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PRINCIPLE: A clinical trial evaluating treatments for suspected and confirmed COVID-19 for recovery at home

Submission date
20/03/2020

Recruitment status
No longer recruiting

Registration date
22/03/2020

Overall study status
Completed

Last Edited
07/07/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The COVID-19 pandemic is having a devastating effect on people's health and society. So far, no treatments for COVID-19 have been proven to be effective in well-conducted clinical trials. Most cases of probable COVID-19 are being managed in the community. An ideal treatment for patients with suspected COVID-19 in the community is one that is safe, with few side-effects, can be provided by existing NHS services, helps patients recover quicker, and prevents hospital admissions.
Setting up a new clinical trial each time a possible treatment becomes available is time-consuming and inefficient. This study is a platform, randomised controlled trial in primary care that can rapidly test low-risk treatments for people at higher risk of complications from the illness. Using an efficient, open (no placebo) clinical trial design in conditions of current usual care, this trial aims to give rapid answers about the effectiveness of trial treatments. The platform trial will be flexible; it will allow further treatments to be added into the trial while the trial is already in progress, should such suitable treatments become available. The overall goal is to find treatments suitable for widespread use in the community that will help affected people recover sooner and prevent hospital admissions.

Who can participate?
Patients throughout the UK with a positive COVID-19 test (PCR test of Lateral Flow) in the last 14 days and symptoms of COVID-19 (e.g. continuous cough and/or high temperature) that started within the last 14 days, aged 18 years and over. The study website https://www.principletrial.org provides more information on how to take part.

What does the study involve?
Participants will be randomly allocated to receive usual treatment for COVID-19 or usual treatment plus the study treatment. In this study the study treatment can be changed. Please see the trial website https://www.principletrial.org/ for details of the current study treatment.

What are the possible benefits and risks of participating?
By taking part in this study, participants will be contributing towards the understanding of how

doctors can treat COVID-19 and how the symptoms progress. This may help to reduce the duration and severity of symptoms when people fall ill and reduce the burden on the NHS during this crisis. Most participants will also receive a swab, and will be told if the swab is positive or not for COVID-19. With any medicine, including ones that are already used within the NHS, there is a risk of side effects. Participants will be able to report whether they are experiencing any of these symptoms in the daily diary.

Where is the study run from?
All participating GP practices in England, managed by the University of Oxford Primary Care and Vaccines Clinical Trials Unit co-operative (UK) and all potential participants in the UK can enrol through the trial website.

When is the study starting and how long is it expected to run for?
March 2020 to July 2023

Who is funding the study?
UKRI/NIHR

Who is the main contact?
Prof. Christopher Butler - Chief Investigator
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Type(s)
Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
2020-001209-22

Integrated Research Application System (IRAS)
281958

Study information

Scientific Title
Platform Randomised trial of Treatments in the Community for Epidemic and Pandemic Illnesses (PRINCIPLE)

Acronym
PRINCIPLE

Study objectives
Current hypothesis as of 18/01/2021:
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.

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Previous hypothesis as of 08/06/2020:
Trial treatments will be superior to standard care at reducing the need for hospital admission or death for patients aged ≥50 years with comorbidity, and aged ≥65 with or without comorbidity and suspected COVID-19 infection during time of prevalent COVID-19 infections.

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Previous hypothesis:
Trial treatments (hydroxychloroquine in the first instance) will be superior to standard care at reducing the need for hospital admission or death for patients aged ≥50 years with comorbidity, and aged ≥65 with or without comorbidity and suspected COVID-19 infection during time of prevalent COVID-19 infections.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 26/03/2020, NHS REC South Central - Berkshire (Health Research Authority, Skipton House, 80 London Road, London, SE1 6LH, United Kingdom; +44 (0)2071048046; berkshire.rec@hra.nhs.uk), ref: 20/SC/0158

Study design
Pragmatic platform randomized controlled trial of interventions for COVID-19 in primary care

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
COVID-19 (SARS-CoV-2 infection)

Interventions
Current intervention as of 23/03/2022:
The study treatment of Favipiravir is 9 x 400 mg tablets (1800 mg) to be taken on day 1 (5 tablets AM, 4 tablets PM) and then 2 x 400 mg tablets (800 mg) twice daily for four days (maintenance dose) - a total of 25 tablets, over 5 days. The study treatment of Ivermectin will be 3 mg tablets once daily (300 µg/kg body weight) for 3 days.

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Previous interventions as of 27/01/2022:
The study treatment of Favipiravir is 9 x 200mg tablets (1800mg) to be taken twice a day on day 1 (loading dose) and then 4 x tablets (800mg) twice daily for four days (maintenance dose) - a total of 50 tablets, over 5 days. The study treatment of Ivermectin will be 3mg tablets once daily (300µg/kg body weight) for 3 days.

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Previous interventions as of 12/05/2021:
The study treatment of Favipiravir is 9 x 200mg tablets (1800mg) to be taken twice a day on day 1 (loading dose) and then 4 x tablets (800mg) twice daily for four days (maintenance dose) - a total of 50 tablets, over 5 days. The study treatment of Colchicine is 500mg tablet once daily for 14 days. The study treatment of Ivermectin will be 3mg tablets once daily (300µg/kg body weight) for 3 days.

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Previous interventions as of 26/04/2021:
The PRINCIPLE trial platform is currently evaluating usual care alone vs usual care plus Colchicine vs usual care plus Favipiravir.

A platform trial, in contrast to say a traditional two-arm design, allows multiple arms to be considered simultaneously, and interventions can be dropped and replaced as evidence emerges for effectiveness or lack of it. The intent is to establish an on-going trial infrastructure within a master protocol that uses all the data already accumulated for the assessment of current and subsequently introduced interventions. New interventions will only be added after submission to the appropriate approval bodies.

The evaluation of any new interventions will be governed by the master protocol, including adaptive and decision criteria. In addition, the inclusion of any new interventions will require supplementary appendices to the protocol and SAP.

The study treatment of Favipiravir is 9 200mg tablets (1800mg) to be taken twice a day on day 1 (loading dose) and then 4 tablets (800mg) twice daily for four days (maintenance dose). A total of 50 tablets, over 5 days. The study treatment of Colchicine is 500mg once daily (tablet) for 14 days.

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Previous intervention as of 18/01/2021:

The PRINCIPLE trial platform is currently evaluating usual care alone vs usual care plus inhaled budesonide (a steroid used to treat asthma).

A platform trial, in contrast to say a traditional two-arm design, allows multiple arms to be considered simultaneously, and interventions can be dropped and replaced as evidence emerges for effectiveness or lack of it. The intent is to establish an on-going trial infrastructure within a master protocol that uses all the data already accumulated for the assessment of current and subsequently introduced interventions. New interventions will only be added after submission to the appropriate approval bodies.

The evaluation of any new interventions will be governed by the master protocol, including adaptive and decision criteria. In addition, the inclusion of any new interventions will require supplementary appendices to the protocol and SAP.

The study treatment is 400 µg/day budesonide as Pulmicort turbohaler®. Participants in this arm will take 2 puffs twice a day for 14 days.

The comparator is usual care.

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Previous intervention as of 01/10/2020:

The PRINCIPLE trial platform is currently evaluating usual care alone vs usual care plus doxycycline (an antibiotic).

A platform trial, in contrast to say a traditional two-arm design, allows multiple arms to be considered simultaneously, and interventions can be dropped and replaced as evidence emerges for effectiveness or lack of it. The intent is to establish an on-going trial infrastructure within a master protocol that uses all the data already accumulated for the assessment of current and subsequently introduced interventions. New interventions will only be added after submission to the appropriate approval bodies.

The evaluation of any new interventions will be governed by the master protocol, including adaptive and decision criteria. In addition, the inclusion of any new interventions will require supplementary appendices to the protocol and SAP.

The study treatment is doxycycline 100 mg capsules. Participants in this arm will take 200 mg on the first day (as a single dose or in divided doses with a 12-h interval) followed by 100 mg a day for 6 days (7-day course in total). The capsules are for oral administration.

The comparator is usual care.

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Previous intervention as of 16/06/2020:

The PRINCIPLE trial platform is currently evaluating usual care alone vs usual care plus azithromycin (a commonly used antibiotic that is anti-inflammatory, treats community acquired pneumonia and bacterial chest infections, and has antiviral properties).

A platform trial, in contrast to say a traditional two-arm design, allows multiple arms to be considered simultaneously, and interventions can be dropped and replaced as evidence emerges for effectiveness or lack of it. The intent is to establish an on-going trial infrastructure within a master protocol that uses all the data already accumulated for the assessment of current and subsequently introduced interventions. New interventions will only be added after submission to the appropriate approval bodies.

The evaluation of any new interventions will be governed by the master protocol, including adaptive and decision criteria. In addition, the inclusion of any new interventions will require supplementary appendices to the protocol and SAP.

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

The comparator is usual care.

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Previous intervention as of 10/06/2020:

The trial will initially be two-arm, comparing usual care to usual care with hydroxychloroquine or azithromycin treatment.

The trial will be implemented in the first instance in practices that are already part of the RCGP RSC Network. Currently, over 500 practices are part of this network, with 100 already offering a sentinel viral swabbing service which is being scaled up and due to the pandemic, all practices in the UK have been asked to join the RCGP RSC Network.

A platform trial, in contrast to say a traditional two-arm design, allows multiple arms to be considered simultaneously, and interventions can be dropped and replaced as evidence emerges for effectiveness or lack of it. The intent is to establish an on-going trial infrastructure within a master protocol that uses all the data already accumulated for the assessment of current and subsequently introduced interventions. New interventions will only be added after submission to the appropriate approval bodies.

The PRINCIPLE trial will begin as a 1:1 randomised trial of usual care plus study-specific medication (in the first instance hydroxychloroquine) versus usual care alone but the study design has the capability to add additional interventions over time (such as azithromycin). The evaluation of any new interventions will be governed by the master protocol, including adaptive and decision criteria. In addition, the inclusion of any new interventions will require supplementary appendices to the protocol and SAP.

The initial drug is hydroxychloroquine sulphate 200 mg tablets. The tablets are for oral administration. One tablet (200 mg) hydroxychloroquine to be taken twice daily for 7 days by mouth (14 tablets in total). 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, UK. Marketing authorisation number is PL 17780/0748.

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

The second study treatment is azithromycin 250mg capsules. Participants in this arm will take 500 mg (two capsules) once daily for 3 days. The capsules are for oral administration.

The comparator is usual care.

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Previous intervention as of 08/06/2020:

The trial will initially be two-arm, comparing usual care to usual care with hydroxychloroquine /azithromycin treatment.

The trial will be implemented in the first instance in practices that are already part of the RCGP RSC Network. Currently, over 500 practices are part of this network, with 100 already offering a sentinel viral swabbing service which is being scaled up and due to the pandemic, all practices in the UK have been asked to join the RCGP RSC Network.

A platform trial, in contrast to say a traditional two-arm design, allows multiple arms to be considered simultaneously, and interventions can be dropped and replaced as evidence emerges for effectiveness or lack of it. The intent is to establish an on-going trial infrastructure within a master protocol that uses all the data already accumulated for the assessment of current and subsequently introduced interventions. New interventions will only be added after submission to the appropriate approval bodies.

The PRINCIPLE trial will begin as a 1:1 randomised trial of usual care plus study-specific medication (in the first instance hydroxychloroquine) versus usual care alone but the study design has the capability to add additional interventions over time. The evaluation of any new interventions will be governed by the master protocol, including adaptive and decision criteria. In addition, the inclusion of any new interventions will require supplementary appendices to the protocol and SAP.

The initial drug is hydroxychloroquine sulphate 200 mg tablets. The tablets are for oral administration. One tablet (200 mg) hydroxychloroquine to be taken twice daily for 7 days by mouth (14 tablets in total). 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, UK. Marketing authorisation number is PL 17780/0748.

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

Comparator is usual care.

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Previous intervention:

The trial will initially be two-arm, comparing usual care to usual care with hydroxychloroquine treatment.

The trial will be implemented in the first instance in practices that are already part of the RCGP RSC Network. Currently, over 500 practices are part of this network, with 100 already offering a sentinel viral swabbing service which is being scaled up and due to the pandemic, all practices in the UK have been asked to join the RCGP RSC Network.

A platform trial, in contrast to say a traditional two-arm design, allows multiple arms to be considered simultaneously, and interventions can be dropped and replaced as evidence emerges

for effectiveness or lack of it. The intent is to establish an on-going trial infrastructure within a master protocol that uses all the data already accumulated for the assessment of current and subsequently introduced interventions. New interventions will only be added after submission to the appropriate approval bodies.

The PRINCIPLE trial will begin as a 1:1 randomised trial of usual care plus study-specific medication (in the first instance hydroxychloroquine) versus usual care alone but the study design has the capability to add additional interventions over time. The evaluation of any new interventions will be governed by the master protocol, including adaptive and decision criteria. In addition, the inclusion of any new interventions will require supplementary appendices to the protocol and SAP.

The initial drug is hydroxychloroquine sulphate 200 mg tablets. The tablets are for oral administration. One tablet (200 mg) hydroxychloroquine to be taken twice daily for 7 days by mouth (14 tablets in total). 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, UK. Marketing authorisation number is PL 17780/0748.

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

Comparator is usual care.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Azithromycin, hydroxychloroquine sulphate, doxycycline, inhaled budesonide (Pulmicort turbohaler®), colchicine, favipiravir, ivermectin

Primary outcome(s)
Current primary outcome measure as of 18/01/2021:

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.The trial has co-primary endpoints:
1. Time taken to self-reported recovery, defined as the first instance that a participant reports feeling recovered from possible COVID-19
2. Hospitalisation and/or death

Both collected within 28 days of randomisation from patient report, study partner report, medical records, daily online symptom scores .

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Previous primary outcome measure as of 10/06/2020:

Hospital admission or mortality related to suspected COVID-19 infection assessed using reports of patients' medical records, from enrolment up to 28 days after completing treatment

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Previous primary outcome measure as of 08/06/2020:

Hospital admission or mortality related to suspected COVID-19 infection.

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Previous primary outcome measure:

Hospital admission or death, for patients aged ≥50 years with comorbidity, and aged ≥65 years with or without comorbidity and suspected COVID-19 infection during time of prevalent COVID-19 infections, measured by hospital admission or mortality related to suspected COVID-19 within 28 days

Key secondary outcome(s))

Current secondary outcome measures as of 27/01/2022:

1. All cause of death or non-elective/urgent hospitalisation
2. Patient-reported illness severity
3. Duration of severe symptoms and symptom recurrence, measured by patient report on day recovered
4. Contacts with the health services, reported by patients and captured by reports of patients' medical records where the practice is a member of the RCGP RSC network
5. Consumption of antibiotics, measured using bi-weekly reports from participants' primary care medical records
6. Hospital assessment without admission, measured using patient report/carer report/medical record in primary care and hospital care
7. Oxygen administration, measured using patient report/carer report/medical record in primary care and hospital care
8. Intensive Care Unit admission, measured using patient report/carer report/medical record in primary care and hospital care
9. Mechanical ventilation, measured using patient report/carer report/medical record in primary care and hospital care
10. Duration of hospital admission
11. Negative effects on well being
12. New infections in household
13. To investigate the safety of treatments that are not licensed in the UK

Previous secondary outcome measures as of 26/04/2021:

1. Patient-reported illness severity
2. Duration of severe symptoms and symptom recurrence, measured by patient report on day recovered
3. Contacts with the health services, reported by patients and captured by reports of patients' medical records where the practice is a member of the RCGP RSC network
4. Consumption of antibiotics, measured using bi-weekly reports from participants' primary care

medical records
5. Hospital assessment without admission, measured using patient report/carer report/medical record in primary care and hospital care
6. Oxygen administration, measured using patient report/carer report/medical record in primary care and hospital care
7. Intensive Care Unit admission, measured using patient report/carer report/medical record in primary care and hospital care
8. Mechanical ventilation, measured using patient report/carer report/medical record in primary care and hospital care
9. Duration of hospital admission
10. Negative effects on well being
11. New infections in household
12. To determine if effects are specific to those with a positive test for SARS-CoV-2
13. To investigate the safety of treatments that are not licensed in the UK

Measured using the following methods/timepoints:
1. Daily online symptoms score and diary
2. Telephone call or text on days 7, 14, and 28 if data not being received online
3. GP notes review where available through RSC network after 28 days
4. HES/ONS data linkage after 28 days where patients have been assessed in hospital
5. Swab result available once processed from GP record and from the supporting PHE laboratory
6. Evaluation of overall safety of drugs by the monitoring of pre-defined Adverse Events

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Previous secondary outcome measures as of 18/01/2021:

1. Patient-reported illness severity
2. Duration of severe symptoms and symptom recurrence, measured by patient report on day recovered
3. Contacts with the health services, reported by patients and captured by reports of patients' medical records where the practice is a member of the RCGP RSC network
4. Consumption of antibiotics, measured using bi-weekly reports from participants' primary care medical records
5. Hospital assessment without admission, measured using patient report/carer report/medical record in primary care and hospital care
6. Oxygen administration, measured using patient report/carer report/medical record in primary care and hospital care
7. Intensive Care Unit admission, measured using patient report/carer report/medical record in primary care and hospital care
8. Mechanical ventilation, measured using patient report/carer report/medical record in primary care and hospital care
9. Duration of hospital admission
10. Negative effects on well being
11. New infections in household
12. To determine if effects are specific to those with a positive test for SARS-CoV-2

Measured using the following methods/timepoints:
1. Daily online symptoms score and diary
2. Telephone call or text on days 7, 14 and 28 if data not being received online

3. GP notes review where available through RSC network after 28 days
4. HES/ONS data linkage after 28 days where patients have been assessed in hospital
5. Swab result available once processed from GP record and from the supporting PHE laboratory

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Previous secondary outcome measures as of 08/06/2020:

1. Duration of severe symptoms, measured by patient report on day recovered
2. Time taken to self-report recovery, measured by patient report on day recovered
3. Contacts with the health services, reported by patients and captured by reports of patients' medical records where the practice is a member of the RCGP RSC network
4. Consumption of antibiotics, measured using bi-weekly reports from participants' primary care medical records
5. Hospital assessment without admission, measured using patient report/carer report/medical record in primary care and hospital care
6. Oxygen administration, measured using patient report/carer report/medical record in primary care and hospital care
7. Intensive Care Unit admission, measured using patient report/carer report/medical record in primary care and hospital care
8. Mechanical ventilation, measured using patient report/carer report/medical record in primary care and hospital care
9. Swab results either at baseline or day 5 for SARS-CoV-2 will indicate an 'Intention to Treat Infected' group within the overall cohort for sub-analysis. Blood test on recovery (optional) for evidence of historic COVID-19.
10. Follow up swab at day 5 (if available) will indicate ongoing viral shedding, allowingcomparison between groups
11. Negative effects on well-being measured using WHO-5 Well-Being Index

Measured using the following methods/timepoints:
1. Daily online symptoms score and diary
2. Telephone call or text on days 7, 14 and 28 if data not being received online
3. GP notes review where available through RSC network after 28 days
4. HES/ONS data linkage after 28 days where patients have been assessed in hospital
5. Swab result available once processed from GP record and from the supporting PHE laboratory

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Previous secondary outcome measures:

1. Duration of severe symptoms, measured by patient report on day recovered
2. Time taken to full recovery of illness, measured by patient report on day recovered
3. Contacts with the health services, reported by patients and captured by reports of patients' medical records where the practice is a member of RSC
4. Consumption of antibiotics, measured using bi-weekly reports from participants' primary care medical records
5. Hospital assessment without admission, measured using patient report/carer report/medical record in primary care and hospital care
6. Oxygen administration, measured using patient report/carer report/medical record in primary care and hospital care
7. Intensive Care Unit admission, measured using patient report/carer report/medical record in primary care and hospital care

8. Mechanical ventilation, measured using patient report/carer report/medical record in primary care and hospital care
9. Swab results for COVID-19 will indicate an “Intention to Treat Infected” group within the overall cohort for sub-analysis, to determine if effects are specific to those with the infection's syndrome but who test positive for COVID-19

Measured using the following methods/timepoints:
1. Daily online symptoms score and diary
2. Telephone call or text on days 7, 14 and 28 if data not being received online
3. GP notes review where available through RSC network after 28 days
4. HES/ONS data linkage after 28 days where patients have been assessed in hospital
5. Swab result available once processed from GP record and from the supporting PHE laboratory

Completion date
11/07/2023

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 27/01/2022:
1. Participant or their legal representative, is willing and able to give informed consent for participation in the study, and is willing to comply with all trial procedures
2. A positive test for SARS-CoV-2 infection within the past 14 days (patient reported PCR test or lateral flow test result), with symptoms consistent with COVID-19*
3. Symptoms must have started within the past 14 days and be ongoing
4. Participant is aged 18 or over

*These symptoms may include, but are not limited to: a high temperature; a new, continuous cough; loss or change to your sense of smell or taste; sore throat; shortness of breath; general feeling of being unwell; muscle pain; diarrhoea and vomiting.

Previous participant inclusion criteria as of 26/04/2021:
1. Participant is willing and able to give informed consent for participation in the study
2. Participant is willing to comply with all trial procedures
3. Suspected COVID-19 using the NHS syndromic definition, or symptoms consistent with COVID-19 (including, but are not limited to, shortness of breath, general feeling of being unwell, muscle pain, diarrhoea and vomiting) and with a positive test for SARS-CoV-2 infection within the past 14 days
4. Aged 65 years or over, aged 18-64 and is experiencing shortness of breath as part of COVID-19 illnesses, or aged 18-64 and has any of the following underlying health conditions:
4.1. Known weakened immune system due to a serious illness or medication (e.g. chemotherapy);
4.2. Known heart disease and/or a diagnosis of high blood pressure
4.3. Known chronic lung disease (e.g. asthma)
4.4. Known diabetes
4.5. Known mild hepatic impairment;
4.6. Known stroke or neurological problem;
4.7. Self-report obesity or body mass index ≥35 kg/m²

Previous participant inclusion criteria as of 08/06/2020:

1. Participant is willing and able to give informed consent for participation in the study
2. Participant is willing to comply with all trial procedures
3. Onset of symptoms of possible COVID-19 in the community (continuous cough and/or high temperature) should be within 14 days of inclusion OR a positive test for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND the participant is 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 they must have had them for fewer than 15 days.
4. Patients aged ≥50-64 years with any of the following listed comorbidities OR patients aged ≥65 years with or without comorbidity:
4.1. Known weakened immune system due to serious illness or medication (e.g. chemotherapy)
4.2. Known heart disease and/or hypertension
4.3. Known asthma or lung disease
4.4. Known diabetes not treated with insulin
4.5. Known mild hepatic impairment
4.6. Known stroke or neurological problem

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Previous inclusion criteria:

1. Participant is willing and able to give informed consent for participation in the study
2. Participant is willing to comply with all trial procedures
3. Onset of symptoms of possible COVID-19 in the community (continuous cough and/or high temperature) should be within 7 days of inclusion
4. Patients aged ≥65 with or without comorbidity, and patients aged ≥50 years with the following listed comorbidities:
4.1. Known weakened immune system due to serious illness or infection (e.g. chemotherapy)
4.2. Known heart disease
4.3. Known asthma or lung disease
4.4. Known diabetes not treated with insulin
4.5. Known mild hepatic impairment
4.6. Known stroke or neurological problem

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
11768

Key exclusion criteria

Current participant exclusion criteria as of 27/01/2022:
1. Patient currently admitted in hospital
2. Almost recovered (generally much improved and symptoms now mild or almost absent)
3. Judgement of the recruiting clinician deems ineligible.
4. Previous randomisation to an arm of the PRINCIPLE trial
5. Known or suspected pregnancy
6. Breastfeeding
7. Women of childbearing potential (premenopausal female that is anatomically and physiologically capable of becoming pregnant*), or male with a partner of childbearing potential, not willing to use highly effective contraceptive** for the 28-day duration of the trial.

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

Previous participant exclusion criteria as of 26/04/2021:
1. Patient currently admitted in hospital
2. Almost recovered (generally much improved and symptoms now mild or almost absent)
3. Judgement of the recruiting clinician deems ineligible
4. Previous randomisation to an arm of the PRINCIPLE trial

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

Previous participant exclusion criteria as of 16/06/2020:

1. Patient currently admitted in hospital
2. Almost recovered (generally much improved and symptoms now mild or almost absent)
3. Judgement of the recruiting clinician deems ineligible
4. Patient already taking an intervention arm medication (hydroxychloroquine or azithromycin) or other macrolides or ketolides

5. Exclusion criteria related to azithromycin:
5.1. Pregnancy
5.2. Breastfeeding
5.3. Known severe hepatic impairment
5.4. Known severe renal impairment
5.5. Known myasthenia gravis
5.6. Previous adverse reaction to, or currently taking, azithromycin or other macrolides or ketolides
5.7. Patients taking the following drugs: hydroxychloroquine or chloroquine, sotalol, amiodarone, ciclosporin, digoxin, bromocriptine, cabergoline, ergotamine, ergometrine, methysergide or any ergot derivatives
5.8. Already taking antibiotics for an acute condition Known congenital or documented QT

prolongation
5.9. Known allergy to soya or peanut due to the risk of hypersensitivity reactions

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Previous exclusion criteria as of 08/06/2020:

1. Patient currently admitted in hospital
2. Almost recovered (generally much improved and symptoms now mild or almost absent)
3. Judgement of the recruiting clinician deems ineligible
4. Patient already taking an intervention arm medication (hydroxychloroquine or azithromycin) or other macrolides or ketolides

Additional exclusions specific to each intervention arm are listed below. Participants can take part in the study if they are eligible to be randomised to at least one intervention arm as well as the control arm.

5. Exclusion criteria related to hydroxychloroquine:
5.1. Pregnancy
5.2. Breastfeeding
5.3. Known severe hepatic impairment
5.4. Known severe renal impairment
5.5. Known porphyria
5.5. Type 1 diabetes or insulin dependent type 2 diabetes mellitus
5.6. Known G6PD deficiency
5.7. Known myasthenia gravis
5.8. Known severe psoriasis
5.9. Known severe neurological disorders (especially those with a history of epilepsy—may lower seizure threshold)
5.10. Previous adverse reaction to, or currently taking, hydroxychloroquine or chloroquine
5.11. Patients currently taking the following drugs: penicillamine, amiodarone, ciclosporin, digoxin, azithromycin or other macrolides or ketolides
5.12. Known congenital or documented QT prolongation
5.13. Known retinal disease

6. Exclusion criteria related to azithromycin:
6.1. Pregnancy
6.2. Breastfeeding
6.3. Known severe hepatic impairment
6.4. Known severe renal impairment
6.5. Known myasthenia gravis
6.6. Previous adverse reaction to, or currently taking, azithromycin or other macrolides or ketolides
6.7. Patients taking the following drugs: hydroxychloroquine or chloroquine, sotalol, amiodarone, ciclosporin, digoxin, bromocriptine, cabergoline, ergotamine, ergometrine, methysergide or any ergot derivatives
6.8. Already taking antibiotics for an acute condition Known congenital or documented QT prolongation
6.9. Known allergy to soya or peanut due to the risk of hypersensitivity reactions

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Previous exclusion criteria:

1. Pregnancy
2. Breastfeeding
3. Known severe hepatic impairment
4. Known severe renal impairment
5. Known porphyrias
6. Type 1 diabetes or insulin-dependent Type 2 diabetes mellitus
7. Known G6PD deficiency
8. Known myasthenia gravis
9. Known severe psoriasis
10. Known severe neurological disorders (especially those with a history of epilepsy — may lower seizure threshold)
11. Previous adverse reaction to, or currently taking, hydroxychloroquine
12. Known retinal disease
13. Judgement of the recruiting clinician deems ineligibility

Date of first enrolment
25/03/2020

Date of final enrolment
12/12/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Open to all eligible participants throughout the UK
Please go to https://www.principletrial.org/participants/how-to-join-the-trial to enrol
Oxford
United Kingdom
OX3 9DU

Study participating centre
All participating GP practices in England
United Kingdom
-

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
Office of the Chief Medical Officer

Results and Publications

Individual participant data (IPD) sharing plan
Selected, de-identified individual participant data for outcome measures will be available on request, accompanied by a protocol outlining hypotheses and proposed analytic methods, by contacting the corresponding author: requests will be considered by a Departmental Committee. A contract should be signed.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	Azithromycin results	20/03/2021	08/03/2021	Yes	No
Results article	Doxycycline results	27/07/2021	02/08/2021	Yes	No
Results article	Budesonide results	10/08/2021	16/08/2021	Yes	No
Results article	Ivermectin results	29/02/2024	05/03/2024	Yes	No
Results article	Favipiravir results	29/08/2024	02/09/2024	Yes	No
Results article	Hydroxychloroquine results	04/07/2025	07/07/2025	Yes	No
Protocol article		18/06/2021	21/06/2021	Yes	No
Abstract results	Budesonide arm; NAPCRG 50th Annual Meeting — Abstracts of Completed Research 2022	01/01/2023	24/03/2023	No	No
HRA research summary			28/06/2023	No	No
		20/01	24/01		

Other publications		/2022	/2022	Yes	No
Participant information sheet	Participant information sheet	11/11 /2025	11/11 /2025	No	Yes
Protocol file	version V4.0	02/07 /2020	07/09 /2020	No	No
Statistical Analysis Plan	version 5.0	14/12 /2021	10/05 /2024	No	No
Study website	Study website	11/11 /2025	11/11 /2025	No	Yes