NIHR | Oxford Biomedical Research Centre

UKRI Medical Research Council

Making clinical trials mainstream:

COVID and beyond

Martin Landray

Nuffield Department of Population Health

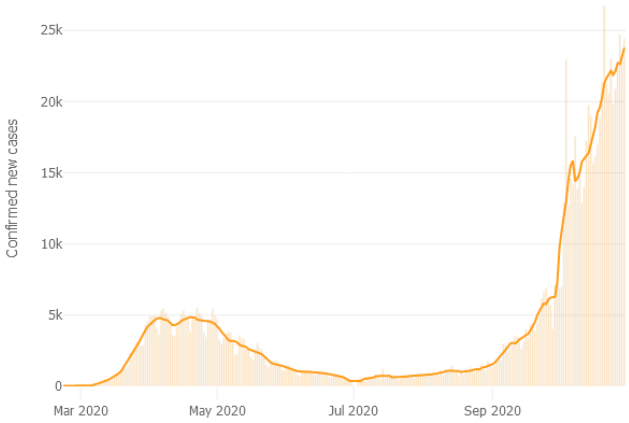
University of Oxford

Background

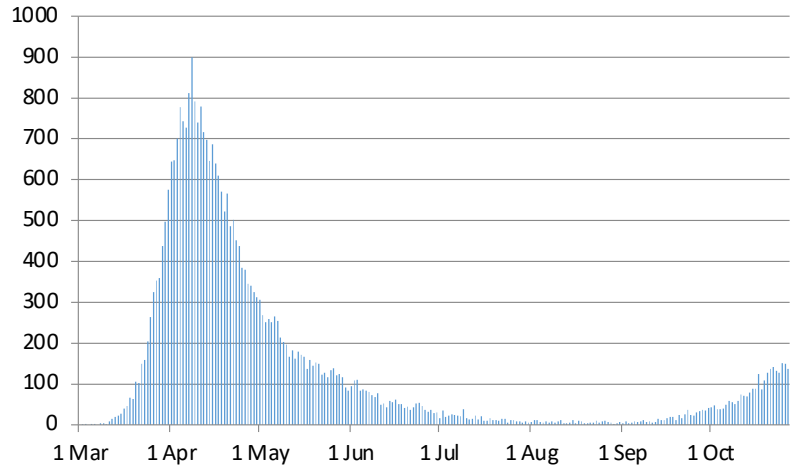
Unprecedented clinical challenge:

- 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



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**

Committee for Medicinal Products for Human Use: A call to pool EU research resources into large-scale, multi-centre, multi-arm clinical trials against COVID-19 (16 March 2020)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- CHMP... considers it **critical to generate robust and interpretable evidence** that would allow prompt definition of which investigational or repurposed medicinal products are effective and safe for the treatment of COVID-19.
- **Randomised controlled studies with a control arm** without antivirals or other experimental agents, as none yet has proven efficacy, **would allow generation of data that could lead to timely regulatory decisions** and could promptly guide clinicians in defining best treatment options for COVID-19.
- **Such studies need to be prioritised**, considering that they would allow the best use of available supply of investigational agents.
- The **CHMP is concerned about the amount of planned small studies or compassionate use programmes** across Europe that are **unlikely to be able to generate the required level of evidence** to allow clear-cut recommendations. **Such studies would not be in the best interests of patients.**
- **Multi-arm clinical trials investigating different agents simultaneously have the potential to deliver results as rapidly as possible across a range of therapeutic options** according to the same evaluation criteria.

Quality in clinical trials

"Clinical trials should incorporate quality in their scientific and operational design, conduct and analysis."

CTTI Monitoring Recommendations
2011
www.ctti-clinicaltrials.org/files/Monitoring/Monitoring-Recommendations.pdf

CTTI

Quality in clinical trials

"Quality" in clinical trials is defined as the

absence of errors that matter to decision making

i.e. errors which have a meaningful impact on the safety of trial participants or the credibility of the results (and thereby the care of future patients)

CTTI Quality by Design Recommendations 2015

www.ctti-clinicaltrials.org/qbd

CTTI

ICH GCP Addendum: Quality Management

"The sponsor should implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials"

*"**The methods used** to assure and control the quality of the trial **should be proportionate to the risks inherent in the trial and the importance of the information collected**."*

ICH E6 (R2) 2016

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

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

Looking back to move forward...

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.

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**."

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

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: .....

OR: PATIENT STICKER,
IF ALL DETAILS PROVIDED

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

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 calendar pack interrupted, or not given

TICK ✓ APPARENT SIDE-EFFECTS OF STREPTOKINASE/PLACEBO INFUSION
Significant hypotension during, or just after, infusion
Anaphylactic shock
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 site(s).....
"Minor" bleed (not transfused) ...../...../.....
Cardiac rupture ...../...../.....
Reinfarction ...../...../.....
Ventricular fibrillation ...../...../.....
Other cardiac arrest ...../...../.....
Stroke, probable cerebral haemorrhage ...../...../..... Likely residual disability (if alive):
Stroke, infarct or unknown type ...../...../..... Non-significant/ Moderate/ Severe
Discharge alive from hospital ...../...../.....
Death in hospital ...../...../..... and underlying cause, if not cardiac: .....

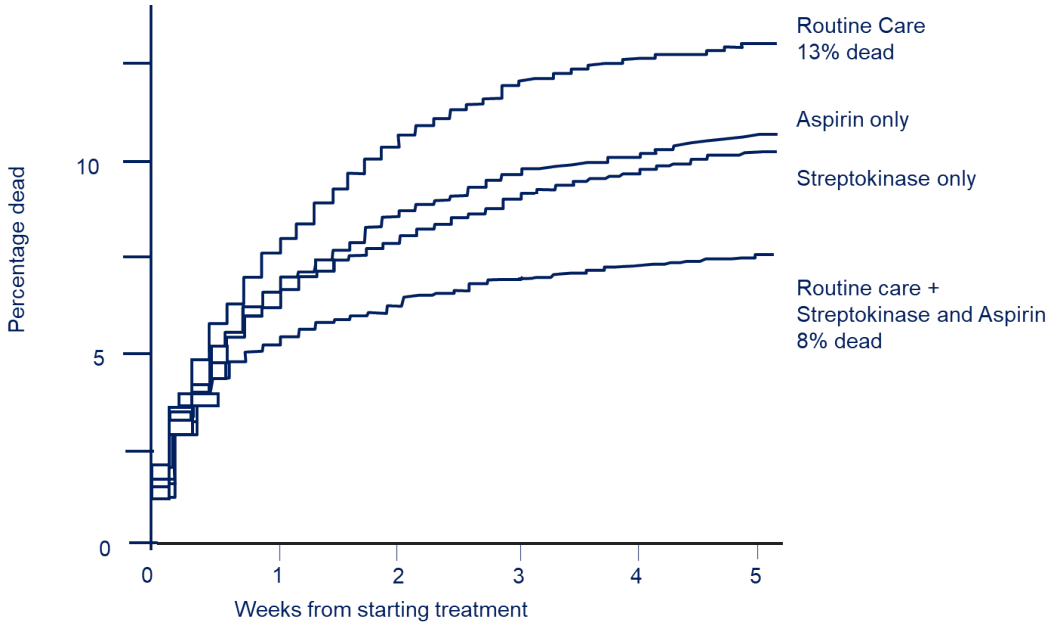
TICK ✓ TREATMENT IN HOSPITAL
Steroids prior to streptokinase/placebo infusion
Subcutaneous heparin
Intravenous heparin
Oral anticoagulant
Intravenous beta-blocker
Non-trial aspirin
Other anti-platelet agent(s)

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



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

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.

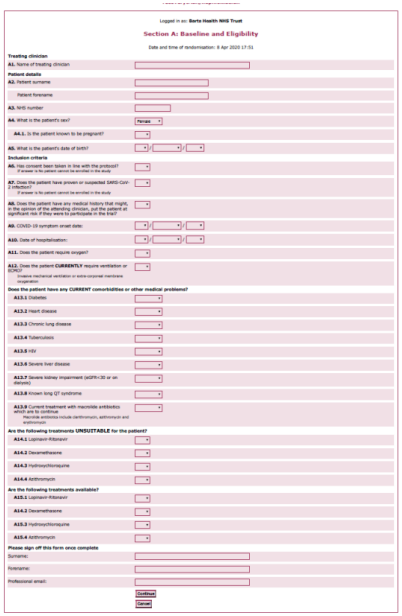
4. Access to my medical information: I agree that medical information collected by the doctors and hospitals which provide me with care and which may be located in local or national health and research organizations (including hospital admission, civil registration, audit and research data) may be provided 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*



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 them 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

A15.2 Dexamethasone

A15.3 Hydroxychloroquine

A15.4 Azithromycin

Please sign off this form once complete

Surname:

Forename:

Professional email:

Confirm

Cancel

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.**

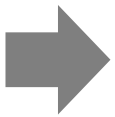
The tasks that they are required to perform under this protocol are similar to those that they perform in the other aspects of their roles as NHS staff.

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.

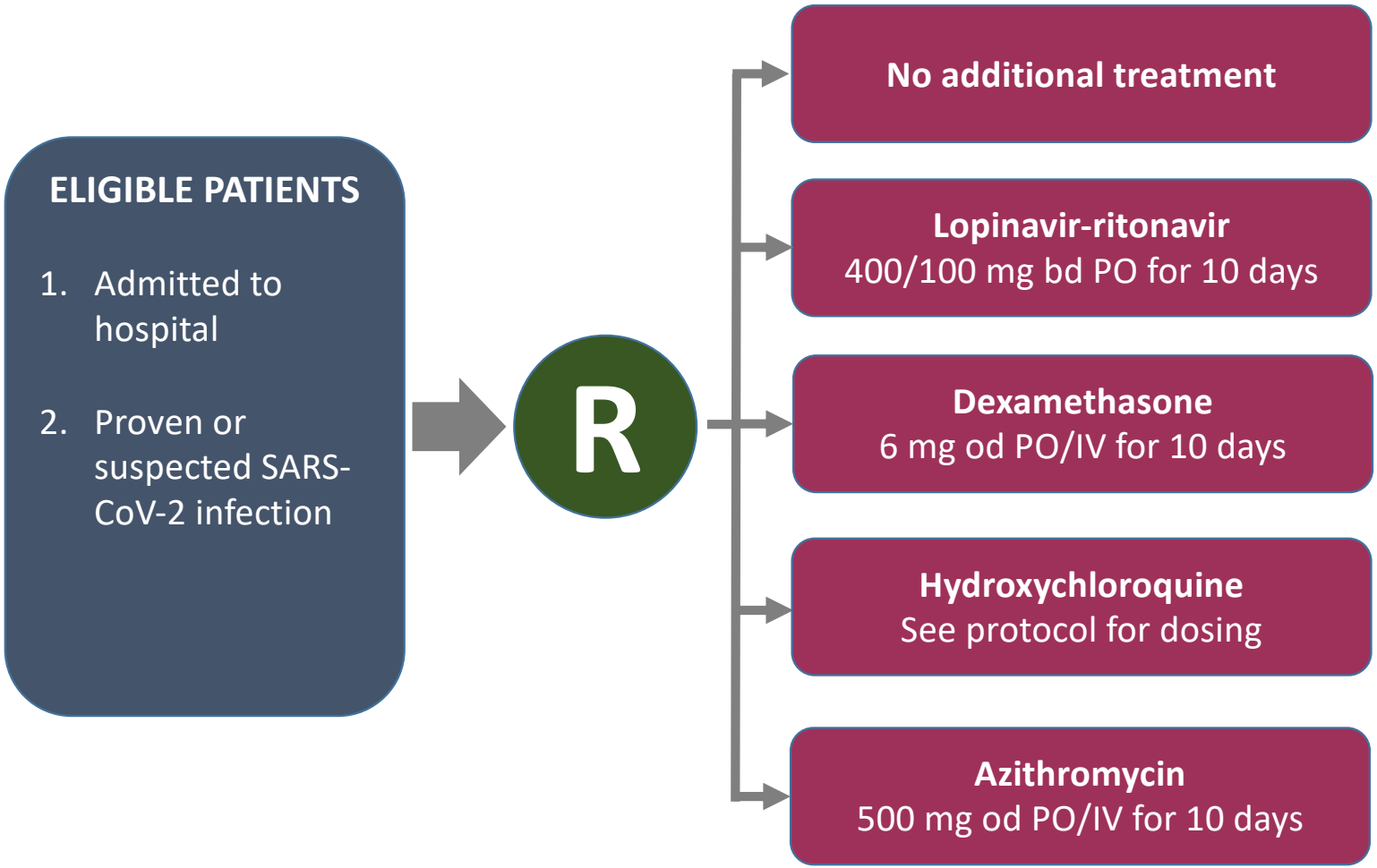
RECOVERY trial design

ELIGIBLE PATIENTS

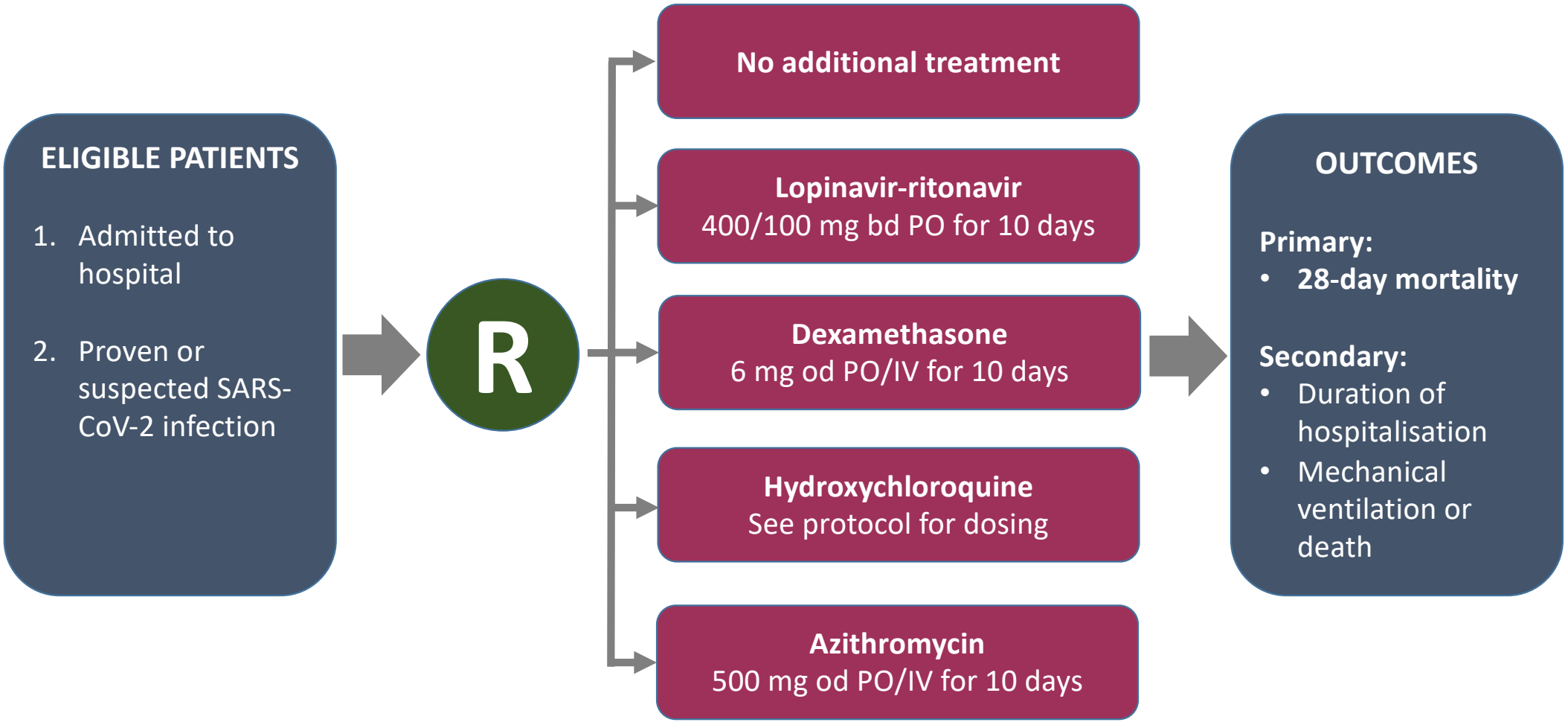
1. Admitted to hospital
2. Proven or suspected SARS-CoV-2 infection



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

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*"

Centrally collected routine data

Hospitalisation datasets

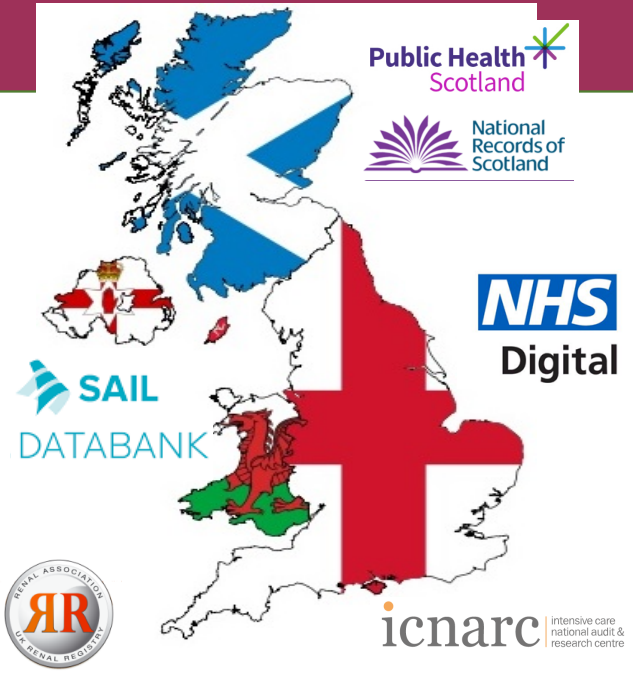
- ✓ Scottish Morbidity Records (SMR)
- ✓ Hospital Episode Statistics Admitted Patient Care (HESAPC)
- ✓ Secondary Uses Service Admitted Patient Care (SUSAPC)
- ✓ Patient Episode database for Wales (PEDW)

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)

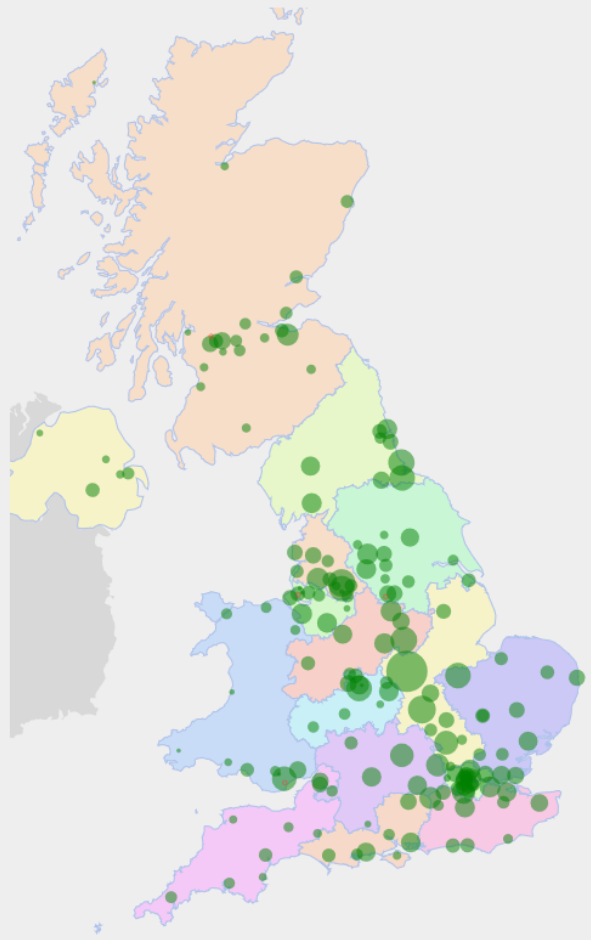
Critical care datasets

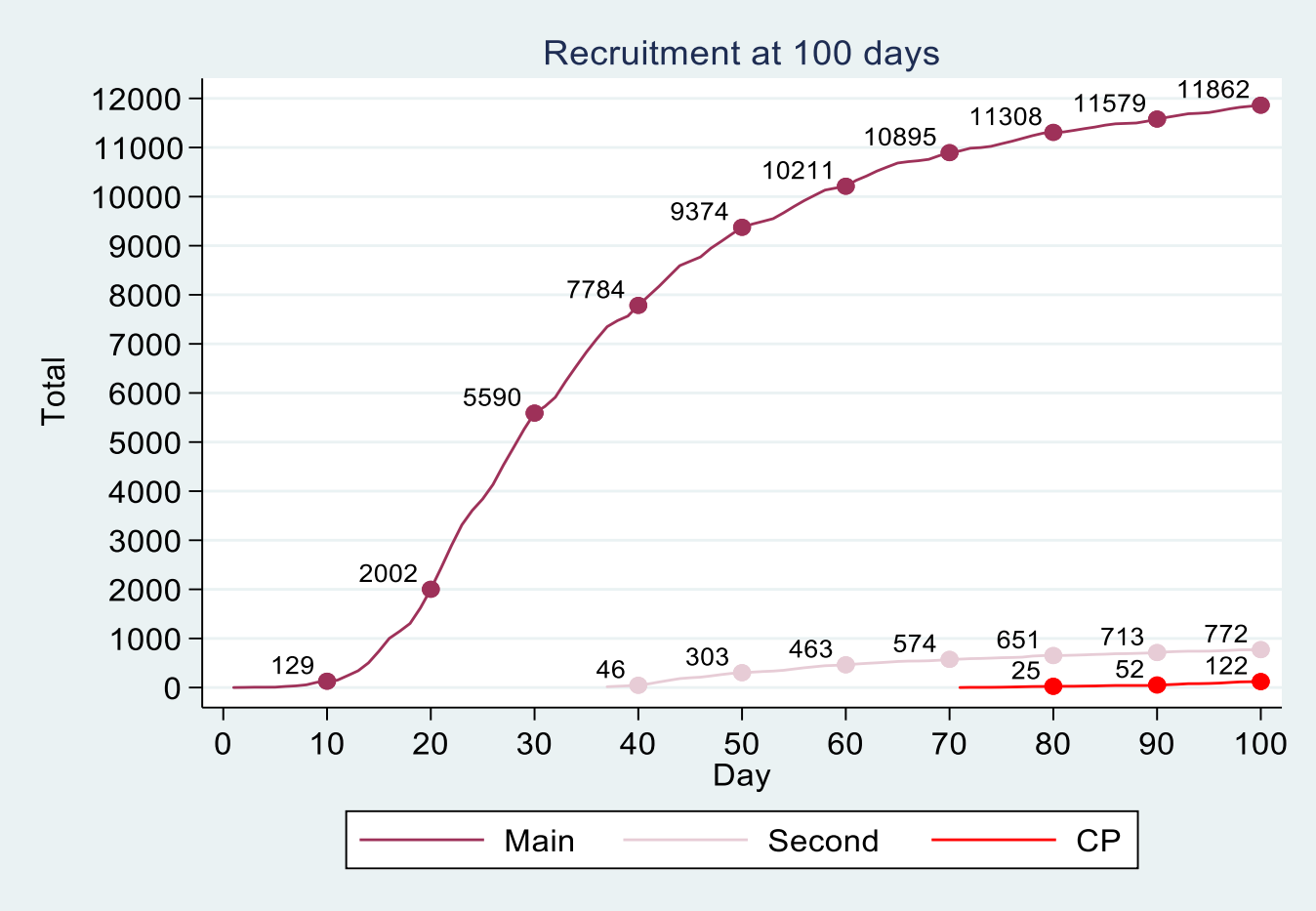
- ✓ Scottish Intensive Care Society Audit Group (SICSAG)
- ✓ Intensive Care National Audit and Research Centre (ICNARC)
- ✓ HES Critical Care Dataset (CCDS)
- ✓ PEDW Critical Care Dataset (CCDS)

COVID datasets

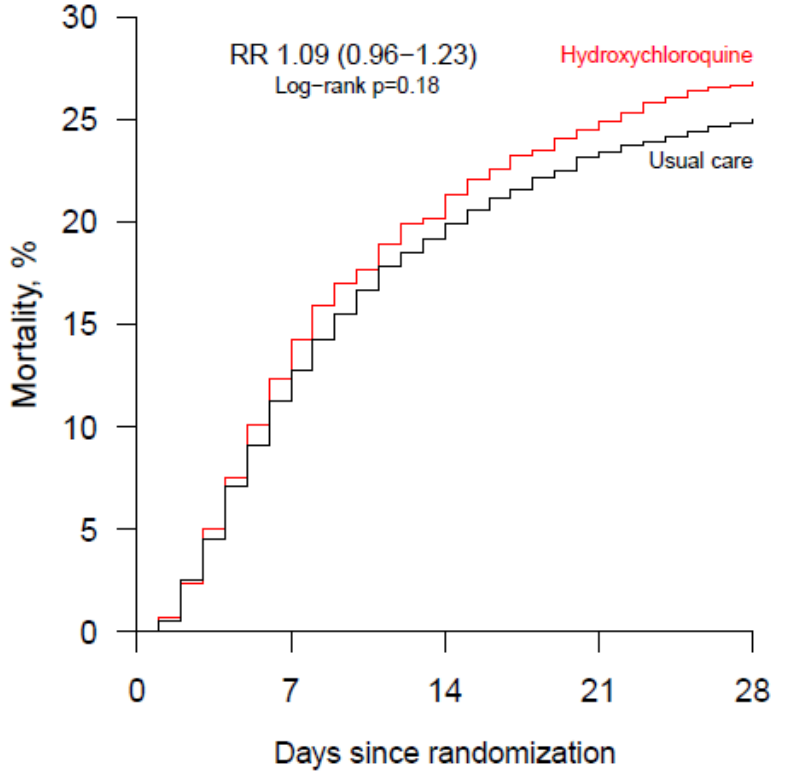
- ✓ COVID-19 Hospitalisation in. England Surveillance System
- ✓ Second Generation Surveillance System (SGSS)
- ✓ Electronic Communication of Surveillance in Scotland (ECOSS)
- ✓ Welsh Results Reporting Service (WRRS)

RECOVERY – rapid and widespread recruitment

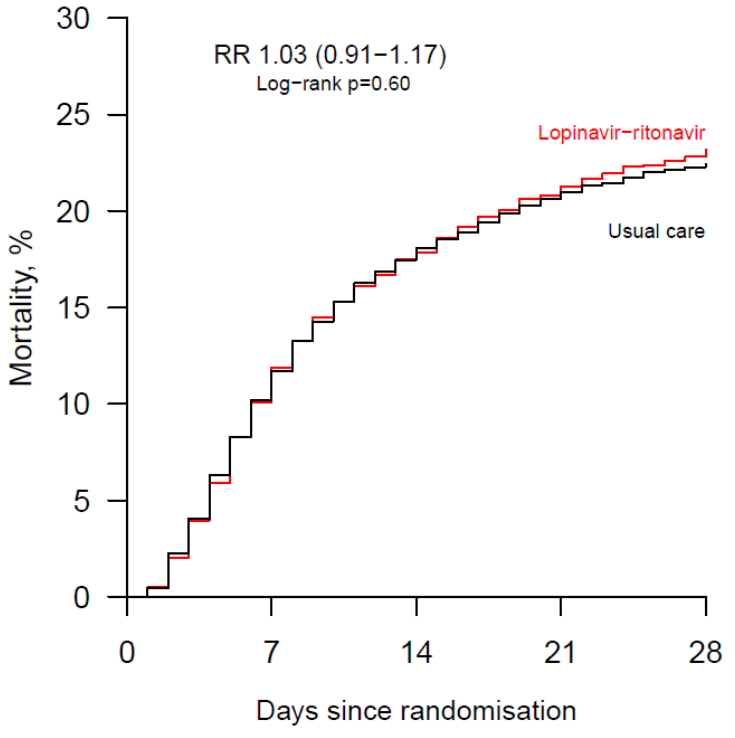




Hydroxychloroquine & Lopinavir-ritonavir: Widely recommended – shown to be ineffective



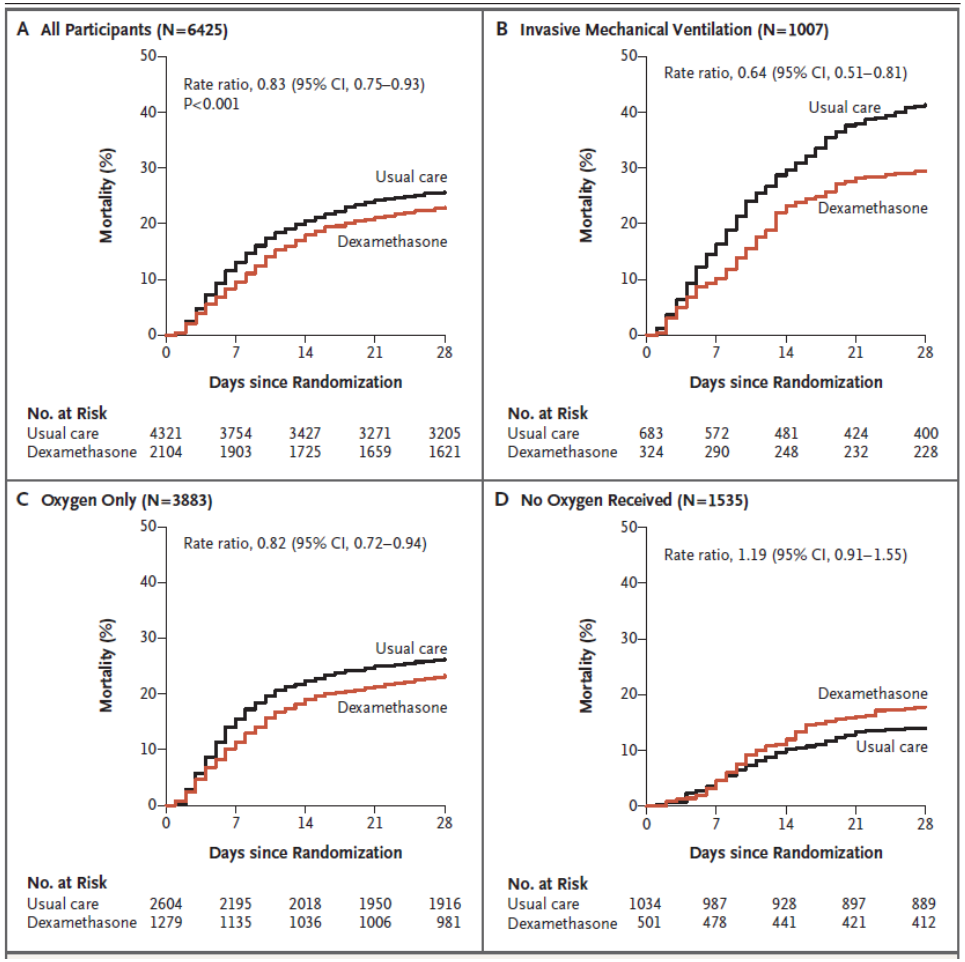
Number at risk					
Active	1561	1337	1227	1161	1125
Control	3155	2750	2525	2410	2346

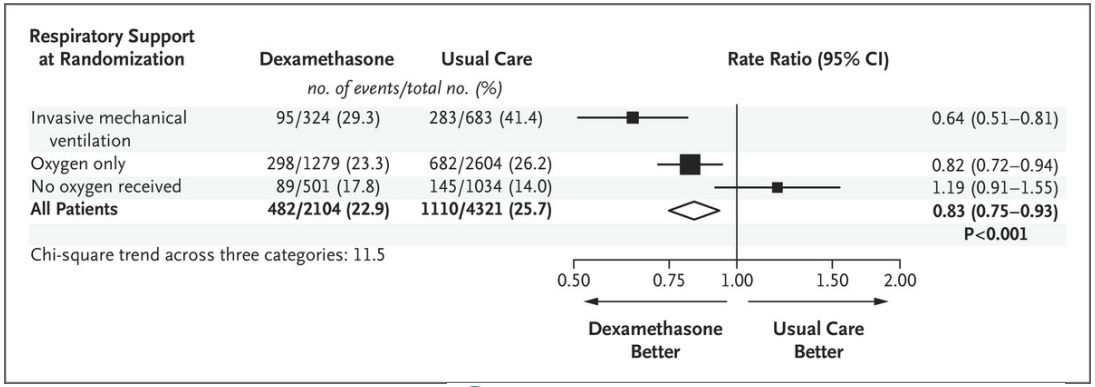


Number at risk					
Active	1616	1422	1325	1269	1238
Control	3424	3018	2799	2700	2650

Dexamethasone:
Reduces mortality in patients requiring oxygen or ventilation

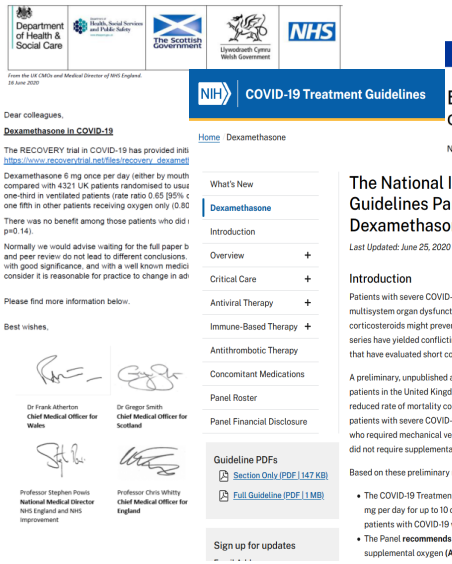
DOI: 10.1056/NEJMoa2021436



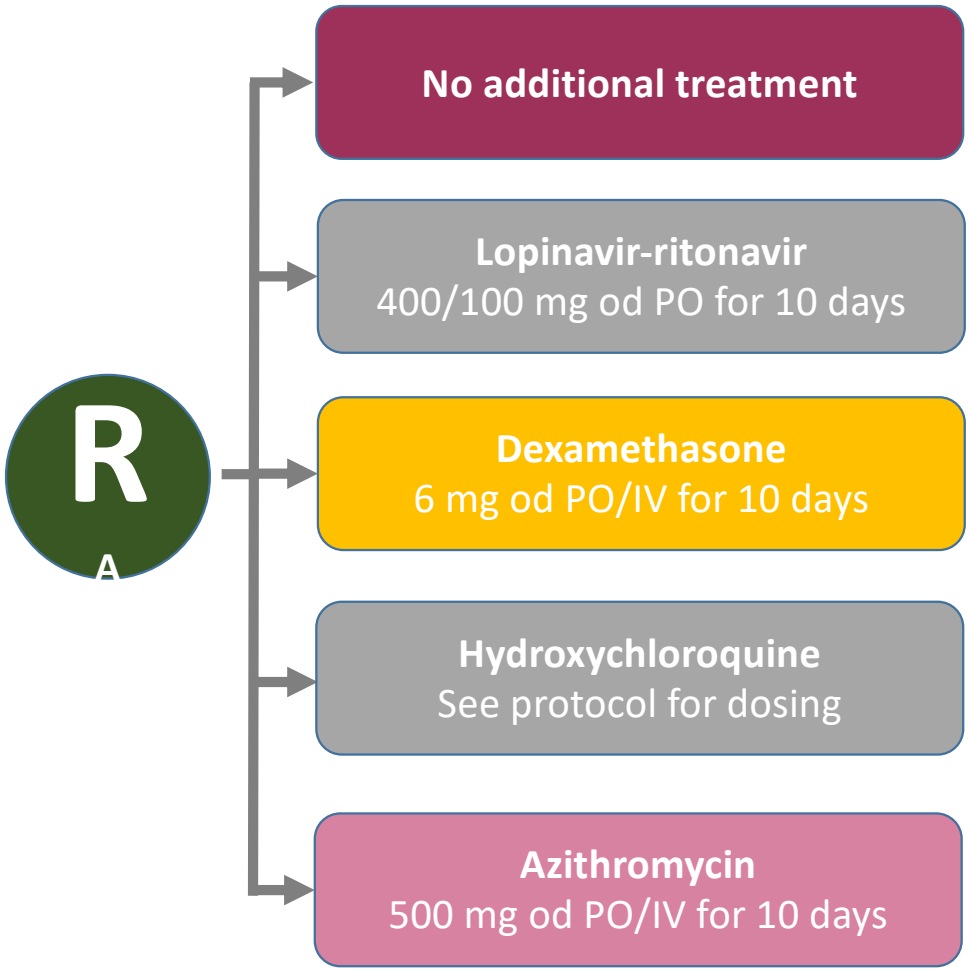


Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

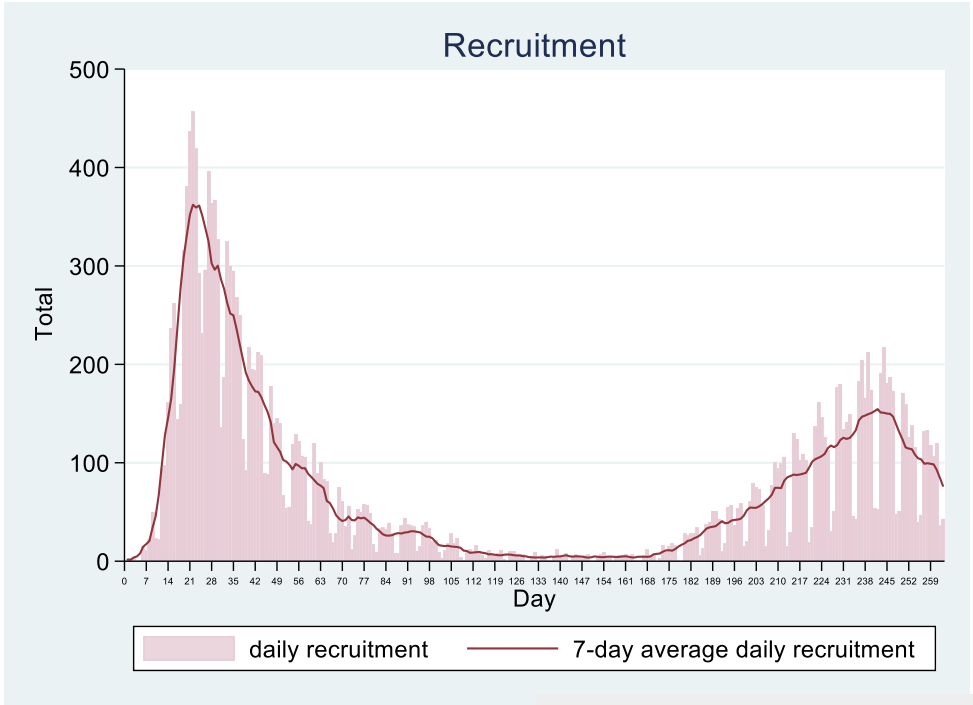
Chi-square trend across three categories: 11.5

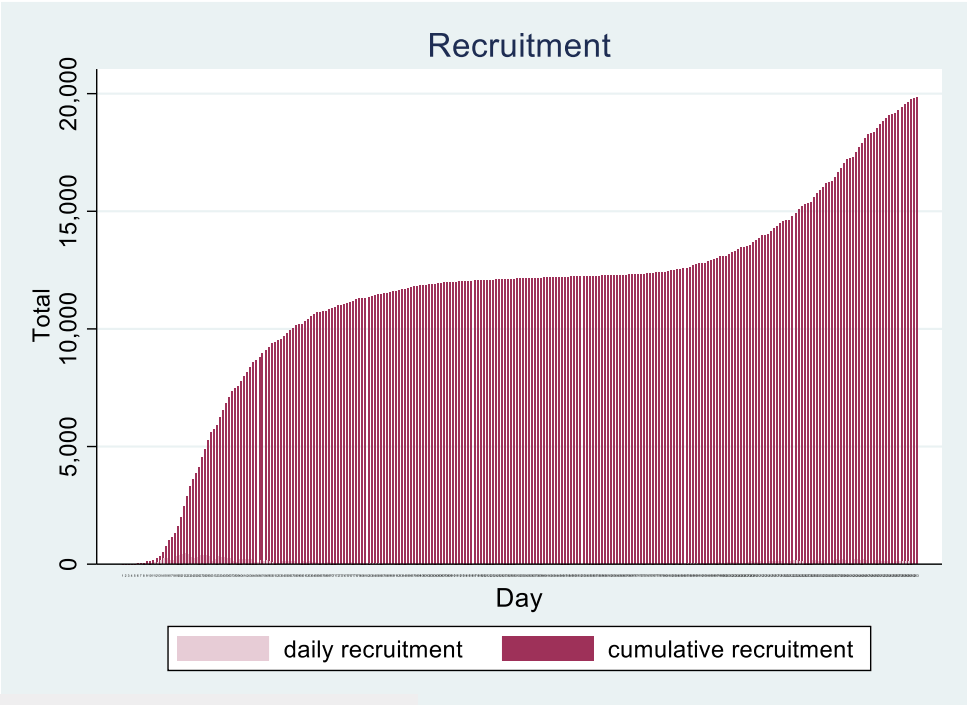


RECOVERY – studying multiple treatments



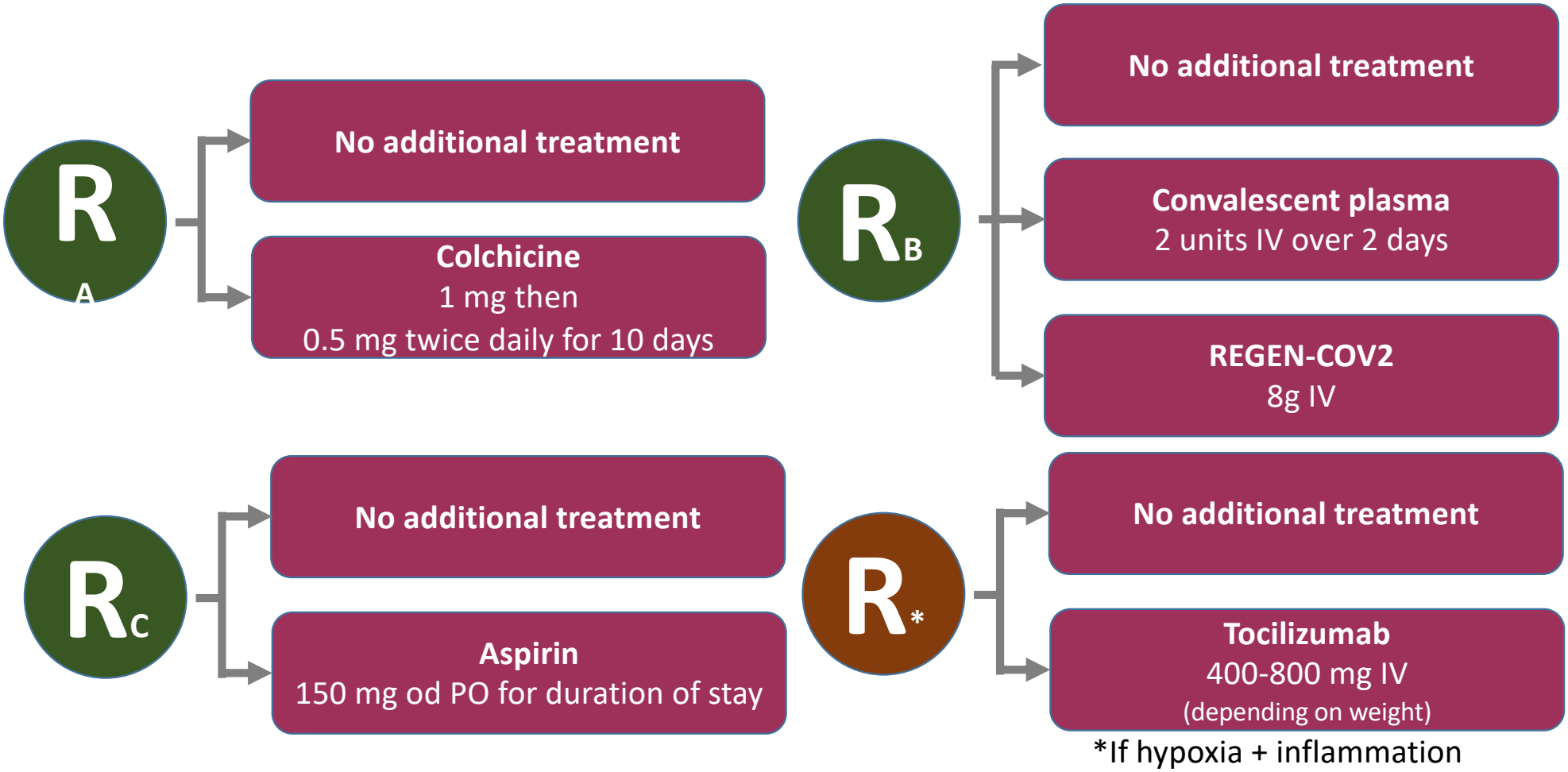
RECOVERY – the second wave is upon us





Active Sites	Recruiting Sites	Participants	Phase 2 rands.	Phase 3 rands.	Phase 4 rands.
176	174	20000	2166	6803	2018

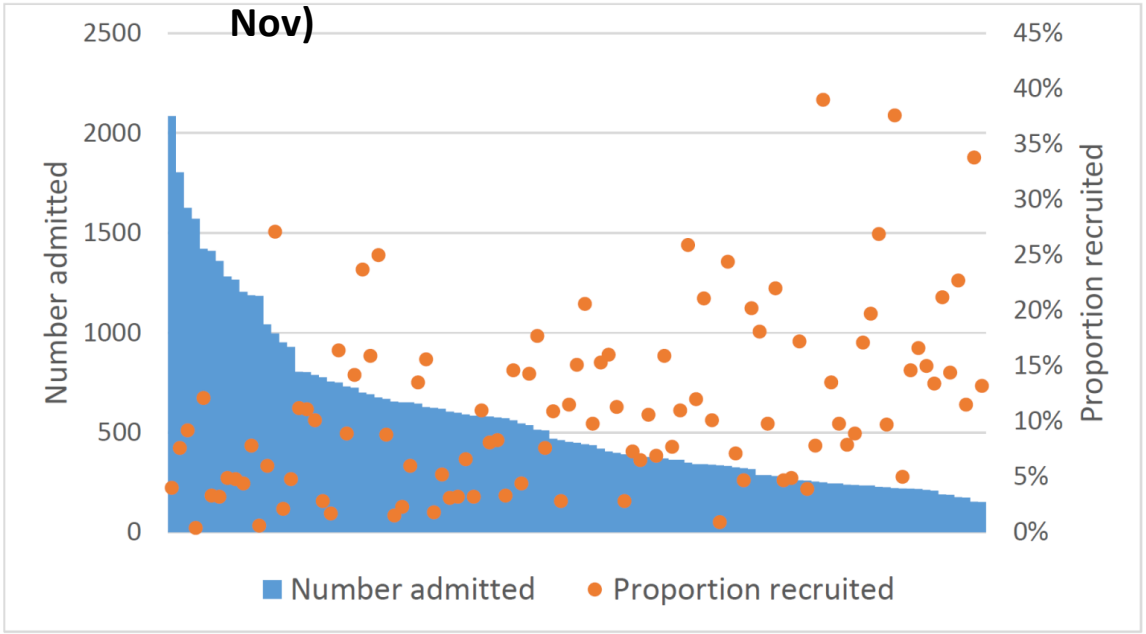
RECOVERY – studying multiple treatments



*If hypoxia + inflammation

Clinical trials as a core component of clinical care

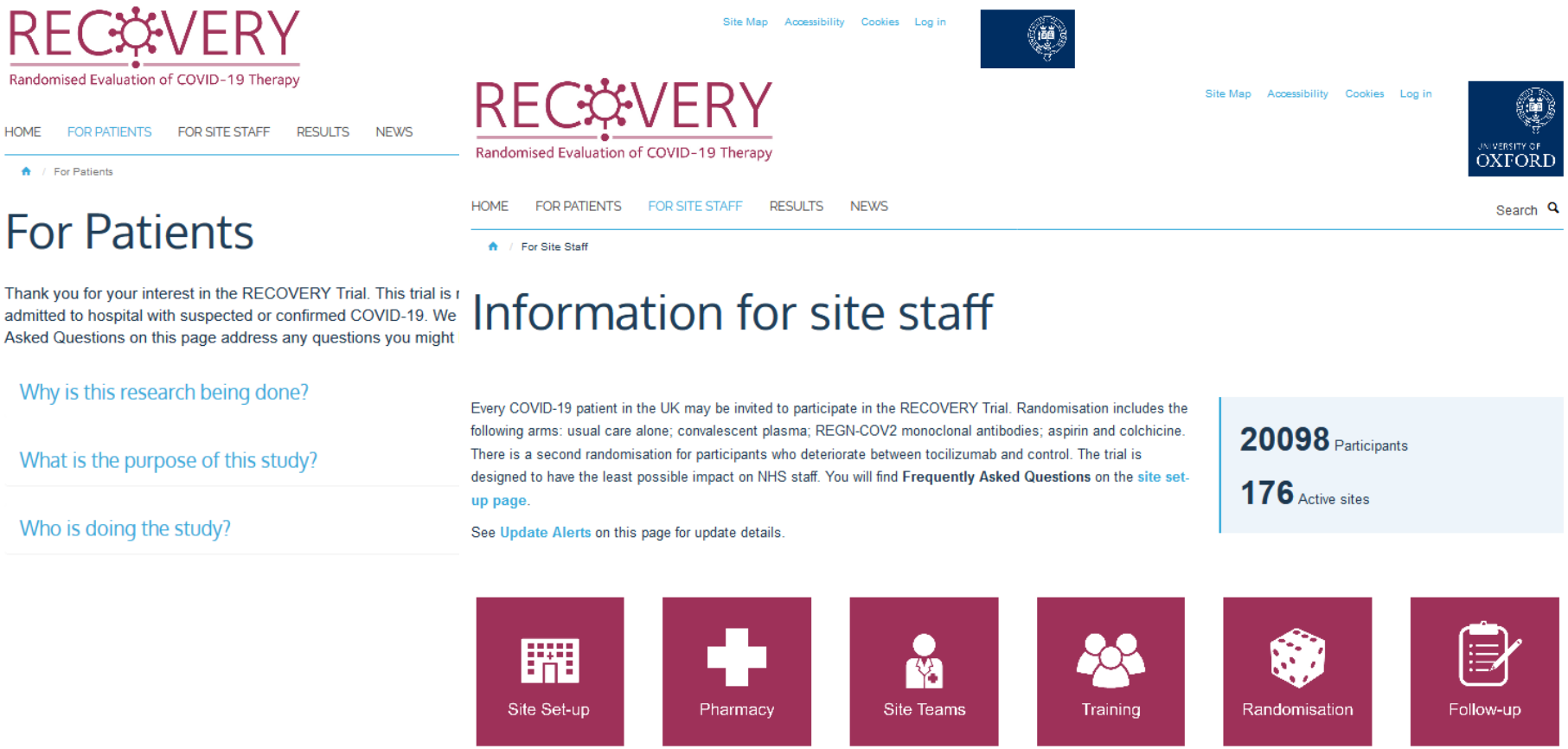
Recruitment by hospital Trust (1 Oct – 30 Nov)



"[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"
NHS Consultant & Local Principal Investigator

"We have been very pleased to have been able to help contribute to this effort that has helped to provide some clear answers."
NHS Consultant & Local Principal Investigator

Communication: www.recoverytrial.net



RECOVERY
Randomised Evaluation of COVID-19 Therapy

HOME FOR PATIENTS FOR SITE STAFF RESULTS NEWS

For Patients

For Patients

Thank you for your interest in the RECOVERY Trial. This trial is r
admitted to hospital with suspected or confirmed COVID-19. We
Asked Questions on this page address any questions you might

Why is this research being done?

What is the purpose of this study?

Who is doing the study?

Site Map Accessibility Cookies Log in

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Site Map Accessibility Cookies Log in

UNIVERSITY OF OXFORD

HOME FOR PATIENTS FOR SITE STAFF RESULTS NEWS

Search

For Site Staff

Information for site staff

Every COVID-19 patient in the UK may be invited to participate in the RECOVERY Trial. Randomisation includes the following arms: usual care alone; convalescent plasma; REGN-COV2 monoclonal antibodies; aspirin and colchicine. 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 Alerts** on this page for update details.

20098 Participants

176 Active sites

Site Set-up

Pharmacy

Site Teams

Training

Randomisation

Follow-up

Opinion

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**.

https://www.nytimes.com/2020/09/01/opinion/coronavirus-clinical-research.html

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

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
- 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