Institution: Lancaster University		
Unit of Assessment: 10, Mathematical Sciences		
Title of case study: Clinical trial designs by Lancaster University statisticians result in rapid discovery of COVID19 treatments		
Period when the underpinning research was undertaken: 2012-20		
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:**
- Thomas Jaki - John Whitehead - Andrew Titman - Pavel Mozgunov	- Lecturer, now Professor in Statistics - Emeritus Professor in Statistics - Lecturer now Senior Lecturer in Statistics - Lecturer in Statistics	- 01/06/07-present - 01/10/07-present - 10/06/08-present - 01/10/15-present
Period when the claimed impact occurred: Jan 1st 2020 – Dec 31st 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Lancaster University statisticians have played a leading role in the global response to the Covid-19 pandemic. Drawing on a sustained body of Lancaster University research into the design of adaptive clinical trials (carried out since 2007) Prof Jaki, Dr Mozgunov, and Dr Titman played a central role in the design and ongoing adaptation of the world-leading RECOVERY clinical trial and AGILE trial platform. Their novel designs were chosen as they allow for extremely rapid and more accurate decision-making than standard designs. These novel statistical methodologies have resulted in the following headline impacts:

- **Discovery of the first effective treatment** (dexamethasone) for hospitalised patients suffering from severe COVID-19 symptoms. It is estimated to have saved over 12,000 lives in the UK, and up to 650,000 globally by 1 January 2021.
- **Rapid identification of ineffective treatments** (including hydroxychloroquine, lopinavir-ritonavir, and azithromycin), enabling health services across the globe to focus resource on more effective treatments.
- **Identification of safe and correct dosages for a novel treatment** (EIDD-2801), which has rapidly progressed to later phase trials to test efficacy in frontline services.
- **Brought about changes to policy and published guidance** offered by national and international bodies, including: the UK Government, World Health Organisation (WHO), European Medicines Agency (EMA) and the National Institutes for Health in the US.

2. Underpinning research (indicative maximum 500 words)

Lancaster statisticians have developed a large corpus of fundamental research into the design of early and late phase clinical trials, and especially in adaptive trial designs, where the allocation of patients to treatments in later stages of the trial depends on the outcomes of earlier patients in the trial. These methods allow quicker and/or more accurate decision-making leading to faster development of novel treatments and savings in development costs. These features are critically important in an epidemic situation, and Lancaster's trial designs have played a pivotal role in the rapid development of COVID-19 treatments. The research underpinning this case study falls into two strands:

2.1 Multi-arm multi-stage (MAMS) trials

In contrast to traditional studies, which compare a single novel treatment to a control, these designs consider evaluating multiple treatments in one study simultaneously and have the potential to drop ineffective arms before the trial ends. They result in more efficient use of patients, since they compare multiple treatments to a single control arm and avoid allocating patients unnecessarily to ineffective treatments that can be eliminated quickly from the trial. The research article [3.1] develops a novel multi-arm multi-stage design where several active treatments are compared to a common control. The design allows for early stopping and at each stage retains only the treatments that are sufficiently promising. The design is the first MAMS design to control the familywise error rate in the strong sense (a common regulatory requirement) and enables analytic sample size calculations. The work presented in [3.4] expands the MAMS framework to enable unplanned modifications, which allows new treatments to be added to

an existing trial. Building on the experience of using these designs, general guidance for MAMS trials has been produced [3.2]. A novel estimation approach for these methods was developed [3.3] to ensure adequate analysis and enable (nearly) unbiased estimation.

2.2 Adaptive dose-finding trials

In the early phases of treatment development, it is important to rapidly establish safe and effective doses of a treatment that will be subsequently studied in larger trials. The Lancaster group has a long record of developing bespoke adaptive methodologies to do so in an efficient manner in advanced clinical trials. While dose-finding designs are conventionally developed for non-randomized settings, the methodology of [3.5] brings randomization to dose-finding, which has proven to be essential if symptoms of the disease overlap with common side effects of the treatment as for COVID-19. This method was adapted and deployed in the AGILE platform [3.6] to provide a method for rapidly finding optimal dose of multiple COVID-19 candidate treatments. The Lancaster Group has also developed a number of adaptive dose-finding methodologies for trials of dose- schedules. The methods in [3.7] allow for efficient dose-schedule finding for drugs with unknown optimal mode of administration. Building on these, trial designs for several AGILE platform compounds were proposed. The Lancaster Group has also extensively contributed to the implementation of novel adaptive methodologies in clinical trials in various therapeutic areas and actively collaborated with pharmaceutical companies to accelerate their use in practice. The computational and communication tools developed during these projects fed into a more effective and rapid implementation of novel methodologies in the AGILE platform.

3. References to the research (indicative maximum of six references)

Multi-arm multi-stage:

3.1 Magirr D., **Jaki T.**, and **Whitehead J.** (2012) 'A generalized Dunnett test for multi-arm multistage clinical studies with treatment selection', *Biometrika*, 99(2), pp. 494-501. **Cited >80 times** https://doi.org/10.1093/biomet/ass002.

3.2 Wason J., Magirr D., Law M., and **Jaki T.** (2016) 'Some recommendations for multi-arm multi-stage trials', *Statistical Methods in Medical Research*, 25(2), pp.716-727 https://doi.org/10.1177/0962280212465498.

3.3 **Whitehead J.**, Desai Y., and **Jaki T.** (2020) 'Estimation of treatment effects following a sequential trial of multiple treatments', *Statistics in Medicine*, 39(11), pp.1593-1609 https://doi.org/10.1002/sim.8497.

3.4 Magirr D., Stallard N., and **Jaki T.** (2014) 'Flexible sequential designs for multi-arm clinical trials', *Statistics in Medicine*, 33(19), pp.3269-3279. https://doi.org/10.1002/sim.6183.

Dose-finding:

3.5 **Mozgunov P.**, **Jaki T.**, and Paoletti X. (2019) 'Randomized dose-escalation designs for drug combination cancer trials with immunotherapy', *Journal of Biopharmaceutical Statistics*, 29(2), pp.359-77. https://doi.org/10.1080/10543406.2018.1535503.

3.6 **Jaki T.,** Barnett H., **Titman A.,** and **Mozgunov P.** (2020) 'A Seamless Phase I/II Platform Design with a Time-To-Event Efficacy Endpoint for Potential COVID-19 Therapies', (Preprint arXiv: 2010.06518) https://arxiv.org/abs/2010.06518.

3.7 **Mozgunov P.** and **Jaki T.** (2019), 'An information theoretic phase I–II design for molecularly targeted agents that does not require an assumption of monotonicity,' *Journal of the Royal Statistical Society*, Series C, Applied Statistics, 68(2), pp. 347-367 https://doi.org/10.1111/rssc.12293.

4. Details of the impact (indicative maximum 750 words).

Statisticians based at Lancaster University have played a leading role in helping to identify the effectiveness of established and novel treatments as part of the RECOVERY trial and AGILE platform, helping to save lives and mitigate the harmful effects of COVID-19 at a national and global scale. Their rapid design and implementation of efficient Multi-Arm Multi-Stage (MAMS) and sequential dose-finding trials, the production of guidance documents for practitioners and clinicians, and their expert consultation as members of steering committees on major national trials, have resulted in a series of world-leading clinical breakthroughs.

4.1 Impact of Lancaster University statisticians on the statistical approach adopted by RECOVERY trial: RECOVERY is the UK's leading national clinical trial for COVID-19 treatments in hospitalized patients. It has so far enrolled 23,000 patients, across 176 sites, to test 5 different treatments, making it the largest trial of its kind in the world. Jaki, as the lead statistician on the RECOVERY trial steering committee, was responsible for the design and implementation of the MAMS approach adopted by the trial, which drew on methodologies he devised in [3.1] and [3.2]. As Professor Peter Horby, Chief Investigator of the RECOVERY trial has said of the contribution made by Lancaster University research: *"Underpinning this trial has been the design of Professor Thomas Jaki, who is Co-Investigator of the trial and member of the trial steering committee. Building on our earlier collaboration on clinical trial designs for epidemic infectious diseases, Prof. Jaki and I worked closely together during the early stages of the pandemic on the design of clinical trials for Covid-19."* He goes on to describe how Jaki used his research insights in [3.1] and [3.4] in the *"initial design of the study and has been integral in subsequent modifications of the platform. This efficient design together with the pragmatism of the study have been key to deliver policy-changing evidence for treatments of COVID-19 in record time"* [5.1]. The research methodologies also continue to inform the ongoing development and modification of the RECOVERY trial as it ventures into later phase testing and research: *"The trial is currently entering a new phase in which more experimental treatments (rather than re-purposed agents) will be explored within the platform and Prof Jaki is contributing substantially to the design of these evaluations once more. This includes the imminent addition of a paediatric Phase II sub-study with Bayesian methods"* [3.1] and [5.1].

4.2 Global adoption of dexamethasone as the first confirmed effective treatment for COVID-19: A major impact of the trial, and a direct consequence of its innovative statistical approach, was the rapid identification of dexamethasone as the first effective treatment for COVID-19 patients – formally announced on 16 June 2020 [5.2]. This breakthrough showed that it was effective in up to one-third of hospitalised cases and has since resulted in the successful treatment of over 20,000 patients in the UK as well as 650,000 worldwide [5.1]. It was heralded by the New York Times as *"a major discovery"* that has *"transformed COVID-19 care worldwide,"* and demonstrates *"the critical need for randomised trials to separate drugs we hope work from treatments we know work"* [5.3a]. Likewise, an article in Nature ascribed the trial's success to its *"short, flexible protocol – just 20 pages long – that laid out the design and data and regulatory requirements, [which] allowed trial arms to be halted or added"* in an adaptive and rapid manner [5.3b]. The Director-General of the World Health Organisation (WHO), Dr Tedros Adhanom Ghebreyesus, has also publicly applauded the work of RECOVERY: *"This is the first treatment to be shown to reduce mortality in patients with COVID-19 requiring oxygen or ventilation support,"* describing it as a *"lifesaving scientific breakthrough"* [5.3c].

These findings resulted in widespread changes to national and international policy guidelines. On the 2nd September, the WHO announced a change in their guidance on the use of Corticosteroids (such as dexamethasone), stating how *"work on this guidance began on 22 June when the RECOVERY trial published a preliminary report on the impact of Corticosteroids"* [5.4]. The findings produced by the RECOVERY trial fed into the WHO's own meta-analysis as part of the SOLIDARITY trial, which looked at data from seven clinical studies investigating the benefits of dexamethasone (the largest of which was RECOVERY) and found the discovery to be robust [5.4]. The European Medical Agency also changed their product information and guidelines in September 2020, following an extensive review of the data provided by RECOVERY, and concluded *"that dexamethasone can be considered a treatment option for patients who require oxygen therapy (from supplemental oxygen to mechanical ventilation)"* [5.5a-b]. These changes in guidance from leading international bodies has resulted in the adoption of the drug in healthcare systems across the globe.

4.3 Identification of hydroxychloroquine, lopinavir-Ritonavir and azithromycin as ineffective treatments for COVID-19: The MAMS trial methods, developed by Lancaster University statisticians and deployed in RECOVERY, resulted in the quick elimination of two treatments (hydroxychloroquine and lopinavir-ritonavir) that were found to be ineffective in combatting the symptoms associated with COVID-19, even pointing to potential harmful effects for patients in both cases and has more recently disqualified a third (azithromycin). The most significant of these discoveries was hydroxychloroquine, which had been widely described as a

potential *"miracle cure"* on social media and by various public figures, including the former President of the United States. This led to global stockpiling, price hikes, and shortages of the drug, with negative consequences for neighbouring fields of health in which the drug is commonly used; for example, 60% of rheumatologists in Africa reported shortages of the drug, leading some to reduce doses for their patients to prolong supply [5.6a]. Against expectation, the RECOVERY trial's randomised testing model very rapidly demonstrated hydroxychloroquine's ineffectiveness, concluding on 5 June 2020, just 78 days from the trial's start, that *"there was no clinical benefit from use of hydroxychloroquine for hospitalised patients with COVID-19"* [5.6b]. This finding resulted in the WHO halting its trial of the drug on 17 June [5.8], and the National Institutes of Health following suit on 20 June [5.6c].

Another drug that had been widely cited as a potential cure was lopinavir-ritonavir – an antiviral treatment commonly used to treat HIV/AIDS. The MAMS design for the RECOVERY trial meant that within the same trial it was shown that, as in the case of hydroxychloroquine, there was no clinical benefit associated with its use versus ordinary care [5.7a-b]. This finding had a major global impact, with healthcare services discontinuing its use, and the WHO halting its own trial of the drug at the same time as hydroxychloroquine [5.8]. Following these initial results (achieved in just three months), the Executive Chair of the Medical Research Council, Professor Fiona Watt, applauded the statistical methodologies and efficiency of these trials, stating publicly that *"The UK's RECOVERY trial is the world's largest randomised trial of potential COVID-19 treatments and has worked with unprecedented speed to start delivering the answers we need."* She goes on to note that *"whilst it is disappointing that lopinavir/ritonavir, like hydroxychloroquine, has been found to be ineffective, the earlier findings with dexamethasone were positive. Researchers and health professionals are now focusing their efforts, and patient care, on other promising drugs"* [5.7a]. Since then, RECOVERY identified azithromycin as another ineffective drug, a result that has again been lauded by the Chair of the Medical Research Council: *"Although it is disappointing that azithromycin isn't an effective treatment for hospitalised COVID-19 patients, negative results are important so that clinicians can focus patient care on drugs that have been shown to work. This is particularly vital for antibiotics like azithromycin, because inappropriate use of antibiotics contributes to bacteria in the body becoming resistant"* [5.9].

4.4 The adoption of Lancaster University's MAMS and adaptive dose-finding methodologies to the AGILE platform and testing of novel treatments for COVID-19: Alongside the need to test existing treatments for their efficacy in fighting COVID-19, there is also an urgent need to explore the potential of novel ones. Trialling novel treatments brings the additional hurdle of identifying safe and effective dose levels. The AGILE trial platform, established in July 2020, brought together experts from the Universities of Lancaster, Liverpool, and Southampton, to tackle these and other problems associated with the identification and trialling of novel drugs. Drawing on their established expertise in the development of adaptive dose-finding [3.5-7] and MAMS [3.1-4] trials, the Lancaster group, headed by Jaki, Mozgunov, and Titman, were tasked with designing and implementing a novel trial infrastructure capable of simultaneously evaluating treatment candidates to find safe and effective dose levels, and thus accelerate progress toward later phase clinical trials [5.10]. Their designs have proven fundamental to AGILE's ongoing success, as Professor Saye Khoo, the platform's Chief Investigator has put it: *"Professor Thomas Jaki, Dr Pavel Mozgunov, and Dr Andrew Titman at Lancaster University have led the development of the AGILE trial design.... their innovative approach… has played a critical role in the rapid set up of the AGILE trial platform and its success to date.'* Moreover, their methods have enabled *'AGILE to carry out extensive national-level trials in an efficient and rapid way. These innovations significantly reduce the time taken to identify safe dose levels and drug effectiveness, resulting in more rapid trials than possible using conventional methods"* [5.10].

Trials for four drugs are currently underway with a further four due to commence in 2021 [5.10]. Currently, the trial consists of four novel compounds: EIDD-2801, VAL-083, VIR-7831, and VIR-7832. EIDD-2801 was one of the first drugs to be included as part of the trial and has seen the most success to date. The Lancaster group established the trial design for both phase 1 and 2 in April, the trial was then approved in July and the first patient randomised in phase 1 in September 2020. Thanks chiefly to the efficiency of the statistical methodologies deployed by the Lancaster group, it commenced phase 2 in November with renewed financial backing (just 2.5 months after the randomisation of the first patient in phase 1). The co-founder and CEO of Ridgeback

Biotherapeutics, who are the company producing and funding the drug, stated that the rapid testing of EIDD-2801 represents *"a tremendous trans-continental effort to bring EIDD-2801 into a Phase 2 efficacy protocol to benefit COVID-19 patients in the U.K. immediately following Phase 1"* [5.11]. Trials of VIR-7831 and VIR-7832 have also seen significant progress toward the end of the REF-period, with GlaxoSmithKline and Vir Biotechnology agreeing to invest over GBP3million in late December to accelerate early-phase development as part of the AGILE programme [5.12]. Though trials are ongoing and remain in an early stage, AGILE's success was recognised by the UK government, when on 16th December 2020 it was officially designated a *"national platform"* (alongside RECOVERY), meaning that all early phase trials of novel drugs intending to use NHS resource must now go through the AGILE platform [5.13]. Consequently, two of the UK's four national platforms are now underpinned by Lancaster University research.

5. Sources to corroborate the impact (indicative maximum of ten references)

5.1 Testimonial letter provided by Principal Investigator RECOVERY Trial: demonstrating Jaki's contribution to the design of the randomised MAMS trial that underpins RECOVERY, and the impact of the trial nationally and internationally.

5.2 Press Release by RECOVERY trial: Low-cost dexamethasone reduces death by up to one third in hospitalised patients (16 June 2020)

5.3 News media coverage of the discovery of Dexamethasone as an effective treatment: a) New York Times Article: Where Is America's Groundbreaking Covid-19 Research? (Sept. 2020) b) Nature article: How we accelerated clinical trials in the age of coronavirus (Aug. 2020) c) WHO press release: WHO welcomes preliminary results about dexamethasone (16 June 2020)

5.4 Press Release by WHO announcing change of guidance on effectiveness of Corticosteroids: WHO updates clinical care guidance with corticosteroid recommendations (Sept. 2020)

5.5 EMA press releases relating to dexamethasone: a) Press release announcing rapid review of dexamethasone following findings published by RECOVERY: EMA starts review of dexamethasone (July 2020) b) Press release announcing EMA adoption of dexamethasone as an effective treatment for COVID-19: EMA endorses use of dexamethasone (18 Sept. 2020)

5.6 News media coverage of hydroxychloroquine findings: a) Article discussing drug shortages in Africa: COVID-19 and African rheumatology: progress in adversity (Sept. 2020) b) Press Release by RECOVERY trial: No clinical benefit from use of hydroxychloroquine (June 2020) c) National Institutes of Health Press Release: NIH halts clinical trial of hydroxychloroquine (20 June 2020)

5.7 News media coverage of lopinavir-ritonavir findings: a) Press Release by RECOVERY trial: No clinical benefit from use of lopinavir-ritonavir (29 June 2020) b) The Pharmaceutical Journal article discussing trial methods and findings: Lopinavir/ritonavir 'not effective' (June 2020 - hard copy available)

5.8 WHO Press Release: WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19 (4 July 2020)

5.9 Article by UKRI: Azithromycin has no benefit for hospitalised COVID-19 patients (14 December 2020)

5.10 Testimonial from Chief Investigator for AGILE Clinical Trial Platform demonstrating the impact of the Lancaster team on the design, implementation and ongoing maintenance of the trial underpinning the AGILE platform.

5.11 News article announcing commencement of phase 2 trials of EIDD-2801: Ridgeback Biotherapeutics Announces Potential COVID-19 Treatment EIDD-2801 (7 July 2020)

5.12 GBP3million Investment for trial of VIR-7831 and VIR-7832: Two new therapies to be tested in ground-breaking COVID-19 clinical trial (January 2021)

5.13 Guidance from the department of Health and Social Care on national platform clinical trials: Guidance: making a proposal for COVID-19 therapeutics clinical trials (16 December 2020)