Randomized trials for better health

Martin Landray
University of Oxford

Rationale for randomisation

Major public health crisis

- For hospitalised patients, 25-30% mortality
- For ventilated patients, 30-40% mortality

Huge uncertainty about treatment

- Many candidate drugs
- Many opinions (from many sources)
- No reliable data (uncontrolled case series, inconclusive randomized trials)
- Unlikely to be a single “big win” but moderate benefits would be important

- **Large-scale randomisation required to identify effective treatments**

Lessons from the past…
Second International Study of Infarct Survival (ISIS2)

"**By far the most important determinant of the success of ISIS is the extent to which**, in those busy hospitals where the majority of acute MI patients are actually admitted, **the responsible physicians and nurses choose to enter their patients**. Hence, **the extra work must be – and is – absolutely minimal**."

STATISTICS IN MEDICINE, VOL. 3, 409–420 (1984)

WHY DO WE NEED SOME LARGE, SIMPLE RANDOMIZED TRIALS?

SALIM YUSUF* RORY COLLINS AND RICHARD PETO
Clinical Trial Service Unit, Radcliffe Infirmary, Oxford, UK

The criteria for a good trial are similar in many serious diseases: first and foremost, ask an 'important' question and, secondly, answer it 'reliably'. These two very general criteria obviously require further elaboration, but even as they stand they can suggest some surprisingly specific consequences for clinical trial design. Particularly, they can be used to suggest both the possibility and the desirability of *large, simple randomized* trials of the effects on *mortality* of various *widely practicable* treatments for *common* conditions.

PATIENT IDENTIFIERS (Please PRINT):
(for central monitoring of certified causes of death)

Hospital: .....
Surname/Family name: .....
All given name(s): .....
Date of birth: day: ..... / month: ..... / year: .....
Address: .....

Maiden name: .....
(if available)
Family doctor: .....
(if available)

ISIS 2
Second International Study of Infarct Survival
NOTIFICATION OF DISCHARGE OR PRIOR DEATH

OR: PATIENT STICKER,
IF ALL DETAILS PROVIDED

TICK ✓ PRE-TREATMENT CHARACTERISTICS
Female
Previous myocardial infarction
Previous diabetes

TICK ✓ ANY DEVIATIONS FROM TRIAL TREATMENT
STREPTOKINASE/PLACEBO infusion interrupted, or not given
ASPIRIN/PLACEBO calender pack interrupted, or not given

TICK ✓ APPARENT SIDE-EFFECTS OF STREPTOKINASE/PLACEBO INFUSION
Significant hypotension during, or just after, infusion
Anaphylactic shock
Rigor
Rash
Other (specify, eg, respiratory distress) .....

TICK ✓ MAIN EVENTS (FATAL OR NOT) AFTER RANDOMISATION, AND ENTER DATE (FIRST) OCCURRED
day / month / year
"Major" bleed (transfused) ..... / ..... / ..... and sites).....
"Minor" bleed (not transfused) ..... / ..... / .....
Cardiac rupture ..... / ..... / .....
Reinfarction ..... / ..... / .....
Ventricular fibrillation ..... / ..... / .....
Other cardiac arrest ..... / ..... / .....
Stroke, probable cerebral haemorrhage ..... / ..... / ..... Likely residual disability (if alive): Non-significant/ Moderate/ Severe
Stroke, infarct or unknown type ..... / ..... / .....
Discharge alive from hospital ..... / ..... / .....
Death in hospital ..... / ..... / ..... and underlying cause, if **not** cardiac: .....

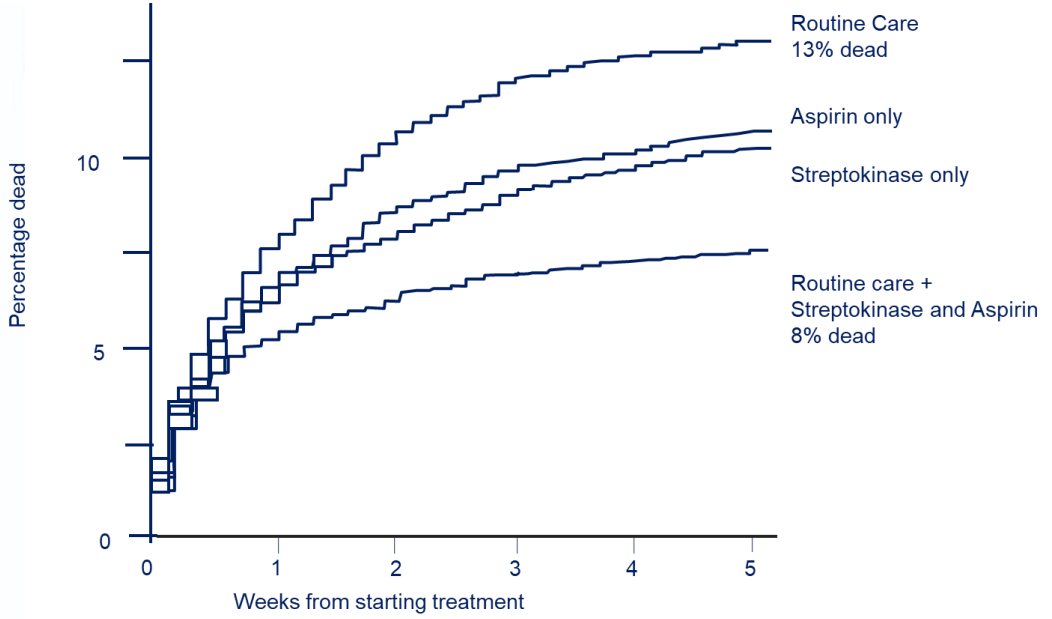
TICK ✓ TREATMENT IN HOSPITAL
Steroids prior to streptokinase/placebo infusion
Subcutaneous heparin
Intravenous heparin
Oral anticoagulant
Intravenous beta-blocker
Non-trial aspirin
Other anti-platelet agent(s)

TICK ✓ DRUGS ON DISCHARGE
Oral anticoagulant
Non-trial aspirin
Other anti-platelet agent(s)
Beta-blocker

NAME OF PERSON COMPLETING FORM (please PRINT): .....

PLEASE SEND: — TOP COPY OF THIS FORM (retain bottom green copy)
— AND PRE-RANDOMISATION ECG (original or good photocopy)
TO: ISIS-2, FREEPOST, OXFORD OX2 6BR, UK (no stamp required within UK)

THANK YOU VERY MUCH



Randomised controlled trials don't have to be complicated... they must be practical

- **Simple eligibility:** Hospitalised patients with SARs-CoV-2
- **Important outcome:** mortality (use of ventilation, duration of hospitalisation)
- **Randomization:** assigns patient between suitable and available treatments
- **Follow-up:** 1 page case report form + extensive linkage to NHS datasets via NHS DigiTrials

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.

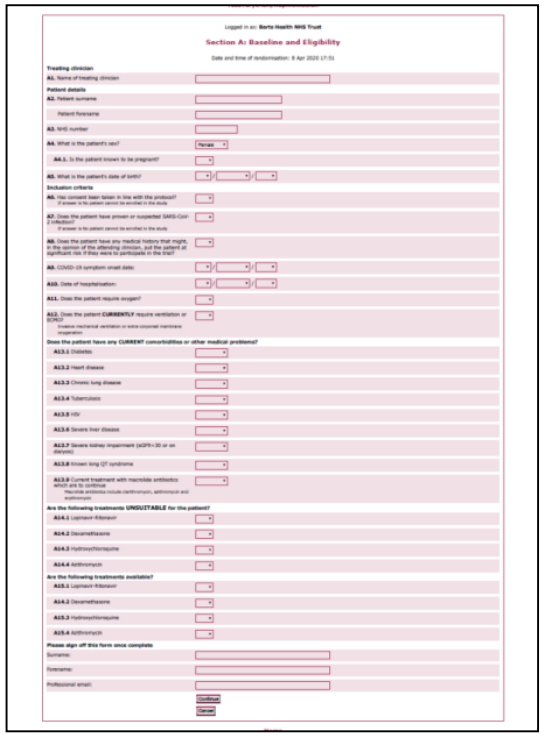
5. **Data stored on computer:** I understand that information about my progress in the study will be recorded on a computer database, and that this data will be stored on computers supervised by the University of Oxford. I understand that this information will be kept securely and confidentially.

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.

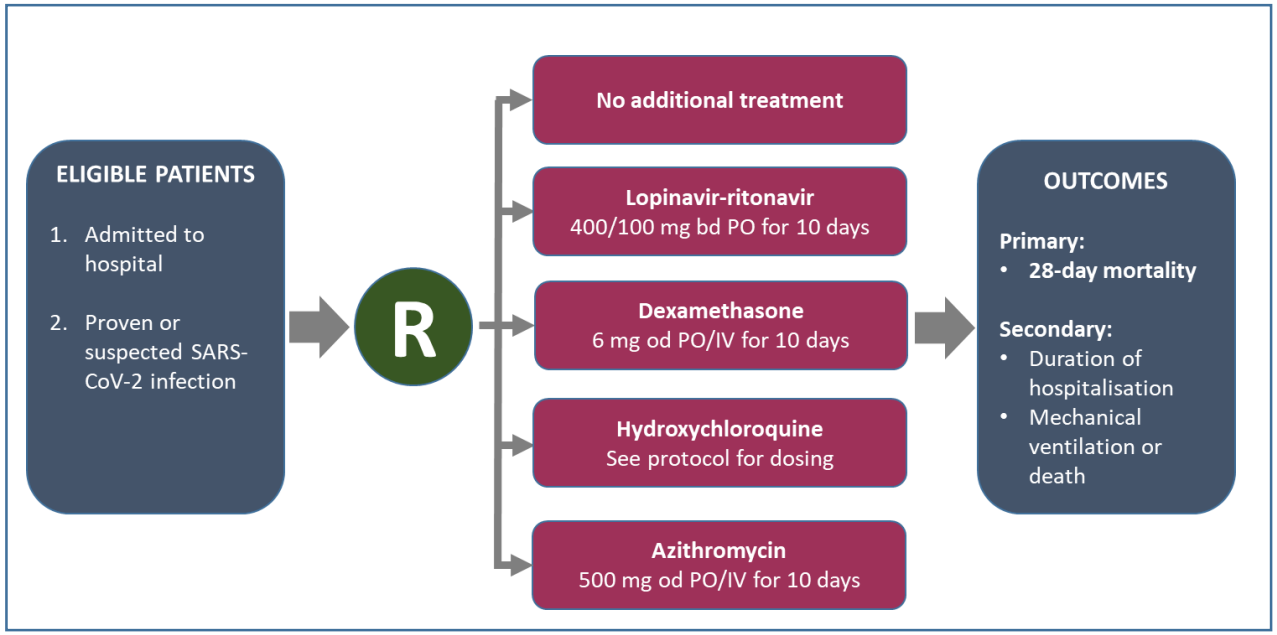
PRINTED name of participant | Signature | Today's date

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

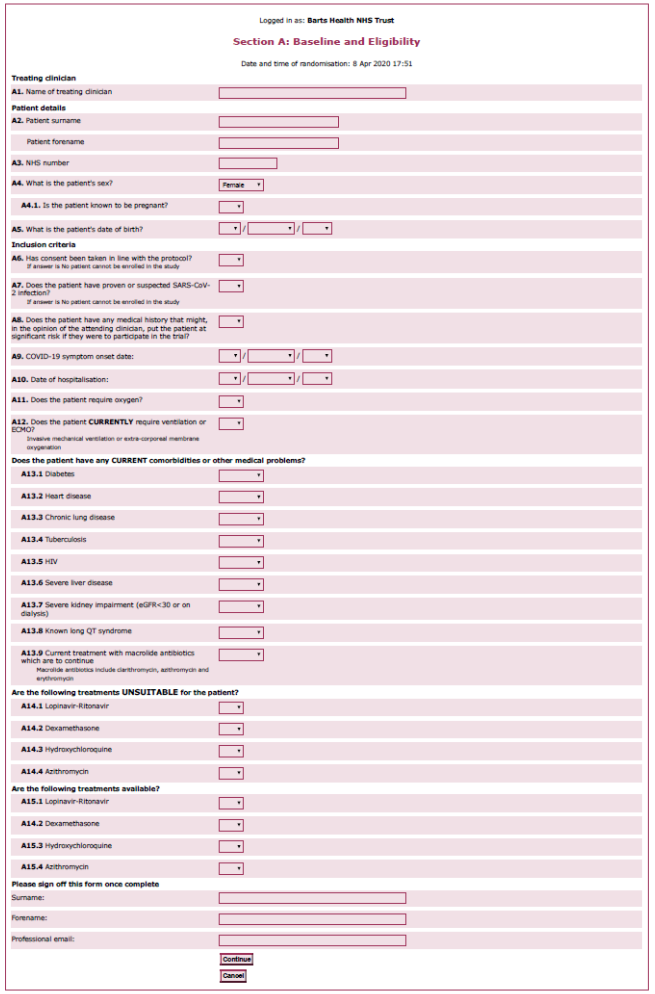


Section A: Baseline and Eligibility



Randomisation

- **Simple data entry** (online)
  - Patient details
  - Inclusion criteria
  - Key co-morbidities
  - Any treatments for which the patient is not suitable
  - Any treatments not available in hospital pharmacy
- **Randomly assigns** participant between suitable and available treatments
- **Doctor prescribes** allocated treatment on usual hospital drug chart



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

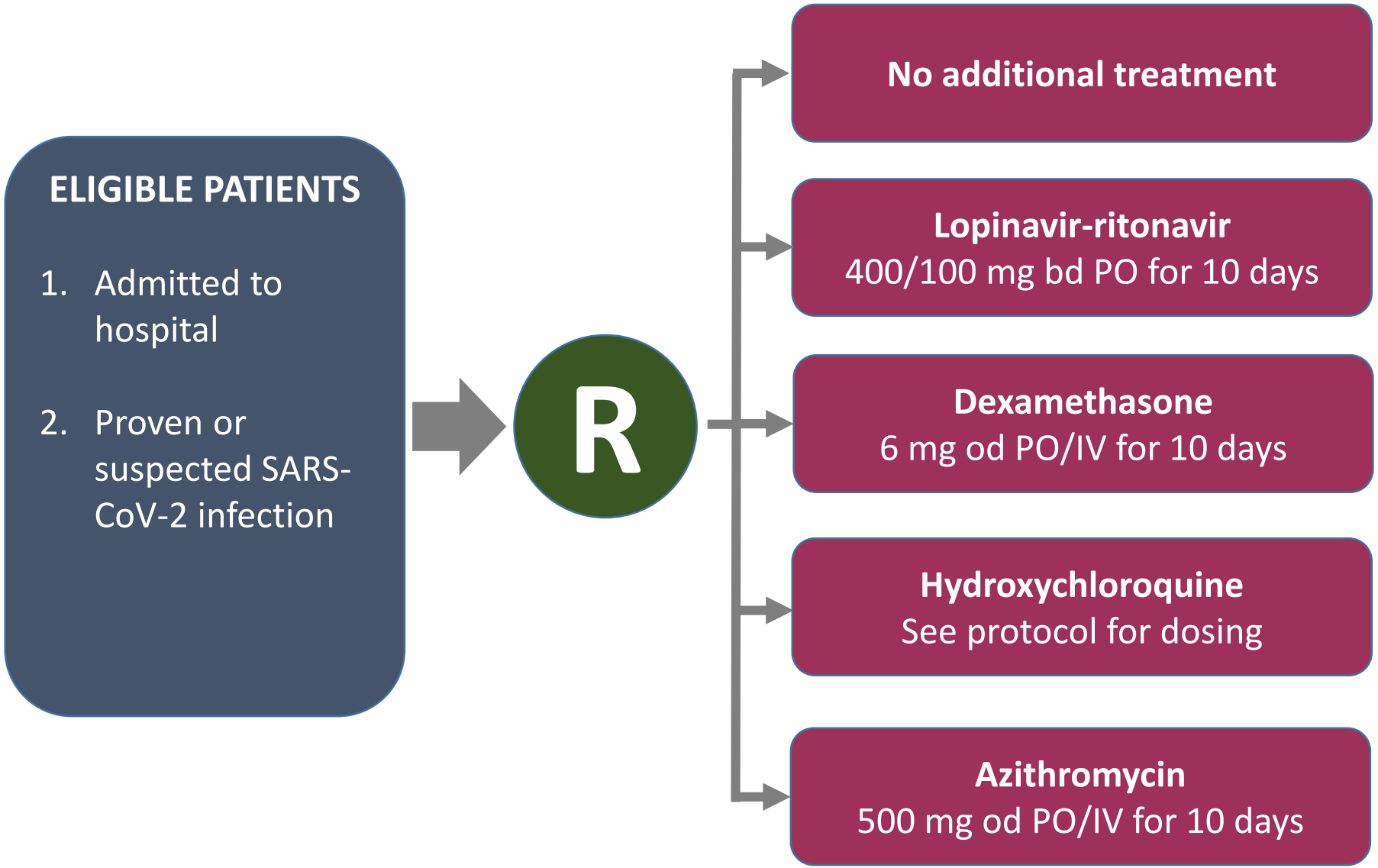
Cancel

RECOVERY trial design

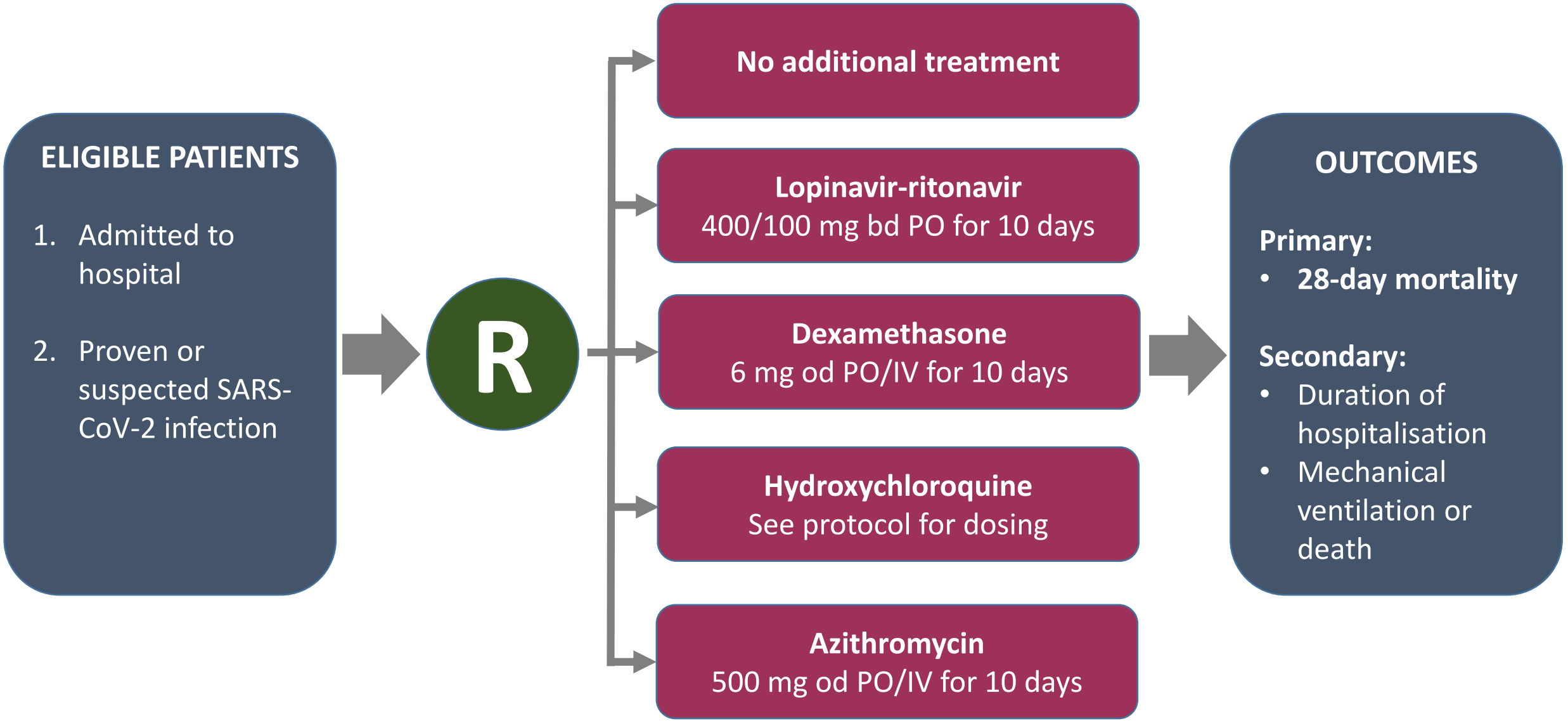
ELIGIBLE PATIENTS

1. Admitted to hospital
2. Proven or suspected SARS-CoV-2 infection

RECOVERY trial design



RECOVERY trial design



Follow-up

- **Simple on-line form at death, discharge or 28 days**
  - Vital status (and presumed cause of death)
  - Hospitalisation status (with date of discharge)
  - Use of ventilation (with days of use and type)
  - Use of renal dialysis or hemofiltration
  - Documented new major cardiac arrhythmia (since 12 May)
  - Use of study medications (and remdesivir, since 28 May)
  - COVID-19 test result

- **Additional assessment of safety of convalescent plasma at 72 hrs**
  - Sudden worsening of respiratory status, severe allergic reaction
  - Temperature >39C or >2C rise above baseline
  - Sudden hypotension, clinical haemolysis

Follow-up

- **Linkage to national health 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
- **Pre-specified analyses at 6 months**
- **Permission to follow-up via record linkage for up to 10 years**

Protocol section 2.3

Centrally collected routine data

Hospitalisation datasets

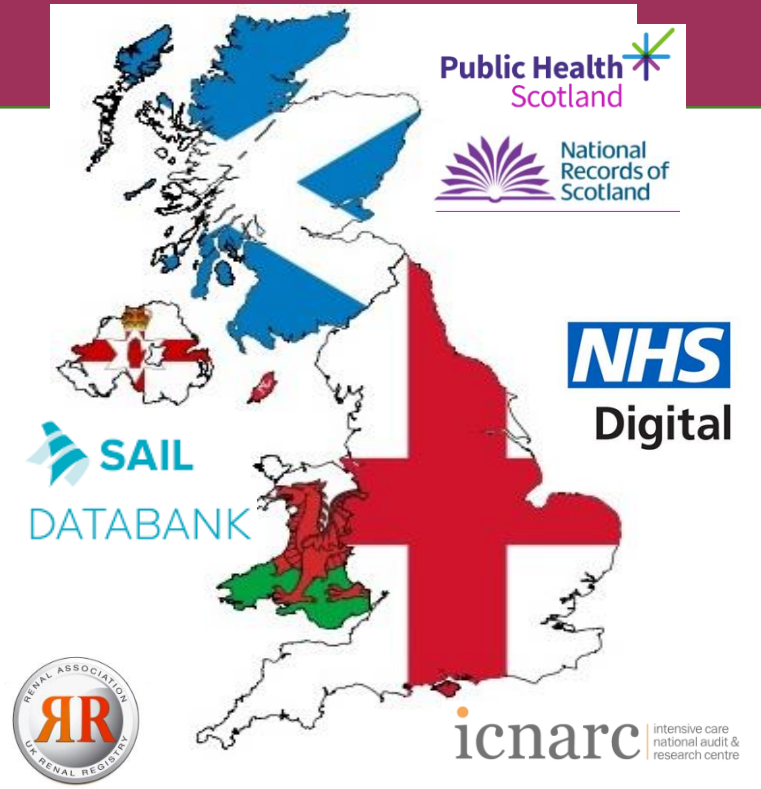
- ✓ Scottish Morbidity Records (SMR)
- ✓ Hospital Episode Statistics Admitted Patient Care (HESAPC)
- ✓ Secondary Uses Service Admitted Patient Care (SUSAPC)
- ✓ Patient Episode database for Wales (PEDW)

Mortality datasets

- ✓ Personal Demographics Service
- ✓ Civil Registrations
- ✓ NHS Scotland Central Register PDS
- ✓ Welsh Demographics Extract

Disease specific datasets

- ✓ UK Renal Registry
- ✓ Cancer Registry



Primary care datasets

- ✓ Business Services Authority (BSA) prescribing and dispensing data
- ✓ General Practice Extraction Service (GPES) Data for pandemic planning and research (GDPPR)

Critical care datasets

- ✓ Scottish Intensive Care Society Audit Group (SICSAG)
- ✓ Intensive Care National Audit and Research Centre (ICNARC)
- ✓ HES Critical Care Dataset (CCDS)
- ✓ PEDW Critical Care Dataset (CCDS)

COVID datasets

- ✓ COVID-19 Hospitalisation in. England Surveillance System
- ✓ Second Generation Surveillance System (SGSS)
- ✓ Electronic Communication of Surveillance in Scotland (ECOSS)
- ✓ Welsh Results Reporting Service (WRRS)

Quality-by-Design Principles

- **In assessing any risks to patient safety and well-being, a key principle is that of proportionality.**

- **Risks associated with participation in the trial must be considered in the context of usual care.**

- At start, there were no proven treatments for COVID-19, basic hospital care (staffing, beds, ventilatory support) may well be overstretched, and mortality for hospitalised patients may be around 10% (or more in those who are older or have significant co-morbidity).

Protocol section 5.1

Quality by Design: Considerations for RECOVERY

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

- Randomisation of relevant population; Comprehensive follow-up
- Communicate and collaborate
- Transparency (with research, medical, patient, public, media, etc)

Informed consent

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 mechanical ventilation before they do so. However, a few percent 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 an 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 them) 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 10 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

RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

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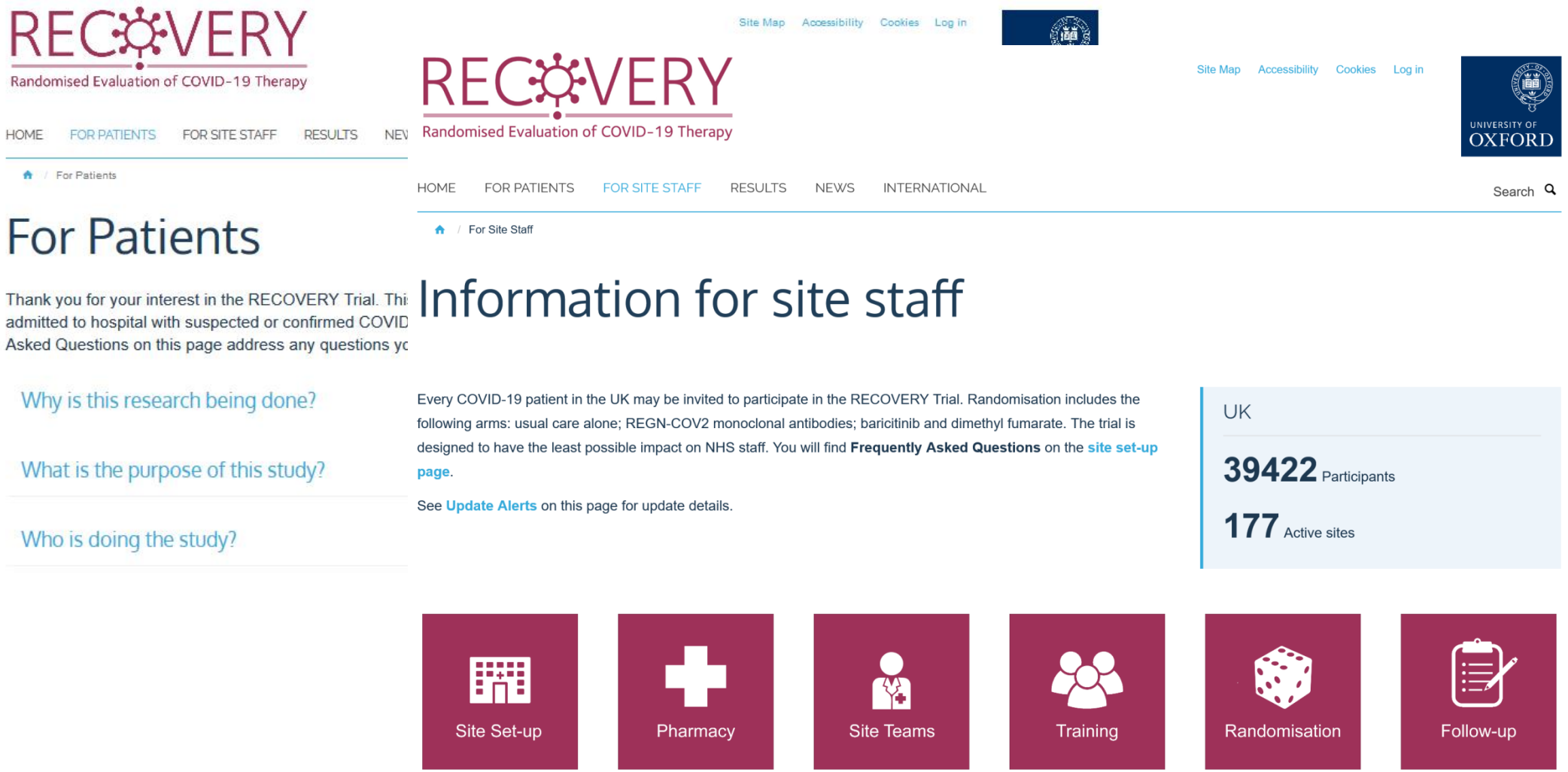
6. Agreement to take part: I have read the information (or had it read to me), had an opportunity to ask questions and agree to take part in the above study.

.....	.....	...../...../.....
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*

Transparency: www.recoverytrial.net



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. All study materials, including protocol and related documents, will be available online and there will be a 24 hour telephone service, supported by medical staff and trained coordinating centre research staff.

Training site staff

- Protocol deliberately specifies that trial *"will be carried out by medical staff attending patients with COVID-19 and by hospital research nurses, medical students and other staff with appropriate education, training, and experience."*

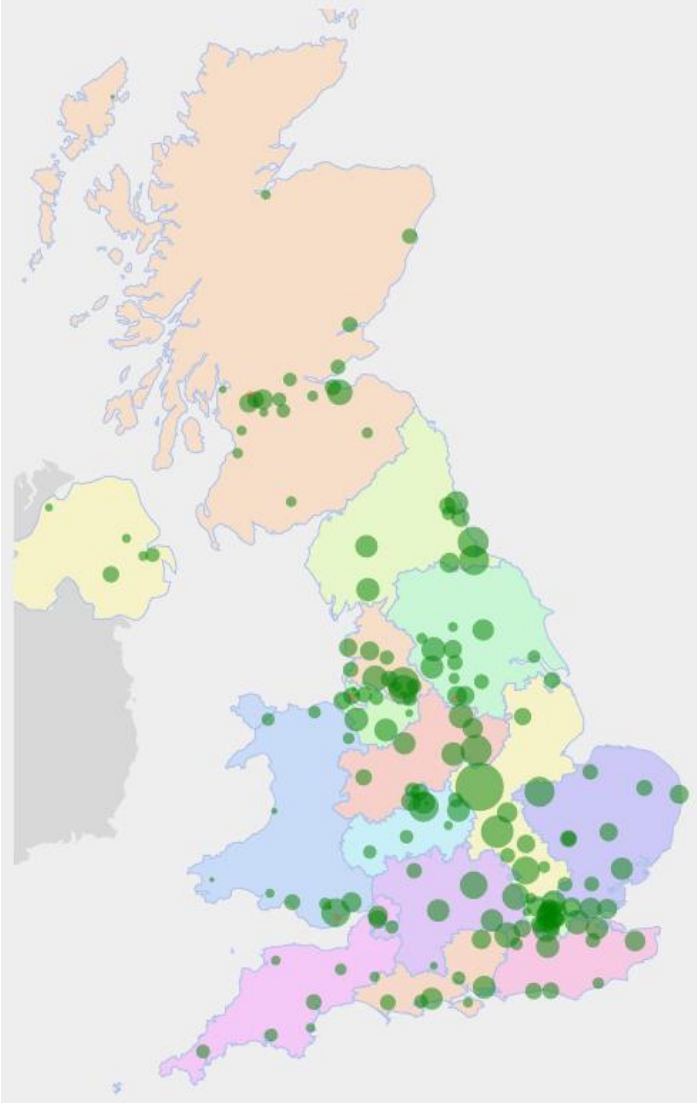
- Online videos provided for staff to watch and then self-certify (with NDPH receiving a copy)

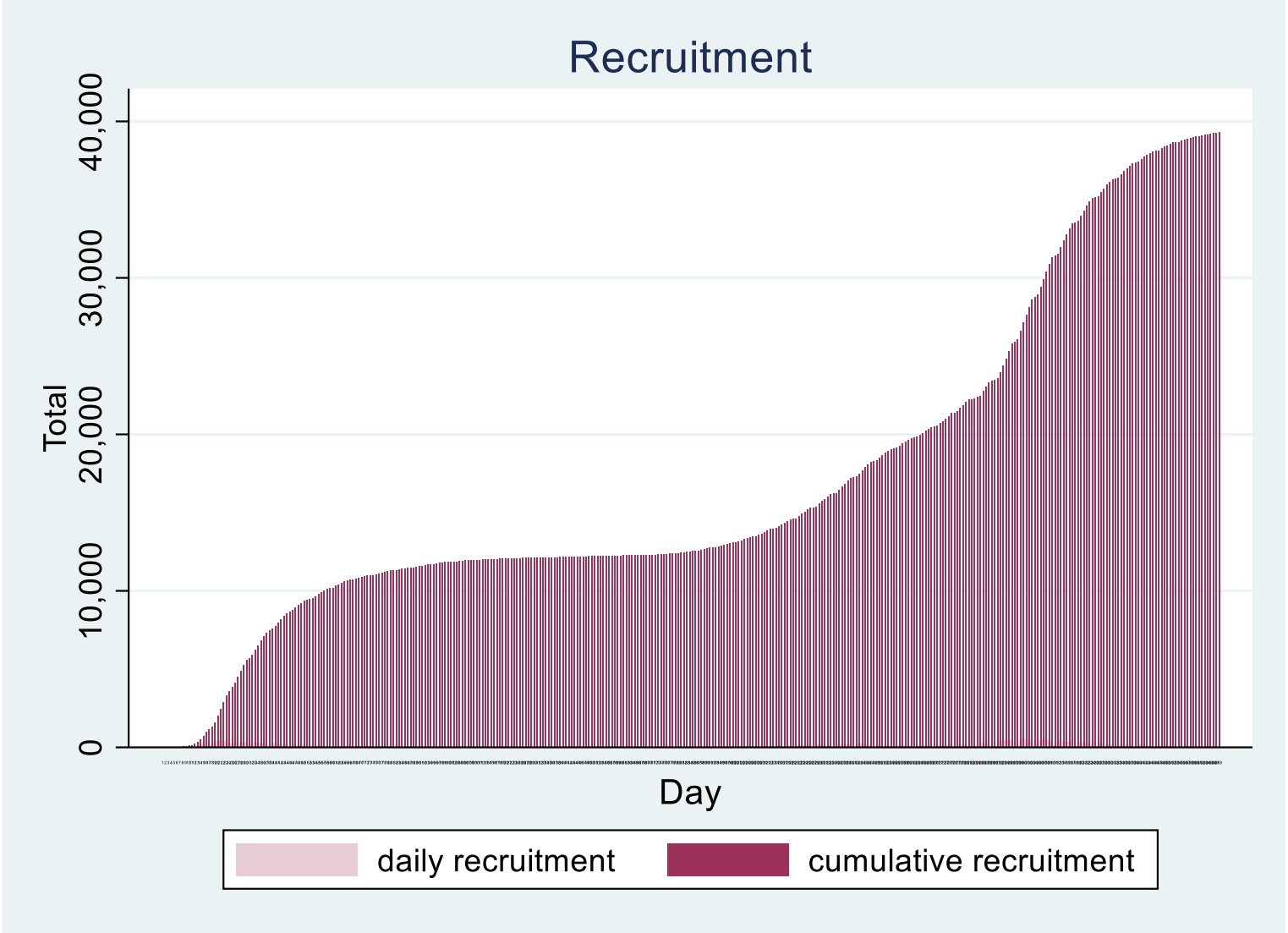
- Certificate in GCP training **not** required

Adverse event reporting

- **Suspected Serious Adverse Reactions** – expedited reporting
- **All deaths (with cause of death)** – eCRF and record linkage
- **Other serious or non-serious adverse events** – not routinely captured
- **Additional assessments may be added** – e.g. cardiac arrhythmia, transfusion and infusion reactions, bleeding
- **Independent Data Monitoring Committee**
  - to "*determine if, in their view, the randomised comparisons in the study have provided evidence on mortality that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies*"

COVID can affect anyone... RECOVERY is open to everyone

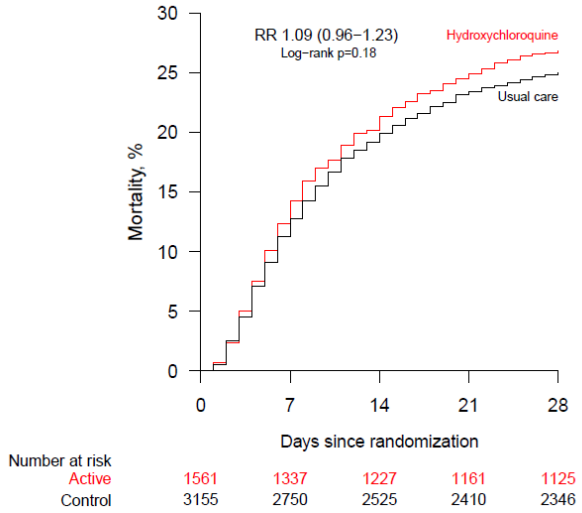




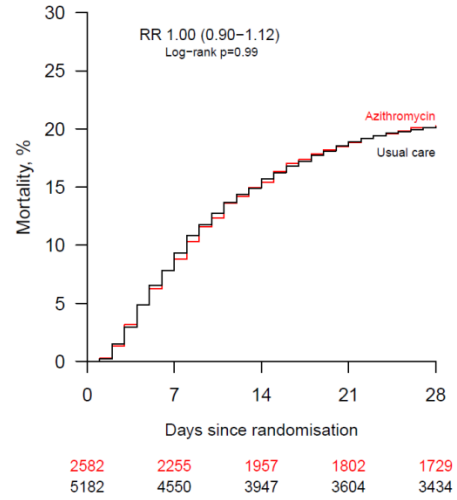
Widely recommended, loudly promoted, widely used...

Hydroxychloroquine, lopinavir, azithromycin, convalescent plasma...

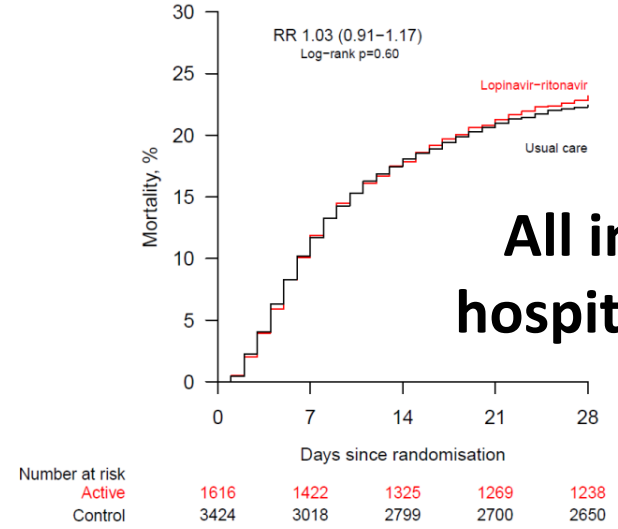
Hydroxychloroquine



Azithromycin

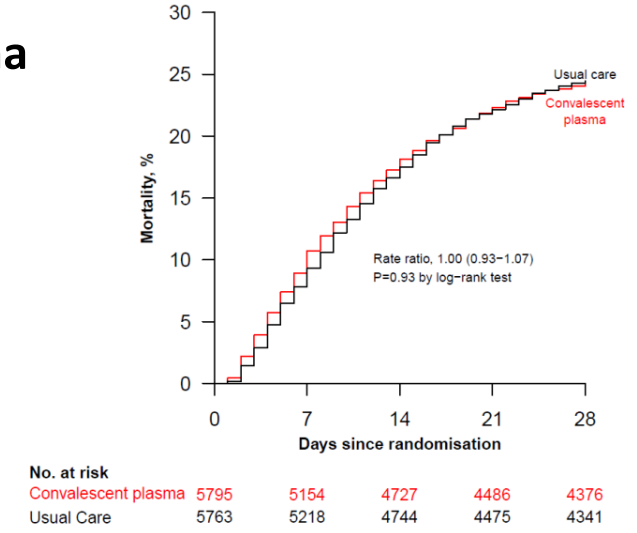


Lopinavir



All ineffective for hospitalised patients

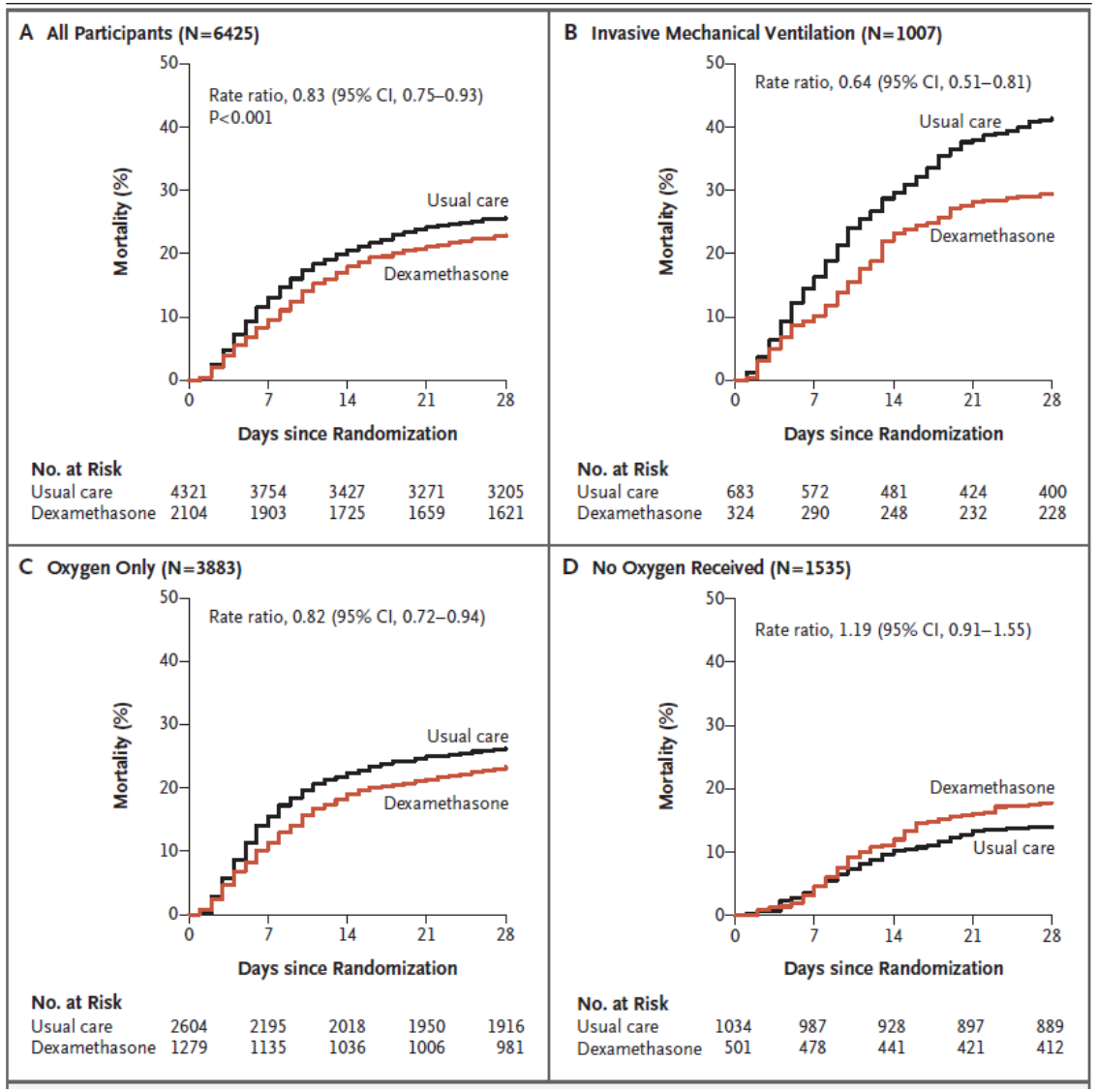
Convalescent plasma



Dexamethasone:

Reduces mortality in patients requiring oxygen or ventilation

DOI: 10.1056/NEJMoa2021436



CEM/CMO/2020/026

Dear colleagues,

Dexamethasone in COVID-19

The RECOVERY trial in COVID-19 has provided initial results of the dexamethasone arm https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_final.pdf

Dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for ten days was compared with 4321 UK patients randomised to usual care alone. Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021).

There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14).

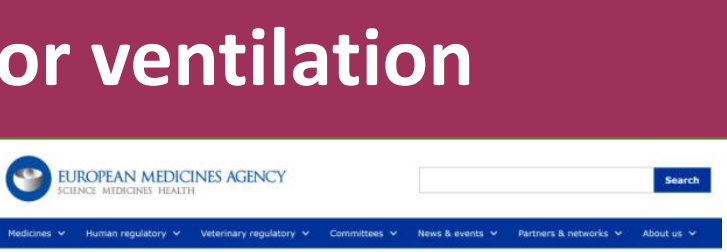
Normally we would advise waiting for the full paper before changing practice, to ensure final analysis and peer review do not lead to different conclusions. However, given this clear mortality advantage, with good significance, and with a well known medicine which is safe under these circumstances we consider it is reasonable for practice to change in advance of the final paper.

Please find more informati

Best wishes,

Dr Frank Atherton
Chief Medical Officer for Wales

Professor Stephen Powis
National Medical Director
NHS England and NHS Improvement



EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation

News 18/09/2020

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

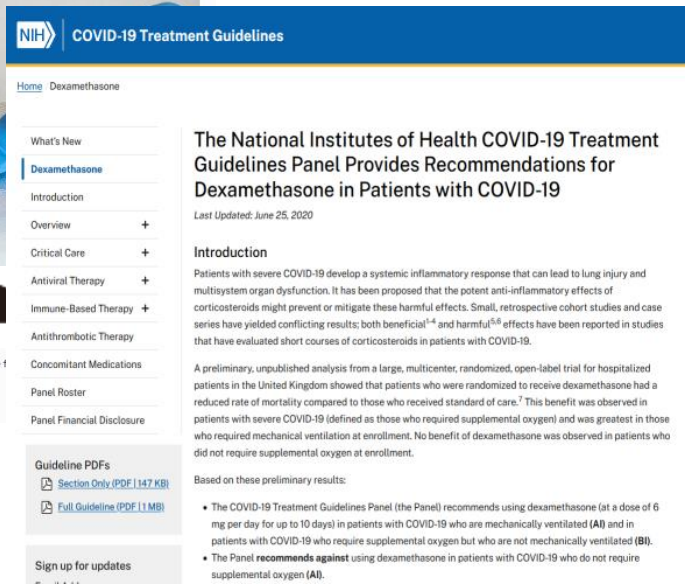
NATIONAL / SCIENCE & HEALTH

Japan approves dexamethasone as second drug for coronavirus treatment

thejapan

The health ministry has approved the use of the steroid drug dexamethasone f patients. | GETTY IMAGES / VIA KYODO

KYODO



NIH COVID-19 Treatment Guidelines

Home Dexamethasone

What's New
Dexamethasone
Introduction
Overview
Critical Care
Antiviral Therapy
Immune-Based Therapy
Antithrombotic Therapy
Concomitant Medications
Panel Roster
Panel Financial Disclosure

Guideline PDFs
Section Only (PDF | 147 KB)
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The National Institutes of Health COVID-19 Treatment Guidelines Panel Provides Recommendations for Dexamethasone in Patients with COVID-19

Last Updated: June 25, 2020

Introduction

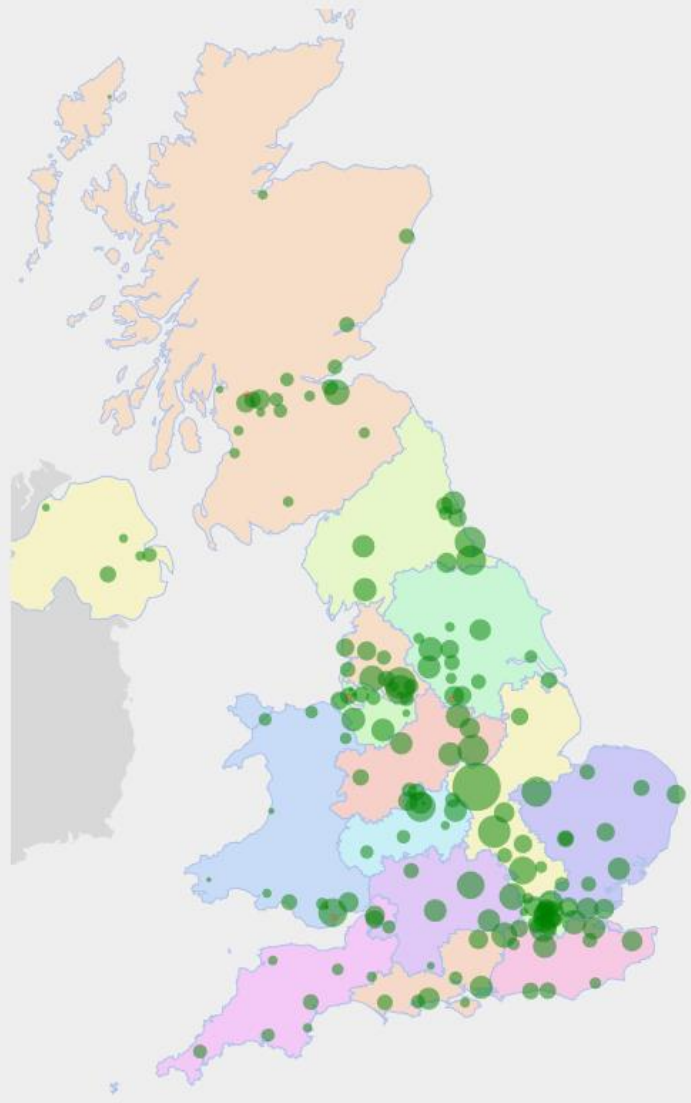
Patients with severe COVID-19 develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these harmful effects. Small, retrospective cohort studies and case series have yielded conflicting results; both beneficial[1-4] and harmful[5,6] effects have been reported in studies that have evaluated short courses of corticosteroids in patients with COVID-19.

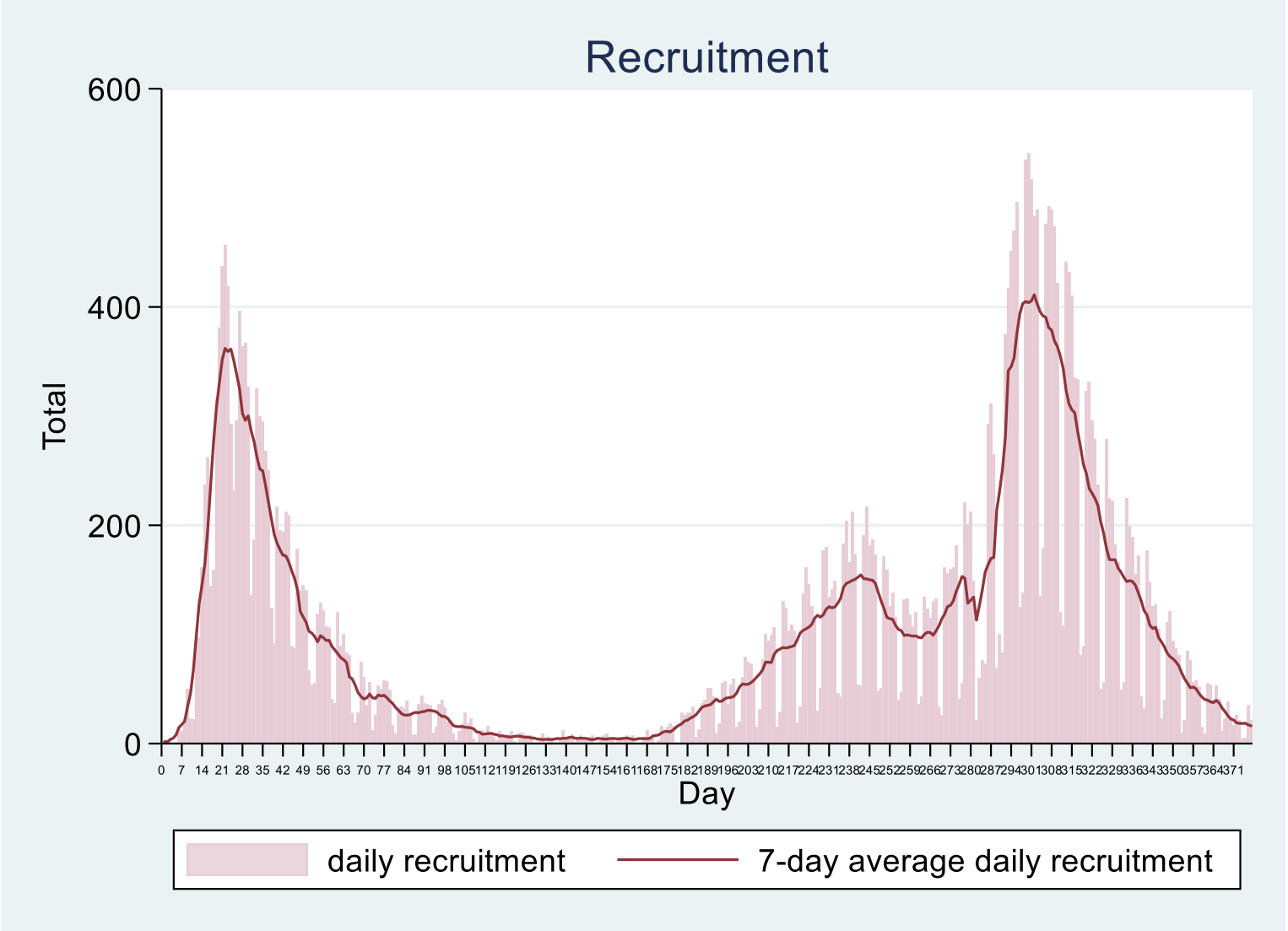
A preliminary, unpublished analysis from a large, multicenter, randomized, open-label trial for hospitalized patients in the United Kingdom showed that patients who were randomized to receive dexamethasone had a reduced rate of mortality compared to those who received standard of care.[7] This benefit was observed in patients with severe COVID-19 (defined as those who required supplemental oxygen) and was greatest in those who required mechanical ventilation at enrollment. No benefit of dexamethasone was observed in patients who did not require supplemental oxygen at enrollment.

Based on these preliminary results:

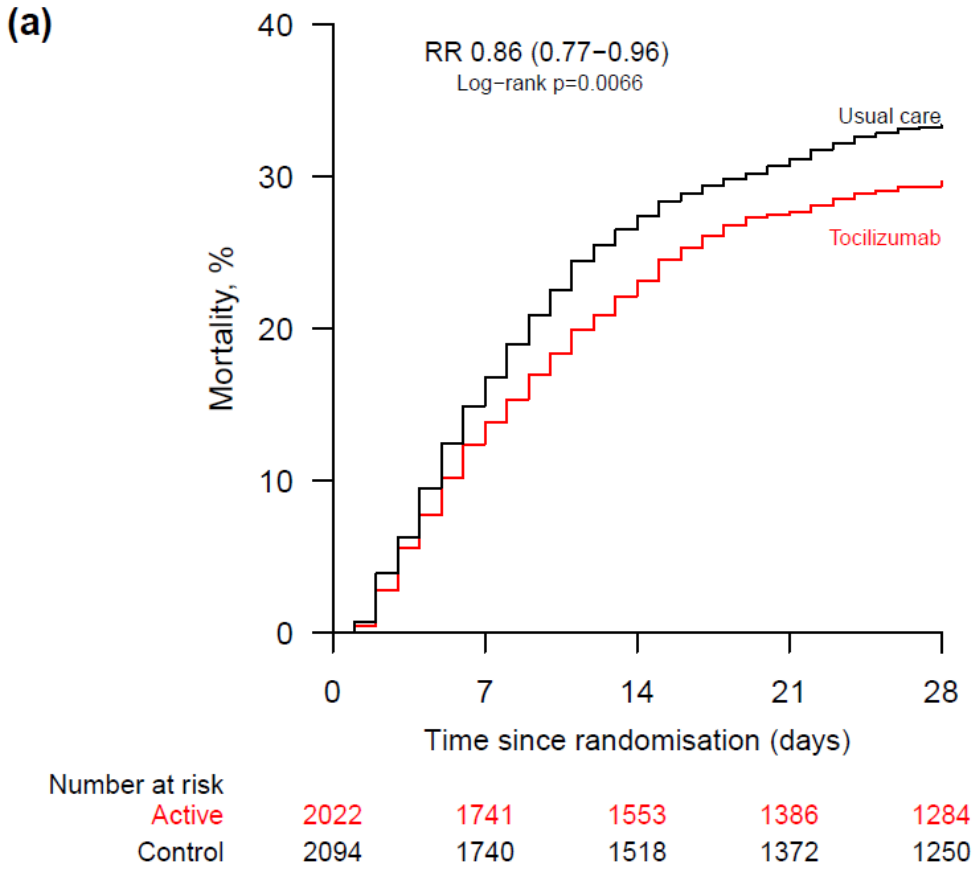
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated **(AI)** and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using dexamethasone in patients with COVID-19 who do not require supplemental oxygen **(AI)**.

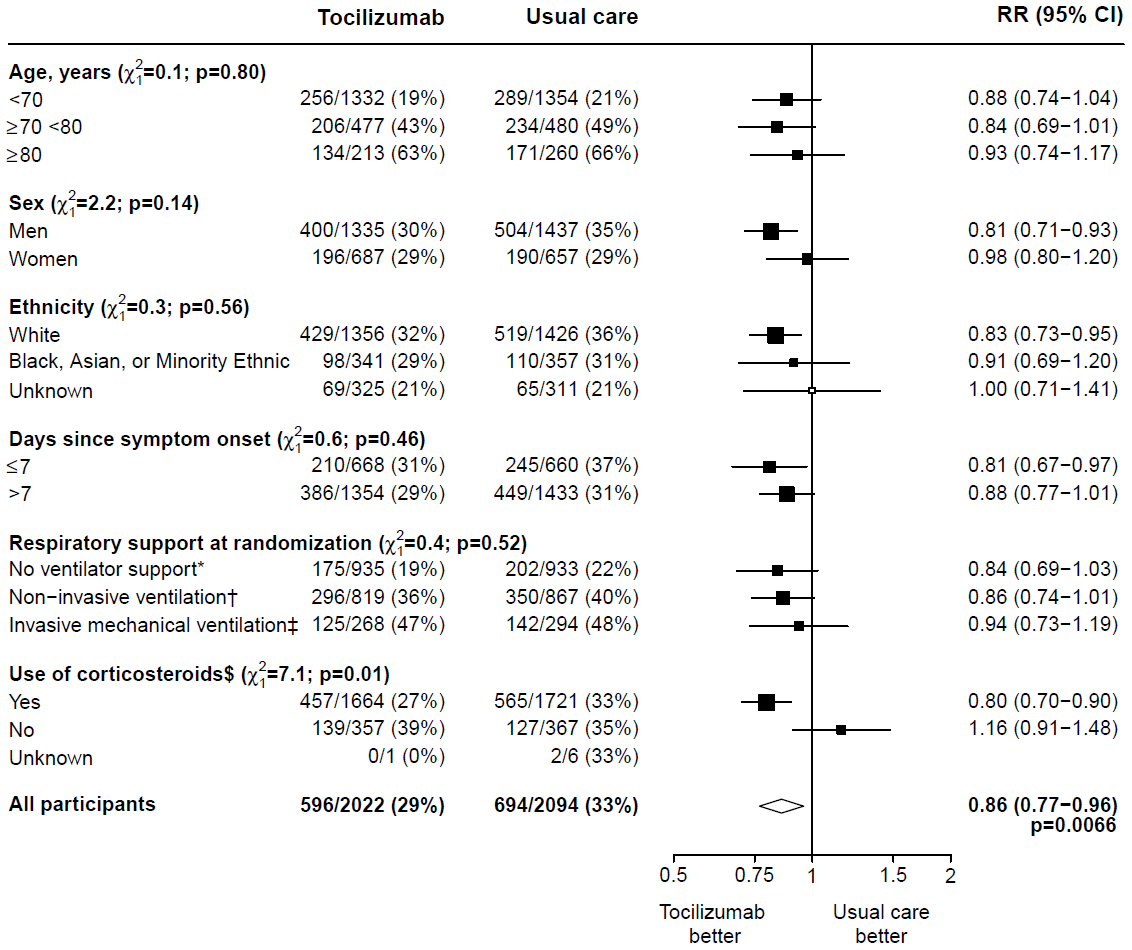
RECOVERY – rapid and widespread recruitment





Tocilizumab:
Reduces mortality in patients with hypoxia and inflammation



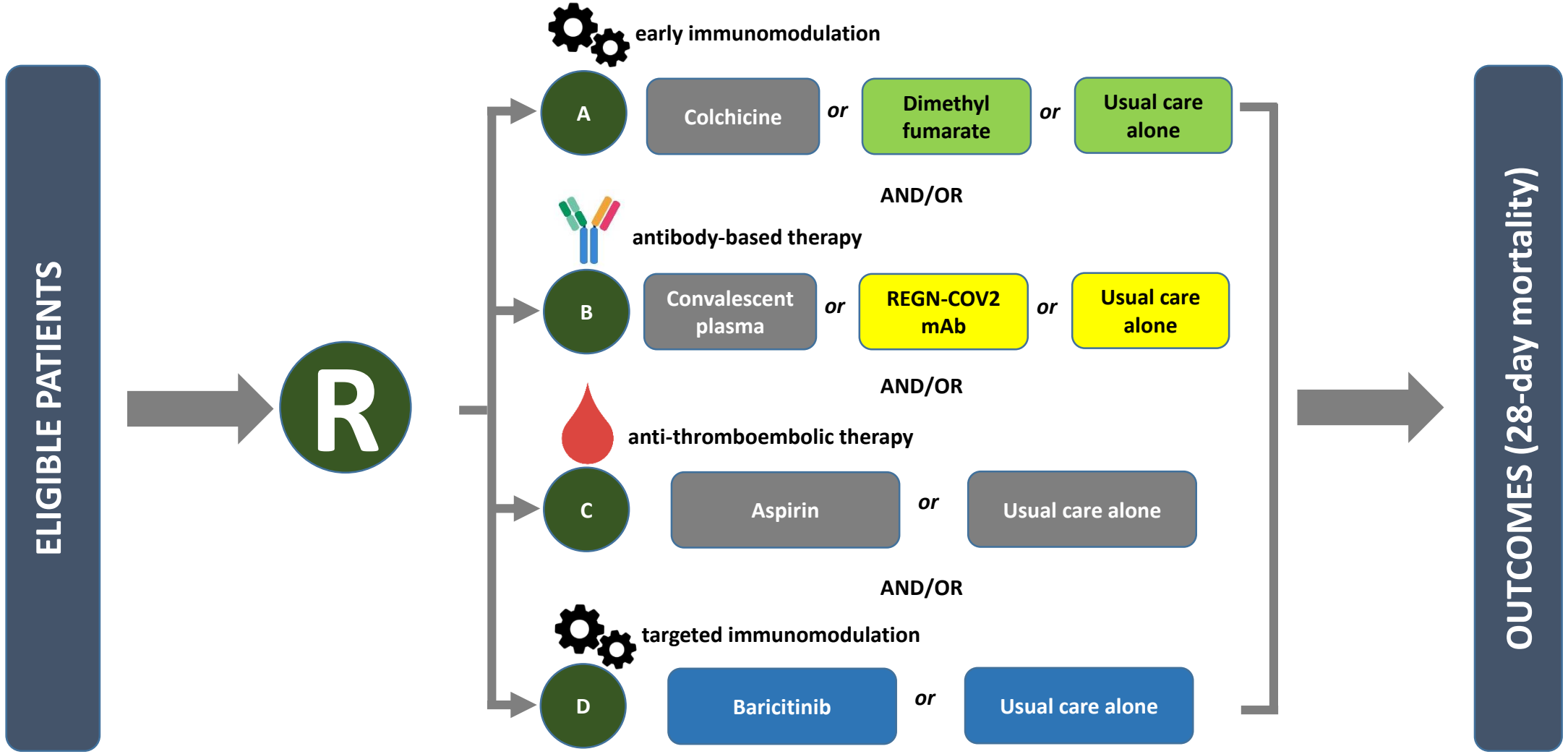


Benefits additional to dexamethasone

Preliminary data

www.medrxiv.org/content/10.1101/2021.02.11.21249258v1

Factorial designs - efficient evaluation of multiple treatments

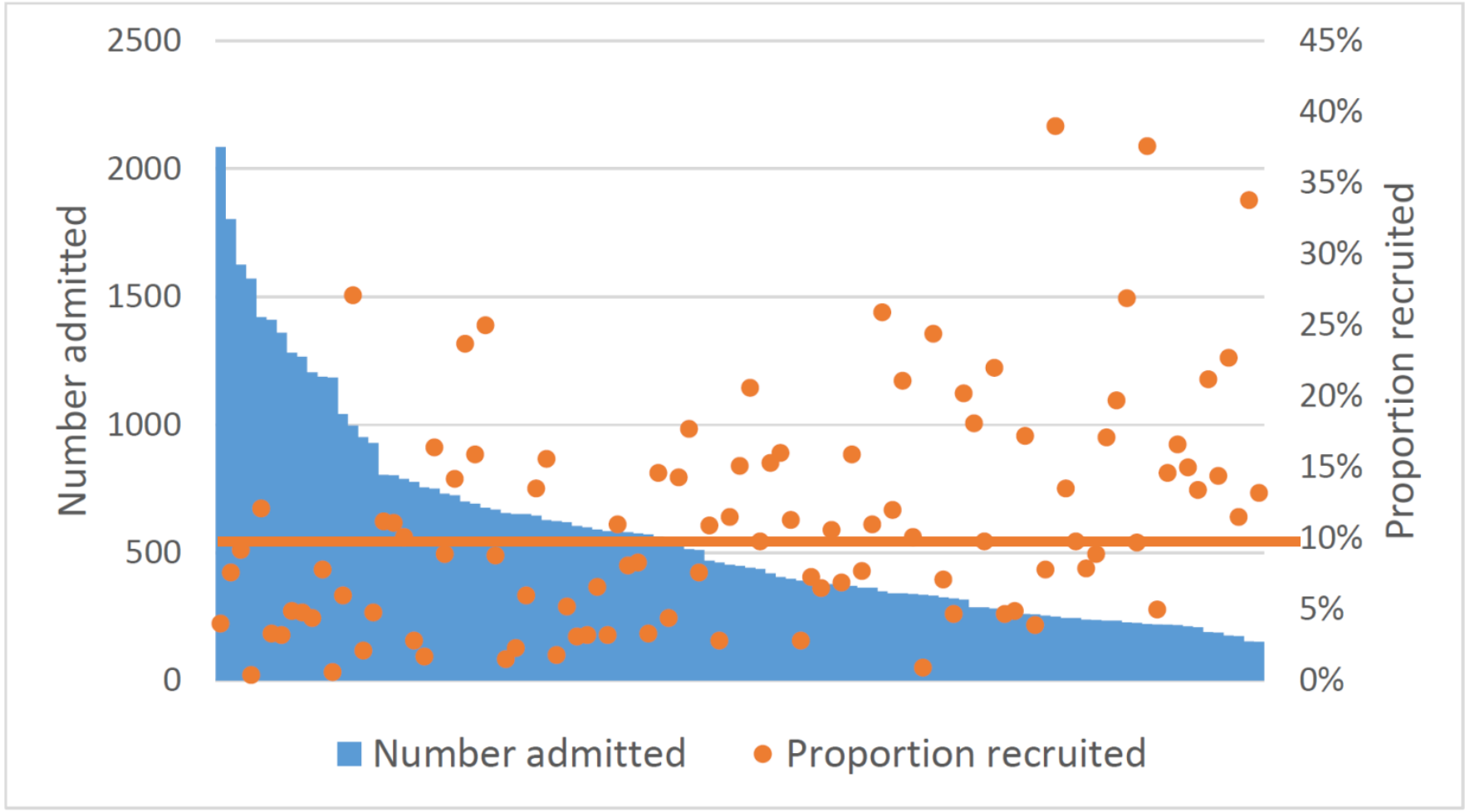


Efficient evaluation of multiple treatments

Anti-viral	Immunomodulatory	Anti-thrombotic
1600 Hydroxychloroquine ✗	2000 Dexamethasone ✓	7300 Aspirin ?
1600 Lopinavir-ritonavir ✗	2000 Tocilizumab ✓	**Anti-inflammatory**
5800 Convalescent plasma ✗	1500 Baricitinib	2500 Azithromycin ✗
4800 REGN-COV2 Antibody cocktail	50 Dimethyl fumarate	5600 Colchicine ✗

Clinical trials as a core component of clinical care

Recruitment by hospital Trust (1 Oct – 30 Nov)



Clinical trials as a core component of clinical care: Comments from NHS consultants/investigators

"Coming in to work each day, people would say to me 'they've chosen the wrong drugs'. I'd say 'let's see'.

I didn't know this [dexamethasone] would work. No one knew which drugs would work. But I thought we should help find out.

Three months on from the start of the trial, we have a therapy which is cheap & readily available. Millions could benefit.

I'm glad we helped contribute 1% of the data. Thank you to the patients who when offered to participate, agreed."

"[The RECOVERY trial] has inspired many of the more junior Doctors in our trust to look again at a career in research and we feel has given an opportunity / access to treatment to our patients that they otherwise would not have"

"We have been very pleased to have been able to help contribute to this effort that has helped to provide some clear answers."

Key lessons

The New York Times

Ezekiel J Emanuel, Cathy Zhang, Amaya Diana
https://www.nytimes.com/2020/09/01/opinion/coronavirus-clinical-research.html

- First, the Recovery trials are **designed to be easy to take part in**
- Second, the Recovery **protocol was quickly approved** at the national level and **adopted by all hospitals** in Britain.
- Third, **background patient data provided by the National Health Service helped to simplify the research process.**
- Fourth, support from **leaders in government health care ensured widespread cooperation** by hospitals.
- Fifth, Britain has a **national system of research nurses** who were rapidly redeployed to work on Covid-19 research
- And last, the British effort was **incorporated as part of everyday clinical care in hospitals**.

New opportunities for clinical trials

Smart design & streamlined operations

+

Integrated with routine healthcare & data systems

+

Enlightened regulatory approaches

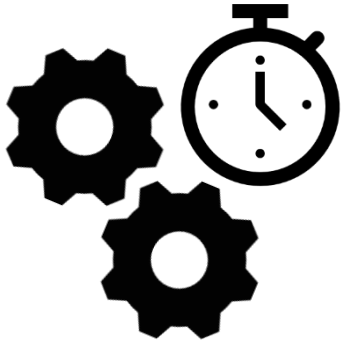
Better patient care and public health

Six key qualities of a good RCT

Produces a scientifically sound answer to a relevant question

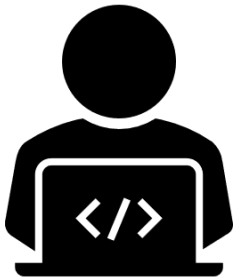
Respects the rights & well-being of participants

Designed to be feasible & conducted by appropriately experienced individuals



Streamlined proportionate, coordinated, and efficient systems oversee trial quality

Systems in place to address clinical safety



Appropriate data collection, security, handling, record-keeping, processing and publication.

Randomised trials are an essential component of high quality clinical care

- Arbitrary use of unproven treatments is a disservice to patient care & public health
- Randomized trials are a critical component of high quality clinical care
- Compelling results change practice

- But trials must be:
  - Feasible for patients and clinical staff
  - Inclusive of relevant patient groups
  - Focused on outcomes that matter

- Requires leadership, coordination, collaboration, fairness, and transparency

These lessons are important not only for the current COVID-19 pandemic

but also for the tackling the burden of many other common diseases

Acknowledgements

- UK Research & Innovation
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- National Institute for Health Research
- Bill & Melinda Gates Foundation
- Department of Health & Social Care

- NIHR Clinical Research Network
- NIHR Oxford Biomedical Research Centre
- NHS DigiTrials
- Medical Research Council Population Health Research Unit

with enormous thanks

to the very many doctors, nurses, & other healthcare & research staff at 177 NHS hospitals

and, most importantly

to the thousands of patients who participate

in this extraordinary project