the SARS-CoV-2 testing process (and result where 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.[22] We will conduct interviews with approximately 30–40 participants in total. We will also interview a sample of healthcare service, location and practice size to achieve a wide range of views of carrying out trial activities, recruiting patients and the work required to set up a clinical trial during a pandemic. We will purposively select approximately 20–25 healthcare workers based on job role, healthcare service and location to achieve a wide range of views. Interviews will be transcribed and thematically analysed using NVivo 12 software.

Ethics, approvals, monitoring and dissemination

The trial has been approved by the University of Oxford Clinical Trials Research & Governance team as study sponsor, the South Central – Berkshire Research Ethics Committee (20/SC/0158), the Health Research Authority (HRA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). The Trial has received Urgent Public Health Level 1a Priority Status by the National Institute of Health Research. 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.

An independent DMSC independent from the sponsor and without competing interests and comprised of three senior medical statisticians and two senior primary care

researchers with expertise in respiratory infections, reviews interim analyses of accruing data to ensure the rights, safety and well-being of the trial participants and advises the TSC about whether interim analyses recieved from the SAC demonstrate futility or success of interventions. Along with the TSC, the DSMC makes recommendations about how the study is operating, any ethical or safety issues and consideres any data from other relevant studies that might impact the trial. The TSC advises the TMG accordingly and has oversight of trial delivery. Any breaches in confidentiality, study protocol or adverse events attributable to this study are reported to the Research Ethics Committee and the MHRA where appropriate. Eligible patients are asked to provide informed consent for study procedures. All participants receive a £20 voucher as a token of recognition their contribution to the study. Trial results will be presented at national and international conferences and published in academic, peer-reviewed journals.

A risk assessment and monitoring plan was prepared before the study opened and is reviewed as necessary to reflect significant changes to the protocol or outcomes of monitoring activities. Monitoring is performed by the PCV-CTU Quality Assurance Manager or delegate.

Safety monitoring

All symptoms, medication side effects and Serious Adverse Events (SAEs) are collected from participant daily diaries, calls to participants/study partners, medical records, notes reviews and extracts form routinely collected medical records.

SAE information is analysed as part of the interim and whole trial analysis and is reviewed at each DMSC meeting.

Trial status

PRINCIPLE was registered on the ISRCTN registry (ISRCTN86534580) on the 22 March 2020. Enrolment started on 2 April 2020. Protocol V.5.0, 11 Spetember 2020.

DISCUSSION

Summary

Evidence-based interventions to treat COVID-19 in community settings are urgently required to reduce the health and social impacts of this pandemic.[4] We outline an open-label, multiarm, prospective, adaptive platform, randomised clinical trial that aims to rapidly evaluate multiple drug treatments for COVID-19 among people at higher risk of complications in the community.

Comparison with other studies

Two other national platform trials are assessing potential COVID-19 treatments in the UK.[23] The REMAP-CAP trial (NCT02735707) is focusing on patients admitted to intensive care units. Treatments under investigation have included lopinavir/ritonavir, hydroxychloroquine,

interferon-beta-1a and an interleukin-1 receptor antatgonist.[24] The RECOVERY trial (ISRCTN50189673) is focusing on hospital inpatients, and investigatory treatments have included lopinavir/ritonavir, dexamethasone, hydroxychloroquine and azithromycin with usual hospital care.[25] Together, these trials are assessing COVID-19 interventions across a range of clinical and community settings. Trials of community use of hydroxychloroquine in the community have been reported,[26 27] but there are few other recruiting platform trials of community-based treatments for COVID-19 capable of evalauting multiple interventions in an ongoing way.

Strengths and limitations

A major strength of PRINCIPLE is its community care focus, positioning it to test interventions for COVID-19 at earlier and milder stages of illness. As an 'in-pandemic' trial, we have designed PRINCIPLE to minimise the burden on existing healthcare services that are often already under strain and have removed the requirement for face-to-face contact for the purposes of the trial to minimise the risk of SARS-CoV-2 transmission.[28] The trial is potentially open to anyone in a participating jurisdiction who meets eligibility requirements. Furthermore, the use of routinely collected data from electronic health records may complement the capture of trial outcomes and safety monitoring. The adaptive design allows flexibility as the pandemic evolves, providing the capability to rapidly test new interventions as they become available. Interventions suitable for pragmatic evaluation in the PRINCIPLE trial have a favourable safety profile and may be suitable for widespread deployment in primary care settings. Therefore, if an intervention proves effective, rapid scale up should be achievable within the UK NHS and potentially also other settings.[29]

A potential weakness is the inclusion of patients with possible COVID-19, rather than laboratory confirmed SARS-CoV-2 infection. However, this reflects clinical practice during the time the participants were recruited, where some were managed on the basis of their clinical syndrome, in the absence of immediate confirmatory swab result as swab testing has not always been available during the conduct of the trial. Our eligibility criteria are based on the UK case definition for primary care,[20] and we will use swab test results, where available, to identify positive SARS-CoV-2 cases for relevant secondary and exploratory analyses in the SARS-CoV-2 positive subgroup.

We deliberately chose to conduct a pragmatic, open-label trial in the context of everyday practice becasue the study hypothesises that the addtion of a medication being investigated will imporve outocmes over an above routine ususal care without that medication, and usual care does not involve provision of a placebo medication. Effect sizes identified by placebo-controlled, efficacy studies with tight inclusion criteria might not be reproduced in routine care,[17 30 31] and it was not feasible to rapidly produce placebo for multiple drug interventions in this 'in-pandemic' platform trial. This pragmatic, open trial design makes our findings more likely to reflect real-world effects in community care, because knowledge of the medication one is taking could affect subsequent help seeking, including presentation at hospitals. Capturing the effect of an intervention on help seeking is an important element in evaluating the consequences of its use. However, the design does not allow us to determine mechanisms of action, for example, how much of the observed effect can be attributed to the biological effects of the drug treatment or to a placebo effect. Meta-analyses of placebo controlled trials of oseltamivir for influenza-like illness found an average benefit of about a day reduction in symptoms.[32 33] This is similar to the estimate of average benefit obtained in a large, open multinational trial of oseltamivir for infleunza-like illness.[12] The lack of placebo is unlikely to significantly affect 'harder' outcomes such as hospitalisation and death, which form part of the PRINCIPLE trial coprimary outcome. In pragmatic trials, the implementation of treatment strategies should resemble clinical practice as closely as possible.[30 34]

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