

Partnership and Collaboration: Lessons learned from the RECOVERY trial

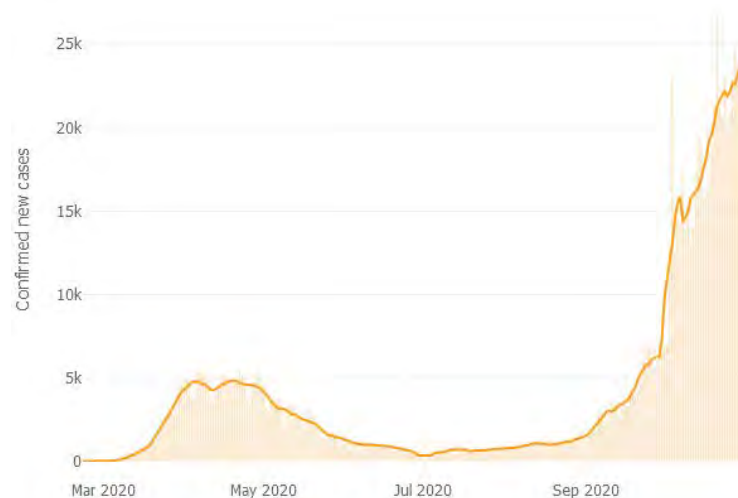
**Martin Landray, University of Oxford,
on behalf of the RECOVERY Collaborative**

Background

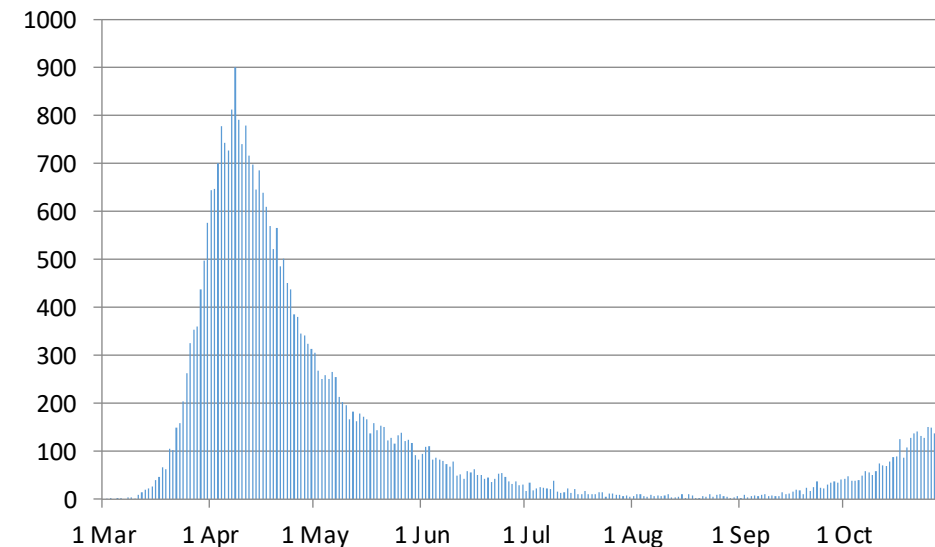
Unprecedented clinical challenge:

- 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

UK New Cases



UK Deaths



Selection of treatments

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

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)

RECOVERY trial - Design

- **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

- **Repurposed antivirals**
 - Hydroxychloroquine
 - Lopinavir-ritonavir
- **Immunomodulatory**
 - Dexamethasone
 - Azithromycin
 - Tocilizumab
- **Targeted anti-SARS-CoV-2**
 - Convalescent plasma

<small>OXFORD MEDICAL RESEARCH UNIT</small> RECOVERY <small>trial 19-07-2020</small>		RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)		 <small>OXFORD</small>
Hospital:		Patient Name:		
<p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>				
_____ PRINTED name of participant		_____ Signature		_____ Today's date
_____ PRINTED name of person taking consent		_____ Signature		_____ Today's date
<p><i>*1 copy for participant; 1 copy for researcher site file; 1 (original) to be kept in medical notes</i></p>				

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

Section A: Baseline and Eligibility

Date and time of registration: 8 Apr 2020 17:55

Treating clinician

A1. Name of treating clinician

Patient details

A2. Patient surname

Firstname

A3. NID number

A4. What is the patient's sex? Female ☐

A5. Is the patient known to be pregnant? ☐

A6. What is the patient's date of birth?

Inclusion criteria

A7. Are current test dates in line with the protocol?
 If answer is 'no' select when it occurred on the date

A8. Does the patient have evidence of completed SARS-CoV-2 infection?
 If answer is 'no' select when it occurred on the date

A9. Does the patient have any medical history that might, in the opinion of the referring clinician, not the patient or significant risk if they were to participate in the trial? ☐

A10. COVID-19 consent signed date

A11. Date of registration

A12. Does the patient require oxygen?

A13. Does the patient CURRENTLY require ventilation on ICU?
 Please tick patient selection in case selection table ☐

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 immunosuppressants and/or is on immunosuppressive treatment (immunosuppressive treatment) ☐

Are the following treatments UNAVAILABLE for the patient?

A14.1 Lipid-lowering treatment ☐

A14.2 Diuretics ☐

A14.3 Hydrocortisone ☐

A14.4 Antithrombotic ☐

Are the following treatments available?

A15.1 Lipid-lowering treatment ☐

A15.2 Diuretics ☐

A15.3 Hydrocortisone ☐

A15.4 Antithrombotic ☐

Please sign off this form once complete

Signature:

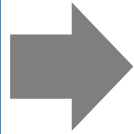
Signature:

Referring clinician:

RECOVERY trial design

ELIGIBLE PATIENTS

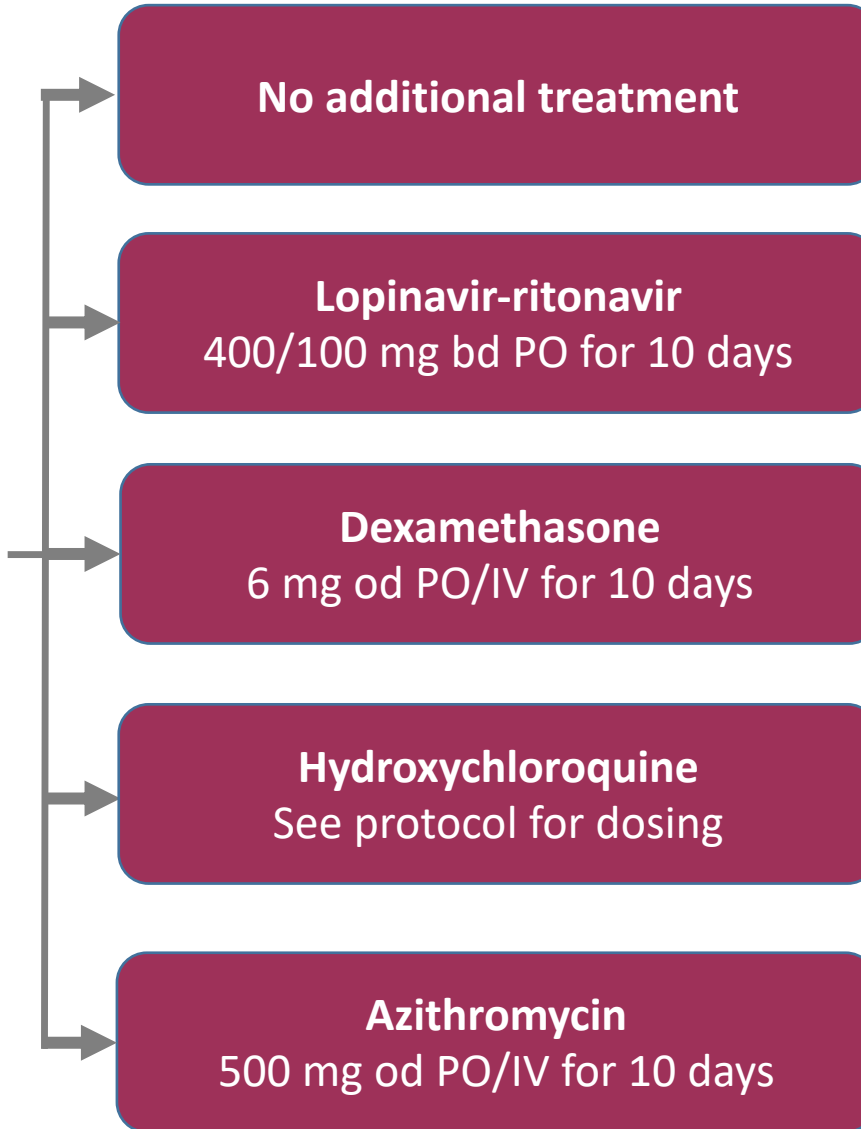
1. Admitted to hospital
2. Proven or suspected SARS-CoV-2 infection



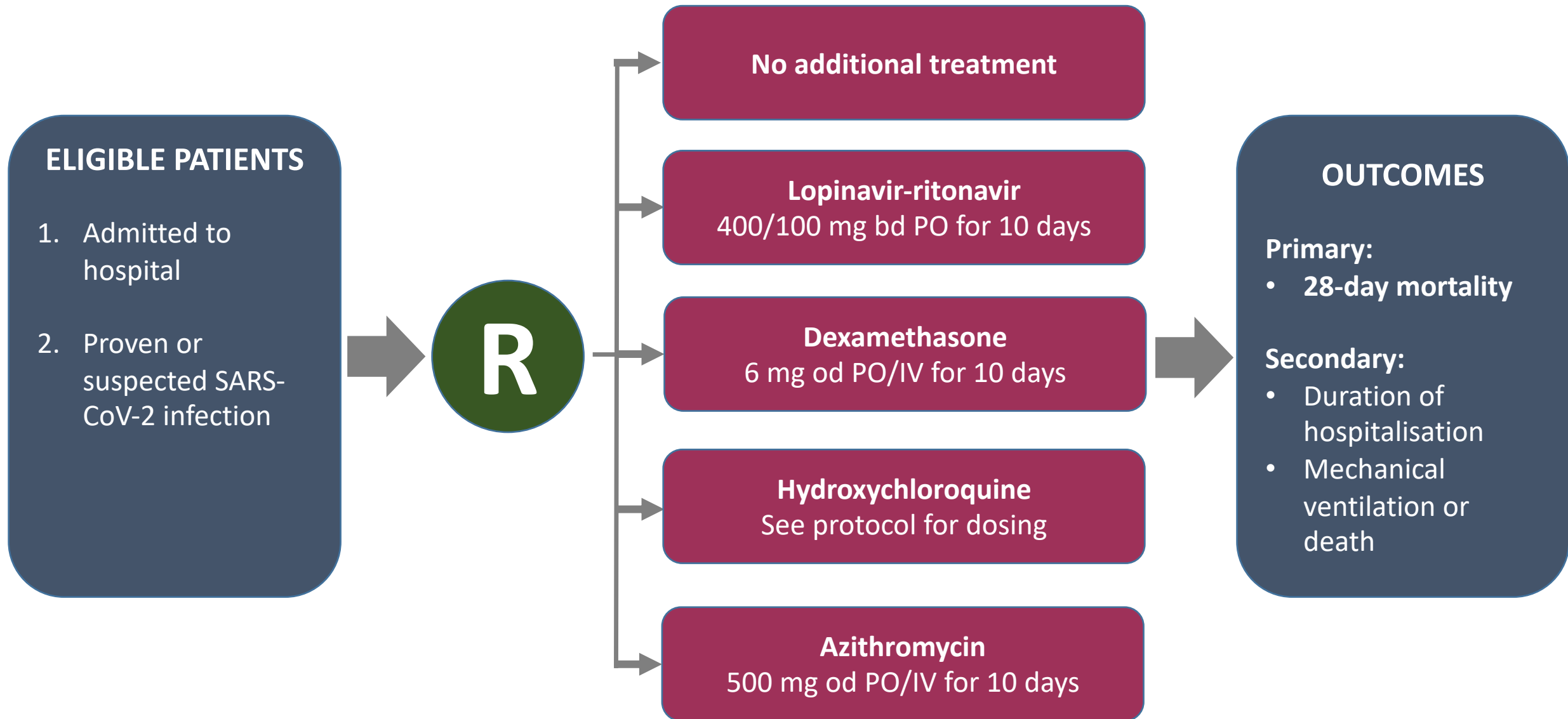
RECOVERY trial design

ELIGIBLE PATIENTS

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



RECOVERY trial design



Centrally collected routine data

Hospitalisation datasets

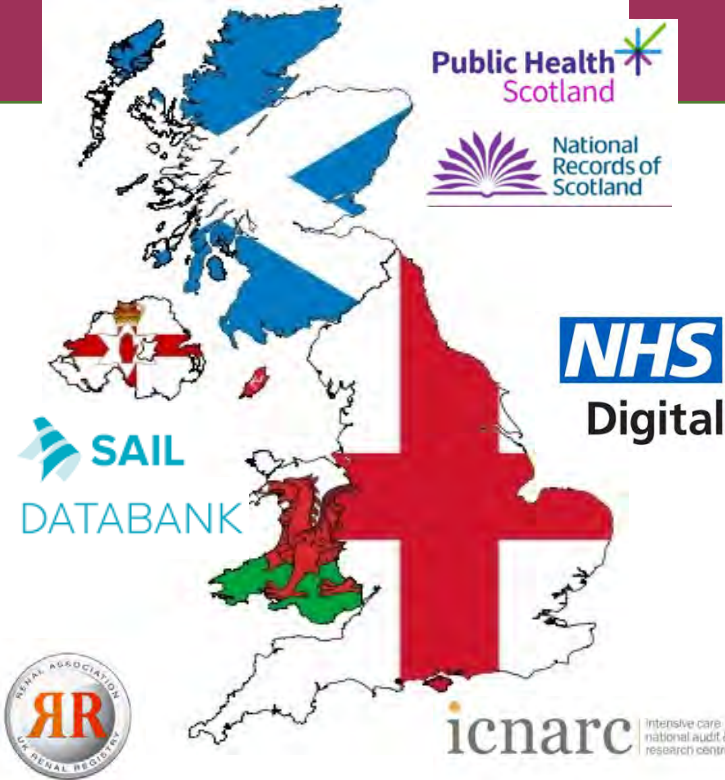
- ✓ Scottish Morbidity Records (SMR)
- ✓ Hospital Episode Statistics Admitted Patient Care (HESAPC)
- ✓ Secondary Uses Service Admitted Patient Care (SUSAPC)
- ✓ Patient Episode database for Wales (PEDW)

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)

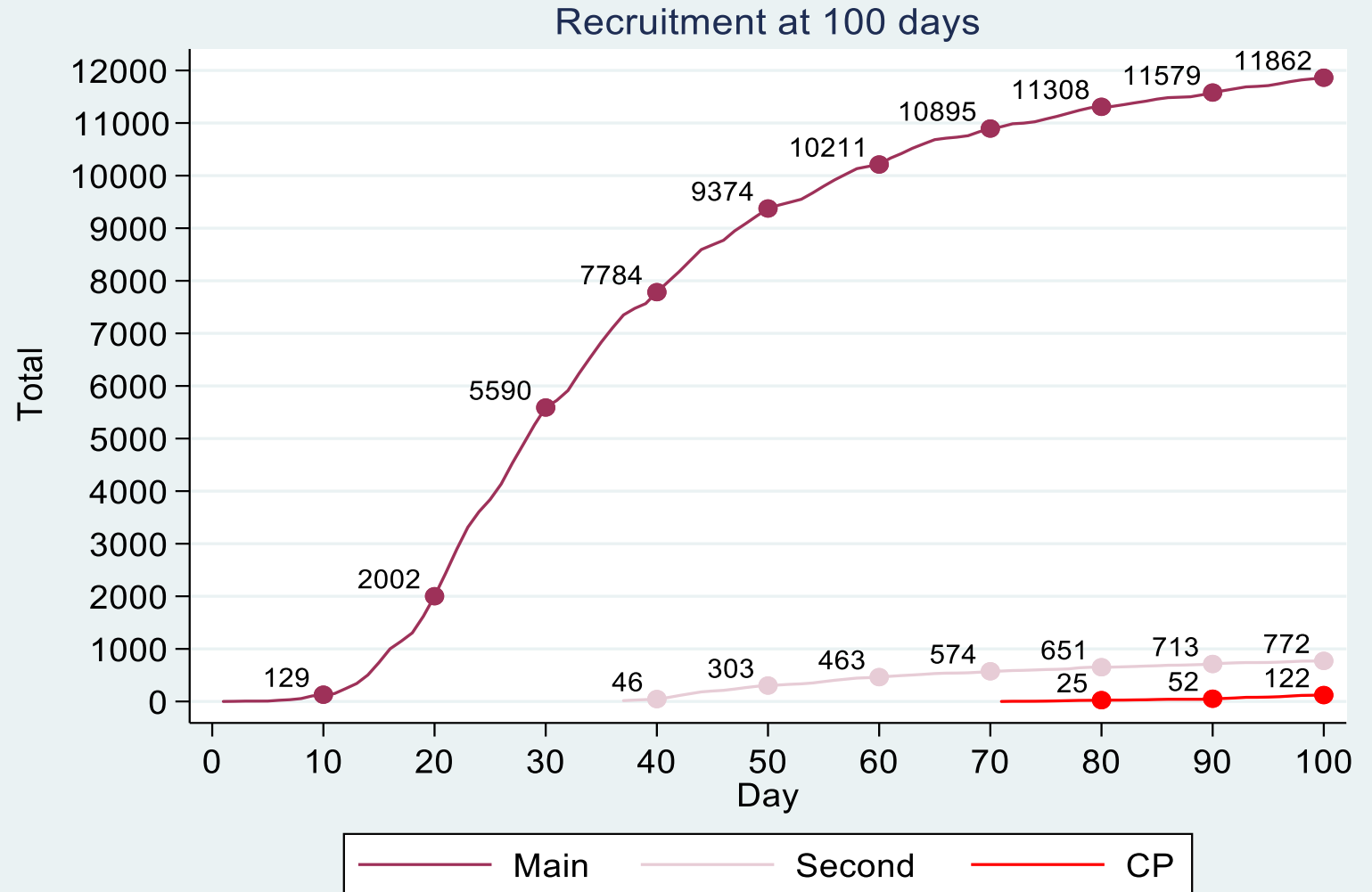
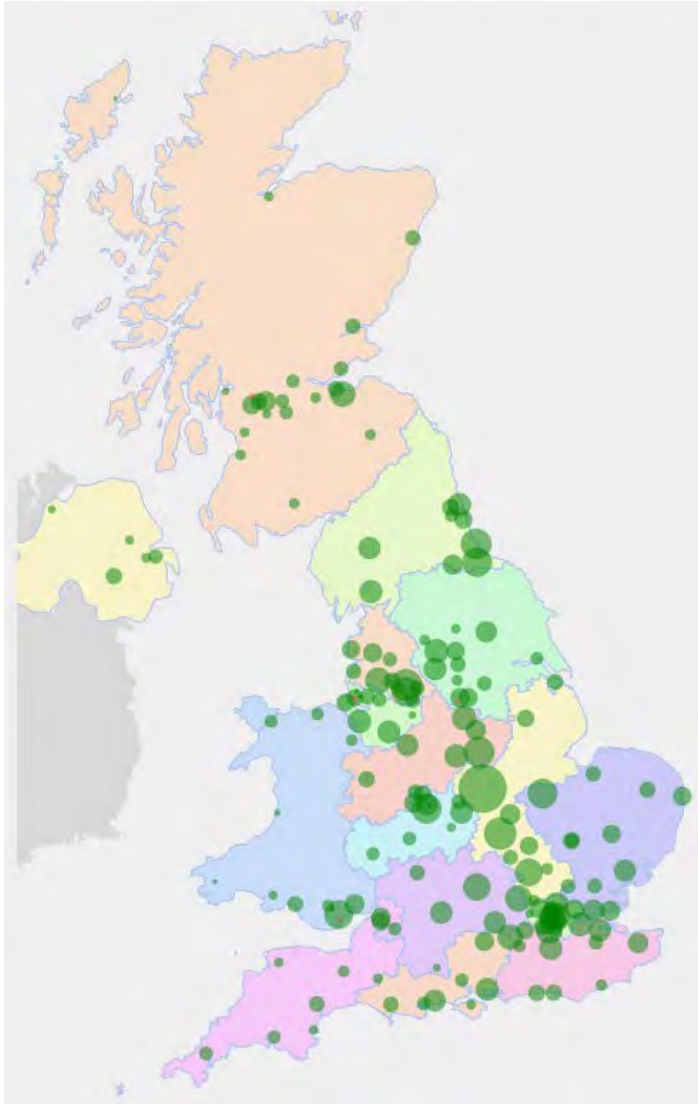
Critical care datasets

- ✓ 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

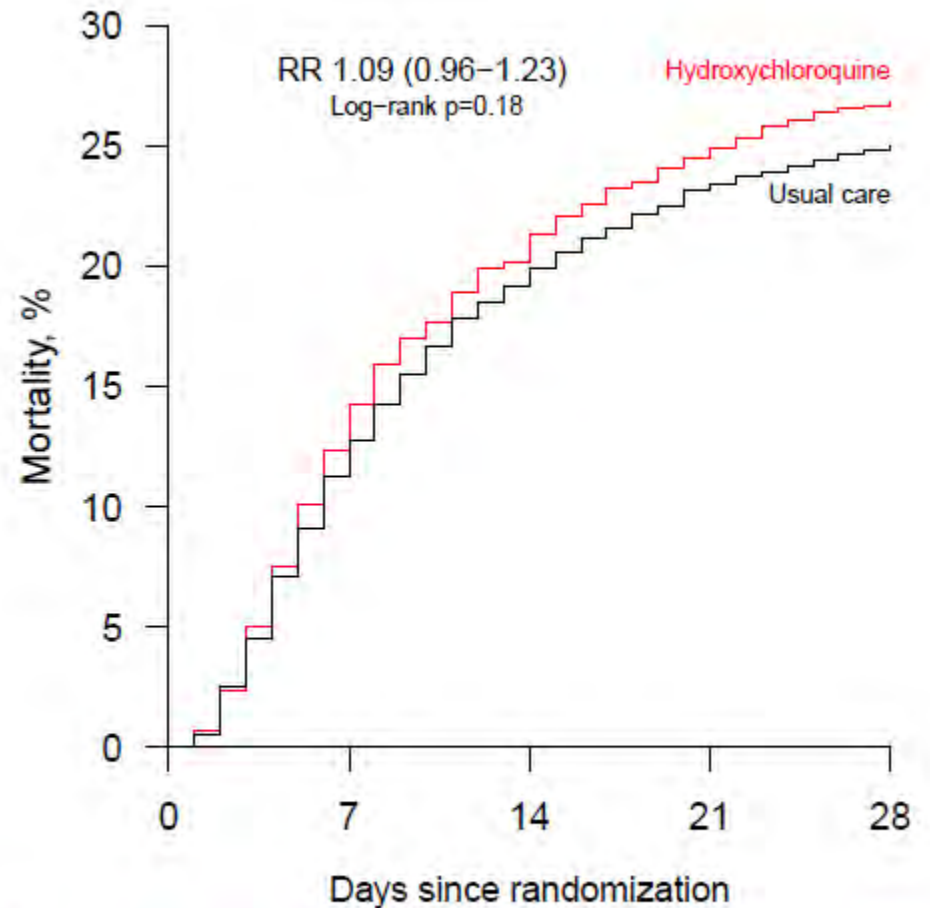
- ✓ COVID-19 Hospitalisation in England Surveillance System
- ✓ Second Generation Surveillance System (SGSS)
- ✓ Electronic Communication of Surveillance in Scotland (ECOSS)
- ✓ Welsh Results Reporting Service (WRRS)

RECOVERY – rapid and widespread recruitment



Hydroxychloroquine: Widely recommended – shown to be ineffective

<https://www.nejm.org/doi/10.1056/NEJMoa2022926>



Number at risk
Active
Control

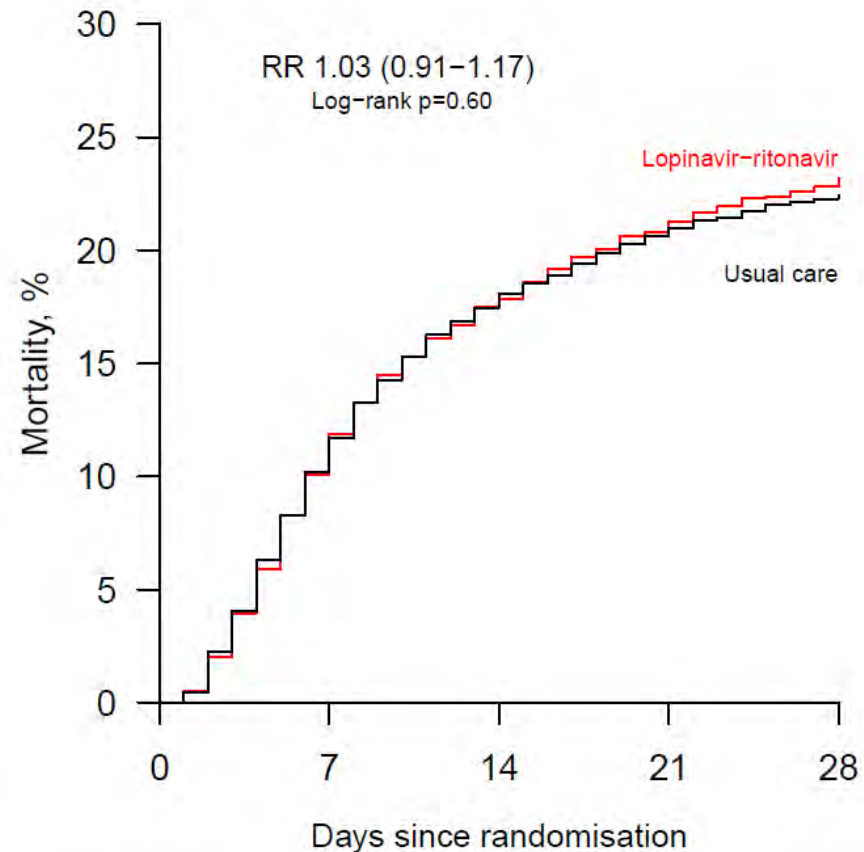
1561 1337 1227 1161 1125
3155 2750 2525 2410 2346



<https://www.nejm.org/doi/10.1056/NEJMoa2022926>

Lopinavir-ritonavir: Widely recommended – shown to be ineffective

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)32013-4/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32013-4/fulltext)



Number at risk					
Active	1616	1422	1325	1269	1238
Control	3424	3018	2799	2700	2650

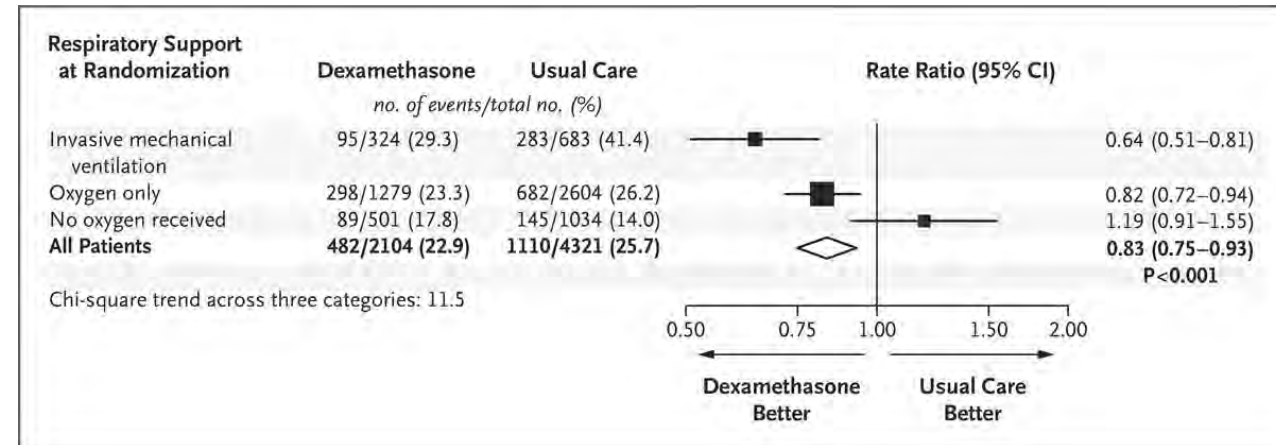
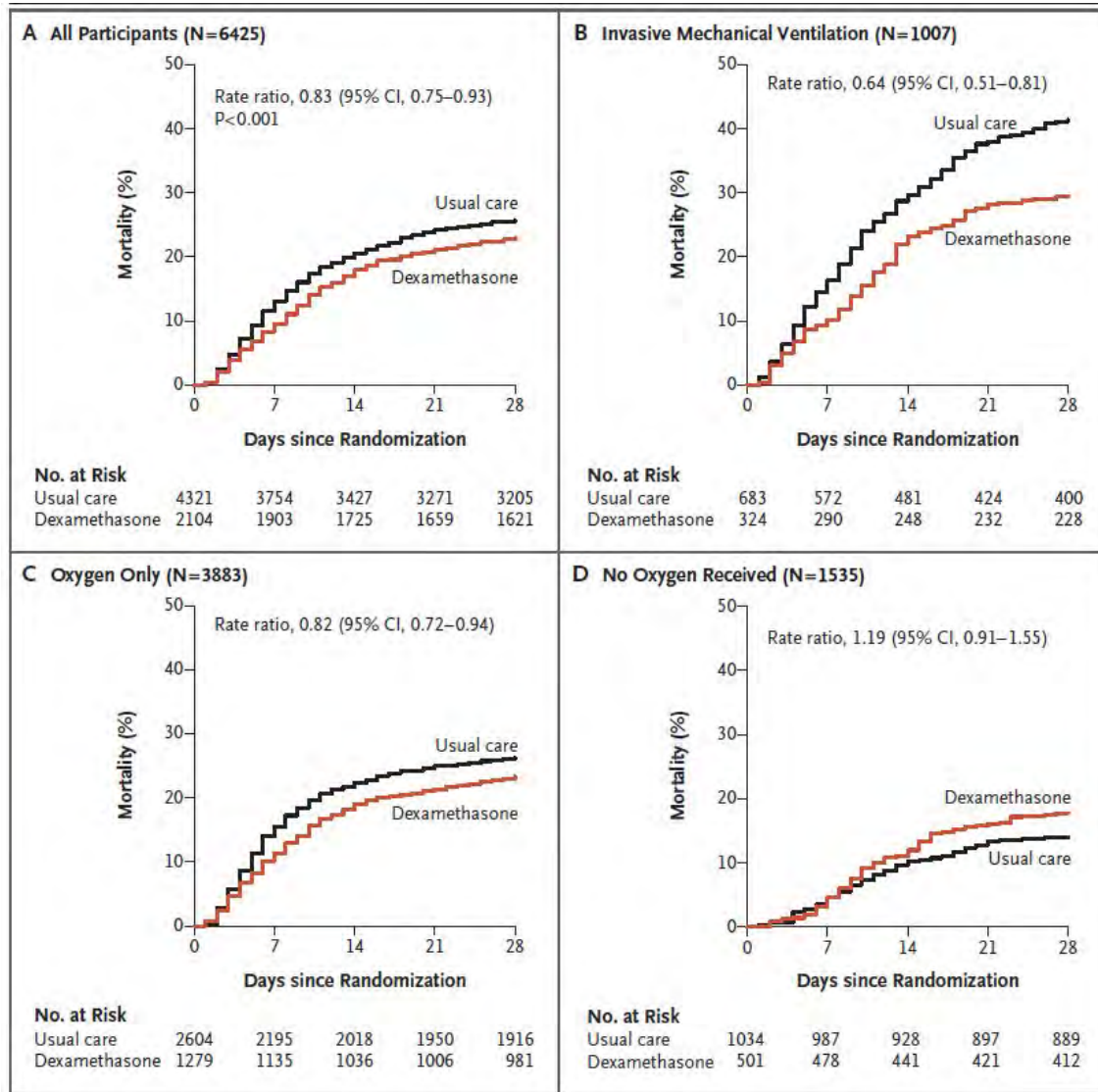


INTERNATIONAL

HIV drug combo found to have no benefit for hospitalised COVID-19 patients in UK trial

Dexamethasone: Reduces mortality in patients requiring oxygen or ventilation

DOI: 10.1056/NEJMoa2021436



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

News 18/09/2020

The National Institutes of Health COVID-19 Treatment Guidelines Panel Provides Recommendations for Dexamethasone in Patients with COVID-19

Last Updated: June 25, 2020

Corticosteroids for COVID-19

LIVING GUIDANCE
7 SEPTEMBER 2020

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

Based on these preliminary results:

- The COVID-19 Treatment Guidelines Panel recommends 10 mg per day for up to 10 days in patients with COVID-19 who require supplemental oxygen.
- The Panel recommends a supplemental oxygen (A).

Sign up for updates

Where Is America's Groundbreaking Covid-19 Research?

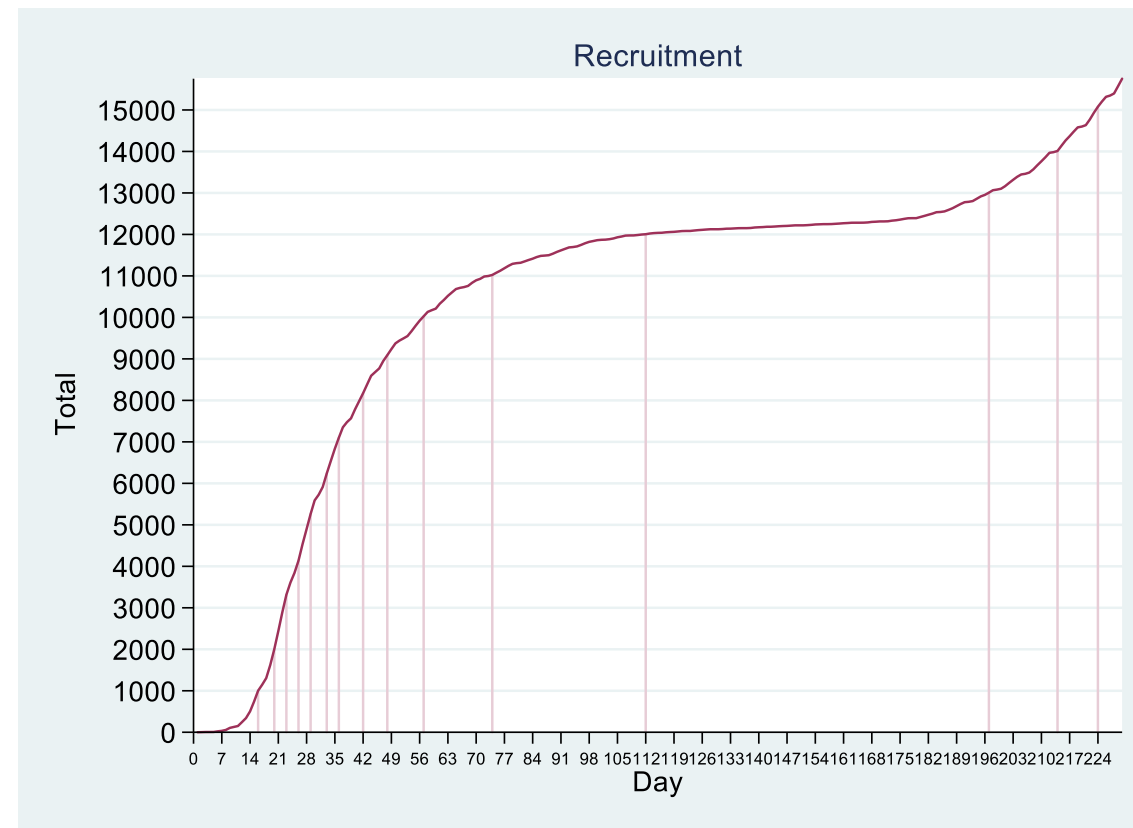
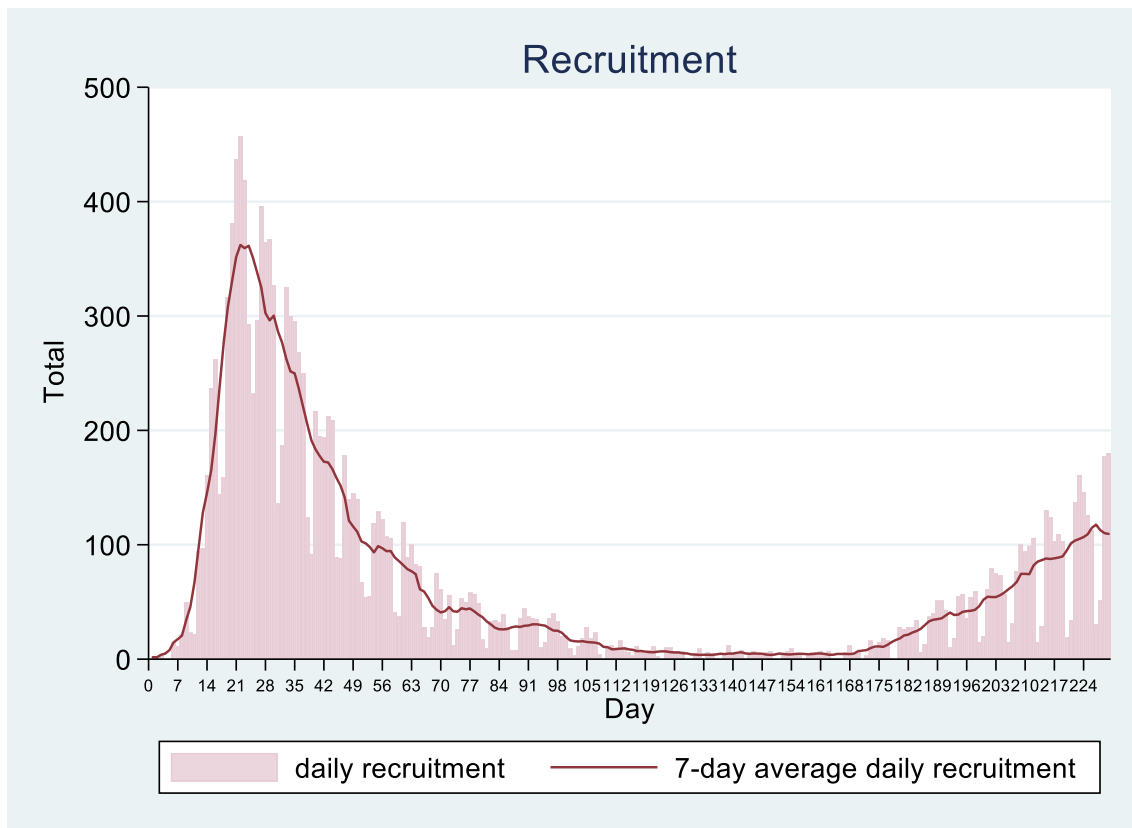
The New York Times

The U.S. could learn a lot from Britain.

By Ezekiel J. Emanuel, Cathy Zhang and Amaya Diana

- 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.**

RECOVERY – the second wave is upon us



RECOVERY – studying multiple treatments

R_A

No additional treatment

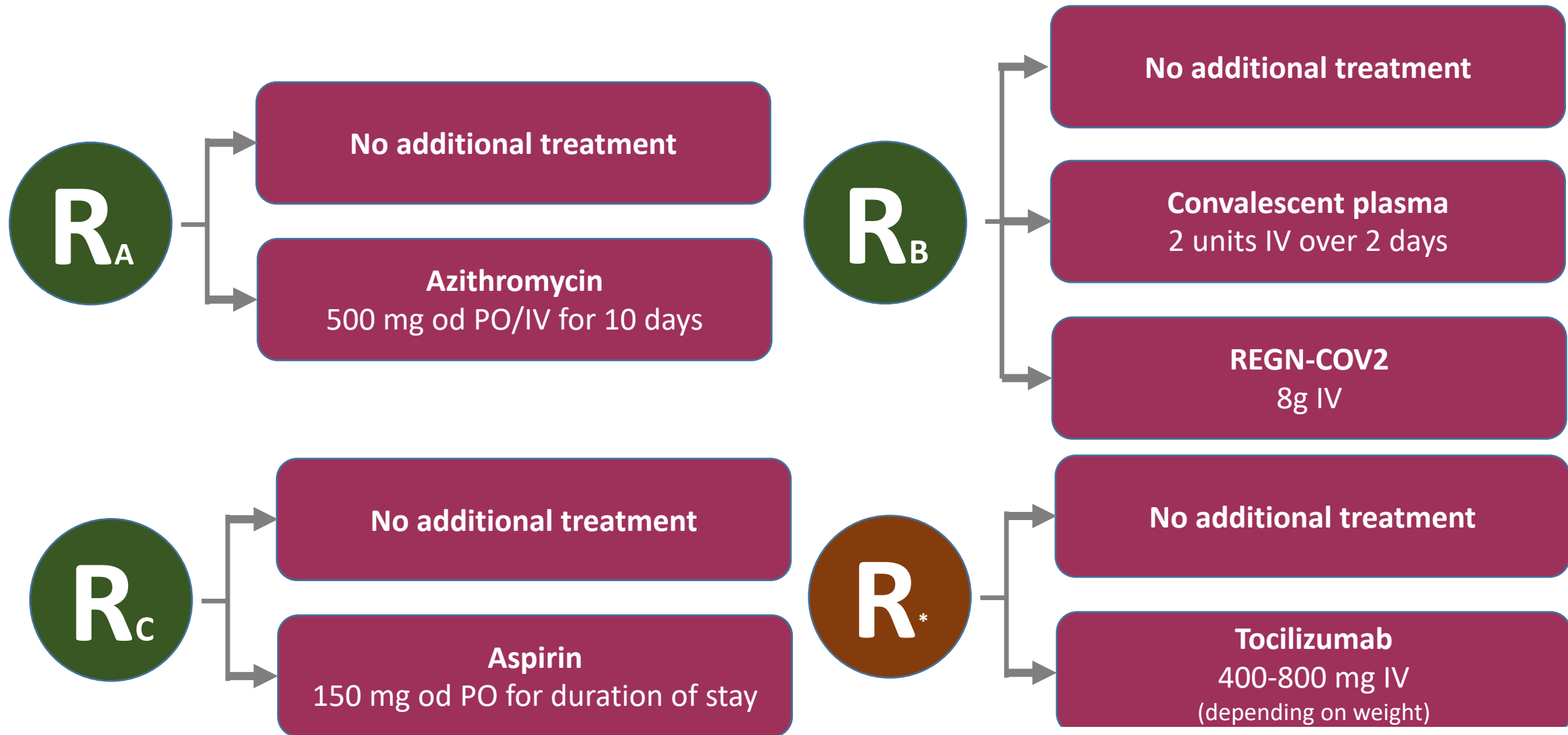
Lopinavir-ritonavir
400/100 mg od PO for 10 days

Dexamethasone
6 mg od PO/IV for 10 days

Hydroxychloroquine
See protocol for dosing

Azithromycin
500 mg od PO/IV for 10 days

RECOVERY – studying multiple treatments



*If hypoxia + inflammation

Randomised trials are an essential component of high quality clinical care

- Arbitrary use of unproven treatments must be avoided
- Large, 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

Communication: www.recoverytrial.net



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[For Patients](#)

For Patients

Thank you for your interest in the RECOVERY Trial. This trial is recruiting patients admitted to hospital with suspected or confirmed COVID-19. We hope the [Frequently Asked Questions](#) on this page address any questions you might have.

[Why is this research being done?](#)

[What is the purpose of this study?](#)

[Who is doing the study?](#)

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[For Site Staff](#)

Information for site staff

Every COVID-19 patient in the UK may be invited to participate in the RECOVERY Trial. Randomisation is currently to one of these arms: usual care; usual care plus lopinavir-ritonavir; usual care plus low-dose dexamethasone (now only recruiting children); usual care plus azithromycin, a commonly used antibiotic; usual care plus convalescent plasma (collected from donors who have recovered from COVID-19 and contains antibodies against the SARS-CoV-2 virus). There is a second randomisation for participants who deteriorate between tocilizumab and control. The trial is designed to have the least possible impact on NHS staff. You will find [Frequently Asked Questions](#) on the [site set-up page](#).

See [Update Alert](#) on this page for update details.

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Search

11891 Participants

176 Active sites



Site Set-up



Pharmacy



Site Teams



Training



Randomisation



Follow-up

Huge thanks to the team...



Huge thanks from the team...



Acknowledgements



- UK Research & Innovation
- Wellcome Trust
- Department for International Development
- National Health Service in England, Wales, Scotland, and Northern Ireland
- NIHR Clinical Research Network
- NIHR Oxford Biomedical Research Centre
- National Institute for Health Research
- Bill & Melinda Gates Foundation
- Department of Health & Social Care
- NHS DigiTrials
- Medical Research Council Population Health Research Unit

with enormous thanks

to the very many doctors, nurses, & other healthcare & research staff at over 176 NHS hospitals
and, most importantly

to the thousands of patients who participate
in this extraordinary project