Institution: University of Nottingham		
Unit of Assessment: UoA1		
Title of case study: Identifying dexamethasone as a lifesaving treatment for ventilated COVID-19 patients		
Period when the underpinning research was undertaken: 2012 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): 1. Professor Wei Shen Lim 2. Professor Lelia Duley 3. Dr Clare Brittain	**Role(s) (e.g. job title):** 1. Consultant Respiratory Physician (NHS) and Honorary Professor of Medicine (University of Nottingham) 2. Professor of Clinical Trials Research 3. Senior Trial Manager	**Period(s) employed by submitting HEI:** 1. Nottingham University Hospital/University of Nottingham 2003– present. 2. March 2011-September 2017 3. February 2013-present
Period when the claimed impact occurred: 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Research into pandemic preparedness at the University of Nottingham was adapted into the dexamethasone arm of the RECOVERY trial, from which dexamethasone was the first drug shown to improve survival of patients with severe respiratory complications from COVID-19. In 2015, researchers at the University of Nottingham developed the multi-centre Adjuvant Steroids in Adults with Pandemic Influenza (ASAP) trial, a clinical trial 'in hibernation' that was ready to be activated in a pandemic, as part of national preparedness planning for public health emergencies. Professor Wei Shen Lim is a core member of the RECOVERY trial team, and influenced the adaption of the ASAP trial in March 2020 to form the **dexamethasone arm** of the RECOVERY trial. This study arm demonstrated that dexamethasone could reduce death rates by **one-third** in ventilated COVID-19 patients. The World Health Organisation, the European Medicines Agency and the National Institutes of Health now recommend dexamethasone and it is now used worldwide for the treatment of ventilated COVID-19 patients.

2. Underpinning research

The problem

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease (COVID-19), emerged in China in late 2019 from a zoonotic source. As of the 15th December 2020, the World Health Organization (WHO) reported over 70,000,000 COVID-19 cases and 1,600,000 deaths globally since the start of the pandemic. A resurgence in the number of new cases in late 2020 and continued growth in some countries threatened high resource and low resource countries alike.

The majority of COVID-19 cases present as asymptomatic or result in only mild disease. However, in a substantial percentage of patients, a respiratory illness requiring hospital care develops, and such infections can progress to critical illness with respiratory failure requiring prolonged ventilation support. Among patients with COVID-19 who were admitted to hospitals in the United Kingdom (UK) during the 2020 pandemic, the case fatality rate was approximately 26%, a percentage that increased to more than 37% among patients who required invasive mechanical ventilation.

At the outset of the pandemic, no therapeutic agents were known to reduce mortality in hospitalised patients with COVID-19. Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It had been proposed that the potent anti-inflammatory effects of glucocorticoids, a class of corticosteroids, might prevent or mitigate these deleterious effects, but the value of these therapeutic interventions had been widely debated. The absence of reliable evidence from large-scale randomised clinical trials meant there was uncertainty about the effectiveness of glucocorticoids in patients with COVID-19.

The research

ASAP trial

In response to delays in research for 2009 influenza A/H1N1, in **2012** the National Institute for Health Research (NIHR) funded a portfolio of projects, which were put on standby in a 'hibernating' state awaiting activation in the event of an influenza pandemic. In response to the COVID-19 pandemic, these NIHR projects were repurposed and activated.

In **2012** Professor Wei Shen Lim led on the development of the multi-centre Adjuvant Steroids in Adults with Pandemic Influenza (ASAP) trial, working with Dr Clare Brittain and Professor Lelia Duley at the University of Nottingham **[1]**. This trial was developed as a 'hiberating' clinical trial that was ready to be activated in a future pandemic, as part of national preparedness planning for public health emergencies. The trial was designed to evaluate whether or not low-dose corticosteroids given as an adjunct to standard treatment is beneficial in patients hospitalised with severe pandemic influenza.

Hurdles to setting up a pandemic trial include planning for pandemic-level pressures on UK NHS resources and co-enrolment of patients to multiple pandemic studies, ensuring adequate geographical distribution of participating sites, maintaining long-term low-level engagement with site investigators, addressing future trial-specific training needs of local investigators and resilience planning in trial management. The ASAP trial was set up with full ethics and regulatory approvals in place, ready for rapid activation at the onset of a pandemic.

RECOVERY trial

Professor Lim is a member of the New and Emerging Respiratory Viruses Threats Advisory Group (NERVTAG) which advises the Department of Health and Social care on emerging viral respiratory threats. NERVTAG recommended the evaluation of low dose steroids in patients hospitalised with COVID-19. In **March 2020**, the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial was established as a randomised clinical trial to test a range of potential treatments for COVID-19, including a study arm investigating the efficacy of low-dose dexamethasone (a steroid treatment). The **dexamethasone arm** of the RECOVERY trial was adapted from the ASAP trial **[2]**.

In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with COVID-19, a total of 2104 patients were randomly assigned to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days and 4321 patients to receive usual care **[3]**. The primary outcome measure was 28-day mortality. In patients hospitalised with COVID-19, the use of dexamethasone reduced deaths by one-third in ventilated patients and by one fifth in other patients receiving oxygen only. There was no benefit among those patients who did not require oxygen or respiratory support. Based on these results, **1 death would be prevented by treatment of around 8 ventilated patients or around 25 patients requiring oxygen alone.**

Professor Lim was actively involved in the **dexamethasone arm** of the RECOVERY trial as the co-investigator on RECOVERY, is a member of the RECOVERY Trial Steering Committee and the Writing Committee and was **joint first author** on the peer-reviewed publication of results **[3] [A]**.

3. References to the research

Research

1. **Lim W**, **Brittain C**, **Duley L**, Edwards S, Gordon S, Montgomery A et al. Blinded randomised controlled trial of low-dose Adjuvant Steroids in Adults admitted to hospital with Pandemic influenza (ASAP): a trial 'in hibernation', ready for rapid activation. Health Technology Assessment. 2015;19(16):1-78. DOI: 10.3310/hta19160
2. Simpson C, Thomas B, Challen K, De Angelis D, Fragaszy E, Goodacre S , S., Hayward, A., **Lim, W. S.**, Rubin, G. J., Semple, M. G. and Knight, M. The UK hibernated

pandemic influenza research portfolio: triggered for COVID-19. The Lancet Infectious Diseases. 2020;20(7):767-769. DOI: 10.1016/S1473-3099(20)30398-4
3. Horby P. **Lim, W. S**., Emberson J. R., Mafham, M., et al. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. New England Journal of Medicine. 2020. DOI: 10.1056/NEJMoa2021436

Grant
2012 NIHR: Double-blinded randomised controlled trial of early low dose steroids in patients admitted to hospital with influenza infection during a pandemic. CI: Professor Wei Shen Lim. £1,658,057.00

4. Details of the impact

Adapted from the ASAP trial, the **dexamethasone arm** of the RECOVERY trial provides evidence that treatment with dexamethasone at a dose of 6 mg once daily for up to 10 days reduces 28-day mortality in patients with COVID-19 who are receiving respiratory support **[2]**. These findings indicate dexamethasone could reduce death rates by one-third in ventilated COVID-19 patients.

Dexamethasone was the first drug tested in the RECOVERY trial and is the first treatment to be shown to improve survival in patients with severe respiratory complications from COVID-19. Dexamethasone is inexpensive, readily available and can be used immediately to save lives worldwide. Given the public health importance of these results, the World Health Organisation (WHO), the European medicines Agency (EMA), and countries such as the United Kingdom (UK) and the United States of America (USA) provided rapid response recommendations of the clinical use of dexamethasone, in order to reduce death rates. In July 2020, it was predicted that approximately 650,000 lives could be saved globally by January 2021 by using dexamethasone to treat COVID-19 patients receiving respiratory support, assuming similar effect sizes in low and middle-income countries **[B]**.

WHO recommends dexamethasone treatment

WHO provides clinical guidance on infectious disease treatment for all countries and health care systems. On **2nd September 2020**, WHO published guidance for clinicians and health care decision-makers on the use of corticosteroids in patients with COVID-19, including the use of dexamethasone following the results from the RECOVERY trial **[C]**. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group used the preliminary published report **[3]** of the dexamethasone arm of the RECOVERY trial on **22nd June 2020** in their appraisal of the value of corticosteroids. WHO partnered with investigators of seven trials on corticosteroids to conduct a meta-analysis of these trials, in order to rapidly provide additional evidence building on data from the RECOVERY trial and to inform guidance development **[D]**.

WHO partnered with the non-profit Magic Evidence Ecosystem Foundation (MAGIC) for methodologic support, to develop and disseminate living guidance for COVID-19 drug treatments **[E]**. WHO recommended systemic corticosteroids, including dexamethasone, for the treatment of patients with severe and critical COVID-19 **[E]**. Corticosteroids are listed in the WHO model list of essential medicines, and are readily available globally at a low cost, making it an effective medicine to recommend across both high-income countries (HICs) and low and middle-income countries (LMICs). In a press release to announce these corticosteroid guidelines for COVID-19 use, the WHO encouraged countries '*to maintain sufficient stocks of corticosteroids to treat COVID-19 and the other disease for which they are effective, while not maintaining excessive stocks which could deny other countries access*' **[C]**.

The WHO recommendation for treating patients with COVID-19 is as follows: '*The panel made two recommendations: a strong recommendation for systemic (i.e. intravenous or oral) corticosteroid therapy (e.g. 6 mg of **dexamethasone** orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 hours) for 7 to 10 days in patients with severe and*

critical COVID-19, and a conditional recommendation not to use corticosteroid therapy in patients with non-severe COVID-19' **[E, pg.7]**.

United Kingdom recommends dexamethasone treatment
Following the demonstrated clinical benefit in COVID-19 patients in the dexamethasone RECOVERY trial study arm, on the **24th June 2020** the UK Government recommended dexamethasone for the management of hospitalised patients with COVID-19 who require oxygen or ventilation **[F]**. Out of hospital treatment was recommended as not appropriate.

The UK Government's Chief Scientific Adviser, Sir Patrick Vallance, said: '*This is tremendous news today from the RECOVERY trial showing that dexamethasone is the first drug to reduce mortality from COVID-19. It is particularly exciting as this is an inexpensive widely available medicine.*

This is a ground-breaking development in our fight against the disease, and the speed at which researchers have progressed finding an effective treatment is truly remarkable. It shows the importance of doing high quality clinical trials and basing decisions on the results of those trials' **[G]**.

For the UK, in July 2020 it was estimated that using dexamethasone to treat COVID-19 patients receiving respiratory support may prevent **approximately 12,000 deaths** by January 2021 **[B]**.

European Medicines Agency recommends dexamethasone treatment
In September 2020, the European Medicines Agency (EMA) reviewed evidence resulting from the dexamethasone RECOVERY trial study arm and concluded that dexamethasone can be considered a treatment option for patients with COVID-19 who require oxygen therapy **[H]**. The recommended dose in adults and adolescents is 6mg once a day for up to 10 days, the same treatment used in the RECOVERY trial study arm.

National Institutes of Health recommends dexamethasone treatment
The National Institutes of Health (NIH), a part of the U.S. Department of Health and Human Services, is one of the world's foremost medical research centres. On the basis of the preliminary report from the dexamethasone arm of the RECOVERY trial, the NIH now recommends using dexamethasone for the treatment of COVID-19 in hospitalised patients who are mechanically ventilated and in hospitalised patients who require supplemental oxygen but who are not mechanically ventilated **[I pg.1]**. The Panel recommends against using dexamethasone for the treatment of COVID-19 in patients who do not require supplemental oxygen.

Recommendation of dexamethasone in individual countries
Canada, Ireland, South Africa, and Belgium are among the various countries that recommend using dexamethasone to treat hospitalised cases of COVID-19 who require oxygen or ventilation, all of which reference the RECOVERY trial as supporting evidence in this recommendation **[J]**. It was predicted that approximately 650,000 lives could be saved globally by January 2021 by using dexamethasone to treat COVID-19 patients receiving respiratory support, assuming similar effect sizes in low and middle-income countries **[B]**.

5. Sources to corroborate the impact

[A] Testimonial from Chief Investigator of RECOVERY trial, University of Oxford, December 2020.
[B] AGUAS, R., Mahdi, A., SHRETTA, R., Horby, P., Landray, M. and White, L., 2020. The potential health and economic impact of dexamethasone treatment for patients with COVID-19. medRxiv DOI: 10.1101/2020.07.29.20164269
[C] WHO updates clinical care guidance with corticosteroid recommendations. September 2020 https://www.who.int/news-room/feature-stories/detail/who-updates-clinical-care-guidance-with-corticosteroid-recommendations

[D] Sterne J, Murthy S, Diaz J, Slutsky A, Villar J, Angus D et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19. JAMA. 2020;324(13):1330 DOI: 10.1001/jama.2020.17023
[E] WHO guidance on corticosteroids for COVID-19. September 2020 https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1
[F] COVID-19 Therapeutic Alert UK – Dexamethasone in the treatment of COVID-19. Department of Health & Social Care. June 2020. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103054
[G] RECOVERY trial Press release - Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19 https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_v2final.pdf
[H] European Medicines Agency endorses use of dexamethasone. September 2020 https://www.ema.europa.eu/en/news/ema-endorses-use-dexamethasone-covid-19-patients-oxygen-mechanical-ventilation
[I] National Institutes of Health COVID-19 Treatment guidelines November 2020 https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/corticosteroids/
[J] Combined evidence document, confirming dexamethasone use for ventilated COVID-19 patients in international countries.