Institution: University of Oxford		
Unit of Assessment: 2 - Public Health, Health Services and Primary Care		
Title of case study: RECOVERY Trial: Global adoption of effective COVID-19 treatments to save lives		
Period when the underpinning research was undertaken: Jan 2000 - 31 Dec 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Prof Martin Landray	Professor of Medicine and Epidemiology	Nov 2000 - present
Prof Richard Haynes	Professor of Renal Medicine and Clinical Trials Medical Research Council (Cat. C)	Sep 2006 - Apr 2009, and Jul 2016 - present May 2009 - Jun 2016
Dr Marion Mafham	Clinical Research Fellow NHS Clinician (Cat. C)	Mar 2003 - Mar 2006, and Dec 2013 - present Apr 2006 - Nov 2013
Prof Jonathan Emberson	Professor of Medical Statistics and Epidemiology	Sep 2004 - present
Prof Edmund Juszczak	Associate Professor and Director of NPEU Clinical Trials Unit	Sep 2017 – Jul 2020
Prof Sir Rory Collins	Professor of Medicine and Epidemiology; Head of Department	Aug 1981 - present
Period when the claimed impact occurred: 19 Mar 2020 – 31 Dec 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the Impact

University of Oxford researchers initiated and led the earliest, fastest, and largest randomised clinical trial of treatments for COVID-19 in 2020: RECOVERY (Randomised Evaluation of COVID-19 Therapy). Research prior to the pandemic on conducting streamlined large-scale clinical trials, by the Nuffield Department of Population Health, was essential for the successful speed and scale of RECOVERY. Results from three arms of RECOVERY announced in June 2020 showed dexamethasone reduces death rates among seriously unwell patients, whereas hydroxychloroquine and lopinavir-ritonavir are ineffective. These findings immediately transformed global clinical guidelines and practice, reversing widespread practice in the early stages of the pandemic. Dexamethasone usage rapidly increased worldwide on the basis of the RECOVERY results, leading to an estimated 650,000 lives saved by the end of 2020.

2. Underpinning research

The University of Oxford's Nuffield Department of Population Health (NDPH) has pioneered streamlined, large-scale clinical trials over several decades. The knowledge, experience and methods from this research were essential for the successful rapid design and implementation of the RECOVERY trial of treatments for COVID-19 in 2020, which was achieved through a new collaboration with Peter Horby (Nuffield Department of Medicine, University of Oxford (UOA1).

Streamlining clinical trials

NDPH research showed that streamlining clinical trials can enable large-scale recruitment, which is essential to achieve sufficient statistical power to detect effects of moderate size that can translate into large public health benefits for common diseases. NDPH has designed and conducted several successful streamlined trials, focusing on quality by keeping protocols simple and collecting only essential information, enabling increased scale without increased time and cost. An illustrative example is the MRC/BHF Heart Protection Study [1], a collaborative study led by University of Oxford researchers including Collins and Peto, which randomised 20,536 UK adults across 69 sites to assess long-term effects of cholesterol-lowering therapy on mortality and morbidity. It provided reliable evidence of the effects of cholesterol-lowering treatments through its large scale, simple eligibility criteria, and focused data collection.

Data linkage

NDPH pioneered the use of routinely collected health data for rapid recruitment and comprehensive follow-up in clinical trials. They led several trials demonstrating that existing clinical and demographic datasets can be used to identify potentially eligible patients, and trial cohorts can be linked to NHS (or similar) data sources supporting rapid large-scale recruitment, reducing burden on trial sites, and simultaneously improving data quality. For example, the 3C Study was a pragmatic randomised controlled trial including sequential randomisations to assess effects of immunosuppression strategies in kidney transplantation [2]. Linkage with routinely collected data captured the primary outcome (transplant function) and key secondary outcomes (including survival, transplant rejection and hospitalisations).

RECOVERY trial design

In March 2020, with COVID-19 spreading rapidly and an urgent need to identify effective treatments, Martin Landray collaborated with Peter Horby to design the RECOVERY platform trial. They formed a University of Oxford-led collaborative team and completed the draft protocol on 10 March 2020. The WHO declared the COVID-19 outbreak to be a pandemic on 11 March, and RECOVERY enrolled the first patient on 19 March 2020. Landray used the principles of streamlining and data linkage, keeping the trial simple so it could be very large. For example, healthcare workers only needed to ask a few questions at enrolment and, in most cases, at only one more data collection point; this minimised burdens on patients and healthcare workers, which was important in the pressured context of the pandemic. Close integration with routine health care datasets through NHS Digital (and equivalents), led by Marion Mafham, enabled access to additional baseline information and complete participant follow-up across the UK.

They chose an adaptive platform trial design, enabling treatments to be added or removed. Enrolled patients were initially randomised between usual care alone, hydroxychloroquine, the corticosteroid dexamethasone, lopinavir-ritonavir (an anti-viral combination treatment) and the antibiotic azithromycin, with further randomisations added including tocilizumab (a monoclonal antibody), convalescent plasma, and others. For dexamethasone, elements of a protocol previously developed by the University of Nottingham were incorporated into RECOVERY.

Key RECOVERY trial results

In less than two months, by 14 May 2020, 10,000 patients had been enrolled to the RECOVERY trial platform and in June 2020 the University of Oxford researchers presented results for three treatments for hospitalised COVID-19 patients. Results from a comparison including 6,435 participants demonstrated that the use of dexamethasone for up to 10 days resulted in lower 28-day mortality than usual care in patients who were receiving invasive mechanical ventilation at randomisation by approximately one third and those who were receiving oxygen by approximately one fifth, but not among patients not receiving respiratory support [3]. By contrast, there was no decrease in 28-day mortality, or other outcomes including length of hospitalisation, for patients receiving hydroxychloroquine (1,542 patients randomised to hydroxychloroquine vs 3,132 patients usual care) [4], or lopinavir-ritonavir (1,596 patients randomised to lopinavir-ritonavir vs 3,376 patients usual care) [5].

3. References to the research

(University of Oxford UOA2 authors in bold.)

1. Heart Protection Study Collaborative Group, **Collins R, Armitage J, Parish S, Sleight P, Peto R**. (2002). MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 360:7–22. DOI: 10.1016/S0140-6736(02)09327-3. Citations: 5894 (WoS, Jan 2021)
2. 3C Study Collaborative Group: **Haynes R, Blackwell L, Staplin N, Herrington WG, Emberson J, Judge PK, Storey BC, Landray MJ**, Harden PN, **Baigent C, Friend P** (2018). Campath, calcineurin inhibitor reduction, and chronic allograft nephropathy (the 3C Study) - results of a randomized controlled clinical trial. *Am J Transplant*. 18:1424–1434. DOI:10.1111/ajt.14619
3. The RECOVERY Collaborative Group, 26 named authors including **Mafham M**, **Linsell L, Juszczak E**, **Emberson J, Haynes R** and **Landray M**. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 384:693-704, preliminary version published 17 July 2020 and available as supplementary material. DOI: 10.1056/NEJMoa2021436

4. The RECOVERY Collaborative Group, 29 authors in writing committee including **Mafham M**, **Linsell L**, **Juszczak E**, **Haynes R**, and **Landray M** (2020). Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*, 383:2030-2040. DOI: 10.1056/NEJMoa2022926.
5. RECOVERY Collaborative Group, 26 authors in writing committee including **Mafham M**, **Linsell L, Emberson J**, **Juszczak E, Haynes R** and **Landray M** (2020). Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 396: 1345–52. DOI: 10.1016/S0140-6736(20)32013-4.

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4. Details of the impact

Between 31 December 2019 and 31 December 2020 there were more than 83,207,000 confirmed cases of COVID-19 worldwide. The case fatality rate has been estimated at approximately 1% in high income countries, or 20-25% of all hospitalised patients. By performing the largest clinical trial of COVID-19 treatments, robustly and at speed, the RECOVERY trial led by the University of Oxford has achieved worldwide impact in guiding treatment, saving lives, and demonstrating the power of evidence-based medicine. For the first time, treatment of an epidemic disease was changed during a pandemic.

Success of speed and scale

The streamlined trial design (built on research including [1, 2]) achieved unprecedented speed in initiation and recruitment, catching the first peak of infections in the UK, essential in a global pandemic with no known effective treatments. On 16 March 2020, the Chief Medical Officer and NHS England Medical Director endorsed RECOVERY and urged all NHS Trusts to adopt the trial, emphasising that it was crucial research and had been kept extremely simple [Ai]. Within 16 days, 1,000 patients had been randomised, 10,000 by 14 May, and 20,000 by 8 December 2020. Participants were recruited at 176 NHS hospital organisations and, during 2020, 10% of hospitalised UK COVID-19 patients were recruited. In August 2020, RECOVERY was selected to be the UK national platform for phase II as well as phase III COVID-19 trials, based on its unique national coverage and recruitment success [Aii].

First COVID-19 treatment that saves lives: Dexamethasone

In March 2020, Landray's collaborator Horby (UOA1) found that corticosteroids were specifically not recommended in most COVID-19 treatment guidelines and chose to include the corticosteroid dexamethasone in the RECOVERY trial [B]. Due to the speed and scale of the trial, it was only three 3 months later that RECOVERY proved that dexamethasone reduces COVID-19 mortality by one third in ventilated patients and approximately one fifth in oxygen-treated patients [3]. In December 2020, corticosteroids remained the only globally-available drugs proven to reduce mortality in severe and critical COVID-19.

Impact on national and international policy and clinical guidelines: It is unprecedented that research results are announced at lunchtime, become policy and practice by evening, and save lives by the weekend. The results were announced on 16 June 2020, a day on which 993 people in the UK died from COVID-19. Within 4 hours, dexamethasone – the world's first coronavirus treatment proven to reduce the risk of death – was recommended for use across the NHS, and the Chief Medical Officer instructed hospitals to act immediately [Ci], stating "*dexamethasone has been demonstrated to have a clear place in the management of hospitalised patients*" and urging clinicians to use it for patients requiring oxygen or ventilation.

In the US, on 17 July 2020 the National Institutes of Health (NIH) [Cii] changed its guidance: *"On the basis of the…(RECOVERY) trial,…(the Panel) recommends using dexamethasone"*. COVID management protocols were revised globally to add recommend dexamethasone, including Saudi Arabia on 17th June [Ciii], South Africa on 20 June [Civ], and India on 27 June [Cv]. On 22 June 2020, the WHO reviewed their guidance on corticosteroids for COVID-19 "*triggered…by the publication of the preliminary report of the RECOVERY trial*" [Cvi]. The WHO conducted a meta-analysis of corticosteroids trials, of which RECOVERY was by far the largest, and the revised guidance, published on 2 Sep 2020, recommended "*systemic corticosteroids rather than no corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence)*" based on the RECOVERY result [Cvi]. On 18 Sep 2020, the European Medicines Authority (EMA), unusually, provided a template for

manufacturers to accelerate submission of amendments to their dexamethasone drug licenses to include the new indication, based on the RECOVERY results [Cvii].

Benefits to patients and global clinical care: Patients in the dexamethasone group in the trial benefited both from increased likelihood of survival and shorter duration of hospitalisation [3]. Health economics analysis [D] estimates that in the UK 12,000 lives (90% confidence interval, 4,250 - 27,000) were saved between 1 July 2020 and 31 December 2020. If dexamethasone has a similar effect size in settings where access to oxygen therapies is limited, in the same period this would translate into approximately 650,000 lives (90% confidence interval 240,000 - 1,400,000) saved globally [D].

Dexamethasone is off-patent, affordably available in most countries, and can be taken by everyone: for less than GBP50, eight patients can be treated, and one life saved. It rapidly became standard of care for the sickest patients across the world. Six days after the RECOVERY result, the drug purchaser Vizient, which supplies approximately half of US hospitals, reported a 610% increase in demand for dexamethasone [Ei]. Independent analysis of US prescribing rates by health care technology company Aetion shows dexamethasone use for COVID-19 in hospital rising from 28% on 14 June 2020 to 52% on 28 June [Eii]. Clinical data reports from International Severe Acute Respiratory and emerging Infections Consortium (ISARIC), gathered from more than 550 sites across 42 countries, show high levels of steroid use globally since the RECOVERY result [F]: for patients admitted since 16 June (until 9 Nov 2020), 70% of those on ventilation and 43% of those on oxygen received steroids.

Adoption of dexamethasone, based on RECOVERY, is widely credited with contributing to the decline in COVID-19 mortality; decreases of 18% in death rates for hospitalised COVID-19 patients have been reported between March and August 2020. For example, clinicians in the US [Gi] and India [Gii] are quoted in academic news articles as attributing decreased mortality to steroids alongside other improvements in patient care.

Preventing harm: hydroxychloroquine and lopinavir-ritonavir

Benefits to patients and healthcare providers: Learning a treatment is not effective is important, as it protects patients from potential harm and avoids wasting resources. Early in the pandemic, in March 2020, both hydroxychloroquine and lopinavir-ritonavir were widely recommended [B], and hydroxychloroquine was championed by US President Donald Trump. RECOVERY announced in press releases on 5 June and 28 June 2020 that hydroxychloroquine [4] and lopinavir-ritonavir [5], respectively, are ineffective for COVID-19. The large scale of RECOVERY allowed a definitive conclusion – and certainty for clinicians – on the lack of benefit of both treatments among hospitalised patients, which had been initially suggested by smaller trials and non-randomised studies. As a direct result of RECOVERY, other clinical trials of both treatments for severe COVID-19 were rapidly halted, including these arms of the WHO's large, international SOLIDARITY trial [Hi,ii]. NDPH researchers made a major contribution to the design and analysis of SOLIDARITY, and the hydroxychloroquine and lopinavir-ritonavir interim results from SOLIDARITY were consistent with RECOVERY [Hiii]. Both treatments have can have serious side-effects, including potentially fatal heart arrhythmias associated with hydroxychloroquine, so preventing unnecessary and ineffective prescribing reduced risks to patients, as well as avoiding raising false expectations. Proving that these drugs do not work avoided wasted resources for healthcare providers.

Impact on policy and clinical guidelines: The US Food and Drug Administration (FDA) had granted emergency use of hydroxychloroquine and chloroquine for COVID-19 on 28 March 2020, and the US government distributed millions of doses to treat patients not enrolled in clinical trials. As a direct result of the RECOVERY finding, the FDA revoked the emergency approval on 15 July 2020 [Ii], stating *"Only randomized controlled trials can answer the question of whether HCQ or CQ is of clinical benefit in hospitalized patients with COVID-19, and the RECOVERY Trial results offer persuasive evidence of a lack of benefit of HCQ".* Hydroxychloroquine is not recommended by the WHO or EMA for COVID-19, with the EMA citing RECOVERY and SOLIDARITY [Iii]. The lopinavir-ritonavir drug regime is no longer recommended for COVID-19 by any international guidelines. Therefore, three RECOVERY results in little more than three weeks turned COVID clinical guidelines on their head: from widespread use of hydroxychloroquine and lopinavir-ritonavir and low use of dexamethasone in March, to the

opposite pattern in July 2020. Subsequently, RECOVERY also found no benefit from azithromycin in patients hospitalised with COVID-19; this was announced on 14 Dec 2020 [Ji] and on 15 Dec the NHS recommended that azithromycin should not be used for these patients [Jii]. This change avoids inappropriate antibiotic use, which can increase antibiotic resistance.

Media coverage, public perception of evidence-based medicine, and trial design

RECOVERY has played a critical role, through media coverage, in changing the public perception of the importance of evidence-based medicine. During 2020, RECOVERY was covered 15,203 times in the media (online, print and broadcast), and #RECOVERYtrial was mentioned 19,000 times on social media. In particular, RECOVERY's power to counter vocal claims of the beneficial effects of hydroxychloroquine has been an influential tool against fake news. The most prominent example is Twitter limiting the account of Donald Trump Jr and ordering him to delete a misleading tweet containing a video on 28 July 2020 after he made claims about the utility of hydroxychloroquine, which RECOVERY had already proved to be false [K]. Twitter also deleted several tweets shared by US President Donald Trump that contained the false claims, and added a note to its trending topics warning about the potential risks of hydroxychloroquine use [K]. In an article about RECOVERY and SOLIDARITY, expert authors including the Director of the Institute for Evidence-Based Heathcare, Bond University, Australia, commented "*it has been refreshing to see how perfectly such weakly founded claims* [of efficacy] *can be swept aside by evidence from properly conducted, large-scale, randomized trials*" [L].

NDPH research demonstrating the value of linkage (e.g. [2]) drove the establishment, in Sep 2019, of NHS DigiTrials, led by Landray, with IBM, Microsoft and NHS Digital [M]. It facilitates the use of routine health care data by any clinical trial team in the UK to enable more and better trials.

5. Sources to corroborate the impact

A. Letters from UK Chief Medical Officers to NHS Trusts: i) 16 March 2020 from Chief Medical Officer of England and NHS England Medical Director, ii) 18 Aug 2020 from Chief Medical Officers of all UK nations
B. A Dagens *et al*. "Scope, quality, and inclusivity of clinical guidelines produced early in the covid-19 pandemic", *British Medical Journal,* 26 May 2020, DOI: 10.1136/bmj.m1936.
C. International recommendations to use dexamethasone for hospitalised COVID-19 patients: i) Alert from UK Chief Medical Officer to NHS Trusts, 16 June 2020; ii) US NIH, COVID-19 treatment guidelines, 17 July 2020; iii) news report of Saudi Arabia Ministry of Health decision, 17 June 2020; iv) news report of South Africa's health ministry decision, 20 June 2020; v) news report on India's health ministry approval, 27 June 2020; vi) WHO Corticosteroids for COVID-19 living guidance, 2 Sept 2020; vii) EMA endorsement and product template, 18 Sept 2020.
D. Aguas R. *et al*. "The potential health and economic impact of dexamethasone treatment for patients with COVID-19", *Nat Comms* 12, 915 (202) DOI: 10.1038/s41467-021-21134-2
E. Reports of increased demand for dexamethasone in the US: i) news release from Vizient Inc; ii) independent analysis of US hospital dexamethasone usage over time by Aetion.
F. ISARIC COVID-19 clinical data report, 20 Nov 2020 DOI: 10.1101/2020.07.17.20155218
G. COVID-19 death rate articles: i) The Conversation, 3 Nov 2020; ii) Nature, 11 Nov 2020
H. WHO SOLIDARITY trial reports: i) WHO news report on stopping hydroxychloroquine, 17 June 2020; ii) WHO news on discontinuing lopinavir-ritonavir and hydroxychloroquine, 4 Jul 2020; iii) SOLIDARITY trial, publication of interim results, *N Engl J Med*, 2 Dec 2020, DOI: 10.1056/NEJMoa2023184, showing no benefits to patients.
I. International guidelines on hydroxychloroquine: i) US FDA revocation of emergency approval, 15 July 2020; ii) EMA guidelines on hydroxychloroquine
J. RECOVERY results on azithromycin: i) press release from RECOVERY trial 14 Dec 2020; ii) NHS alert recommending against use of azithromycin, 15 Dec 2020
K. News report in the Washington Post, 28 July 2020
L. Correspondence "COVID-19 clinical trials: learning from exceptions in the research chaos", *Nature Medicine*, 22 Sep 2020, DOI: 10.1038/s41591-020-1077-z
M. NHS DigiTrials website (https://digital.nhs.uk/services/nhs-digitrials)