PANDEMIC SCIENCES INSTITUTE

The RECOVERY trial

Lessons for leadership in evidence-based healthcare

Peter Horby

Director, Pandemic Sciences Institute

University of Oxford

NMRC Awards Ceremony , Singapore, 23 May 2024

Why do we need to learn from RECOVERY (& other trials)?

Clinical trials were in a crisis before the pandemic began (and still are)

- There is a pressing need for better ways to detect, prevent and treat common and life-threatening diseases, in order to save lives, improve health and relieve pressure on healthcare systems around the world.
- Just **15%** of international cardiovascular treatment guidelines are based on good evidence from RCTs [*Fanaroff, Califf et al JAMA.* 2019;321(11):1069-1080.]
- Randomised clinical trials have become excessively burdensome and unsustainably expensive, failing to generate the evidence needed for sound decision-making about the role of new and established health interventions.

Examples of this crisis

Failure due to bad design

Just **5%** of trial arms in registered trials for COVID-19 were randomized and sufficiently large to achieve a meaningful result

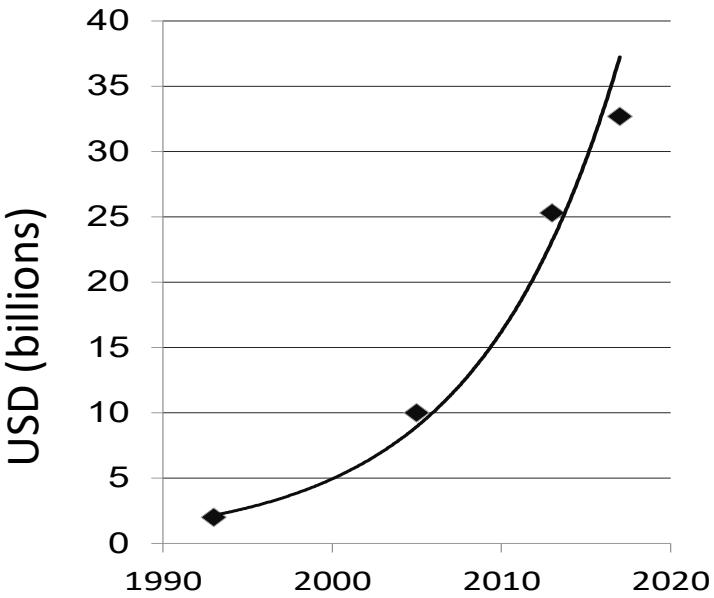
Nature Reviews Drug Discovery
25 Feb 2021

Failure to enrol participants

85% clinical trials fail to recruit to time and target (and those that do, often fail to adequately reflect the diversity of the affected population)

Cost and complexity is growing exponentially

The Contract Research Organization industry is growing by 10% annually



Roberts et al Cancer 2016;
https://doi.org/10.1002/cncr.29994

Cost and time of pivotal clinical trials

- Median cost - $19 million
- Placebo control - $28.8 million
- Clinical outcome - $64.7 million
- Median per patient - $41,117
- Time to complete - 40 months (from approval)

JAMA Intern Med. 2018;178(11):1451-1457.
https://www.nature.com/articles/nrd.2017.21

The consequences

- Promising, innovative treatments never make it to late-phase trials or are developed only for limited indications
- Effective interventions are underused because their true impact is not understood
- Ineffective (or harmful) interventions continue to be used because their flaws go undetected
- Lack of relevant information for patient subgroups (age, gender, ethnicity, co-morbidity etc)

RECOVERY trial

DESIGN

Huge therapeutic uncertainty

- Many candidates
- Many opinions
- No reliable data (uncontrolled case series, inconclusive randomized trials)

"I happen to think it works"

Travel Med Infect Dis. 2020 March-April; 34:101663.

Methods

We conducted an uncontrolled, non-comparative, observational study in a cohort of 80 relatively mildly infected inpatients treated with a combination of hydroxychloroquine and azithromycin.

Brazil's president says hydroxychloroquine to cure his virus #HCQnews

apnews.com

RIO DE JANEIRO (AP) — Brazilian President Jair Bolsonaro says he is confident that he will swiftly recover from the new coronavirus thanks to treatment with hydroxychloroquine, the anti-malaria drug ...

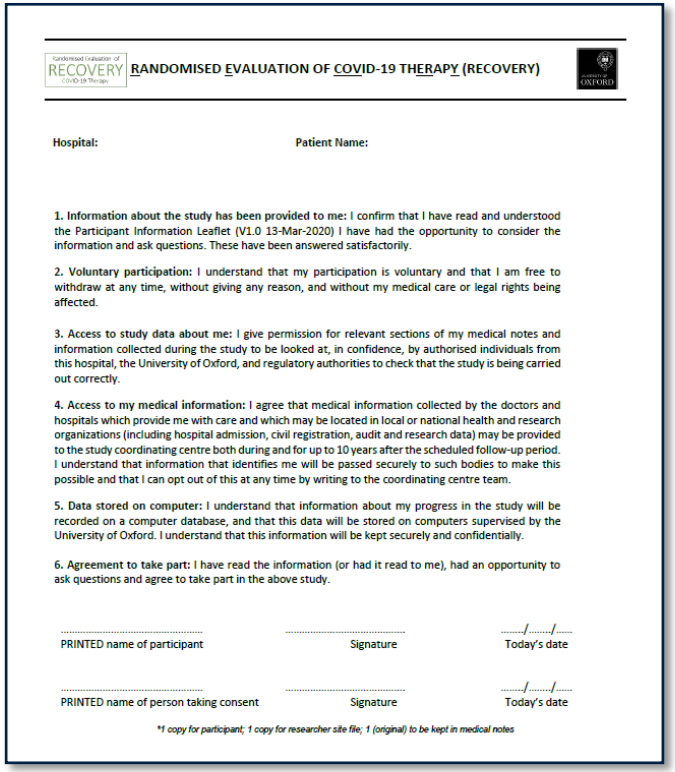
WWW.HCQ.NEWS | WWW.GEORGE.NEWS | WWW.DEFENSETV.ORG

March 2020 – RECOVERY approach

- **Must be quick**
- **Must be big**
  - Unlikely to be a single “big win”
  - Moderate benefits plausible & worthwhile (and may be additive)
  - ~5,000-10,000 participants needed to identify or rule out moderate benefit
- **Must be simple (‘streamlined’)**
  - Embedded in routine care
  - Essential data only
  - Objective and important outcomes
- **Focus on what matters**
  - Safety of participants and respecting their rights
  - Safety of future patients, by ensuring the results of the trial are reliable

RECOVERY trial - Design

- **Simple eligibility:** Hospitalised patients with SARs-CoV-2
- **Randomization:** Assign patient between suitable and available treatments
- **Important outcome:** Mortality (use of ventilation, duration of hospitalisation)



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.

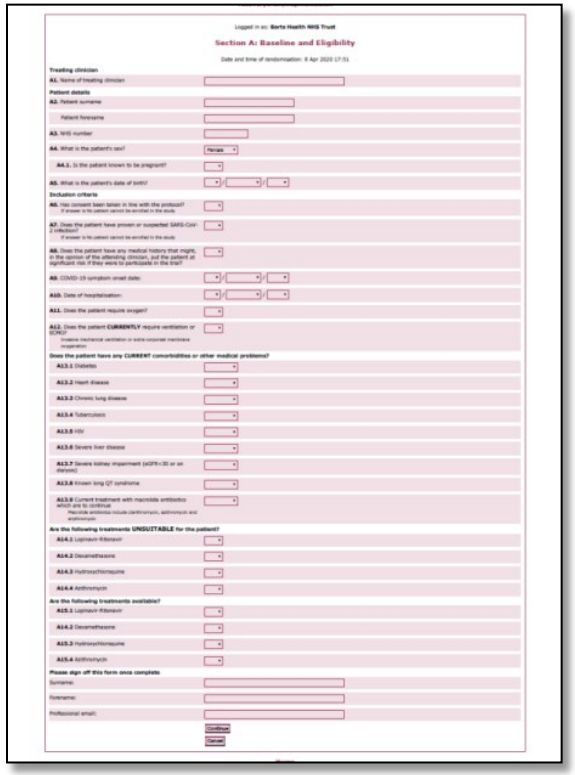
4. Access to my medical information: I agree that medical information collected by the doctors and hospitals which provide me with care and which may be located in local or national health and research organizations (including hospital admission, civil registration, audit and research data) may be provided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

Follow-up

- **Simple on-line form completed by research nurses**
  - Which treatments did the patient receive
  - COVID-19 test result
  - Discharge status & date
  - Use of ventilation

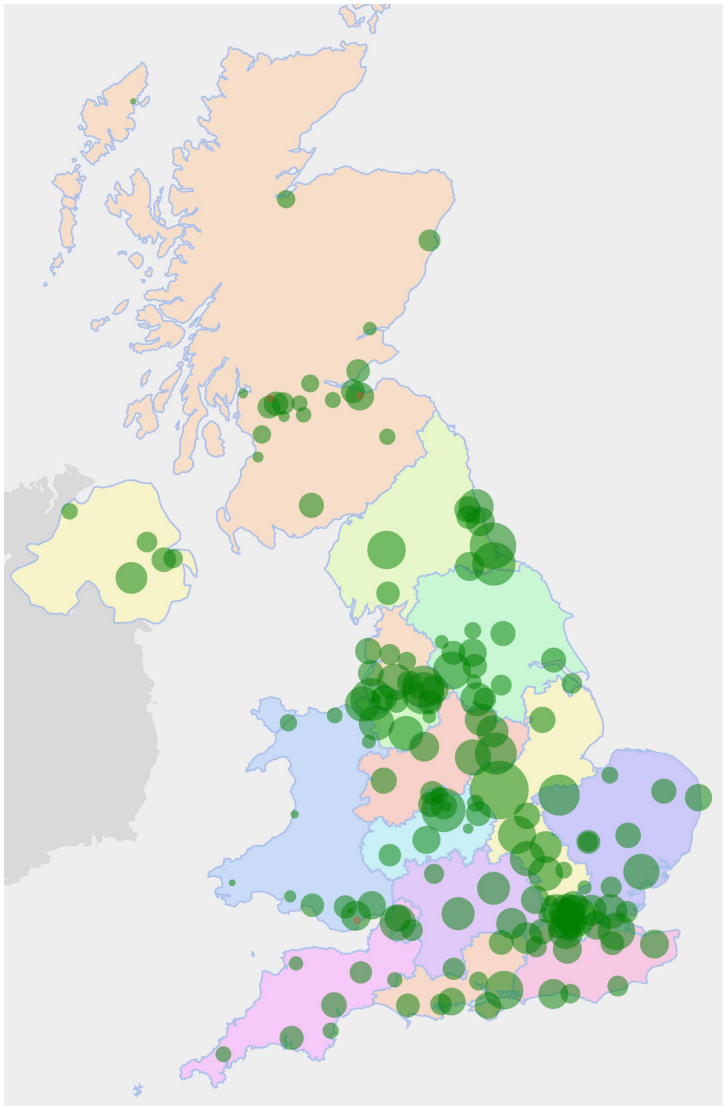
- **Linkage to national data sources**
  - Vital status, death certificate
  - Coded hospital episode statistics (diagnoses, procedures)
  - Intensive Care audit data, SARS-CoV-2 PCR laboratory results
  - Primary care, national outpatient prescribing data

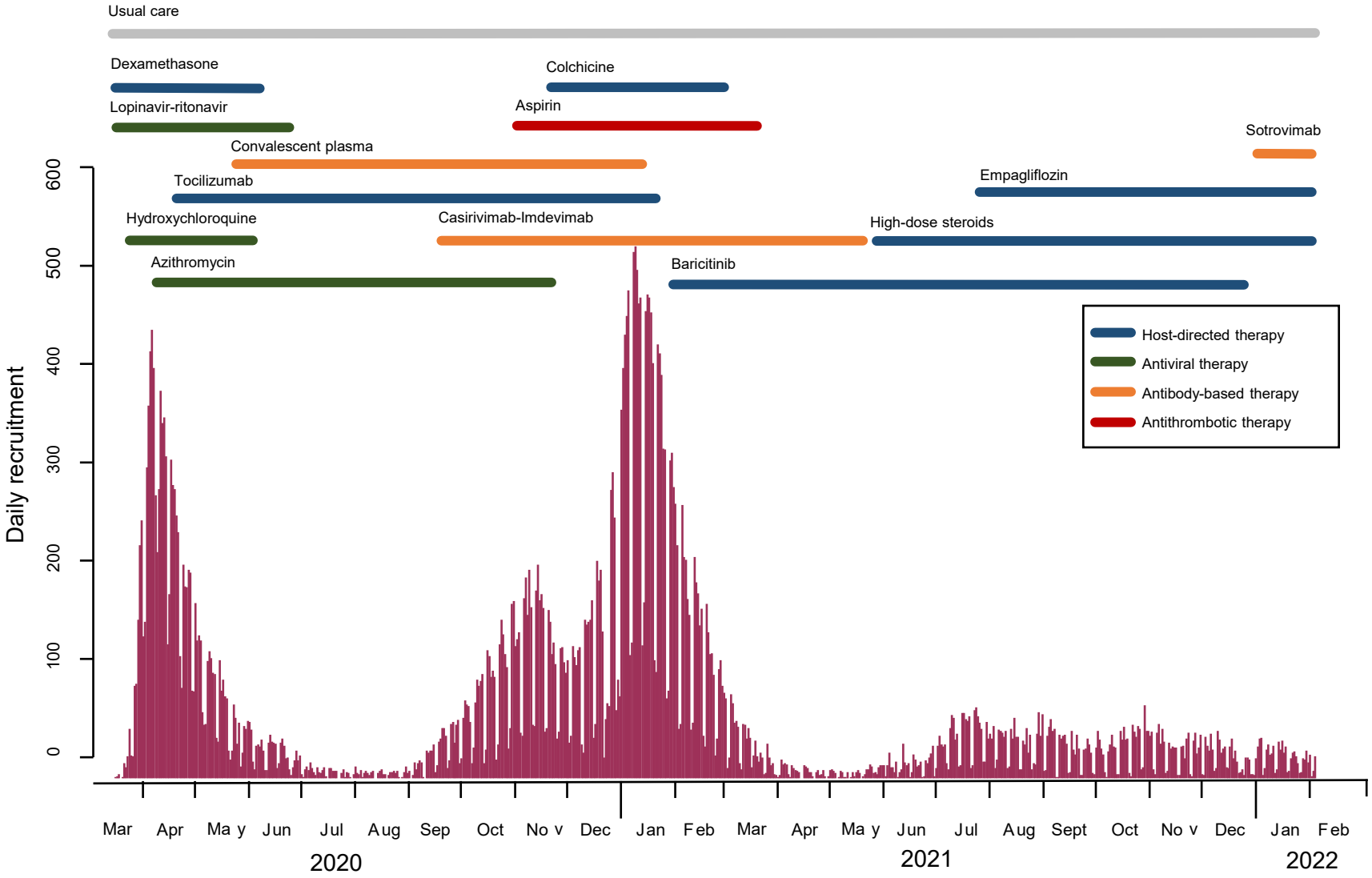
- Permission to follow-up via record linkage for up to 10 years

RECOVERY trial

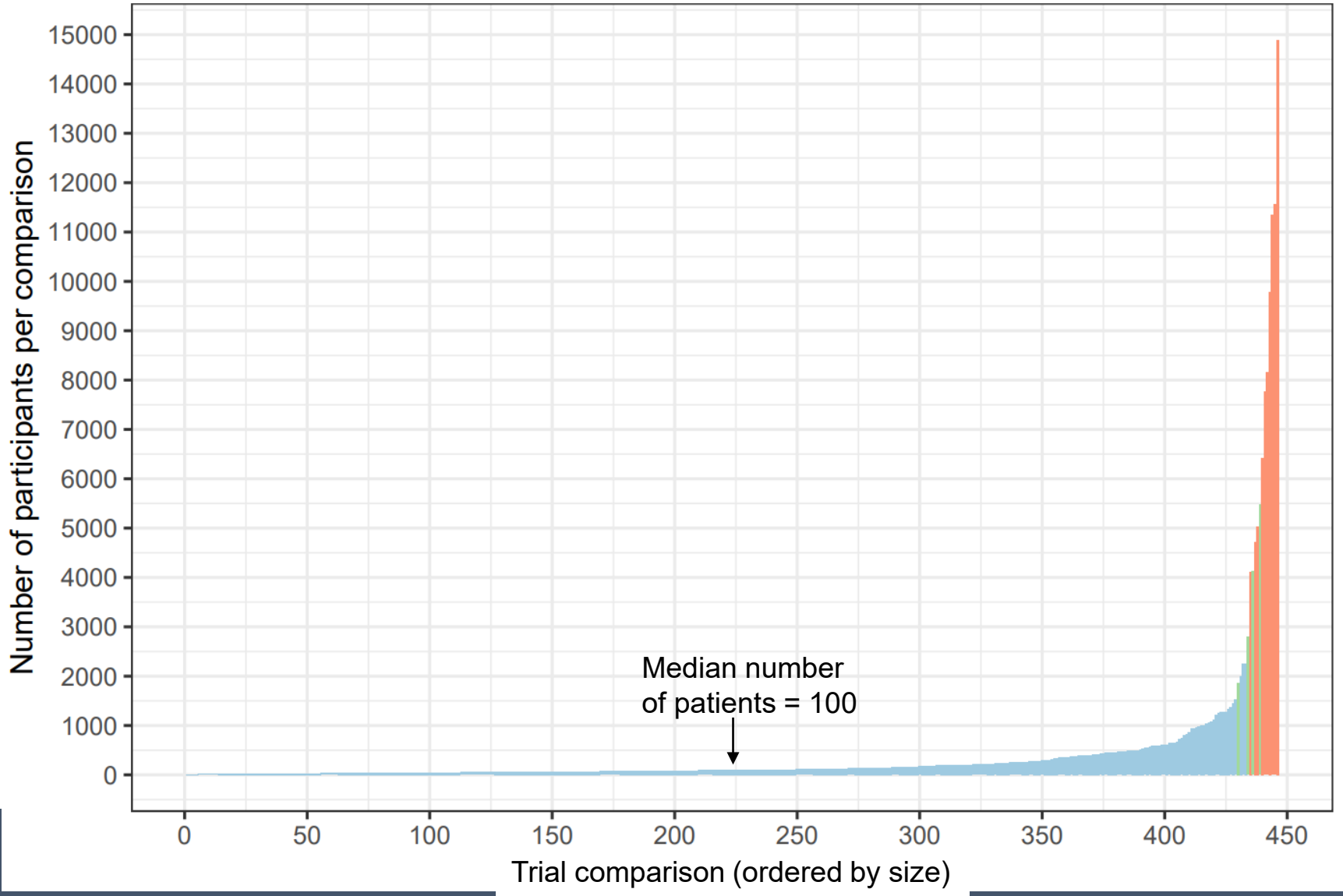
IMPLEMENTATION & RESULTS

Adoption at all acute NHS hospitals





COVID-19 inpatient randomised comparisons reported



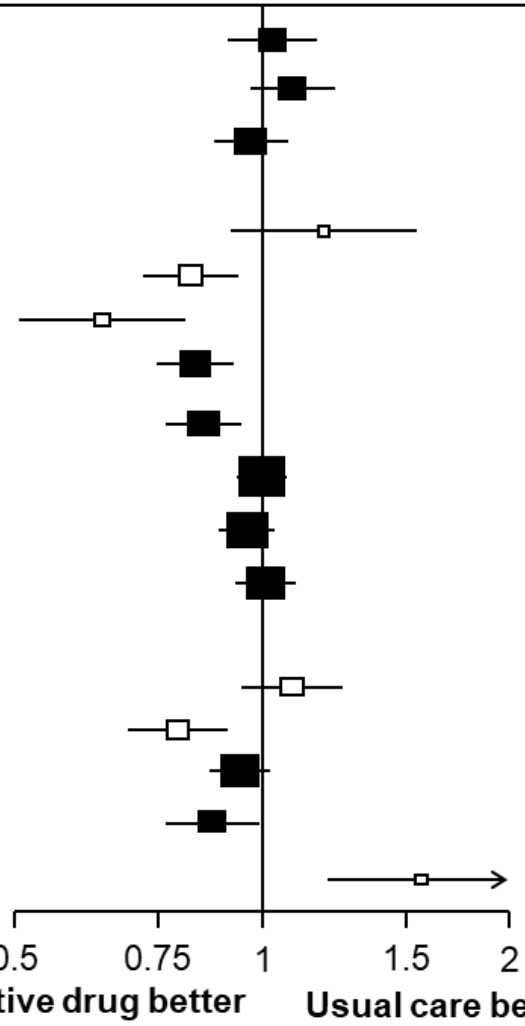
As of Jan 2023,
10 of the 13 largest randomised inpatient treatment comparisons were from RECOVERY

Trial
RECOVERY
SOLIDARITY
Other

Data: covid-nma.com

Published so far…

	Active drug	Usual care	Death rate ratio (95% CI)
Lopinavir-ritonavir	374/1616 (23%)	767/3424 (22%)	1.03 (0.91-1.17)
Hydroxychloroquine	421/1561 (27%)	790/3155 (25%)	1.09 (0.97-1.23)
Azithromycin	561/2582 (22%)	1162/5181 (22%)	0.97 (0.87-1.07)
Dexamethasone			
No oxygen	89/501 (18%)	145/1034 (14%)	1.19 (0.92-1.55)
Oxygen only	298/1279 (23%)	682/2604 (26%)	0.82 (0.72-0.94)
IMV	95/324 (29%)	283/683 (41%)	0.64 (0.51-0.81)
Overall	482/2104 (23%)	1110/4321 (26%)	0.83 (0.75-0.93)
Tocilizumab	621/2022 (31%)	729/2094 (35%)	0.85 (0.76-0.94)
Convalescent plasma	1399/5795 (24%)	1408/5763 (24%)	1.00 (0.93-1.07)
Aspirin	1222/7351 (17%)	1299/7541 (17%)	0.96 (0.89-1.04)
Colchicine	1173/5610 (21%)	1190/5730 (21%)	1.01 (0.93-1.10)
Casirivimab-imdevimab			
Seropositive	410/2636 (16%)	384/2636 (15%)	1.09 (0.94-1.25)
Seronegative	396/1633 (24%)	452/1520 (30%)	0.79 (0.69-0.91)
Overall	943/4839 (19%)	1029/4946 (21%)	0.94 (0.86-1.02)
Baricitinib	514/4148 (12%)	546/4008 (14%)	0.87 (0.77-0.99)
High-dose steroids (in low risk patients)	123/659 (19%)	75/613 (12%)	1.59 (1.20-2.10)



RECOVERY in numbers

	Pre-Covid	RECOVERY
*Time to start**	621 days	14 days
Time to complete	40 months	3 months
Cost (per patient)	$41,117	$500

** Funding agreed to first patient enrolled*

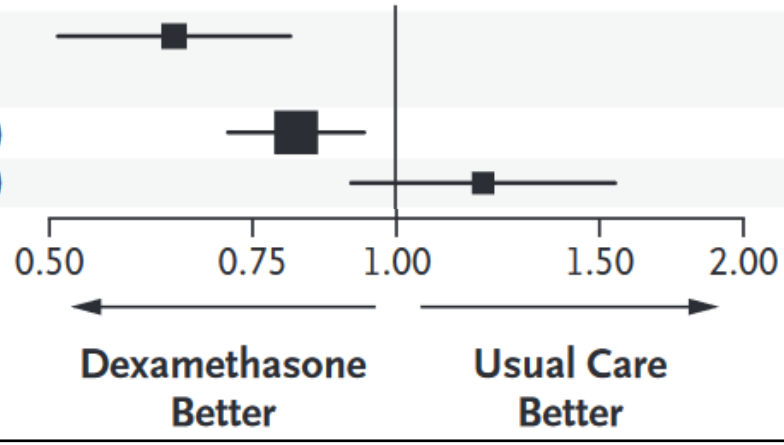
RECOVERY trial

GENERAL LESSONS

Dogma is dangerous - corticosteroids

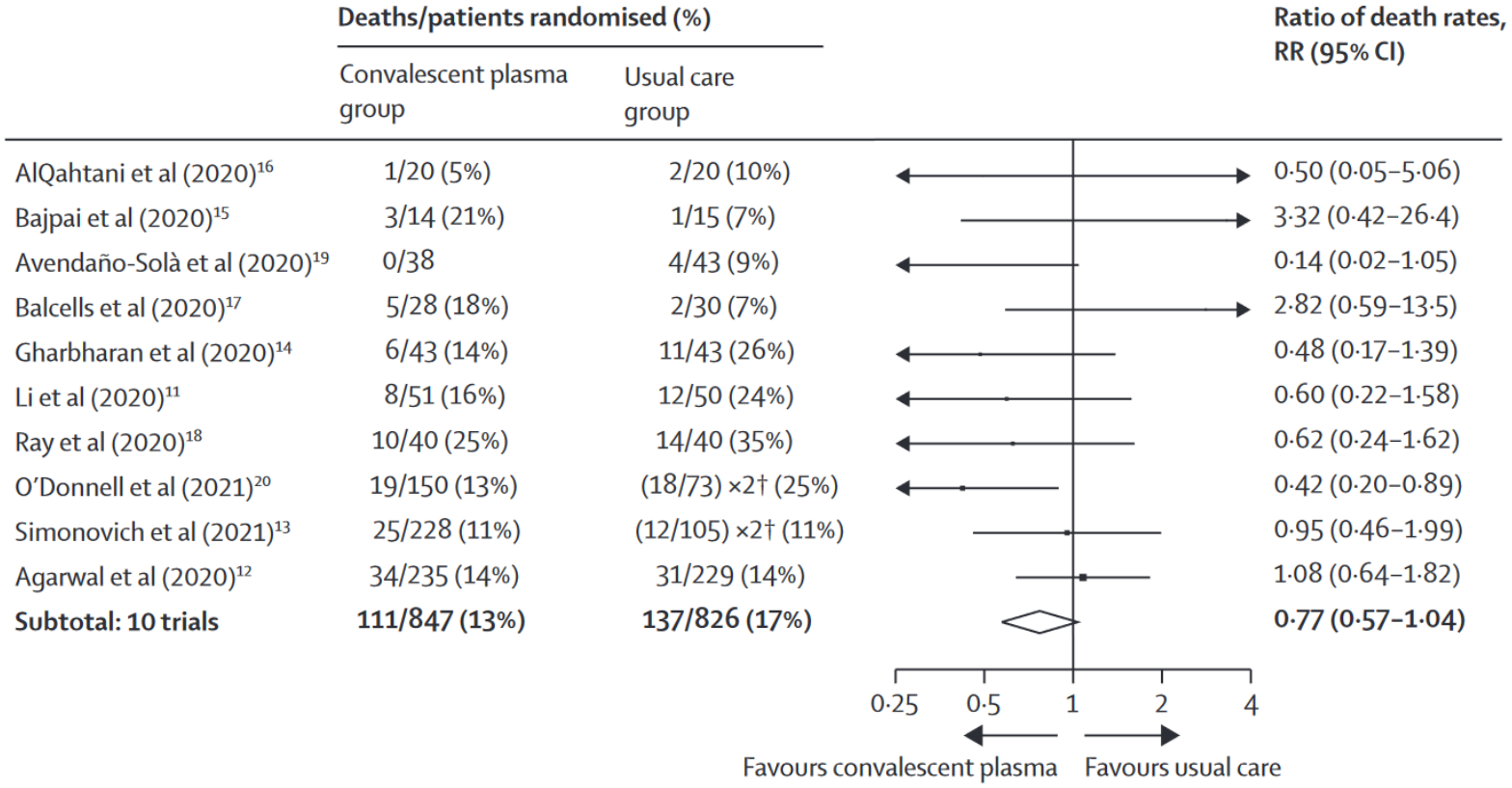
- In void created by lack of evidence, tempting to fill it with opinion
- *"We do not believe it is ethical to randomise patients to dexamethasone, a treatment where there is large body of prior evidence to suggest likely harm."*
  - Signed by 19 doctors (including 9 professors)

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 (0.92–1.55)



Poor evidence leads to poor practice – convalescent plasma

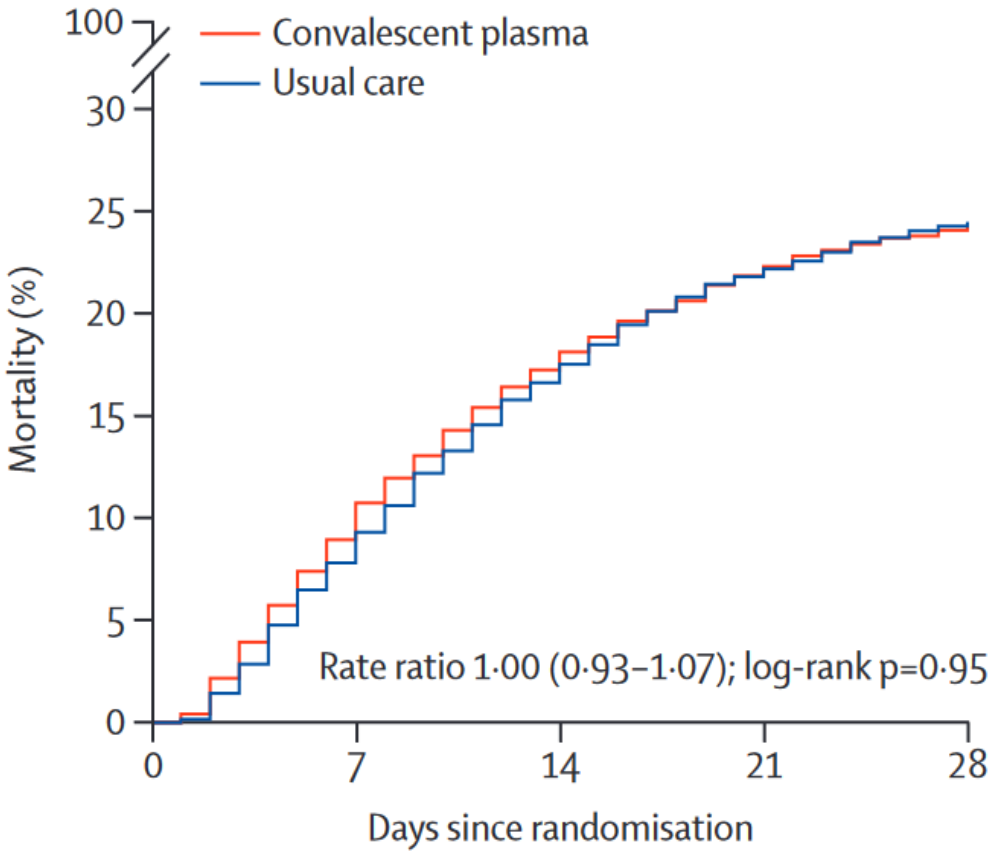
- Strong rationale
- CP given to 500,000 patients in the US
- $800 million spent on US CP program in the first year
- By March 2021, ten trials had included 1,700 inpatients
- One encouraging trial



	Deaths/patients randomised (%)		Ratio of death rates, RR (95% CI)
	Convalescent plasma group	Usual care group	
AlQahtani et al (2020)[16]	1/20 (5%)	2/20 (10%)	0·50 (0·05–5·06)
Bajpai et al (2020)[15]	3/14 (21%)	1/15 (7%)	3·32 (0·42–26·4)
Avendaño-Solà et al (2020)[19]	0/38	4/43 (9%)	0·14 (0·02–1·05)
Balcells et al (2020)[17]	5/28 (18%)	2/30 (7%)	2·82 (0·59–13·5)
Gharbharan et al (2020)[14]	6/43 (14%)	11/43 (26%)	0·48 (0·17–1·39)
Li et al (2020)[11]	8/51 (16%)	12/50 (24%)	0·60 (0·22–1·58)
Ray et al (2020)[18]	10/40 (25%)	14/40 (35%)	0·62 (0·24–1·62)
O'Donnell et al (2021)[20]	19/150 (13%)	(18/73) ×2† (25%)	0·42 (0·20–0·89)
Simonovich et al (2021)[13]	25/228 (11%)	(12/105) ×2† (11%)	0·95 (0·46–1·99)
Agarwal et al (2020)[12]	34/235 (14%)	31/229 (14%)	1·08 (0·64–1·82)
Subtotal: 10 trials	**111/847 (13%)**	**137/826 (17%)**	**0·77 (0·57–1·04)**

Taken together, trials were consistent with **no effect** of CP, or a **40% reduction in mortality**

Poor evidence leads to poor practice – convalescent plasma



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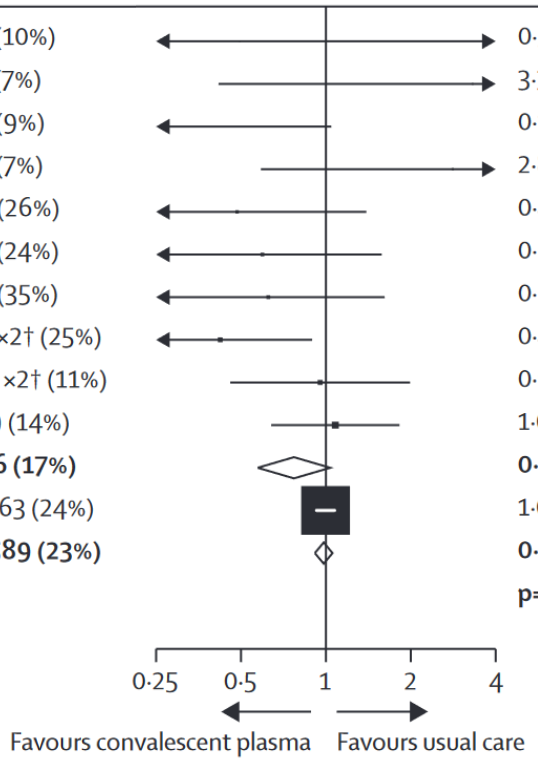
Subtotal: 10 trials	**111/847 (13%)**	**137/826 (17%)**	**0·77 (0·57–1·04)**
RECOVERY	1399/5795 (24%)	1408/5763 (24%)	1·00 (0·93–1·07)
All trials	**1510/6642 (23%)**	**1545/6589 (23%)**	**0·98 (0·91–1·06)**
			p=0·63



11,558 patients randomised

Costly poor practices

Table. Estimated Increases in Dispensed Retail Prescriptions for Selected Products Proposed to Treat or Prevent COVID-19—United States, March-December 2020 vs 2019[a]

Treatment[b]	Baseline No. of prescriptions dispensed per week[c]	Peak week, 2020 (end date)[d]	Peak No. of prescriptions dispensed per week, 2020[d]	No. of prescriptions dispensed above baseline in peak week, 2020	Increase in prescriptions dispensed above baseline in peak week, 2020, %	Weeks >50% above baseline, 2020, No.
Ivermectin	3589	Dec 18, 2020	24 528	20 939	583.4	12
Chloroquine	499	Mar 20, 2020	2966	2467	494.4	2
Zinc[e]	1810	Dec 11, 2020	9110	7300	403.3	32
Hydroxychloroquine	93 640	Mar 20, 2020	267 308	173 668	185.5	4

JAMA Intern Med. 2021;181(6):869-872.

Commercial and Medicare Advantage insurers are spending an estimated **$129.7 million annually** on ivermectin prescriptions for COVID-19

JAMA. 2022;327(6):584-587.

RECOVERY trial

LESSONS FOR HEALTHCARE LEADERSHIP

1. National leadership & commitment to the scientific approach

Department of Health & Social Care

From the Chief Medical Officer & Chief Scientif
Professor Chris Whitty CB FMedSci
&
NHS England Medical Director
Professor Stephen Powis

16 March 2020

Dear Colleague

Randomised Evaluation of COVID-19 Therapy (RECOVERY trial)

I am writing to ask that you provide your fullest support for implementation of the RECOVERY trial in your Trust.

COVID-19 is a global threat to health for which we have no specific treatments. Whilst many products have been proposed to treat COVID-19 patients, none are proven.

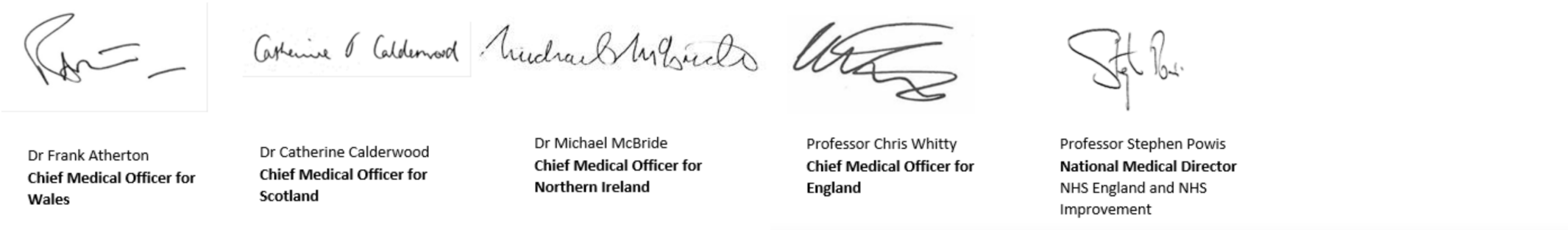
PROFESSOR CHRIS WHITTY
CHIEF MEDICAL OFFICER
DHSC CHIEF SCIENTIFIC ADVISER

PROFESSOR STEPHEN POWIS
NHS ENGLAND MEDICAL DIRECTOR

1. National leadership & commitment to the scientific approach

01 April 2020

The faster that patients are recruited, the sooner we will get reliable results. While it is for every individual clinician to make prescribing decisions, we strongly discourage the use of off-licence treatments outside of a trial, where participation in a trial is possible. Use of treatments outside of a trial, where participation was possible, is a wasted opportunity to create information that will benefit others. The evidence will be used to inform treatment decisions and benefit patients in the immediate future.



Dr Frank Atherton
Chief Medical Officer for Wales

Dr Catherine Calderwood
Chief Medical Officer for Scotland

Dr Michael McBride
Chief Medical Officer for Northern Ireland

Professor Chris Whitty
Chief Medical Officer for England

Professor Stephen Powis
National Medical Director
NHS England and NHS Improvement

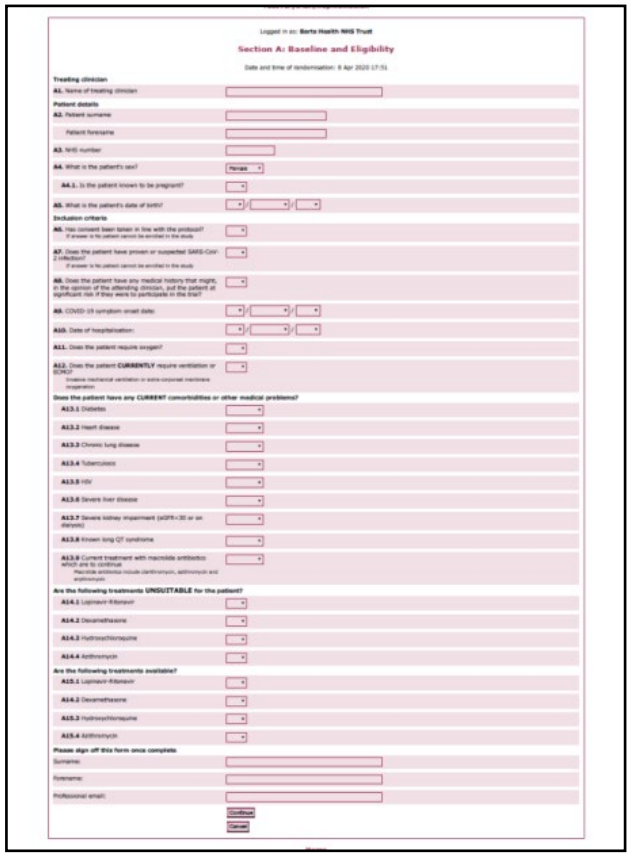
2. Research quality by design

Focus on elements that are ***essential*** to reliable estimation of central question

- *Reality of participants*
- *Randomisation*
- *Follow-up completeness*
- *Safety of participants*
- *Analyses*

Eliminate procedures that are superfluous to central question

One page case record form



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

A15.2 Dexamethasone

A15.3 Hydroxychloroquine

A15.4 Azithromycin

Please sign off this form once complete

Surname:

Forename:

Professional email:

Continue

Cancel

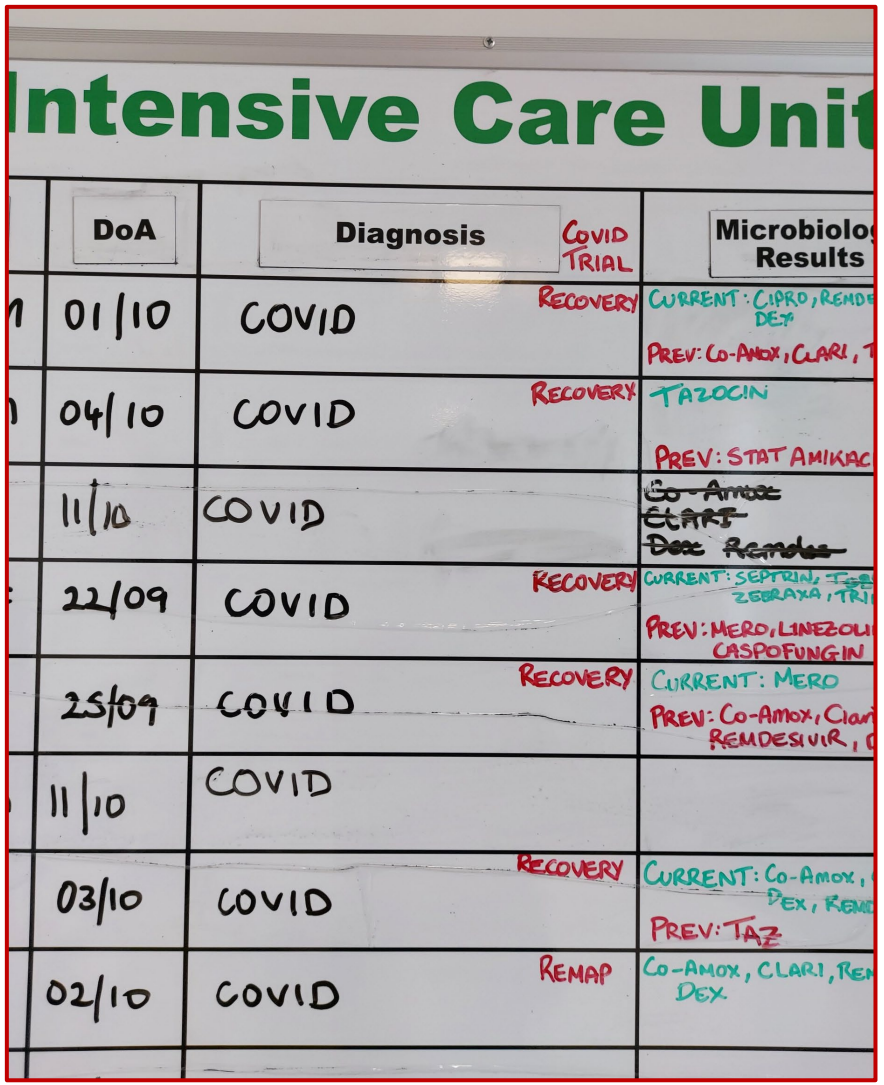
Eight minutes to randomise

N	[Min, Max]	Mean (SD)	Median [IQR]
48595	[0, 89]	8.30 (5.39)	7 [5, 10]

3. Point-of-care trial

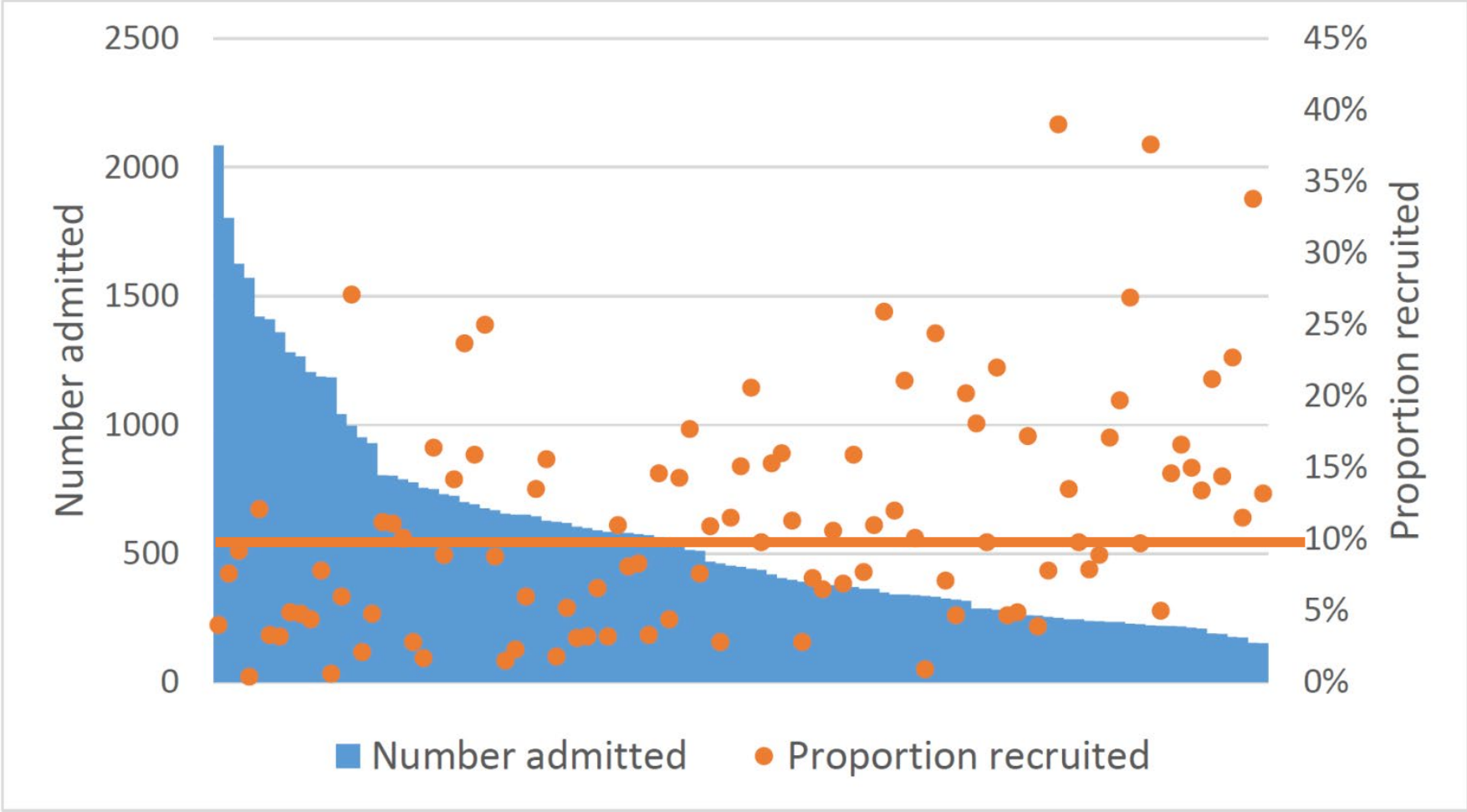
- **Make it (almost) as easy to enroll as to treat**
  - Reduces distractions from critical components
  - Allows participation in routine clinical care settings (not just academic centers)
  - Facilitates larger samples sizes & enhanced statistical power
  - Facilitates participation & representativeness
  - Increases probability of meaningful results that improve care

At peak
500 enrolments per day



Clinical trials can be a core component of care

Recruitment by hospital Trust (1 Oct – 30 Nov)



VIEWPOINT

Benefits of Streamlined Point-of-Care Trial Designs
Lessons Learned From the UK RECOVERY Study

Robert M. Califf, MD
US Food and Drug Administration, Silver Spring, Maryland.

Patrizia Cavazzoni, MD
US Food and Drug Administration, Silver Spring, Maryland.

Janet Woodcock, MD
US Food and Drug Administration, Silver Spring, Maryland.

"Streamlining and quality are not opposed; rather, by applying quality-by-design principles, reliable evidence can be developed with planned, measurable quality when researchers focus on ensuring both the quality of data that address important research questions and trial conduct that protects patient safety."

JAMA Int Med December 2022

4. Quick & proportionate ethical & regulatory review

- No site investigator CVs
- No special labelling of repurposed drugs
- No fixed sample size
- SSARs not all SAEs

Approvals within days

Application	Purpose	Submission date	MHRA	REC	Live	Submission to live
Initial		13 March	17 March	17 March	19 March	**6 days**
Subst. amend. 1	Add hydroxychloroquine	23 March	25 March	24 March	25 March	**2 days**
Subst. amend. 2	Add azithromycin	7 April	8 April	8 April	8 April	**1 day**
Subst. amend. 3	Add tocilizumab	14 April	16 April	16 April	23 April	**9 days**
Subst. amend. 4	Include children	27 April	5 May	30 April	9 May	**12 days**

If RECOVERY had been delayed by just **3 weeks**
dexamethasone result would have been delayed by **4 months**

Role of regulation

- While trialists can demonstrate the value of large, streamlined trials by example, this is not sufficient.
- Much of current practice is driven by regulations, or the over-interpretation of regulations by regulators and others involved in trials.
- What would good regulation look like?

www.goodtrials.org

4. National prioritisation

Urgent Public Health Designation

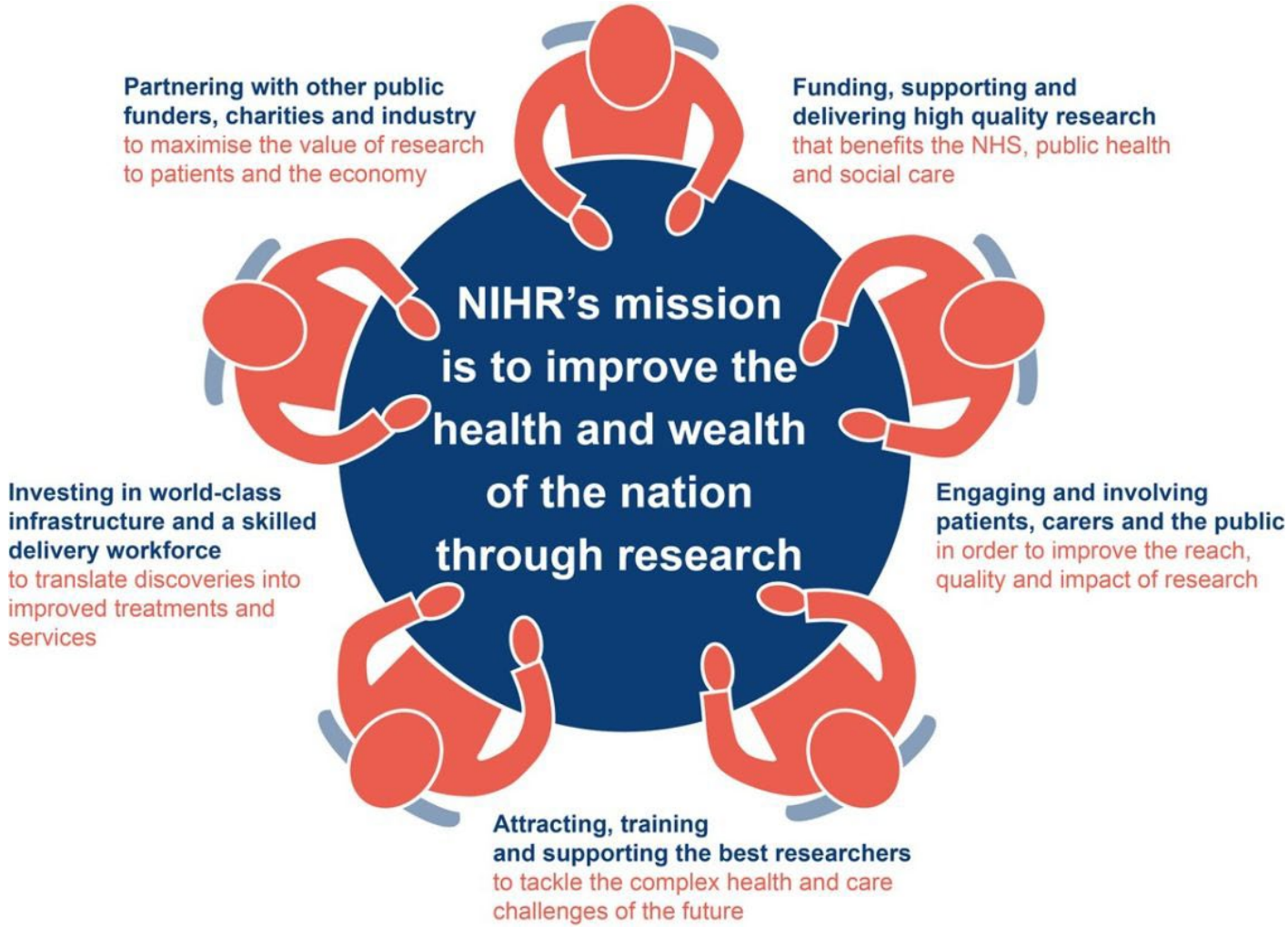
UPH Designation criteria

Your study will be assessed by the UPH Group and assessed against the following criteria:

- How compelling is the science underpinning the proposed study?
- Is it feasible to deliver in the current environment of the NHS and social care?
- Is the study of appropriate scope and scale for national priority status?
- Is the funding appropriate to deliver the proposed outcomes of the study?
- Is there an appropriate management plan to avoid interference with recruitment to other Urgent Public Health studies?
- Will results be relevant to this pandemic?

5. National infrastructure

- Research arm of National Health Service
- Established 2006 as vehicle to implement Government's health research strategy
- National clinical trial agreement template
- National costing framework - Schedule of Events Cost Attribution Tool (SoECAT)



6. Centrally collected routine data used for research purposes

Hospitalisation datasets

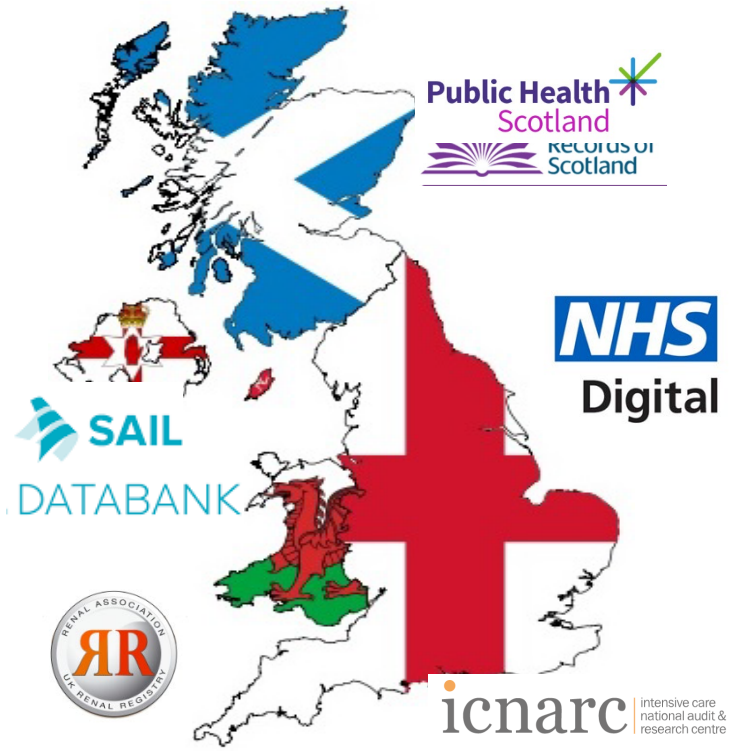
- ✓ Scottish Morbidity Records (SMR)
- ✓ Hospital Episode Statistics Admitted Patient Care (HESAPC)
- ✓ Secondary Uses Service Admitted Patient Care (SUSAPC)
- ✓ Patient Episode database for Wales (PEDW)

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)

Summary

Lessons for the future

- Arbitrary use of unproven treatments damages patient care & public health
- Randomized trials are a critical component of high-quality clinical care
- Compelling results change practice, saving lives & money

- But trials must be:
  - Designed to deliver actionable results
  - Feasible for patients and clinical staff
  - Affordable
  - Inclusive of relevant patient groups
  - Focused on outcomes that matter

Lessons for the future

This requires:

- Health systems to recognise & embrace their role in finding solutions
- Recognition, adoption & adherence to the key principles for good RCTs
- Proportionate regulation
- Long-term platforms for large-scale, collaborative RCTs
- Access to healthcare data
- Healthcare leadership & a commitment to evidence-based medicine

Thank you for your attention

Acknowledgements

- UK Research & Innovation
- National Institute for Health Research
- Wellcome Trust
- Bill & Melinda Gates Foundation
- Department for International Development
- Department of Health & Social Care
- National Health Service in England, Wales, Scotland, and Northern Ireland
- NIHR Clinical Research Network
- NHS DigiTrials
- NIHR Oxford Biomedical Research Centre Unit
- Medical Research Council Population Health Research
- Nuffield Department of Medicine
- Nuffield Department of Population Health
- UO/OUH JRO & RGEA
- MHRA & HRA
- The very many doctors, research nurses, pharmacists, and R&D managers in all participating hospitals
- And, most importantly, **the members of the public who are participating**