The Magic of Randomization

-the RECOVERY experience -

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**

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)

New opportunities for clinical trials

Smart design & streamlined operations

+

Integrated data & technology

+

Enlightened regulatory approaches

⬇

Better patient care and public health

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

RECOVERY 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.

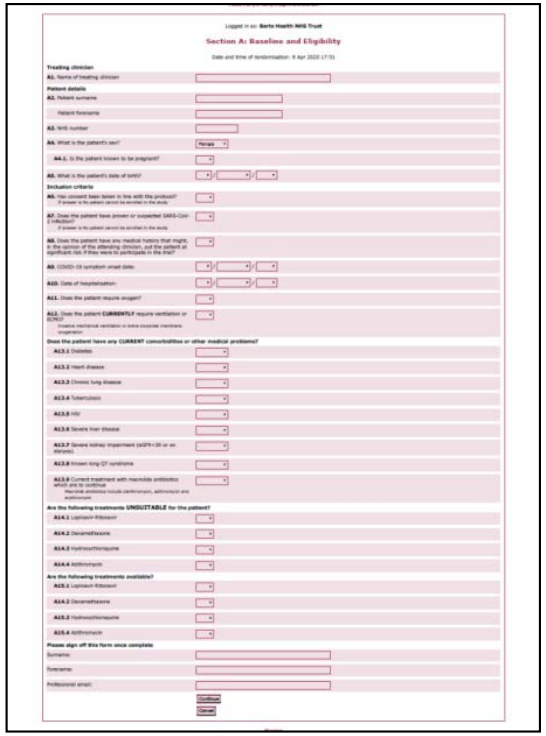
4. **Access to my medical information:** I agree that medical information collected by the doctors and hospitals which provide me with care and which may be located in local or national health and research organizations (including hospital admission, civil registration, audit and research data) may be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

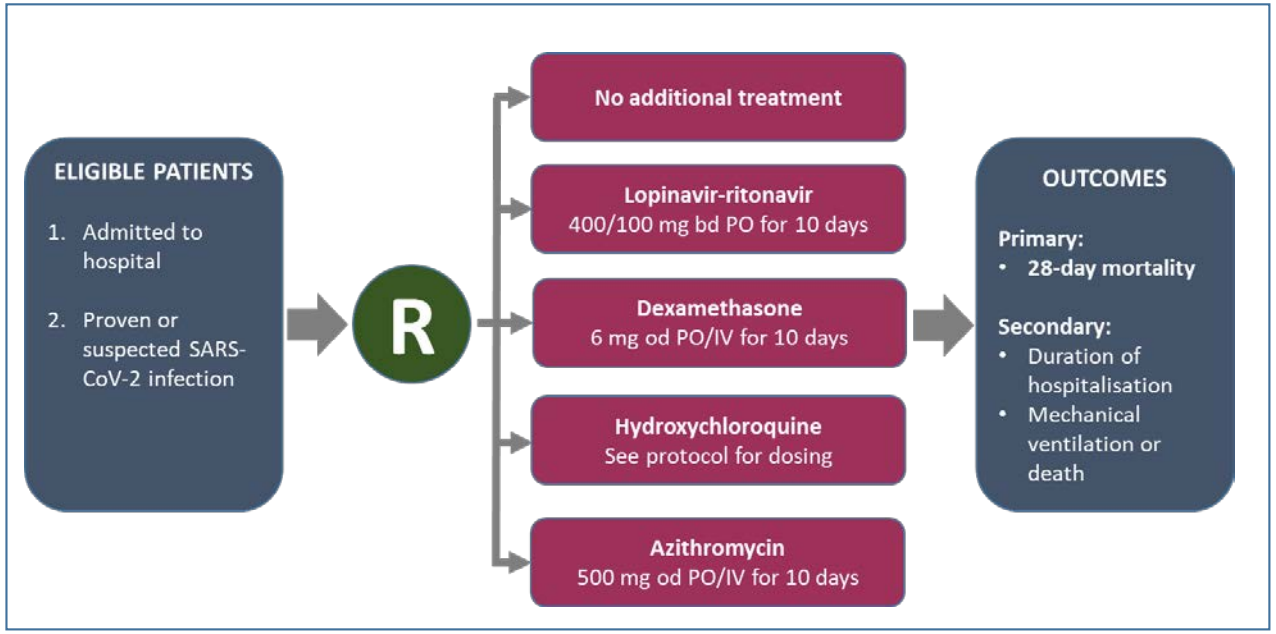
6. **Agreement to take part:** I have read the information (or had it read to me), had an opportunity to ask questions and agree to take part in the above study.

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



Centrally collected routine data

Hospitalisation datasets

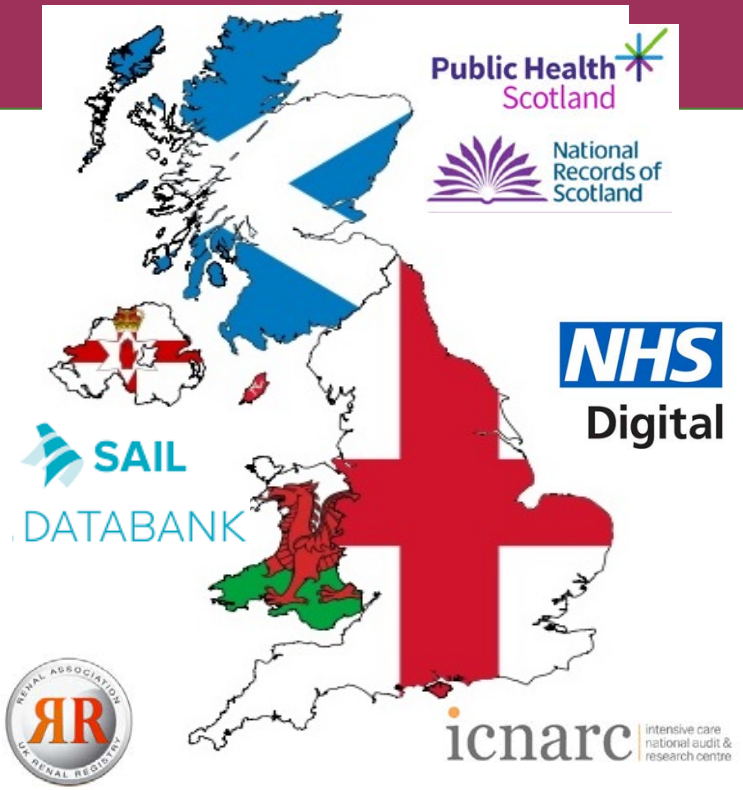
- ✓ Scottish Morbidity Records (SMR)
- ✓ Hospital Episode Statistics Admitted Patient Care (HESAPC)
- ✓ Secondary Uses Service Admitted Patient Care (SUSAPC)
- ✓ Patient Episode database for Wales (PEDW)

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)

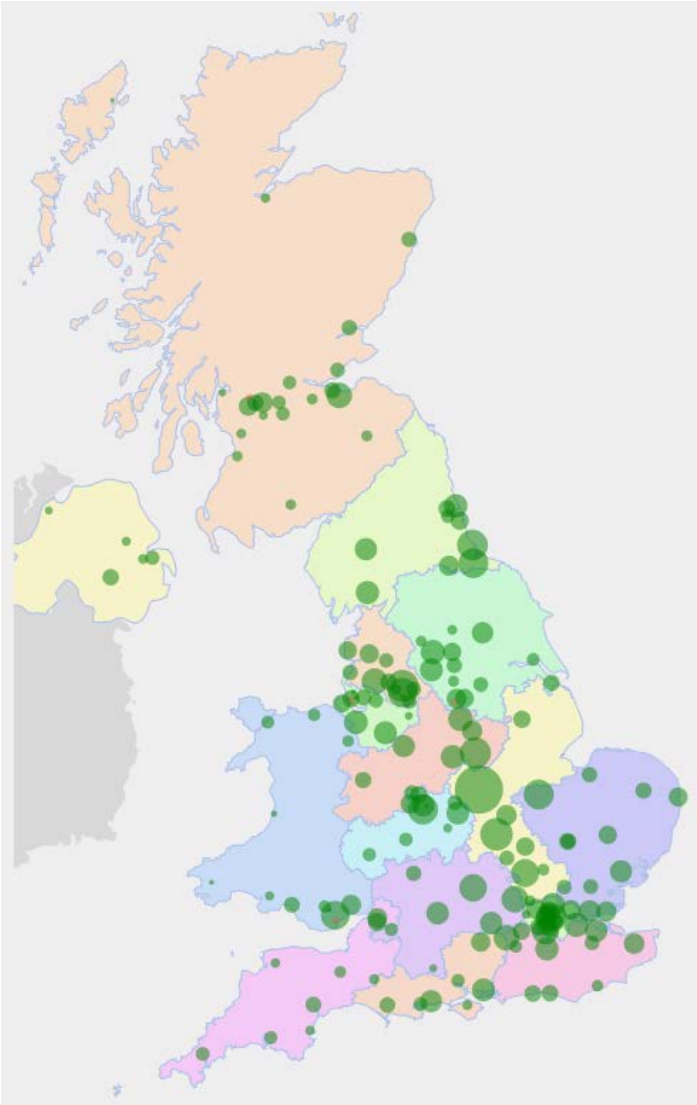
Critical care datasets

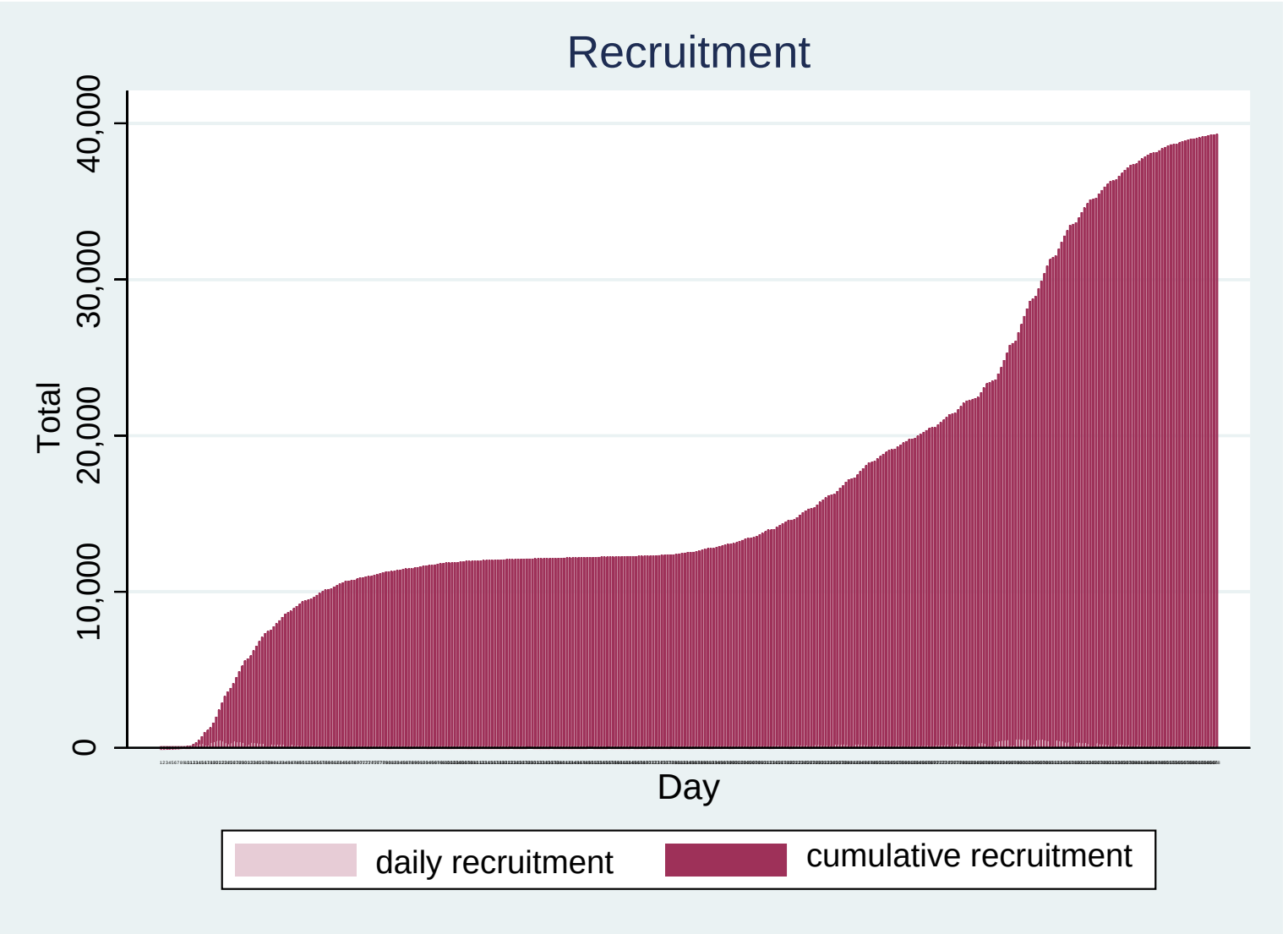
- ✓ Scottish Intensive Care Society Audit Group (SICSAG)
- ✓ Intensive Care National Audit and Research Centre (ICNARC)
- ✓ HES Critical Care Dataset (CCDS)
- ✓ PEDW Critical Care Dataset (CCDS)

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)

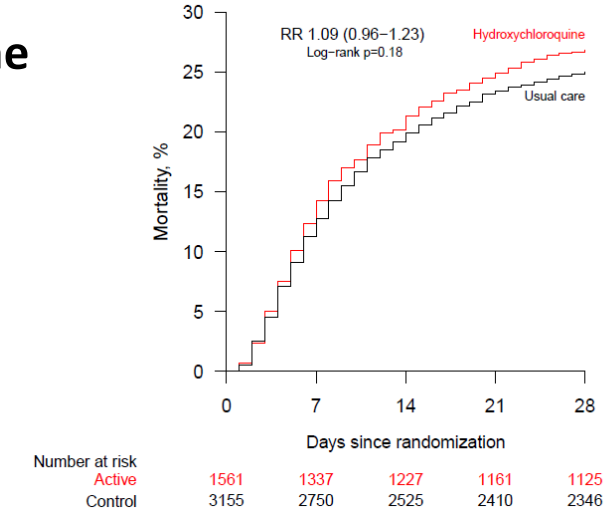
COVID can affect anyone... RECOVERY is open to everyone



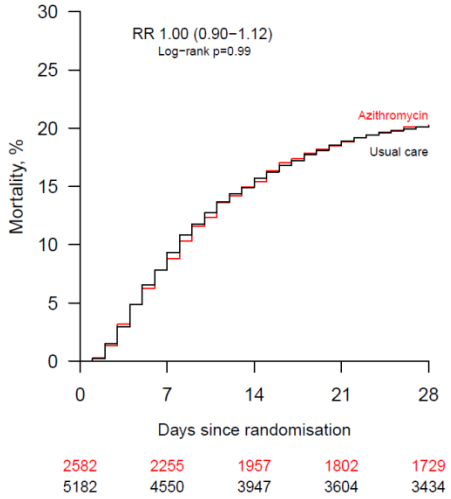


Widely recommended, loudly promoted, widely used...
Hydroxychloroquine, lopinavir, azithromycin, convalescent plasma...

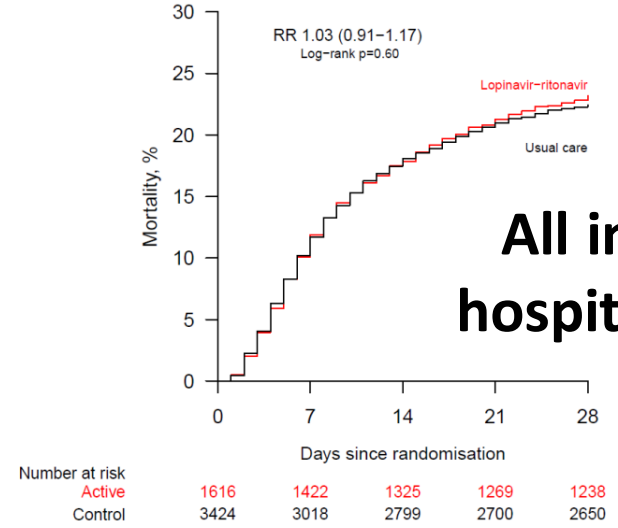
Hydroxychloroquine



Azithromycin

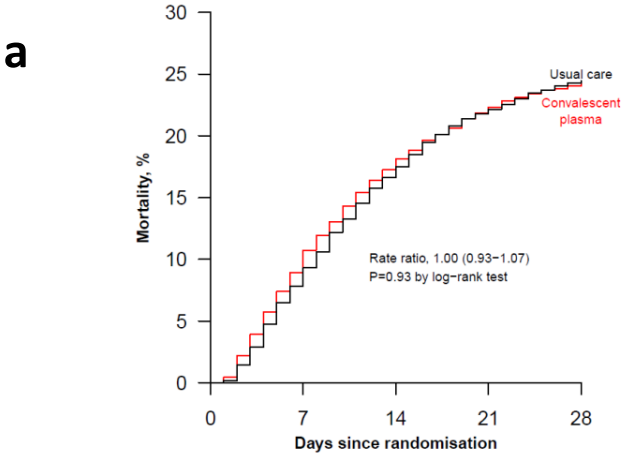


Lopinavir



All ineffective for hospitalised patients

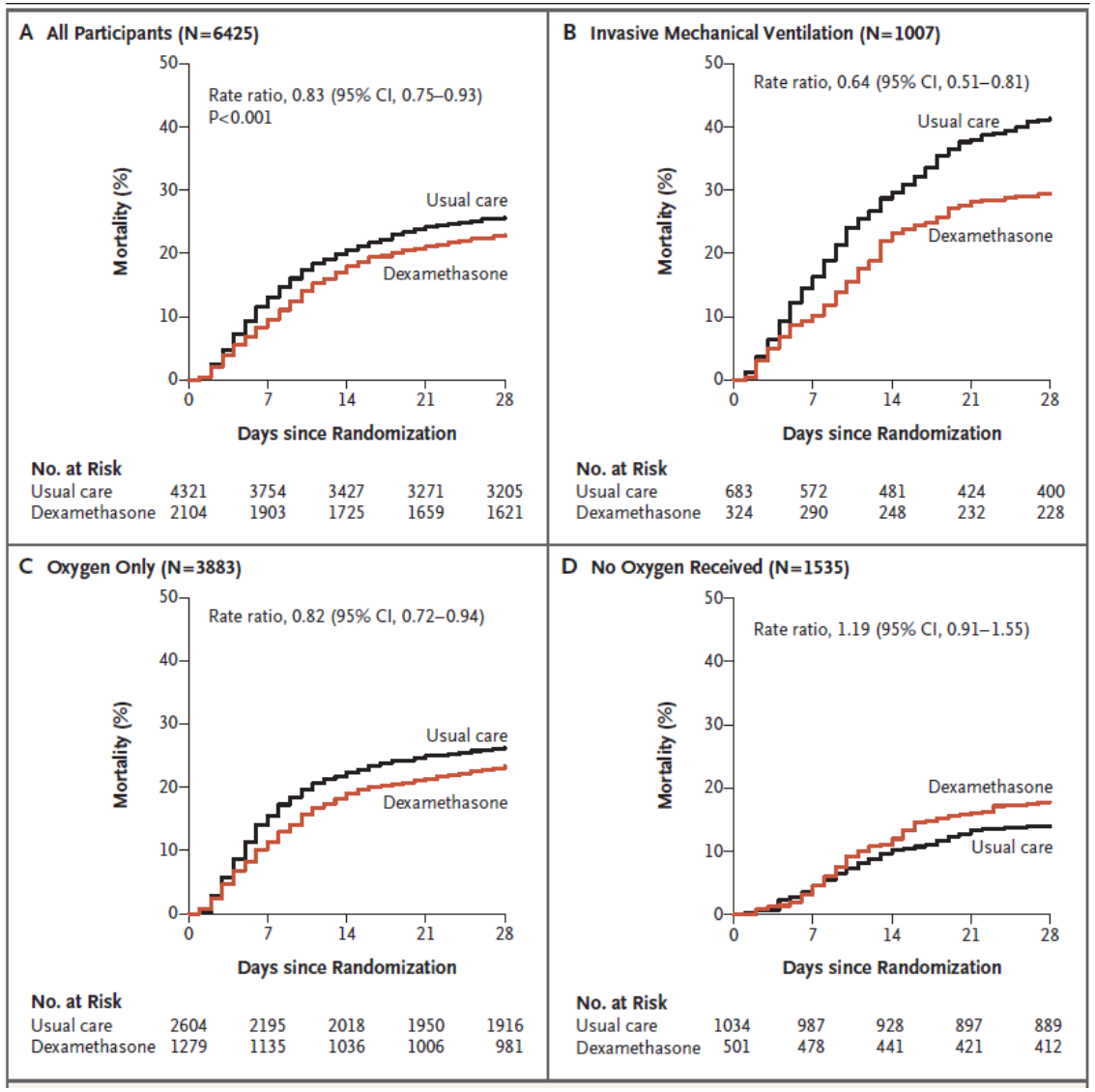
Convalescent plasma

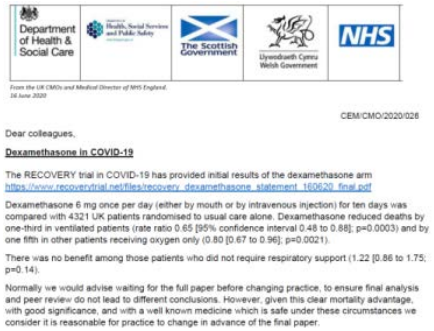


Dexamethasone:

Reduces mortality in patients requiring oxygen or ventilation

DOI: 10.1056/NEJMoa2021436





Department of Health & Social Care · The Scottish Government · Llywodraeth Cymru Welsh Government · NHS

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

NATIONAL / SCIENCE & HEALTH

Japan approves dexamethasone as second drug for coronavirus treatment

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

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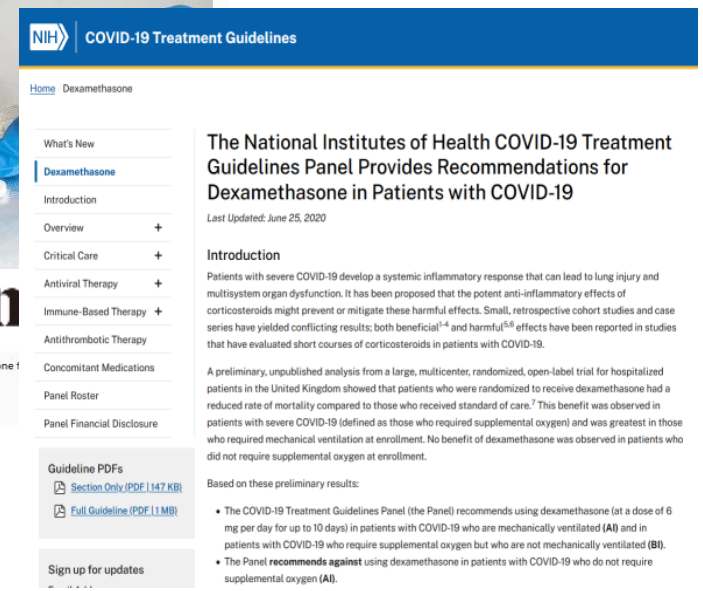
EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation Share

News 18/09/2020

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*



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)
Full Guideline (PDF | 1 MB)

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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.

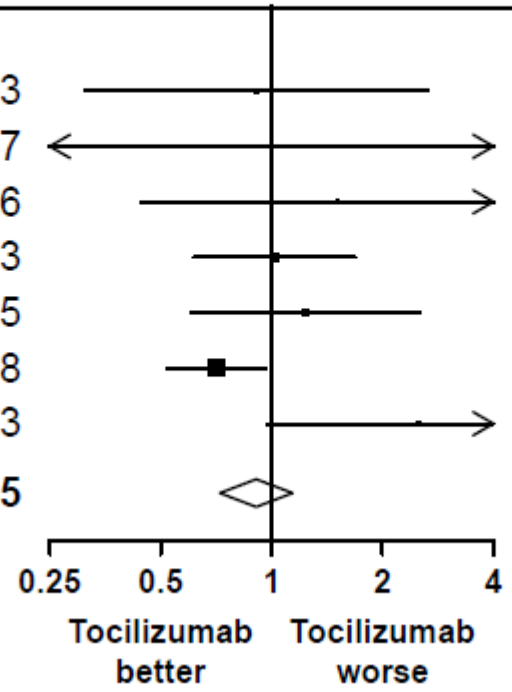
A preliminary, unpublished analysis from a large, multicenter, randomized, open-label trial for hospitalized patients in the United Kingdom showed that patients who were randomized to receive dexamethasone had a reduced rate of mortality compared to those who received standard of care.[7] This benefit 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:

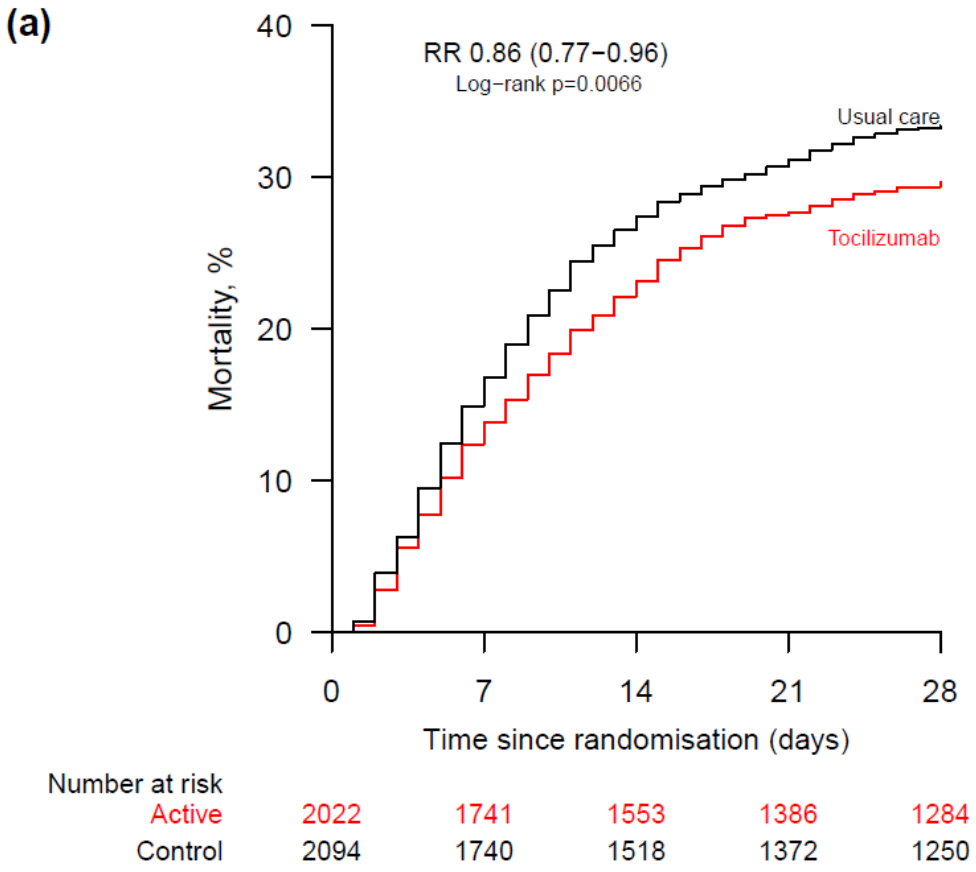
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated **(AI)** and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated **(BI)**.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

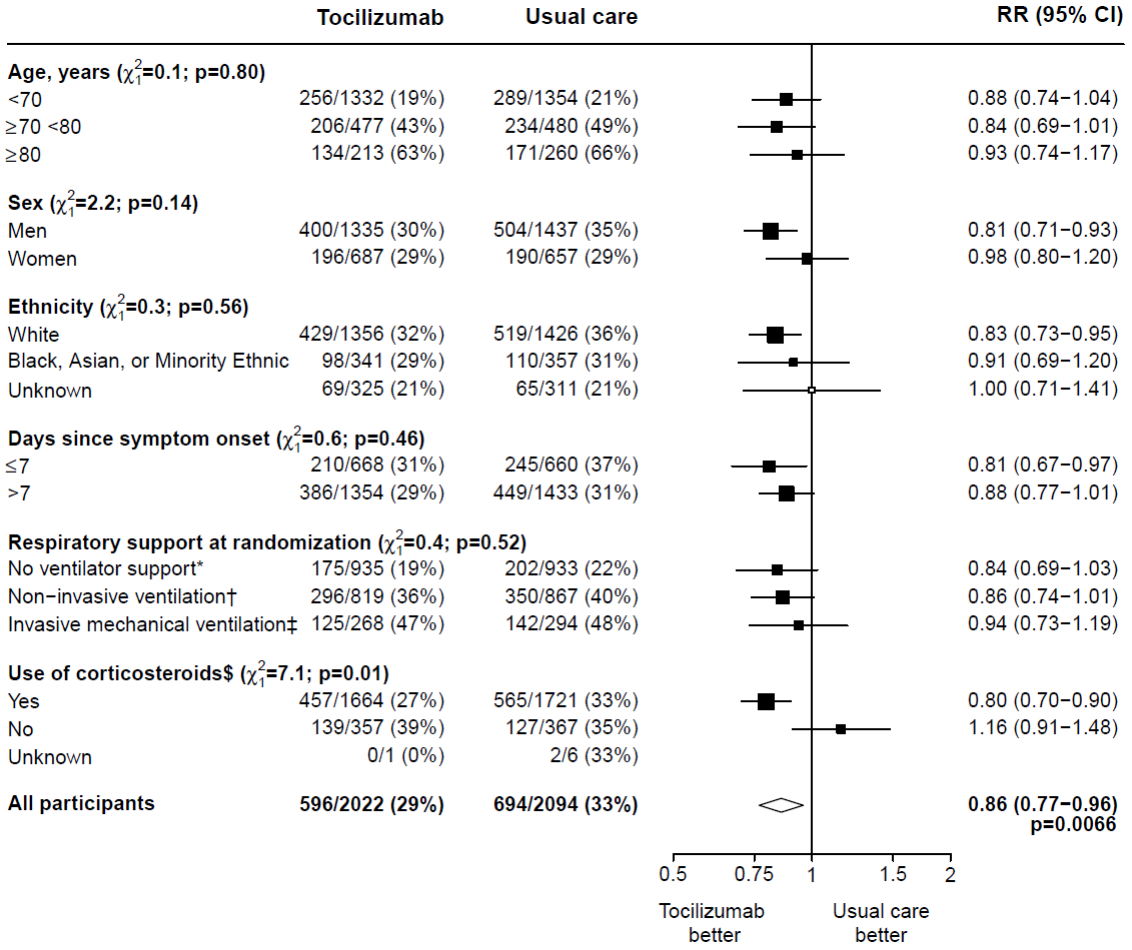
Effect of tocilizumab on 28-day mortality: evidence prior to RECOVERY

	Deaths / Patients randomised (%)		Observed−Expected		Ratio of death rates, RR (95% CI)
	Tocilizumab	Usual care	(O−E)*	Var(O−E)	
COR−IMUNO TOCI	7/64 (10.9)	8/67 (11.9)	−0.3	3.3	0.91 (0.31−2.65)
RCT−TCZ−COVID−19	2/60 (3.3)	1/66 (1.5)	0.6	0.7	2.17 (0.22−21.3)
BACC Bay	9/161 (5.6)	(3/82) x2† (3.7)	1.0	2.6	1.51 (0.44−5.13)
COVACTA	58/294 (19.7)	(28/144) x2† (19.4)	0.3	15.3	1.02 (0.62−1.68)
EMPACTA	26/249 (10.4)	(11/128) x2† (8.6)	1.6	7.5	1.23 (0.60−2.52)
REMAP−CAP	98/353 (27.8)	142/402 (35.3)	−14.2	40.8	0.71 (0.52−0.96)
TOCIBRAS	14/65 (21.5)	6/64 (9.4)	3.9	4.3	2.51 (0.97−6.50)
Subtotal: 7 trials	**214/1246 (17.2)**	**241/1307 (18.4)**	**−7.2**	**74.5**	**0.91 (0.72−1.14)**



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

Effect of tocilizumab on 28-day mortality: evidence after RECOVERY

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

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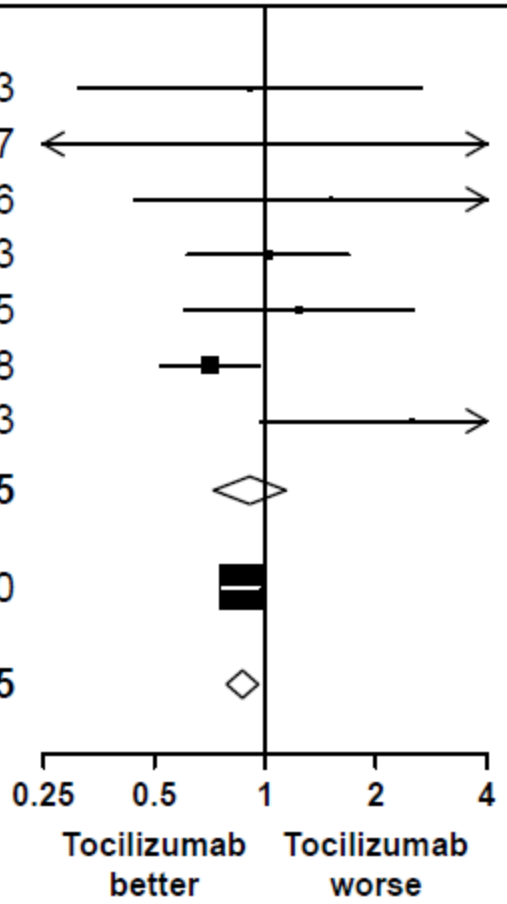
RECOVERY	596/2022 (29.5)	694/2094 (33.1)	−48.2	316.0	0.86 (0.77−0.96)
All trials	**810/3268 (24.8)**	**935/3401 (27.5)**	**−55.4**	**390.5**	**0.87 (0.79−0.96) p=0.005**

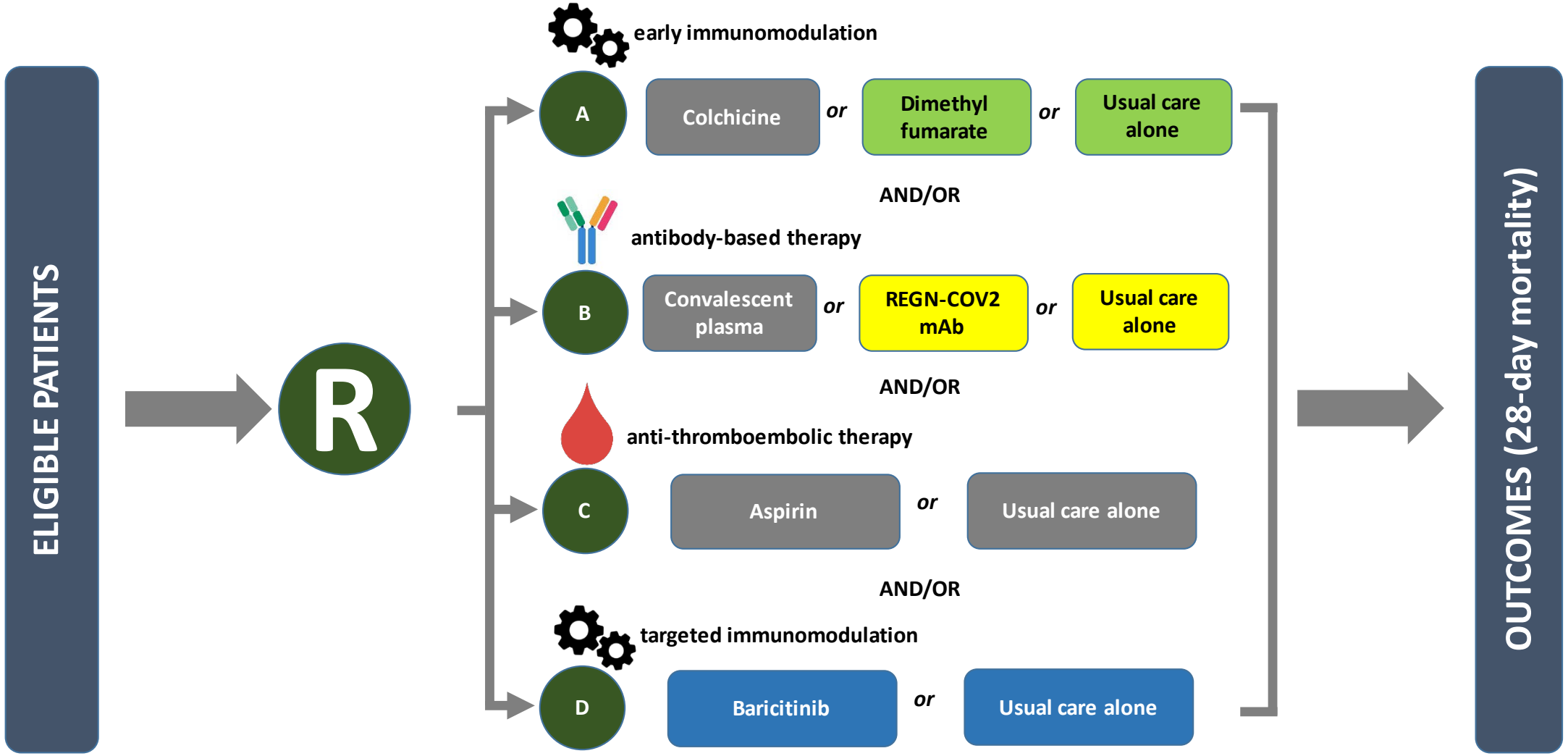
Heterogeneity between RECOVERY and previous trials: χ^2_1=0.2



Preliminary data

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

Factorial designs - efficient evaluation of multiple treatments

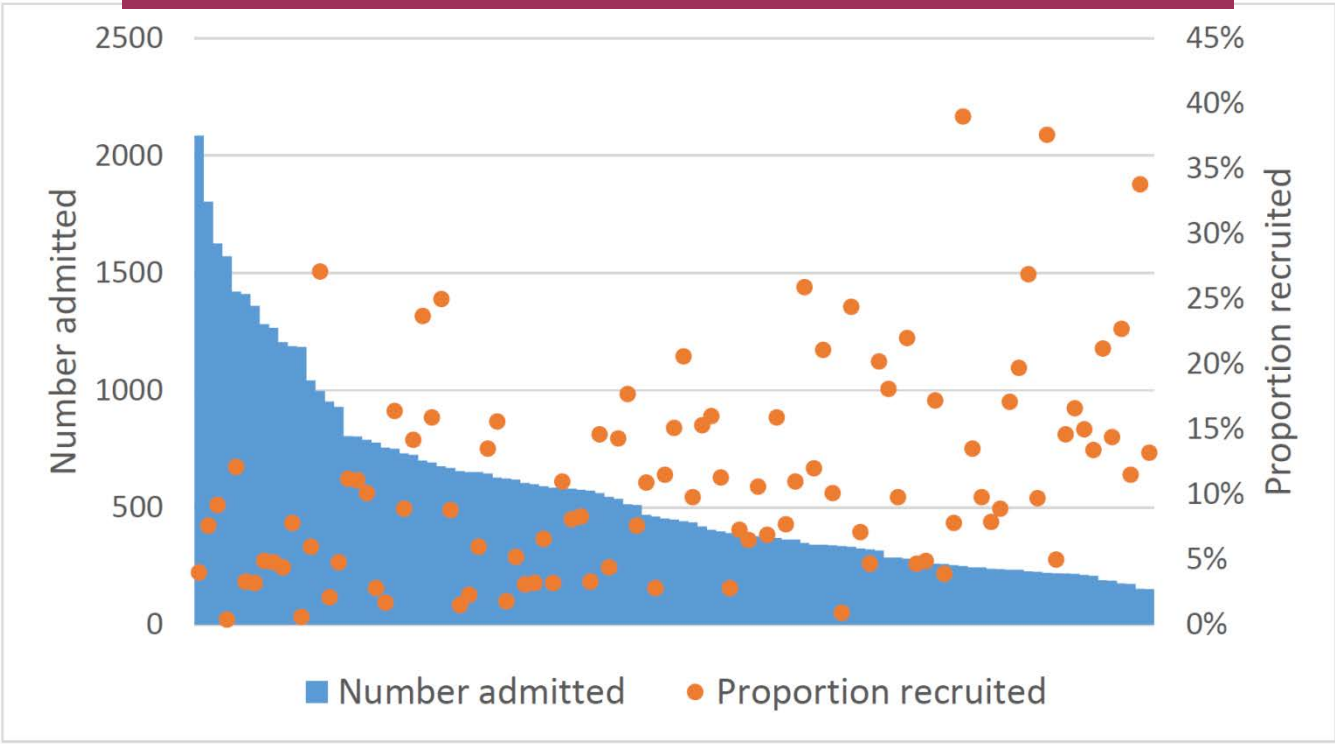


Factorial designs - efficient evaluation of multiple treatments

Anti-viral	Immunomodulatory	Anti-thrombotic
1600 Hydroxychloroquine ✗	2000 **Dexamethasone** ✓	7300 Aspirin
1600 Lopinavir-ritonavir ✗	2000 **Tocilizumab** ✓	**Anti-inflammatory**
5800 Convalescent plasma ✗	1400 **Baricitinib**	2500 Azithromycin ✗
4700 **REGN-COV2 Antibody cocktail**		5600 Colchicine ✗

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

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**.

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
- 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 177 NHS hospitals

and, most importantly

to the thousands of patients who participate

in this extraordinary project