Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Martin Landray

University of Oxford, UK

on behalf of the RECOVERY trial investigators

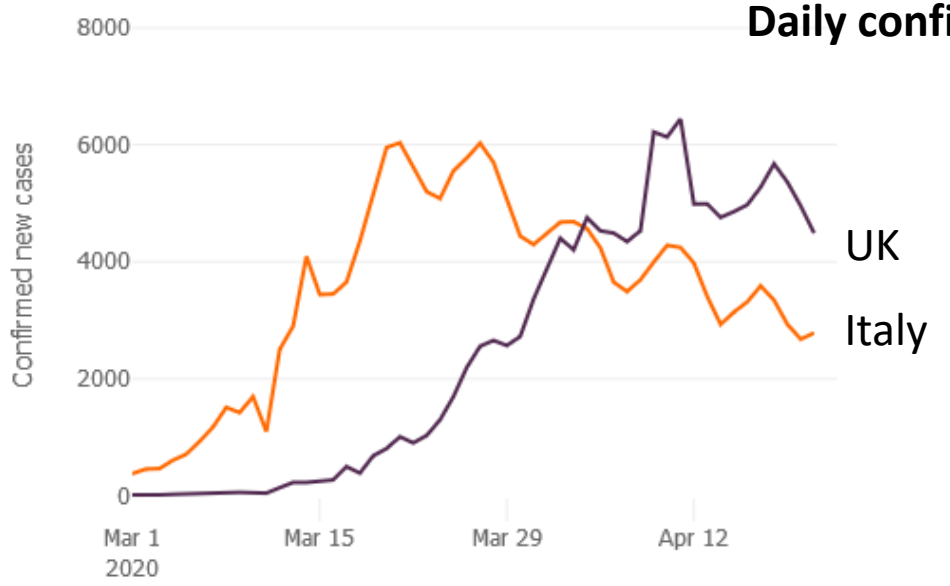
www.recoverytrial.net

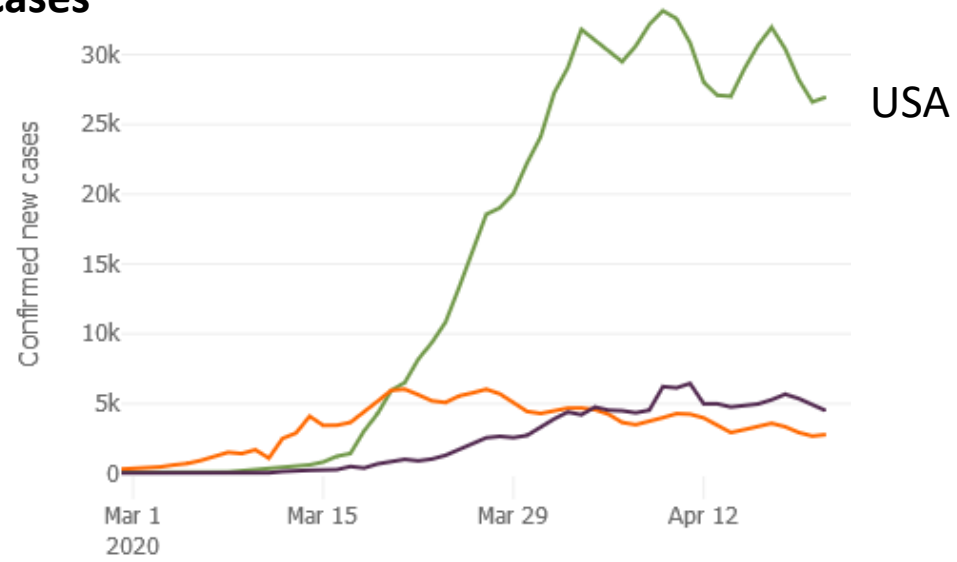
Background

Emerging pandemic caused by a new virus

- For most people, self-limiting viral illness
- For hospitalised patients, 10-20% mortality
- For ventilated patients, 40-50% mortality

Daily confirmed new cases

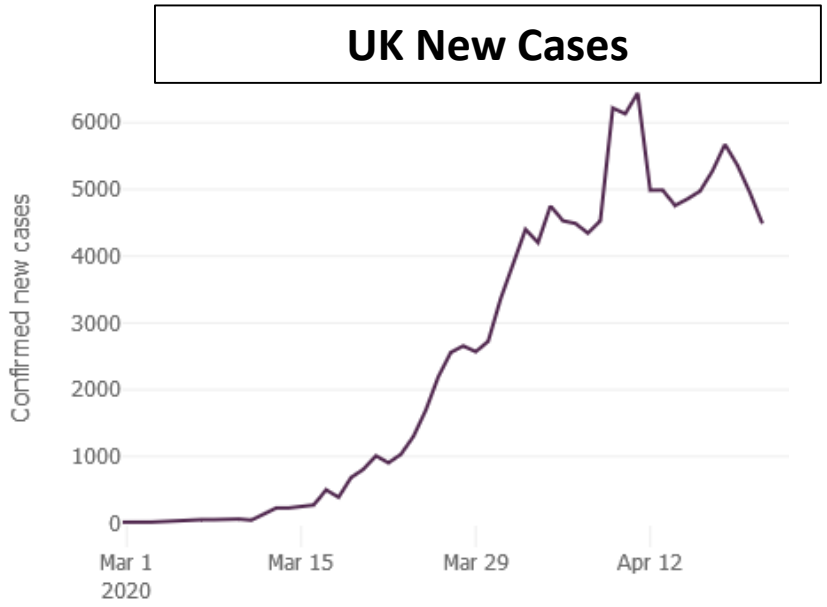


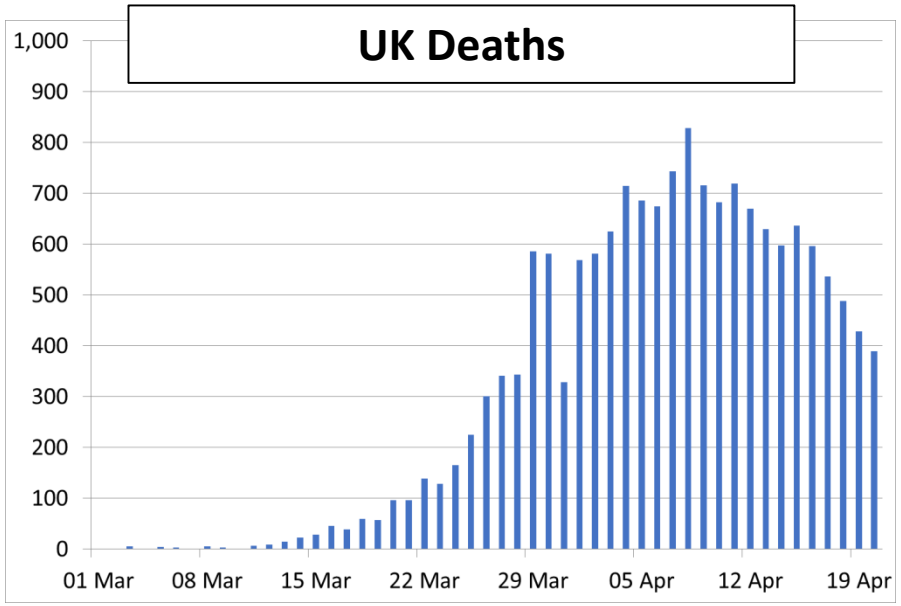


Background

Unprecedented clinical challenge

- Overstretched health service (availability of beds, staff, and ventilators)
- Huge time pressures and personal stress for frontline medical staff
- Large numbers of unwell, anxious, and often elderly patients





Background

Unprecedented clinical challenge

- Overstretched health service (availability of beds, staff, and ventilators)
- Huge time pressures and personal stress for frontline medical staff
- Large numbers of unwell, anxious, and often elderly patients

Huge therapeutic uncertainty

- Many candidates
- Many opinions (from many sources)
- No reliable data (uncontrolled case series, inconclusive randomized trials)

Background

Addressing the therapeutic challenge

- Unlikely to be a single “big win”
- Moderate benefits plausible

Moderate effects are worthwhile

- There were ~15,000 deaths from COVID-19 in the US last week
- Reducing mortality by one-fifth would “save” ~3,000 lives

Background

Differentiating moderate benefits from no benefit (or harm) requires:

- RANDOMIZATION
- Comparison vs. CONTROL group not receiving the drug
- LARGE numbers

For example:

90% power @2P=0.01		**Mortality** 20%	30%
Proportional risk reduction	20%	5,600	3,300
	30%	2,400	1,400

Prioritising treatments to study

Initial prioritisation principles:

- Potentially effective (based on prior pre-clinical & clinical data)
- Major safety issues understood
- Sufficient treatment available for large-scale recruitment
- Potential to rapidly scale up as a clinical treatment (if shown to be effective)

Three broad categories:

- Re-purposed drugs widely used in other conditions
- Drugs normally restricted to specialist settings (e.g. immunomodulation)
- Treatments targeted at SARS-CoV-2 (e.g. convalescent plasma, anti-spike Ab)

Quality by Design

Three key principles:

- Obtain robust results that can rapidly impact care
- Consider well-being of patients
- Consider well-being of staff

Focus only on what matters

- Leave orthodoxy, habits, and traditional practices behind
- Communicate and collaborate
- Transparency (with research, medical, patient, public, media, etc)

A coordinated approach

Coordinated, collaborative approvals

- Single regulatory agency (MHRA)
- Single Ethics Committee (IRB) covers the whole country
- Common contract

Prioritisation of resources

- Chief Medical Officer: clinical trial enrolment is *part of* delivering clinical care
- National Institute for Health Research Clinical Research Network: mobilised research nurses at every hospital
- Department of Health: procured & supplied treatment
- NHS Digital: access to linked national health data from multiple sources

Sticking to the principles of Good Clinical Practice

"Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)." ***(ICH E6(R2) section 2.8).***

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At each hospital, a lead investigator will be responsible for trial activities but much of the work will be carried out by medical staff attending patients with COVID-19 within the hospital and by hospital research nurses, medical students and other staff with appropriate education, training, and experience.

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The tasks that they are required to perform under this protocol are similar to those that they perform in the other aspects of their roles as NHS staff.

Sticking to the principles of Good Clinical Practice

"Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)." ***(ICH E6(R2) section 2.8).***

At each hospital, a lead investigator will be responsible for trial activities but much of the work will be carried out by medical staff attending patients with COVID-19 within the hospital and by hospital research nurses, medical students and other staff with appropriate education, training, and experience.

The tasks that they are required to perform under this protocol are similar to those that they perform in the other aspects of their roles as NHS staff.

No additional training in GCP is required.

RECOVERY trial design

RECOVERY
Randomised Evaluation of COVID-19 Therapy

ELIGIBLE PATIENTS

1. Age ≥18 years
2. Admitted to hospital
3. Proven or suspected SARS-CoV-2 infection

Identification and invitation

RECOVERY
Randomised Evaluation of COVID-19 Therapy

- All adult patients with proven or suspected SARS-CoV-2 infection admitted should be considered for trial

- Should be discussed with senior member of clinical team and assuming
  1. All eligibility criteria are met; and
  2. No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial, the patient should be offered participation

- If one or more of the treatment arms is not available or believed, by the attending clinician, to be contraindicated (or definitely indicted), then the patient can be randomised between the remaining arms

Informed consent

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Randomised Evaluation of COVID-19 Therapy

RECOVERY **RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)**

Invitation to participate

We are inviting adults (aged 18 years or older) who have been admitted to hospital with COVID-19 to consent to join this research study comparing possible treatments. This form gives information about the study including the aims, risks and benefits of taking part.

WHAT YOU SHOULD KNOW ABOUT THIS RESEARCH STUDY:

1) Why is this research being done?

Your doctors have found that you have a lung disease called COVID-19. This condition is caused by a type of virus called SARS-CoV-2, or coronavirus for short.

About 8 out of 10 patients who get coronavirus get better without coming to hospital. Of those who are admitted to hospital, most also get better, but some may need oxygen or medical ventilation before they do so. However, a few people still do not get better.

There are no drugs of proven value against COVID-19 although there are several which may turn out to be helpful (or possibly harmful) when added to the usual standard of care. This study aims to find out whether any of these additional treatments are of any help.

2) What is the purpose of this study?

This study aims to compare several different treatments that may be useful for patients with COVID-19. These treatments have been recommended by the expert panel that advises the Chief Medical Officer in England. Some are tablets and some are injections. Although these treatments show promise, nobody knows if any of them will turn out to be more effective in helping patients recover than the usual standard of care at your hospital (which all patients will receive).

The treatments, given in addition to the usual care at your hospital, are: Lopinavir-ritonavir (commonly used to treat HIV); inhaled interferon (usually given by injection to treat multiple sclerosis, hepatitis C, and some blood disorders); or dexamethasone (a type of steroid, which is used in a range of conditions typically to reduce inflammation). The side-effects are well-known and your doctor will be able to monitor you appropriately.

3) Who is doing the study?

The study is being conducted by researchers at the University of Oxford, which acts as the sponsor for the research, working with doctors at many hospitals across the UK.

4) Who is being included in the study?

Patients may be included in this study if they are at least 18 years of age, have COVID-19 confirmed by a laboratory test for coronavirus, and are in hospital. Patients will not be included if the attending doctor thinks there is a particular reason why none of the study treatments are suitable.

5) What will happen to me if I agree to be included in this study?

If you decide to join, you will be asked to sign the consent form. Next, brief details identifying you and answering a few questions about your health and medical conditions will be entered into a computer. The computer will then allocate you at random (like rolling a dice) to one of the possible treatment options. In all cases this will include the usual standard of care for your hospital. It may also include one additional treatment, which might be given by mouth, injection or inhalation. Neither you nor your doctors can choose which of these options you will be allocated.

Additional information about your health will be recorded and entered into the study computer but no additional visits will be required after you leave the hospital. In some instances, information may be obtained about you from medical records or databases (including genetic or other research databases) if you have provided samples to these) so that the study team can get more detailed or longer term information about the effects of the study treatments on your health for up to 20 years after the end of your participation.

6) What are the possible benefits of being in the study?

We do not know if any of 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.

7) What are the possible risks of being in the study?

Apart from the known side effects of these treatments (which may include tummy upset, flu-like symptoms, and blood test abnormalities), there is the unlikely possibility of a severe reaction to a study drug. Please ask your hospital doctor if you would like more information. Once you have been included in the study, you and your doctors will know which treatment the computer has allocated for you. Your doctors will be aware of whether there are any particular side effects that they should look out for.

8) Can I stop the study treatment or my participation early?

If you or your doctor want to stop the study treatment before the course has been completed, then you are free to do so. If you decide that you do not wish any more information to be collected about you, you are free to say so (although de-identified information that has been collected up to that point will continue to be analysed by the research team).

9) If I have any questions or problems, who can I call?

If you have any questions please speak to your hospital medical team. Further information about the study will also be available on the study website (www.recoverytrial.net).

10) What information do you hold about me and how do you keep it private?

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

11) Do I have to take part?

Joining the study is voluntary. Your decision whether to take part will not affect the care you receive at this hospital.

12) Are there any financial costs or payments?

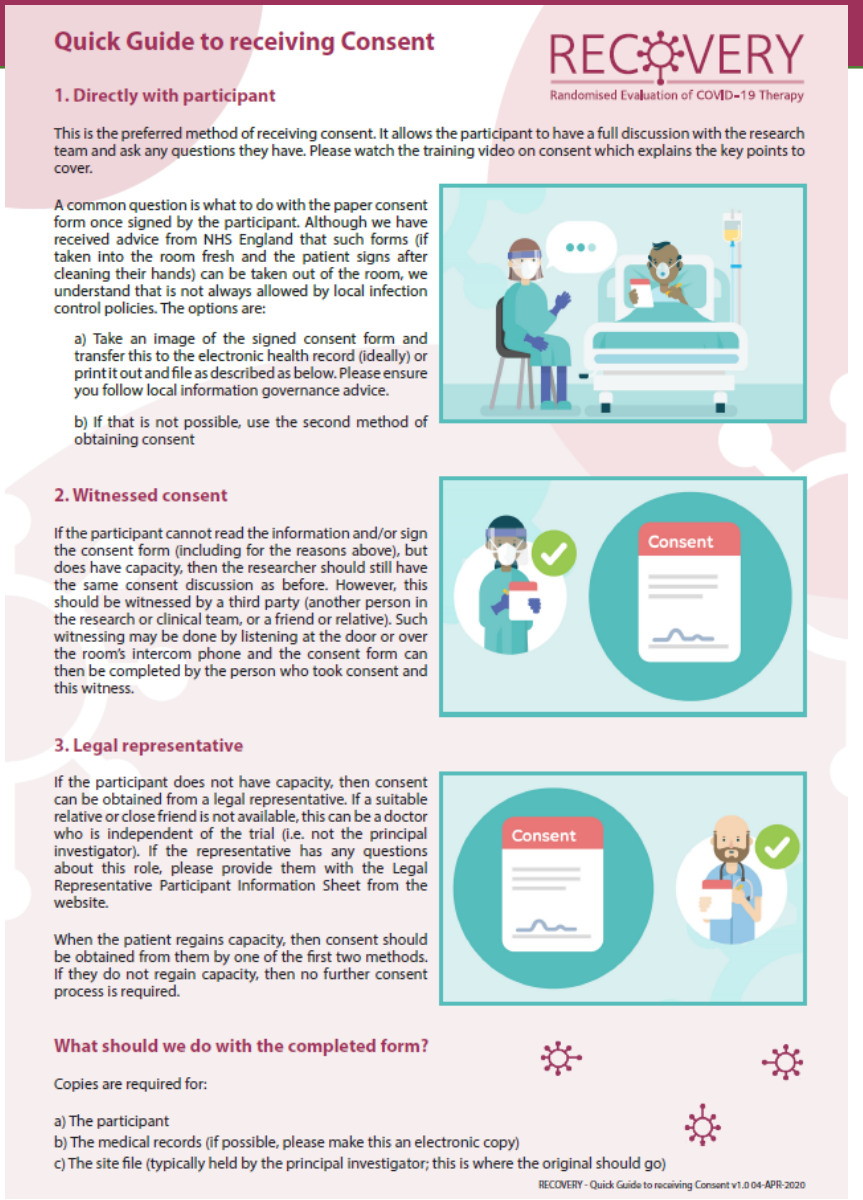
All trial treatments will be free. Neither you nor your medical staff will be paid for your participation in this study.

13) What else can you tell me?

The study is funded by UK Research and Innovation and the National Institute for Health Research, not the makers of any of the study treatments. If we find out any new information that might affect your decision to stay in the study, we will give it to you. 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 study. NHS Indemnity operates in respect of the clinical treatment that is provided.

Informed consent

- Simple 2 page information sheet & 1 page form
- Option for witnessed consent
  - if participant cannot read or sign for themselves
  - If infection control procedures do not allow ICF out of the ‘red zone’
- Option for legal representative
  - if patient lacks capacity



Quick Guide to receiving Consent

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Randomised Evaluation of COVID-19 Therapy

1. Directly with participant

This is the preferred method of receiving consent. It allows the participant to have a full discussion with the research team and ask any questions they have. Please watch the training video on consent which explains the key points to cover.

A common question is what to do with the paper consent form once signed by the participant. Although we have received advice from NHS England that such forms (if taken into the room fresh and the patient signs after cleaning their hands) can be taken out of the room, we understand that is not always allowed by local infection control policies. The options are:

a) Take an image of the signed consent form and transfer this to the electronic health record (ideally) or print it out and file as described as below. Please ensure you follow local information governance advice.

b) If that is not possible, use the second method of obtaining consent

2. Witnessed consent

If the participant cannot read the information and/or sign the consent form (including for the reasons above), but does have capacity, then the researcher should still have the same consent discussion as before. However, this should be witnessed by a third party (another person in the research or clinical team, or a friend or relative). Such witnessing may be done by listening at the door or over the room's intercom phone and the consent form can then be completed by the person who took consent and this witness.

3. Legal representative

If the participant does not have capacity, then consent can be obtained from a legal representative. If a suitable relative or close friend is not available, this can be a doctor who is independent of the trial (i.e. not the principal investigator). If the representative has any questions about this role, please provide them with the Legal Representative Participant Information Sheet from the website.

When the patient regains capacity, then consent should be obtained from them by one of the first two methods. If they do not regain capacity, then no further consent process is required.

What should we do with the completed form?

Copies are required for:

a) The participant
b) The medical records (if possible, please make this an electronic copy)
c) The site file (typically held by the principal investigator; this is where the original should go)

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- Simple 2 page information sheet & 1 page form
- Option for witnessed consent
  - if participant cannot read or sign for themselves
  - If infection control procedures do not allow ICF out of the ‘red zone’
- Option for legal representative
  - if patient lacks capacity

RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

Hospital: **Patient Name:**

1. Information about the study has been provided to me: I confirm that I have read and understood the Participant Information Leaflet (V1.0 13-Mar-2020) I have had the opportunity to consider the information and ask questions. These have been answered satisfactorily.

2. Voluntary participation: I understand that 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. Access to study data about me: I give permission for relevant sections of my medical notes and information collected during the study to be looked at, in confidence, by authorised individuals from this hospital, the University of Oxford, and regulatory authorities to check that the study is being carried out correctly.

4. Access to my medical information: I agree that medical information collected by the doctors and hospitals which provide me with care and which may be located in local or national health and research organizations (including hospital admission, civil registration, audit and research data) may be provided to the study coordinating centre both during and for up to 10 years after the scheduled follow-up period. I understand that information that identifies me will be passed securely to such bodies to make this possible and that I can opt out of this at any time by writing to the coordinating centre team.

5. Data stored on computer: I understand that information about my progress in the study will be recorded on a computer database, and that this data will be stored on computers supervised by the University of Oxford. I understand that this information will be kept securely and confidentially.

6. Agreement to take part: I have read the information (or had it read to me), had an opportunity to ask questions and agree to take part in the above study.

.....	.....	...../...../.....
PRINTED name of participant	Signature	Today’s date
.....	.....	...../...../.....
PRINTED name of person taking consent	Signature	Today’s date

**1 copy for participant; 1 copy for researcher site file; 1 (original) to be kept in medical notes*

RECOVERY trial design

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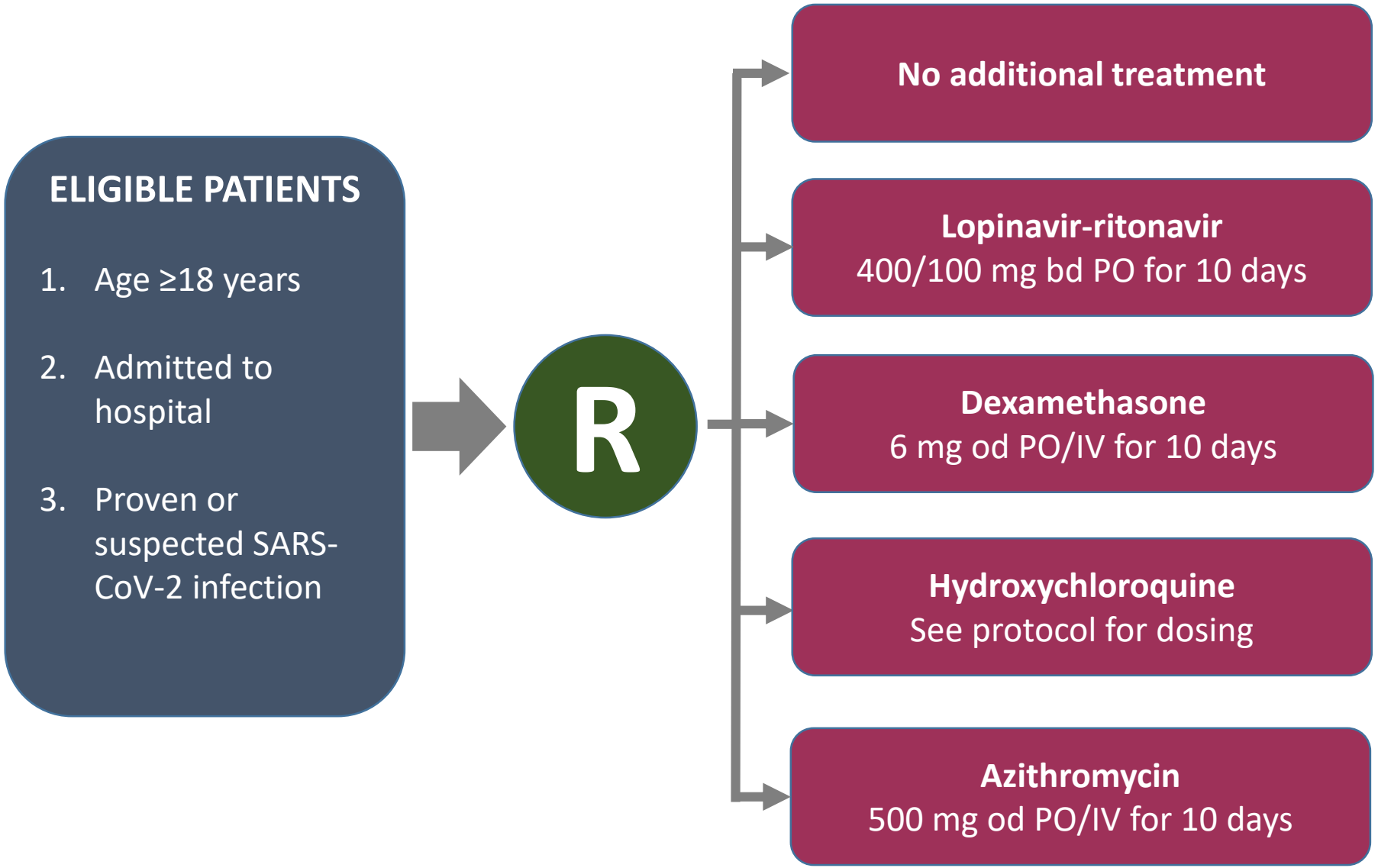
Randomised Evaluation of COVID-19 Therapy



Randomisation

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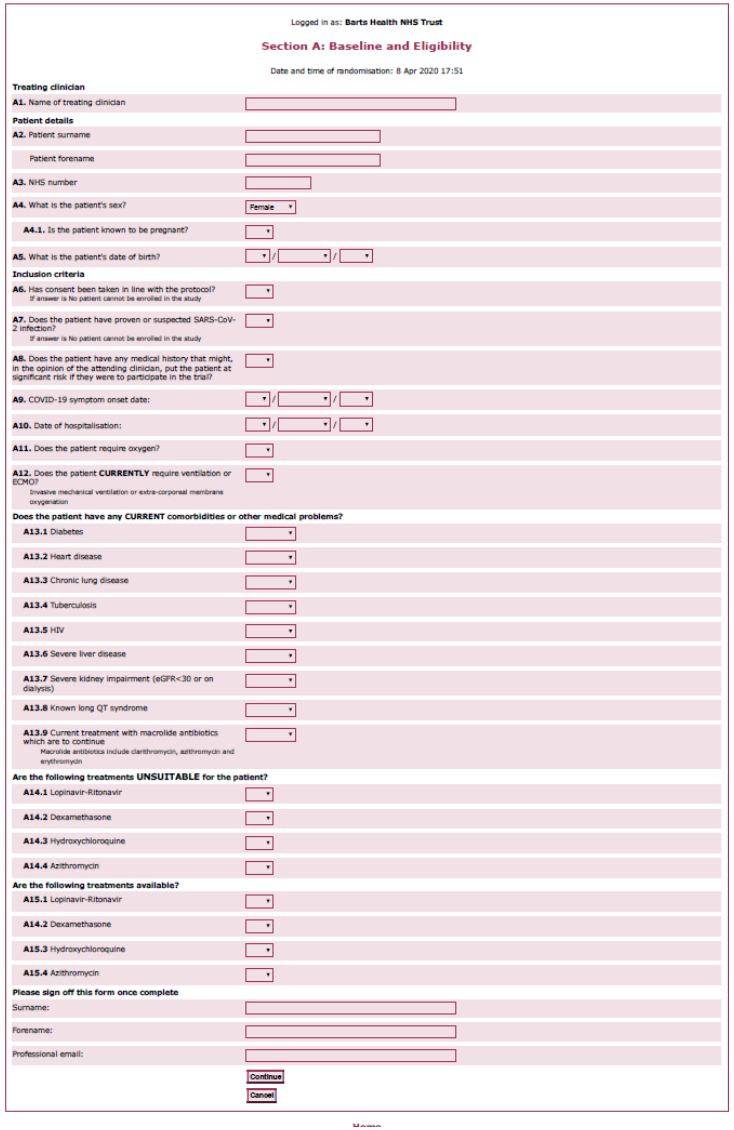

Logged in as: **Barts Health NHS Trust**

Section A: Baseline and Eligibility

Date and time of randomisation: 8 Apr 2020 17:51

Treating clinician

A1. Name of treating clinician

Patient details

A2. Patient surname

Patient forename

A3. NHS number

A4. What is the patient's sex? Female

A4.1. Is the patient known to be pregnant?

A5. What is the patient's date of birth? / /

Inclusion criteria

A6. Has consent been taken in line with the protocol?
If answer is No patient cannot be enrolled in the study

A7. Does the patient have proven or suspected SARS-CoV-2 infection?
If answer is No patient cannot be enrolled in the study

A8. Does the patient have any medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial?

A9. COVID-19 symptom onset date: / /

A10. Date of hospitalisation: / /

A11. Does the patient require oxygen?

A12. Does the patient **CURRENTLY** require ventilation or ECMO?
Invasive mechanical ventilation or extra-corporeal membrane oxygenation

Does the patient have any CURRENT comorbidities or other medical problems?

A13.1 Diabetes

A13.2 Heart disease

A13.3 Chronic lung disease

A13.4 Tuberculosis

A13.5 HIV

A13.6 Severe liver disease

A13.7 Severe kidney impairment (eGFR<30 or on dialysis)

A13.8 Known long QT syndrome

A13.9 Current treatment with macrolide antibiotics which are to continue
Macrolide antibiotics include clarithromycin, azithromycin and erythromycin

Are the following treatments UNSUITABLE for the patient?

A14.1 Lopinavir-Ritonavir

A14.2 Dexamethasone

A14.3 Hydroxychloroquine

A14.4 Azithromycin

Are the following treatments available?

A15.1 Lopinavir-Ritonavir

A14.2 Dexamethasone

A15.3 Hydroxychloroquine

A15.4 Azithromycin

Please sign off this form once complete

Surname:

Forename:

Professional email:

Continue

Cancel

Home

Randomisation

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Treating clinician

A1. Name of treating clinician

Patient details

A2. Patient surname

Patient forename

A3. NHS number

A4. What is the patient's sex?

A5. What is the patient's date of birth? / /
Enter year if full date is not known

Inclusion criteria

A6. Has consent been taken in line with the protocol?
If answer is No patient cannot be enrolled in the study

A7. Has SARS-CoV-2 infection been confirmed?
If answer is No patient cannot be enrolled in the study

A8. Does the patient have any medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial?

Randomisation

RECOVERY
Randomised Evaluation of COVID-19 Therapy

A9. COVID-19 symptom onset date:	/ /
A10. Date of hospitalisation:	/ /
A11. Does the patient require oxygen?	
A12. Does the patient **CURRENTLY** require ventilation or ECMO?	

Does the patient have any CURRENT comorbidities?

A13.1 Diabetes	
A13.2 Heart disease	
A13.3 Chronic lung disease	
A13.4 Tuberculosis	
A13.5 HIV	
A13.6 Severe liver disease	
A13.7 Severe kidney impairment (eGFR<30 or on dialysis)	
A13.8 Known long QT syndrome	

Randomisation

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Are the following treatments unsuitable for the patient?

A14.1 Lopinavir-Ritonavir	
A14.2 Interferon-β1a	
A14.3 Dexamethasone	
A14.4 Hydroxychloroquine	

Are the following treatments available?

A15.1 Lopinavir-Ritonavir	
A15.2 Interferon-β1a	
A15.3 Dexamethasone	
A15.4 Hydroxychloroquine Please check with your PI before changing	No

Please sign off this form once complete

Surname:	
Forename:	
Professional email:	

Randomisation

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Randomisation Program

Call Freefone 0800 138 5451 to contact the RECOVERY team for **URGENT** problems using the Randomisation Program or for medical advice. All **NON-URGENT queries** should be emailed to recoverytrial@ndph.ox.ac.uk

Section B

This patient has been successfully randomised into the RECOVERY trial

Allocated treatment for the RECOVERY trial
Usual standard management

Patient RECOVERY study number
1000016

Please record this study number on the Consent Form and any other trial documentation for this patient and store in the patient's medical notes.

Date and time of randomisation
18/03/2020 19:03

Press the **Print** button below to generate a pdf which can be printed and stored in the patient's medical notes.

Print

Modify contact details

Thank you for entering this patient into the RECOVERY study.
Please click the link below to log out

Log out

Home

RECOVERY trial design

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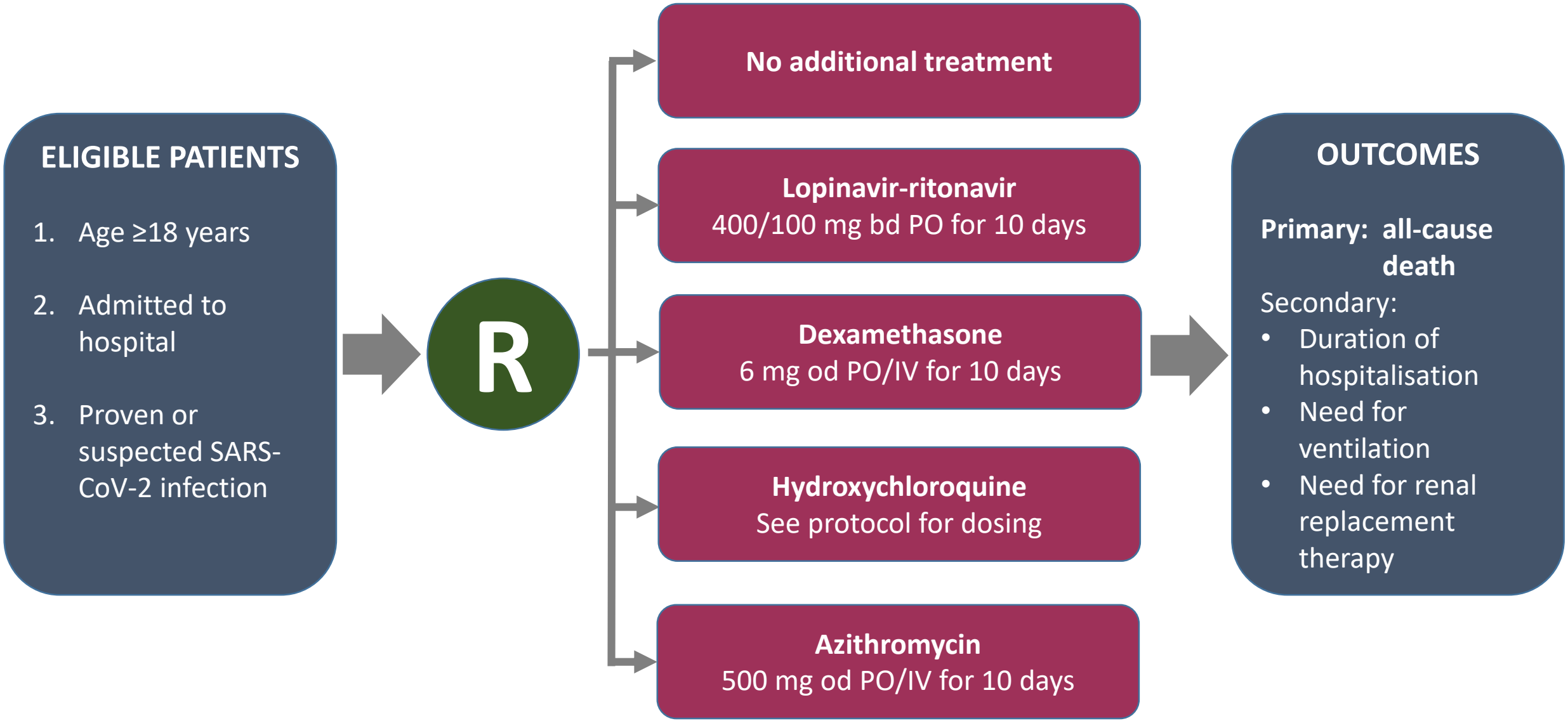

Follow-up

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- Simple on-line form completed by research nurses
  - Which treatments did the patient receive
  - COVID-19 test result
  - Discharge status & date
  - Use of ventilation
- Linkage to national data sources
  - Vital status, death certificate
  - Coded hospital episode statistics (diagnoses, procedures)
  - Intensive Care audit data, SARS-CoV-2 PCR laboratory results
  - Primary care, national outpatient prescribing data
- Permission to follow-up via record linkage for up to 10 years

Adding a second randomisation

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No additional treatment

Lopinavir-ritonavir
400/100 mg bd PO for 10 days

Dexamethasone
6 mg od PO/IV for 10 days

Hydroxychloroquine
See protocol for dosing

Azithromycin
500 mg od PO/IV for 10 days

SECOND RANDOMISATION ELIGIBILITY CRITERIA

Key eligibility criteria
Hypoxia (O_2 sat^n <92% or on O_2 therapy)
+
Inflammation (CRP ≥75 mg/L)

R

Tocilizumab

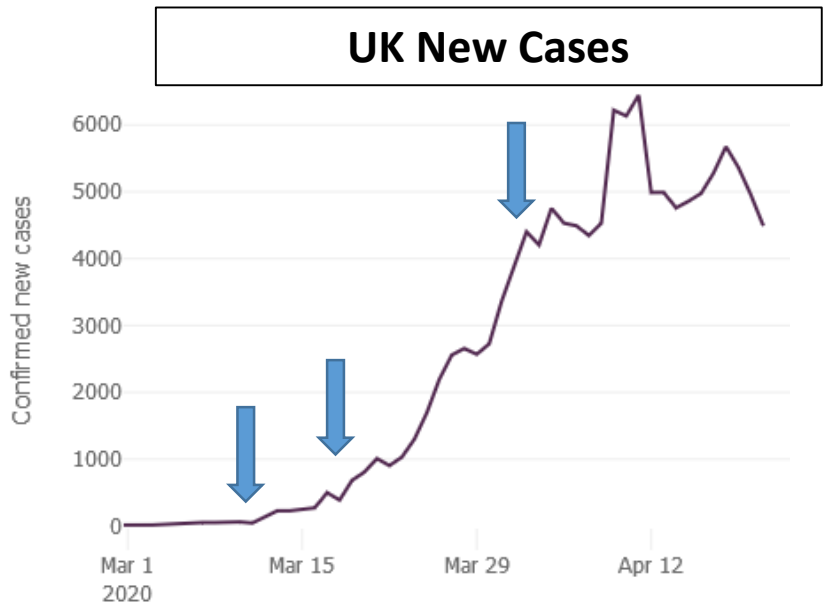
vs

Control

OUTCOMES
1. Mortality at 28 days
2. Need for ventilation; admission duration

Progress: Set-up

Taking the front-foot



10th March	First draft protocol
13th March	Joint regulatory & ethics (IRB) submission
16th March	Regulatory approval. Chief Medical Officer letter to all hospitals.
17th March	IRB committee meeting
18th March	IRB approval received in writing
19th March	First Patient Enrolled (1st protocol +9 days)
3rd April	1000 patients enrolled (FPE + 15 days)

Recruitment

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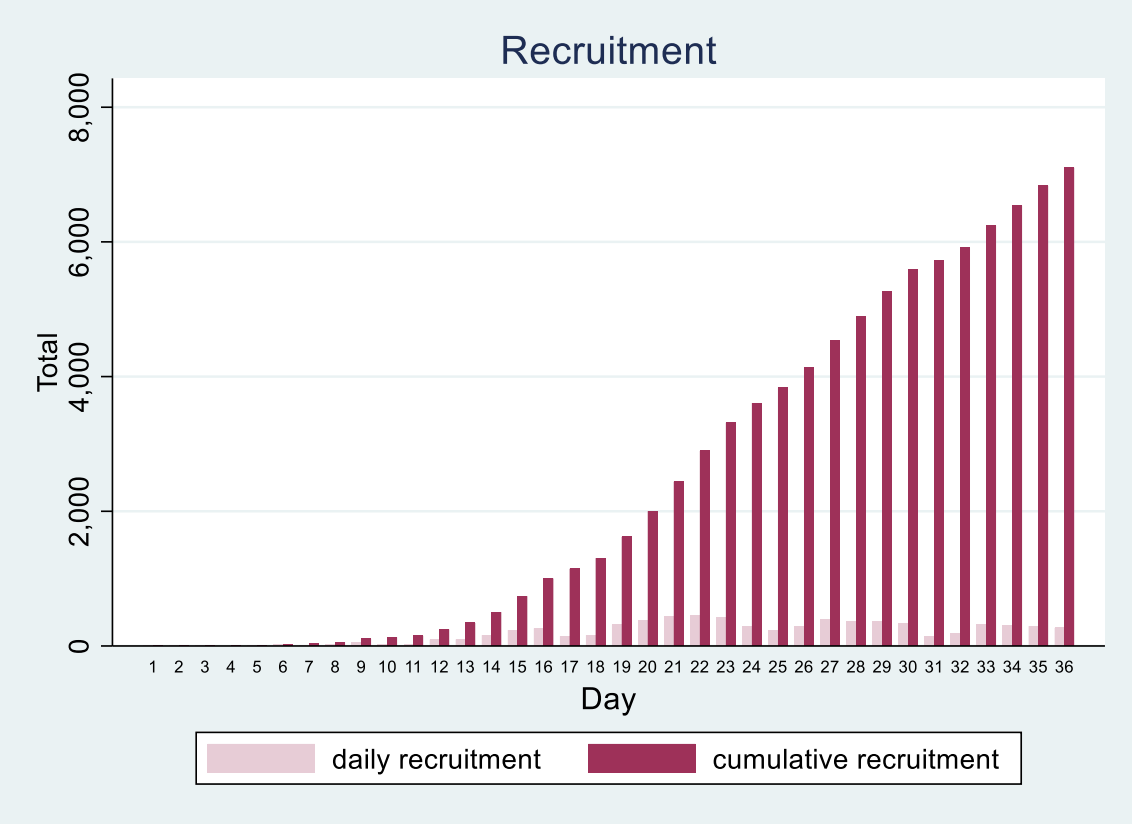
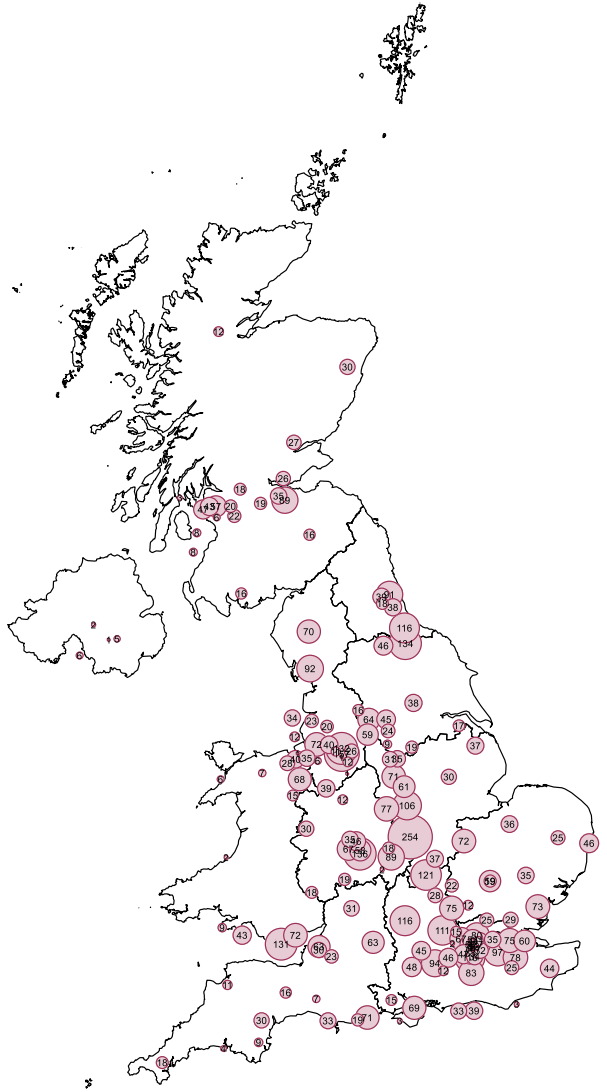
- >7,300 randomised at >160 hospitals
- Typically 300 per day





Acknowledgements

- UK Research & Innovation
- Wellcome Trust
- Department for International Development
- National Health Service in England, Wales, Scotland, and Northern Ireland
- National Institute for Health Research
- Bill & Melinda Gates Foundation
- Department of Health & Social Care

- NIHR Clinical Research Network
- NIHR Oxford Biomedical Research Centre
- Nuffield Department of Medicine
- NHS DigiTrials
- Medical Research Council Population Health Research Unit
- Nuffield Department of Population Health

- The very many doctors, research nurses, pharmacists, and R&D managers at over 160 NHS hospitals
- And, most importantly, the patients who are participating

Thank you

Contact details

RECOVERY

Randomised Evaluation of COVID-19 Therapy

www.recoverytrial.net

recoverytrial@ndph.ox.ac.uk

@martinlandray