Global Collaboration:

Changing the Face of Pandemic Research

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Japanese Society of Intensive Care Medicine

St. Michael's Hospital

February 13, 2021

University of Toronto


SARS
The Dangers Ahead
SEE PAGE 10
SWINE FLU SPREADS!
Feds fear virus could turn deadly in U.S.
Mayor says don't panic as cases confirmed
BEATDOWN
LOST WEEKEND AT FENWAY AS SOX SWEEP YANKS
SEE SPORTS
Coronavirus
coronavirus in U.S.

InFACT: a global critical care research response to H1N1

Published Online
November 10, 2009
DOI:10.1016/S0140-6736(09)61792-X

The H1N1 pandemic presents acute care researchers with an extraordinary challenge and an unprecedented opportunity. By early October, 2009, there had been more than 340 000 reported cases of H1N1 infection in 191 countries, with more than 4100 deaths.[1] WHO initially projected that up to 2 billion people could become infected with the virus over the next 2 years.[2] Although vaccination programmes and other factors should reduce this number, plausible estimates of the number of infected individuals who might benefit from admission to intensive care range from 200 000 to 10 million. Influenza killed at least 50 million people during the 1918 pandemic.[3] Today, with antibiotics and antiviral agents, mechanical ventilation, and the supportive measures available in intensive care, most of those deaths could have been prevented.

and treatment of severe H1N1 disease. In parallel, we will develop a biobank to facilitate studies of genetic susceptibility and clinical biology.

We are starting a programme of collaborative, investigator-led randomised trials of treatment strategies that target both the virus and the host response. Our initial three studies will evaluate inexpensive interventions that are available in both the developed and the developing world: corticosteroids and statins. They use adaptive designs to ensure that results can be quickly incorporated into practice, and that ineffective treatments are dropped. As measures of efficacy, they will measure survival of individual patients and the rapidity with which patients can be liberated from limited intensive-care resources.

We seek to reduce the consequences of severe H1N1 infection in the developed world, where available

- *Lancet* 375:11, 2010

Intensive Care Med (2012) 38:29–39
DOI 10.1007/s00134-011-2409-8

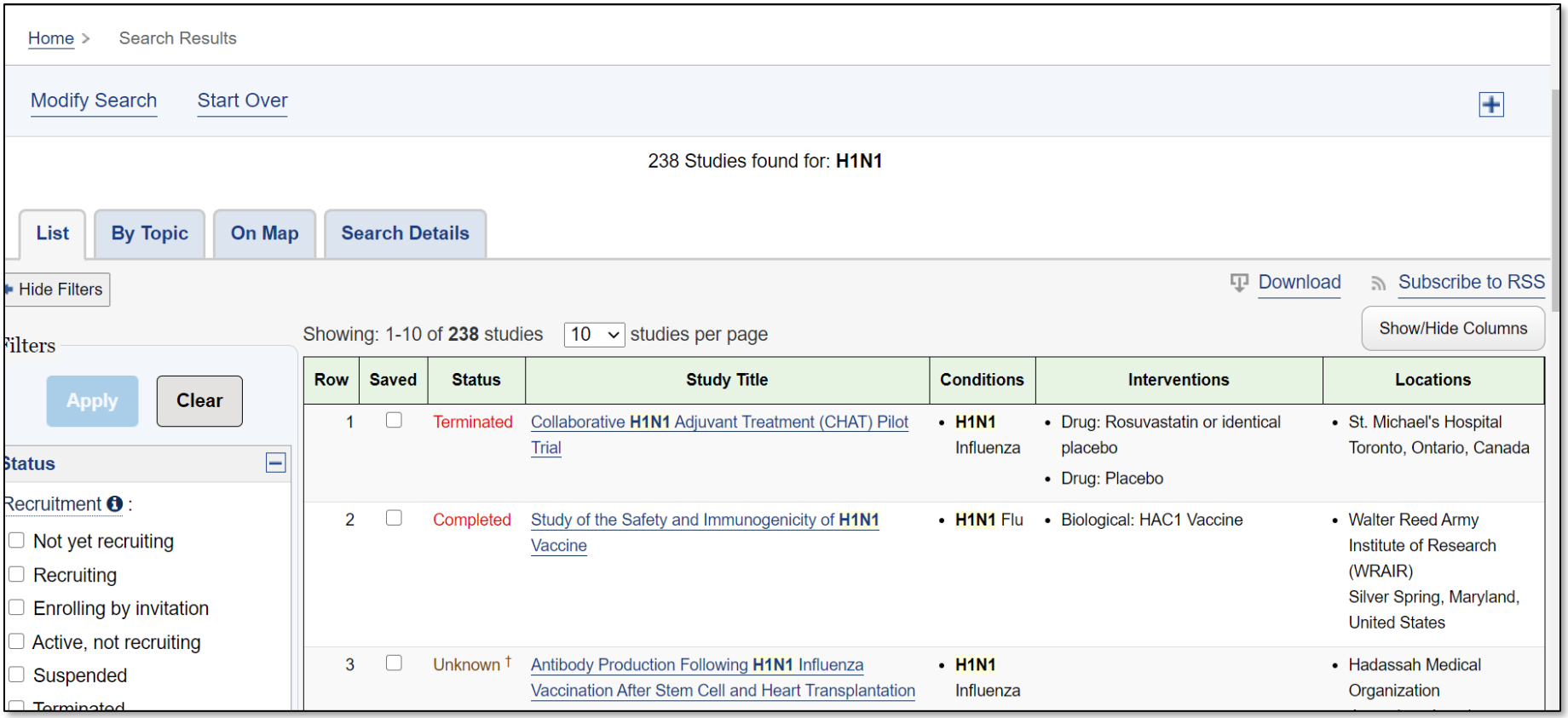
SPECIAL ARTICLE

Djillali Annane
Marion Antona
Blandine Lehmann
Cecile Kedzia
Sylvie Chevret
the CORTIFLU Investigators
and the CRICs, AZUREA, and
REVA/SRLF networks

Designing and conducting a randomized trial for pandemic critical illness: the 2009 H1N1 influenza pandemic

Table 1 Organization of a randomized trial in pandemic critical illness

	What was done?	How long did it take?	How could it be better?	Estimated time saving
Initiative	Investigators led trial	About 4 weeks	Investigators networks should be prepared in advance to launch future pandemic research	4 weeks
Scientific evaluation of the protocol	Independent evaluation by Institute of Microbiology and Infectious Diseases (part of INSERM)	4 weeks' fast-track process	Scientific evaluation should have been anticipated Reviews should have taken no longer than 1 week	3 weeks
Financial evaluation and sponsoring	Independent evaluation by Department for Clinical Research and Development (AP-HP)	3 days' fast-track process	Unlikely to be shorter	–
Ethical evaluation	Independent evaluation by Comité de Protection des Personnes Saint Germain en Laye	3 weeks' fast-track process	Ethical evaluation should have been anticipated Reviews should have taken no longer than 1 week Ethical evaluation should have been run in parallel to the scientific evaluation	3 weeks
Study treatments	Centralized preparation of active treatment and placebo and labeling	6 weeks' fast-track process	Local preparation of active treatment and placebo using commercially available drugs	5 weeks
Activation of study sites	Study materials and drugs were shipped via express mail and conference calls were organized to review all study materials with local investigators and pharmacists 39 sites were activated in 3 consecutive waves	3 weeks	All sites should be activated in one single wave Conference calls worked very well	2 weeks
Assistance for workload associated with patients enrolment	We provided the investigators with technical assistance for completing electronic CRF	–	A dedicated research team should be provided to each study site	–

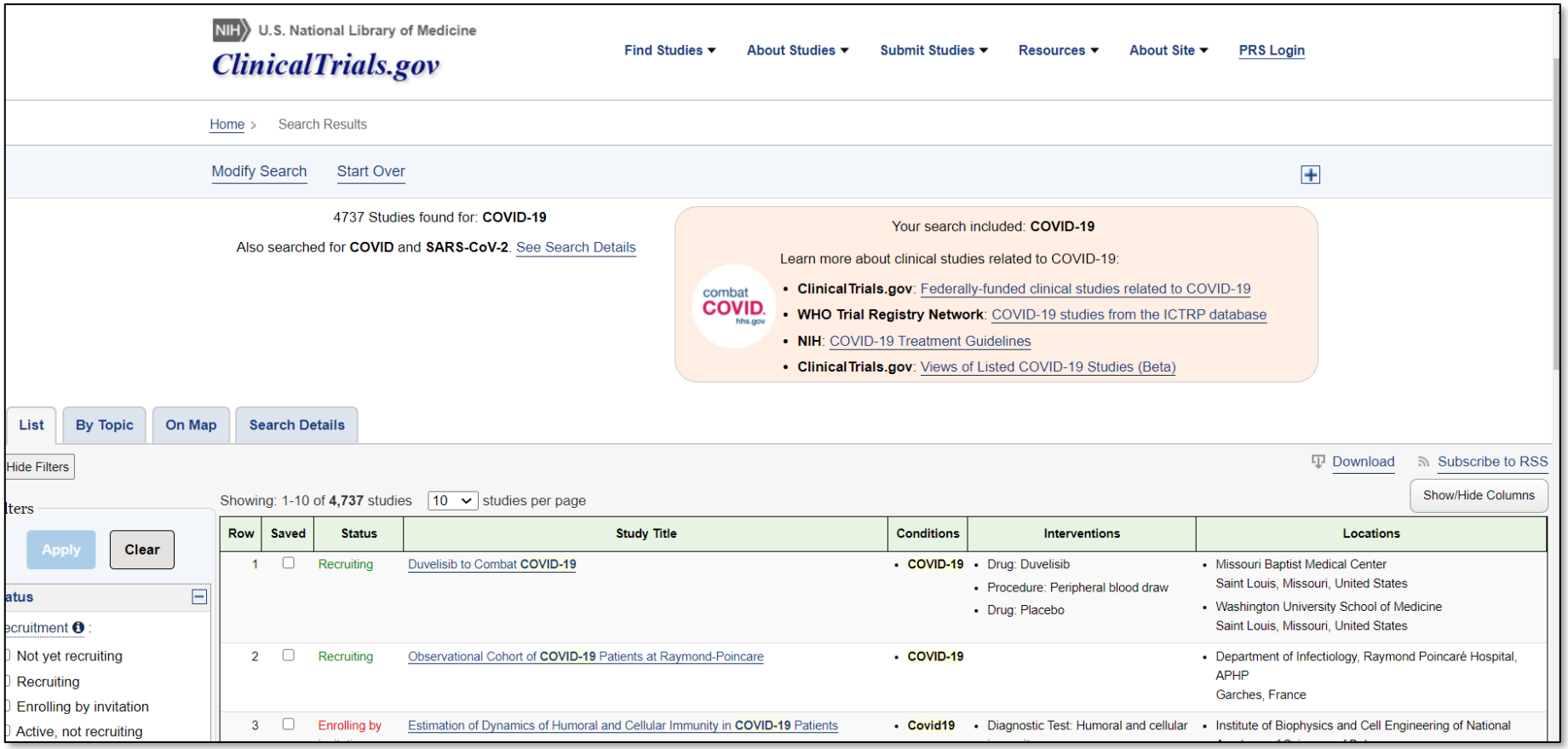


H1N1 Influenza 238 studies

London 2011

Toronto 2011

Pittsburgh 2011



COVID-19 4737 Studies

106 Countries

Why do we need research during a pandemic?

Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury

The 2019 novel coronavirus (2019-nCoV) outbreak is a major challenge for clinicians. The clinical course of patients remains to be fully characterised, little data are available that describe the disease pathogenesis, and no pharmacological therapies of proven efficacy yet exist.

Corticosteroids were widely used during the outbreaks of severe acute respiratory syndrome (SARS)-CoV[1] and Middle East respiratory syndrome (MERS)-CoV,[2] and are being used in patients with 2019-nCoV in addition to other therapeutics.[3] However, current interim guidance from WHO on clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected (released Jan 28, 2020) advises against the use of corticosteroids unless indicated for

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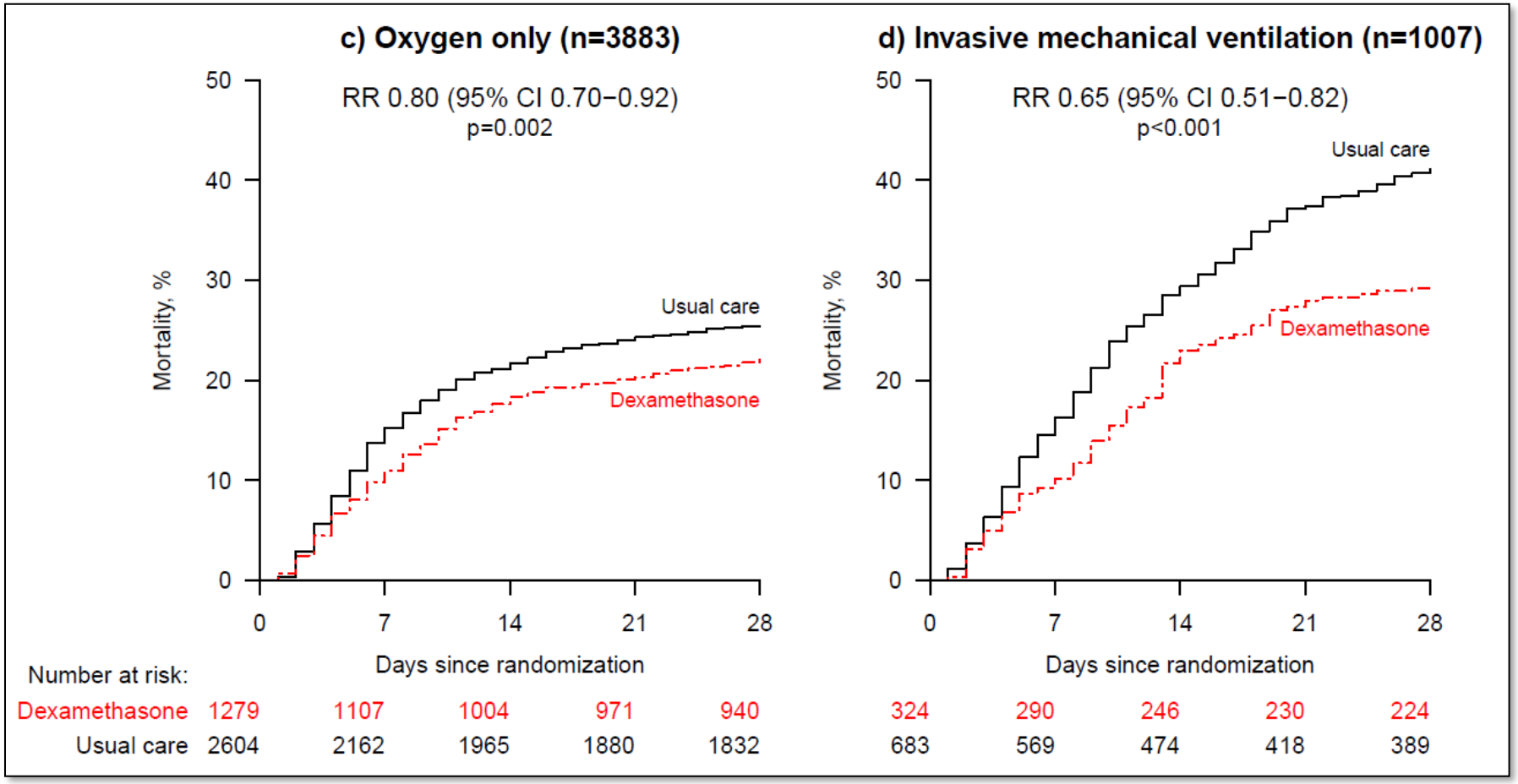
S0140-6736(20)30317-2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*



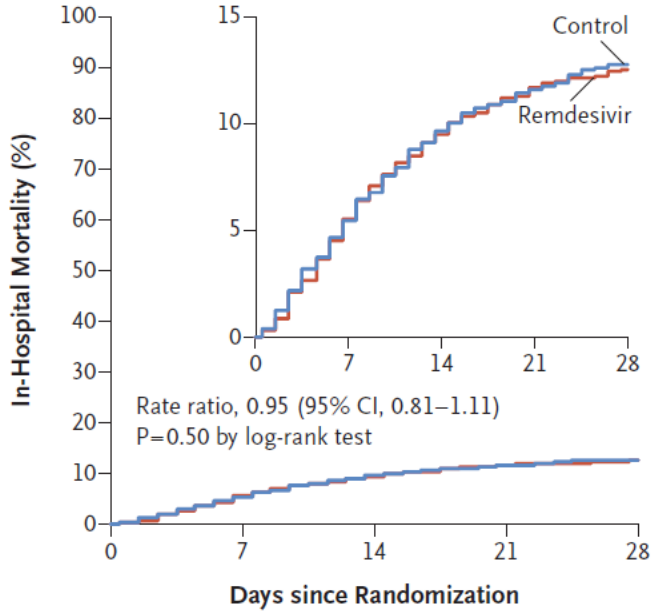
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 11, 2021 VOL. 384 NO. 6

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

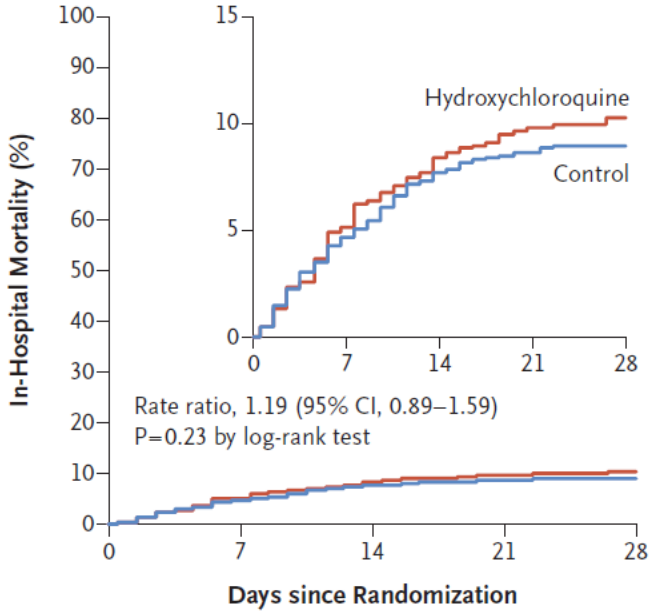
A Remdesivir vs. Its Control



Denominator					
Remdesivir	2743	2159	2029	1918	1838
Control	2708	2138	2004	1908	1833

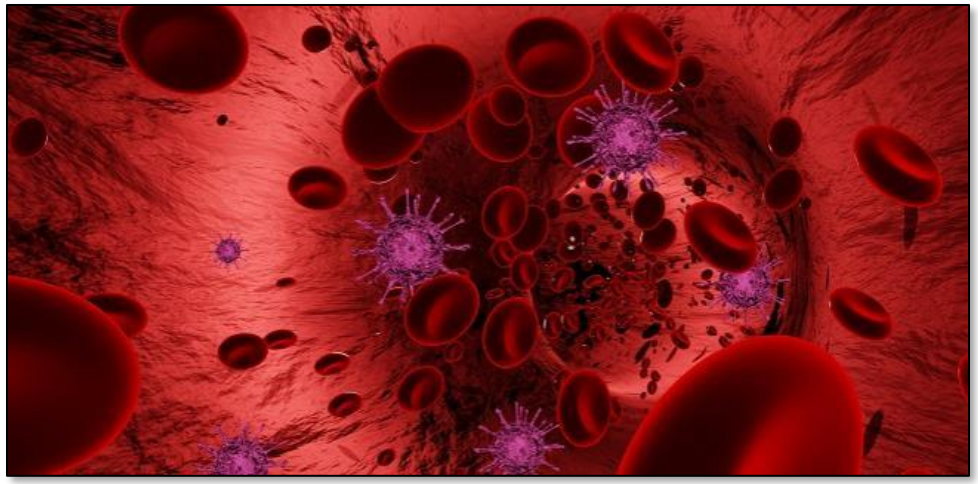
No. Who Died					
Remdesivir	129	90	48	18	16
Control	126	93	43	27	14

B Hydroxychloroquine vs. Its Control

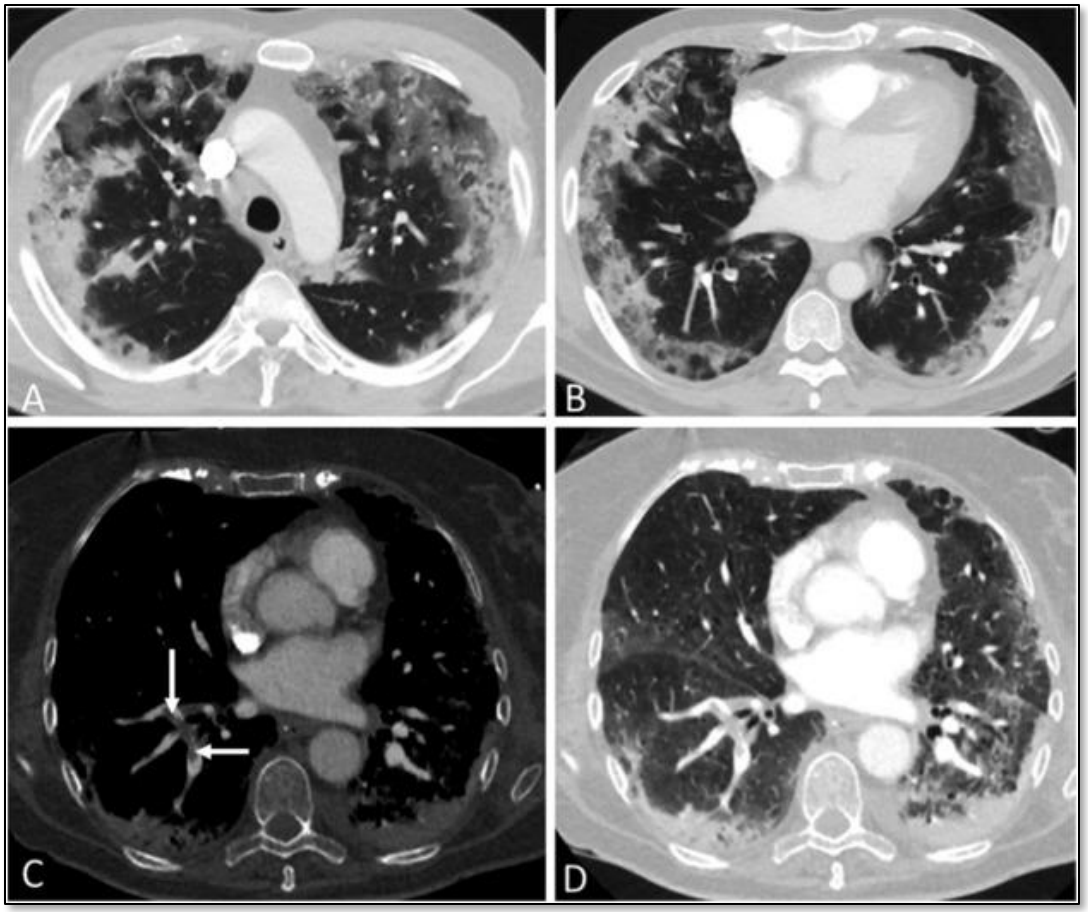


Denominator					
Hydroxychloroquine	947	889	854	838	833
Control	906	853	823	814	809

No. Who Died					
Hydroxychloroquine	48	31	13	6	6
Control	42	27	8	4	3



Coagulopathy in COVID-19



Pre-publication interim data, not from a locked database and not peer reviewed

ATTACC, REMAP-CAP, and ACTIV IV-4a mpRCT

Primary outcome

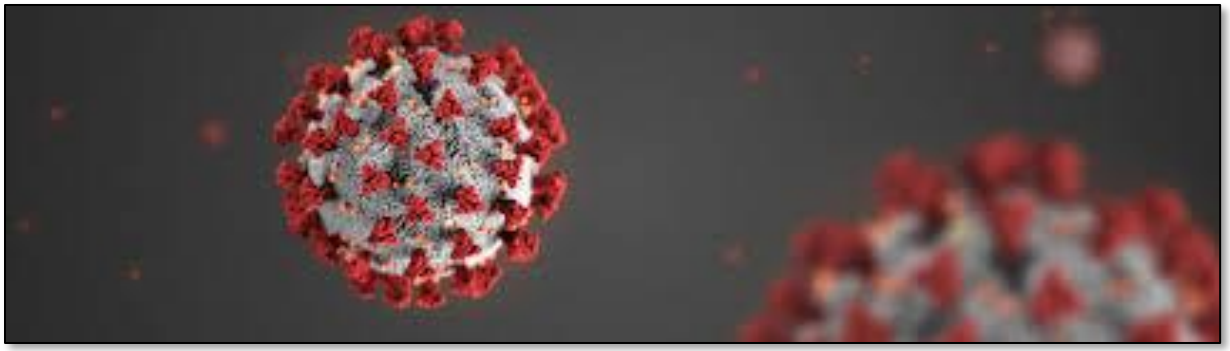
State & D-dimer Strata	Proportional Odds Ratio Median (95% CrI)	Trial Statistical Conclusion
Moderate state, low D-dimer	1.57 (1.14 - 2.19)	**Superiority** [Probability of OR>1 = 0.997]
Moderate state, high D-dimer	1.53 (1.09 - 2.17)	**Superiority** [Probability of OR>1 = 0.991]
Moderate state, missing D-dimer	1.51 (1.06 – 2.15)	n/a⏃
Severe state	0.76 (0.60 – 0.97)	**Futility*** [Probability of OR>1.2 < 0.001]

* Posterior probability of **inferiority** [Probability of OR<1 = 0.985]

⏃ Not evaluated for stopping at interim

OR >1 represents benefit. A higher OR occurs when either mortality is improved and/or if those who survive have reduced requirement for organ support

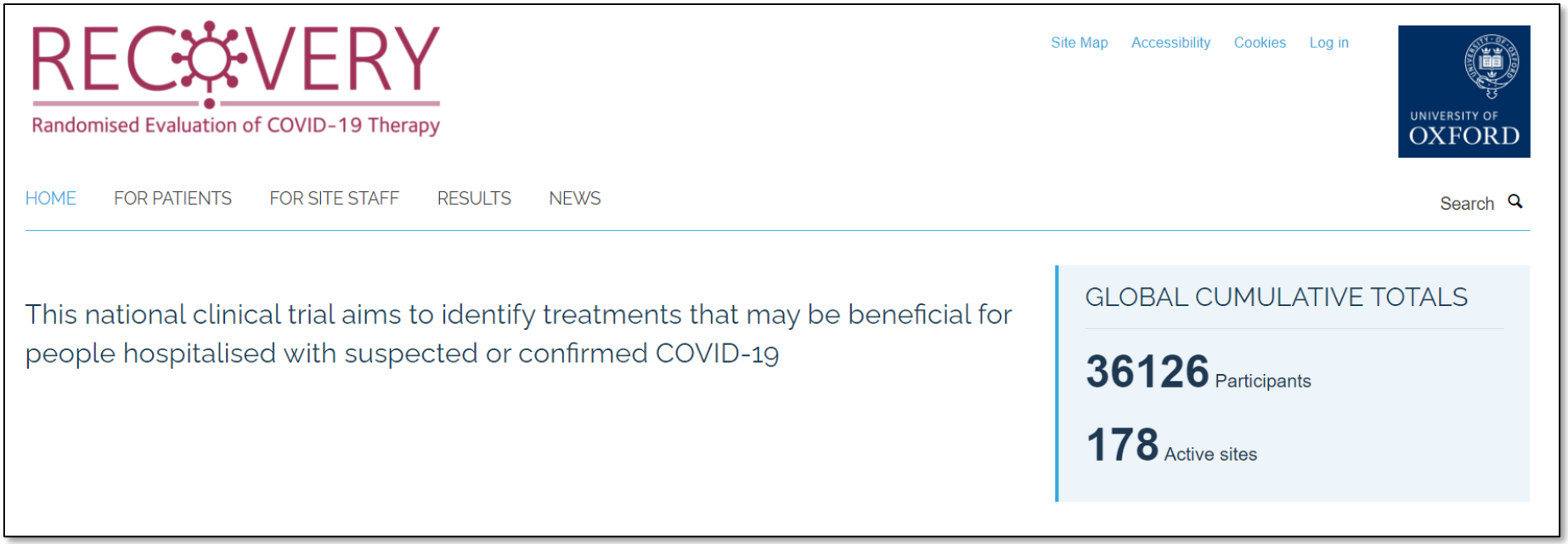
Release date: January 28, 20



How is COVID-19 Changing Clinical Research?

New Trial Designs: The Platform Trial

- Evaluates multiple interventions
- Can add new interventions
- Provides sites with flexibility
- Can evaluate drug-drug interactions
- Provides immediate uptake of findings



- **Colchicine**
- **Regeneron antibody cocktail**
- **Baricitinib**
- **Aspirin**

REMAP-CAP

A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia

11,495

Patient randomisations

10,333

Patient randomisations with suspected or proven COVID-19

31

Available interventions in 12 Domains

6,195

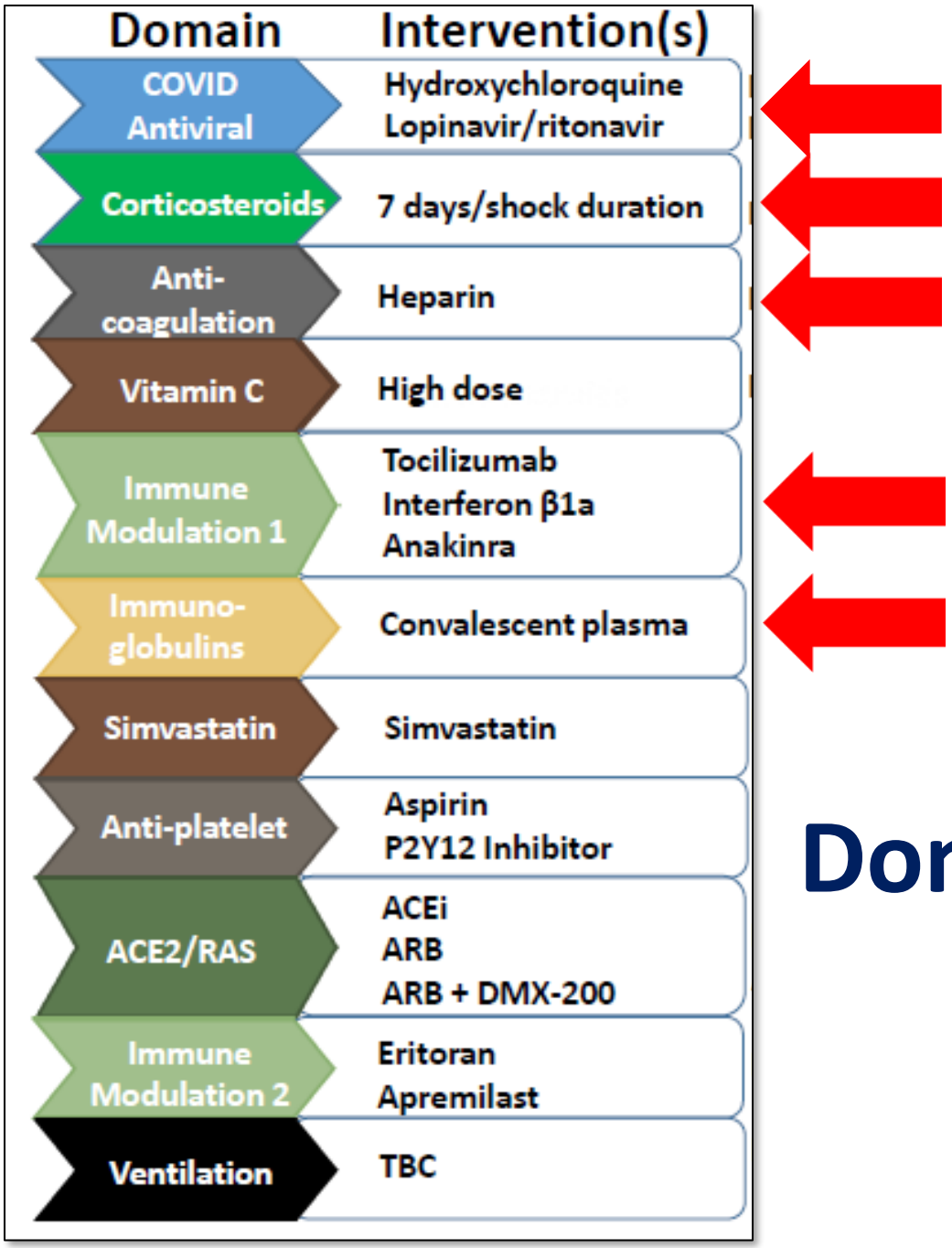
Total patients

5,388

Patients with suspected or proven COVID-19

296

Active Sites



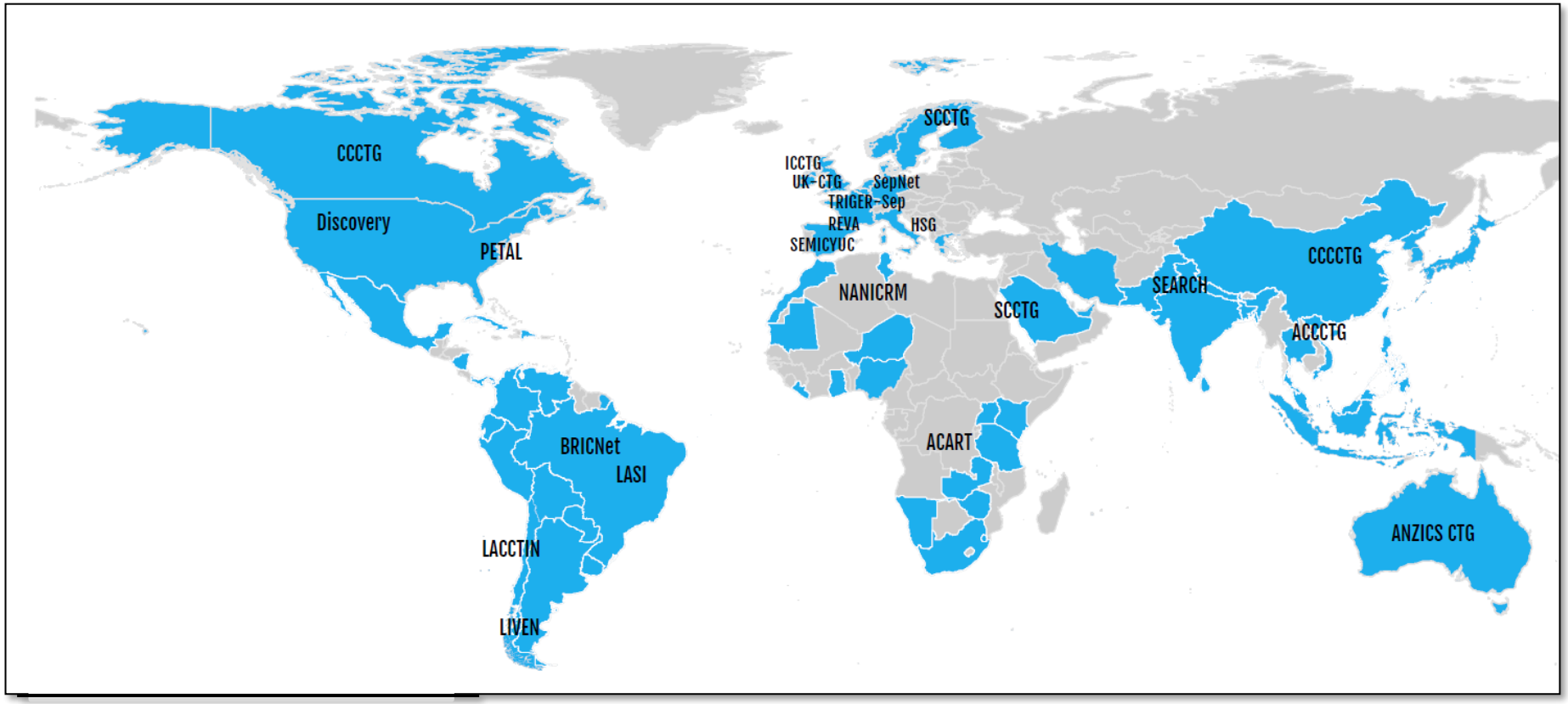
Domain conclusions

New Models of Collaboration

- Amongst specialties
- Across countries
- Amongst funders
- Across studies
- By large teams

- **12000 patients**
- **500 sites**
- **Pragmatic, decentralized**

InFACT


CCCTG
Discovery
PETAL
BRICNet
LASI
LACCTIN
LIVEN
SCCTG
ICCTG
UK-CTG
SepNet
TRIGER-Sep
REVA
HSG
SEMICYUC
NANICRM
SCCTG
ACART
CCCCTG
SEARCH
ACCCTG
ANZICS CTG

Determinants of Citation Impact in Large Clinical Trials in Critical Care: The Role of Investigator-Led Clinical Trials Groups*

John C. Marshall, MD[1]; Wilson Kwong, MSc[1,2]; Kamya Kommaraju, BSc[1]; Karen E. A. Burns, MD, MSc[1]

TABLE 5. The Impact of Organizational Model on Median Annual Citation Rates

Model	No. of Trials (%)	Median (IQR) Annual Citations
Industry led	85 (21.7)	12.3 (5.4–24.1)
Investigator led		
Single center	114 (29.2)	7.0 (3.5–12.9)
2–5 centers	59 (15.1)	11.0 (4.5–22.4)
Multicentre ad hoc group	88 (22.5)	19.1 (9.8–30.4)
Multicentre trials group	45 (11.5)	45.7 (17.3–86.2)[a,b]

IQR = interquartile range.
[a]$p < 0.0001$, Kruskal-Wallis.
[b]$p < 0.0001$ vs ad hoc group.

Crit Care Med
44:663, 2016

The Multiplatform RCT

ATTACC, REMAP, and ACTIV IV (NIH)

An international multiplatform RCT (mpRCT)

- Update:
  - December 18th, DSMB recommending stopping the severe state
    - ~1200 enrolled. Interim efficacy based on ~600 patients
  - Moderate state continues - ~2000 patients enrolled

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

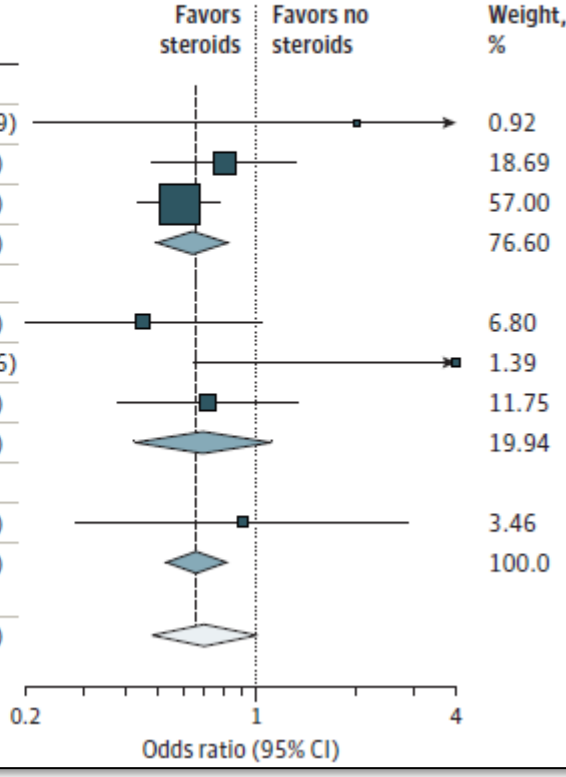
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19

A Meta-analysis

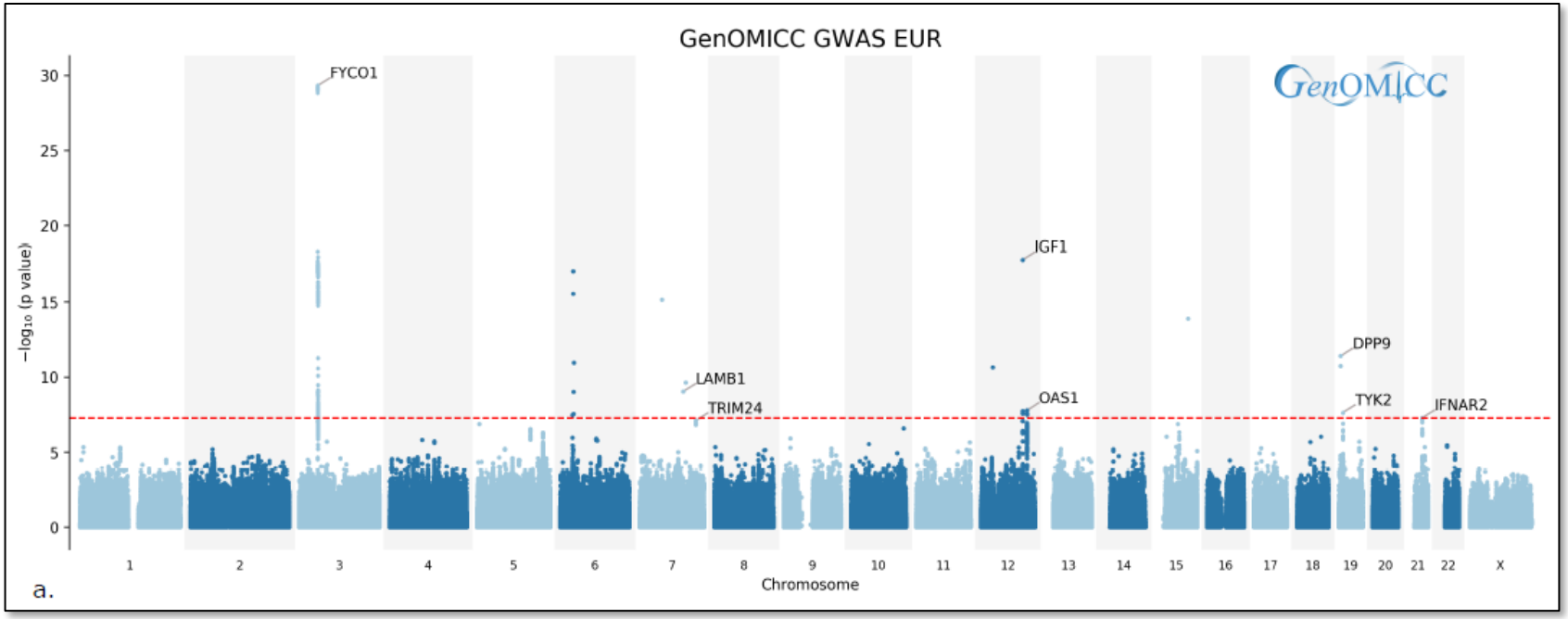
The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)
Dexamethasone					
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)
Hydrocortisone					
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)
Methylprednisolone					
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)



GENETICS OF MORTALITY IN CRITICAL CARE



Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

The Writing Committee for the REMAP-CAP Investigators

ARTICLE INFORMATION

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Author Contributions: Dr Angus had full access to all corticosteroid domain data and all baseline data

NIHR | National Institute for Health Research

- **Hospitals funded to do research**
- **Central coordination reduces duplication**
- **Targets established for recruitment to trials**

Increasing recruitment into covid-19 trials

An urgent priority for the NHS

Ara Darzi, [1] Andrew Goddard, [2] Katherine Henderson, [3] Ravi Mahajan, [4] Clare Marx, [5] Neil Mortensen, [6] Alison Pittard[7]

Since March 2020, UK researchers have established over 70 urgent public health studies to investigate potential treatments, vaccines, and diagnostic tests for covid-19. NHS hospitals have had a vital role in delivering these studies at pace and scale, despite working under extreme pressure. The results are now informing practice worldwide.

In June 2020, the Recovery trial found that dexamethasone, a widely available corticosteroid, improved survival among covid-19 patients on ventilation by 36% (28 day mortality rate ratio 0.64; variation among hospitals and therefore scope for further improvement.

The largest community based covid-19 trial in the UK, Principle,[5 6] evaluates treatments to prevent hospital admission or transmission, including doxycycline and inhaled budesonide. Recruitment has been slow because of the disruption of primary care during the first wave, reaching 2000 participants in December. To aid recruitment Principle now allows patients to participate remotely regardless of the location of their registered general practitioner.

- **7-10% of admissions for COVID-19**
- **20% of all ICU admissions**

Trials save lives. They cannot do so, however, without the participants on which they depend. Recruitment of patients with covid-19 to UK clinical trials must now be prioritised. Although vaccines against

COVID-19 is Changing Clinical Research

- **New trial designs**
- **International collaboration**
- **Acceptance of research as integral to clinical care**
- **Embedding of research into the provision of excellent clinical care**

Thank you!