Witness Name: Professor Anthony Gordon
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UK COVID-19 INQUIRY
MODULE 4

WITNESS STATEMENT OF Professor Anthony Gordon

I, Anthony Gordon, of the Division of Anaesthetics, Pain Medicine and Intensive Care at Imperial College London, Exhibition Road, London SW7 2BX will say as follows: -

Roles and responsibilities

1. I am the UK Chief Investigator (CI) of the Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP). As CI, I take primary responsibility for the conduct of the trial in the UK. This is a global clinical trial consisting of an international network of leading experts, institutions and research networks. As UK CI, I am a member of the International Trial Steering Committee which has overall responsibility for the trial across all regions, and I am delegated responsibility for conduct of the trial in the UK by the trial Sponsor (legally responsible body) in Europe, University Medical Centre Utrecht (UMCU). In the overall international trial, I also chair the Prioritisation Committee (reviewing new interventions to be included in the trial platform) and also the Reporting and Analysis Group, coordinating the scientific reporting of trial results.

2. In the UK, the trial is managed by a team at Imperial College London, in collaboration with the Intensive Care National Audit and Research Centre (ICNARC). At the start of the pandemic the key individuals in the UK trial management were Dr Farah Al-Beidh, UK trial manager at Imperial, Prof Kathy Rowan, Director of ICNARC clinical trials unit and Mr Paul Mouncey, Head of Research at ICNARC. All three were members of the International Trial Steering

Committee. At various times additional trial management personnel from both Imperial and ICNARC helped manage the trial. Initially these people were drafted in from other trials that were on hold in the pandemic, and later new staff were recruited (See **AG/1** INQ000474281). The collaboration between Imperial and ICNARC enabled the trial to have senior clinical academic leadership combined with experienced critical care trials and data management. In addition, as we added new interventions in the pandemic, we added new investigators within the UK, including Prof Danny McAuley (Intensive Care, Queens University Belfast), Prof Manu Shankar-Hari (Intensive Care, University of Edinburgh), Prof Lise Estcourt (Transfusion Haematology, University of Oxford and NHS Blood and Transplant), and Dr Charlotte Bradbury (Thrombosis Haematology, University of Bristol).

Genesis, design and set up

3. We set-up REMAP-CAP after the 2009 H1N1 pandemic with the broad objective to determine and continuously update the optimal set of treatments for patients in hospital due to community-acquired pneumonia. It uses a novel and innovative adaptive trial design to evaluate multiple treatment options simultaneously and efficiently. Our aim was for the trial to be set-up, approved and running in an inter-pandemic period evaluating treatments for severe pneumonia due to common infections and it was designed so that it could easily and rapidly adapt to evaluate treatments for pandemic infections if and when they occurred.

4. We designed the trial using novel, innovative design features and statistical methods to evaluate a range of treatment options as efficiently as possible in a pandemic. We use a type of analysis called Bayesian, that allows answers to be reported as soon as clear results are reached, rather than waiting until fixed numbers of patients have been studied. We test multiple different treatments at the same time and can also look at how these treatments work together (interact). As the trial progresses it also learns from the early results, allocating more patients to treatments that look most encouraging. In this way patients in the trial may benefit even before all the results are known.

5. Although we planned the trial for a pandemic, a number of changes were required to provide valuable answers due to COVID-19. These included modifications to the trial eligibility criteria (to define a new disease that hadn't occurred before), the primary outcome measure (to provide results more rapidly for short-term outcomes that correlate with longer outcomes, and also assess resource use) and timelines for analysing and reporting trial results. The first such amendment to the protocol was made on 31 January 2020. The first patient with COVID-19 was recruited into REMAP-CAP on 9 March 2020. This early recruitment was possible because we already had funding in place (detailed in point 6 below) that meant we had written an initial protocol that could be adapted for a pandemic, obtained regulatory approvals, had data systems in place to capture information and had trial management staff in place to coordinate the conduct of the trial before the pandemic started.

6. Prior to the pandemic the trial was funded by a grant from the EU (£150,515 to Imperial as part of the larger PREPARE grant FP7-HEALTH-2013-INNOVATION-1, #602525) and 12 sites in the UK were recruiting to non-pandemic infections. In early March 2020 we approached the NIHR and DHSC via the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) to expand REMAP-CAP to more sites in the UK. REMAP-CAP then received Urgent Public Health (UPH) badging on 31 March 2020 and additional funding from the NIHR (final total £1,237,495). This enabled us to open as many recruiting sites as possible in the UK. At the maximum we opened 143 different NHS hospital trusts for recruitment. The UPH badge also meant that protocol amendments submitted to the independent Research Ethics Committee (REC), the Medicines and Healthcare products Regulatory Agency (MHRA), the Health Research Authority (HRA) were given an expedited review which enabled rapid roll-out and adaptions over time. This was crucial to successful timely delivery of the trial during the pandemic. These approval timelines were much faster than standard procedures and also some amendments were streamlined, e.g. normally the addition of a new recruiting site or lead investigator at a site requires a substantial amendment. We were given approval in advance to add all hospitals in the UK and regularly update a shared list with the MHRA.

7. We originally designed the trial to evaluate treatments for critically ill patients as this group of patients has the highest rate of mortality, long-term morbidity and use the highest proportion of expensive and limited medical resources, i.e. intensive care beds and mechanical ventilators. In previous pandemics the speed of clinical progression of the infection meant that people who became critically ill would often become critically ill either at hospital admission or very soon after. However, early in the pandemic it became apparent that disease progression of COVID-19 was slower than other viral pneumonias and therefore there would be more patients managed in general wards and so the inclusion criteria for REMAP-CAP were changed to include non-critically ill patients on 18 May 2020. In the UK the majority of patients recruited were critically ill. Of the total of 5,580 patients recruited, approximately 6% were not-critically ill. Globally 10,297 patients with COVID-19 have been recruited.

Oversight, governance, organisational structure and decision-making

8. The global trial is governed by the International Trial Steering Group who remain blinded to emerging data within the trial. (See AG/2 INQ000474280) There is one Core protocol that defines the scientific principles of the trial that applies everywhere in the world. As governance and regulatory processes vary in different regions and countries, these regional specific details are included in Regional Specific Appendices to the Core protocol and the local management of the trial is devolved to regional Sponsors (legally responsible bodies) and regional management committees (RMC). The aim is that the science and clinical details of the trial are universal but managed according to local requirements. The trial is modular so not every region or site has to take part in every part of the platform but where they do, the scientific protocol is the same.

9. There is a Statistical Analysis Committee (SAC), separate from the blinded ITSC via a firewall, who undertake the regular adaptive analyses to inform the independent Data Safety Monitoring Board (DSMB) about emerging results. The DSMB is made up of international, expert, independent clinicians, academics, trialists and statisticians. Based on the reports from the Statistical Analysis Committee and safety reports from the Data Coordination Centre, the DSMB

advise the ITSC when an intervention has reached pre-specified criteria for effectiveness, futility or harm and should be publicly disclosed. The DSMB can also make additional recommendations, usually for safety, from any emerging results and external evidence.

10. Prior to the pandemic the ITSC, SAC, DSMB, and RMCs were all in existence. We grouped the different interventions into domains (interventions with similar modes of action) which were managed by scientific content experts in Domain Specific Working Groups. As the platform expanded new structures and groups had to be introduced quickly to manage the additional workload and these groups included a Data Coordination Centre at ICNARC, a Prioritisation Committee, a Delivery team, a Reporting & Analysis Group, a Data Access Committee, a New Regions team and a Safety Committee.

Working with external organisations and individuals

11. In the UK once the UPH badge was designated we had regular contact with the NIHR, DHSC and Chief Medical Officer (CMO) office. I would attend the twice weekly NIHR UPH committee to provide regular updates about the trial, the Imperial and ICNARC team worked closely with the NIHR CRN (Clinical Research Network) led by Jonathan Sheffield to ensure support for local recruitment and to provide regular recruitment number updates. The support from the CRN was crucial to delivering the trial at scale and pace throughout the UK. When results emerged, we shared these immediately with Jonathan Sheffield, Jonathan VanTam (Deputy CMO) and Charlotte Taylor (DHSC – Therapeutics Taskforce) and results then disseminated to other bodies, eg RAPID C-19, MHRA, NHS-E and NICE.

Participant selection

12. To be eligible for this trial, participants had to be inpatients in hospital acutely unwell with COVID-19. They were identified and approached by clinical / research staff at the local hospital. The trial was explained by these staff to the participants or, if they lacked capacity to consent, to their next-of-kin (via telephone or video link, as visiting was not allowed in hospital) or to independent doctors. Once

consent was obtained then patients were included into the trial and randomised to the different treatment domains which were available at that site, they were eligible for and had agreed to participate in.

13. To ensure rapid recruitment into the trial we ran regular training sessions online for local staff so as many trained investigators were available to recruit, and we produced short summary documents for both participants and staff to allow simple and quick understanding of the trial.
14. We had also obtained regulatory approval to include patients lacking capacity, to be enrolled in the trial without prior consent, due to the emergency nature of the medical condition. In this situation consent to continue is then sought from the participant when capacity returns or from next-of-kin. This was done in line with standard HRA consent processes for such acute medical emergencies. The overwhelming nature of the pandemic meant the consent process was very difficult for sites. Clinically trained research staff were often called into provide extra clinical cover, many staff were absent as they had to quarantine, some hospitals did not allow paper consent forms for infection control reasons, relatives were not at the bedside to discuss the trial, patients were often moved to other hospitals or discharged home before the follow-up consent processes could be completed.
15. The focus of REMAP-CAP recruitment in the UK was critically ill patients in intensive care, as the RECOVERY trial was largely recruiting "less sick" patients on the wards. For interventions not included in the RECOVERY trial, e.g. anti-coagulation, REMAP-CAP included these patients from the general wards. As eligibility for the trial was based largely on being in hospital with severe COVID-19, we expected to recruit the diverse group of patients known to be admitted to ICU with a high proportion of ethnic minorities and participants from areas with high deprivation, as seen in the regular ICNARC reports. Approximately 25% of the patients recruited in REMAP-CAP were from non-White ethnic groups. This was representative of the national percentage of non-White ethnicities admitted to ICU, reported in the ICNARC COVID-19 report of 8 April 2022, where non-White ethnicities made up between 25% and 28.2% of the general ICU population in England, Wales and Northern Ireland. We provided trial information in multiple languages to help participants who did not speak English. We focussed our recruitment and therapeutic selections to treat the highest-risk and most vulnerable patients based on clinical need, regardless of ethnicity or any other characteristic.

16. We did not have a pre-defined fixed sample size. We deliberately designed the trial to analyse the effect of the different treatments in a Bayesian statistical model. More traditional "frequentist" trial statistics require a number of assumptions to be made in advance about the disease and its treatment. This is to define a hypothesis and then test the results with formal statistical tests once the required sample size has been recruited, to determine if any differences seen are chance findings or not. As COVID-19 was a new disease no such assumptions could be reliably made in advance. A Bayesian analytical model works in a different way. Data about the possible effectiveness of the treatments are accumulated by conducting the trial. Regular analyses of these accumulating data in the Bayesian model are undertaken and if predefined thresholds for effectiveness, futility or harm are crossed then the results are reported. A big treatment effect will be declared quickly with fewer patients included, but smaller effects require larger samples sizes. In this way we report if the drug is beneficial or not, as soon as these pre-defined criteria are met, whatever the sample size.
17. Another advantage of the Bayesian method is that after each analysis a numerical probability of the likely benefit of the intervention is provided. Therefore, even if a pre-defined threshold isn't met a likely percentage chance of effectiveness is provided. This benefit was seen once the dexamethasone (steroid) result was reported from the RECOVERY trial in the summer of 2020. We analysed our data at that point and for the steroid that we were evaluating (hydrocortisone), the Bayesian analysis reported there was a 93% chance that hydrocortisone was beneficial. This provided important independent validation of the RECOVERY result, strengthening treatment guidelines and providing support for alternative drugs, which was vital to relieve drug supply issues in a global pandemic.

Therapeutic selection

18. The process for selection of therapeutics to be evaluated changed over time. Initially (January – March 2020) selection was made by the ITSC based on our clinical expertise and was informed by World Health Organisation (WHO) recommendations on likely therapeutics of interest. It rapidly became apparent that there were multiple possible interventions that were being proposed and so a prioritisation committee of REMAP-CAP investigators with varied expertise was set-up in April 2020. We assessed proposals according to four criteria; 1) biological

and clinical rationale, 2) existing safety information, 3) where the proposed intervention would fit within the existing REMAP-CAP protocol, and 4) how feasible was the intervention to be rolled out to multiple sites in multiple countries. In addition, REMAP-CAP was invited to receive recommendations from UK-CTAP (UK COVID-19 Therapeutics Advisory Panel) from September 2020. Both repurposing of existing drugs and new therapeutics were considered and used the same criteria as above. In general, existing drugs had more safety information and were more feasible to roll out to multiple sites and so were far more likely to be prioritised.

19. I think we covered all appropriate domains of therapy suitable for this population, eventually. Some of the immune modulating drugs were hard to obtain for the trial early in the pandemic and were slow to come into the trial. This was due to multiple reasons including initial safety concerns about immunosuppressive treatment in a novel infection, limited supplies in hospitals often with a single manufacturer who may have been reluctant to release drugs to academic investigators, and cost. Although we found several effective immune modulating drugs, others may have been as or more useful and effectiveness of combination therapy remains uncertain. The DHSC were very helpful to arrange and coordinate national supplies of drugs for the trial. We met with members of the DHSC weekly to manage drug supplies from manufacturers, suitable central storage and then regular shipment to recruiting sites.
20. In hindsight the most useful aspect of therapeutic selection was to have an independent body (UK-CTAP) to review the possible interventions and make recommendations about which agents should be prioritized. The sheer number of potentially plausible interventions was too much for any one trial to consider or to have the "in-house" expertise amongst its own investigators to make informed, objective assessments. We were inundated with proposals submitted for inclusion in the trial from a huge range of clinicians, academics, industry or members of the public. It would also have been useful if UK-CTAP could have played a role in coordinating which interventions should be prioritised for which of the UPH trials. This would have been useful because different therapeutics are more likely to have most benefit in different stages of COVID-19 and different trial characteristics may have made one trial a better option to test a drug or even a combination of

therapies. This happened towards the end of the pandemic but would have been useful earlier.

21. In my opinion UK-CTAP did an excellent job of considering the whole range of possible treatments, including small molecule anti-virals and neutralising monoclonal antibodies. As COVID-19 has a more prolonged disease course than other respiratory viral illnesses, by the time patients became sick enough to need hospital and ICU care, direct anti-viral treatments were not shown to be particularly useful to save lives and improve outcomes. Treatments that modulated the body's response to the virus were key to improving care for patients in hospital.

Conduct of the trial in practice

22. Once the trial received UPH badging, we provided regular weekly updates to the NIHR UPH committee in their role as coordinators of UK clinical research during the pandemic. The trial protocol in REMAP-CAP was designed to be modular so that new domains of treatment could be added over time, as appendices, without changing core documents too often. Domains were added when we learnt new things about the disease, e.g. once it became clear that thrombosis (blood clots) were a major issue we added various anti-coagulation (blood thinning) strategies; or new interventions became available, e.g. convalescent plasma once this could be collected from recovered patients. Also the modular design meant that not every hospital had to include every domain or intervention at each hospital, depending on local factors such as drug supply or clinical equipoise (uncertainty) to answer specific questions.
23. We deliberately kept all interventions open-label (i.e. clinical staff, and potentially patients, knew what they were prescribing or receiving) to avoid extra complexity around giving blinded treatments that require placebo medication and also requires additional training. Local clinical staff administered all the treatments in hospital. We liaised with the MHRA to ensure we could keep documentation at hospitals as simple as possible to minimize the burden on over-stretched clinical services, while still maintaining adequate scientific rigor and oversight.
24. We ran regular online training sessions and refreshers to ensure hospital staff were adequately trained in all trial procedures and adaptions. Training delegation logs were kept by sites to demonstrate this training had taken place.

25. Information about patient details, treatment and trial outcomes while in hospital were collected in a trial specific online electronic case report form (eCRF) by local clinical research staff at each site. Longer-term outcomes including quality of life assessment at disability scores at 6 months after inclusion were collected by central trial management staff at Imperial and ICNARC, via telephone calls. The eCRF was dynamic, i.e. only required information relevant for the interventions relevant to each patient. The database has inbuilt queries to try and avoid inconsistent data entries, missing data and obvious data errors. We were not able to undertake onsite monitoring visits due to travel restrictions.

Data analysis, monitoring and management

26. The primary outcome was "Organ Support Free Days". This outcome is a combination of hospital mortality and duration of heart and lung support in intensive care, in those who survived. It is an ordinal scale, meaning low numbers are bad outcomes and higher numbers are better outcomes. Each patient was given a score at the end of their hospital stay. If they died, they were assigned the worst score, -1, i.e. they had the worst outcome. If the patient survived, they were assigned the number of days up to day 21 that they did not require breathing support, i.e. a ventilator, or heart support e.g. drugs used to treat low blood pressure. If a patient survived but had 2 weeks of ventilation they would get a score of 7 but someone who survived and only needed 3 days of ventilation would score 18, i.e. they had a higher (better) score because they had recovered more quickly. This outcome was chosen to measure important short term (in hospital) mortality rates but also measure speed of recovery which was also vitally important when clinical services were so stretched. There were other secondary outcomes looking at safety and long-term outcomes up to 6 months.
27. All the international data from the trial (UK and other countries) were sent to the statistical team (SAC) at intervals. The intervals between analyses varied according to things like recruitment rates and when previous preliminary results required finalising. For each analysis the SAC would run the Bayesian inference model on the full international dataset for all interventions. This model would compare the effect of each treatment within a domain on the primary outcome, organ support free days, compared to all the other possible randomised interventions in that domain. As an illustration, in the immune modulation domain

tocilizumab (an IL6 inhibitor) was compared to patients treated with control (no immune modulation), sarilumab (another IL6 inhibitor) and anakinra (an IL1 inhibitor). Only patients randomised to one of these treatments were compared directly to each other to ensure robust like-for-like comparisons, and the analytical model adjusted for important other factors such as age, sex and time. After each analysis the Bayesian model produces a probability that each treatment is beneficial or not compared to the control and / or other treatments, i.e. does it improve the number of organ support free days. We had pre-defined thresholds to declare if treatments were effective / ineffective, or similar to other treatments. When the primary outcome crossed one of these thresholds, the other outcomes would be analysed when all the patients had completed 21 days of follow-up to be able to produce a report of the full effect (short term efficacy & safety) of the intervention.

Safety monitoring

28. Safety information collected included general serious adverse events and pre-specified safety outcomes of interest for certain interventions, e.g. bleeding events with anti-coagulant treatment and transfusion reactions with convalescent plasma treatment. As is typical of trial conducted in critical care it was complex to collect adverse event data in a population who have an acute life-threatening illness at the time of enrolment. In these situations the analysis of effectiveness (mortality rate and need for organ support) also provides an analysis of overall safety and local investigators were asked to record any serious adverse events that they assessed were likely related to the intervention or the protocol, but not the underlying disease.

Results & Impact

29. In the UK (including the devolved administrations) REMAP-CAP recruited 5580 patients with COVID-19, and 10,297 globally. It has reported on 14 interventions, five that were likely beneficial, three ineffective and six that may have been harmful. The main results in chronological reporting order were:
30. Corticosteroids – September 2020; Among patients with severe COVID-19, treatment with a 7-day fixed-dose course of hydrocortisone, compared with no hydrocortisone, resulted in 93% probability of superiority. This had immediate

impact. MHRA Central Alerting System (CAS) alert CEM/CMO/2020/033 was issued for immediate action "Corticosteroids, and in particular dexamethasone and hydrocortisone, have been demonstrated to have a place in the management of patients with COVID-19." The WHO updated their treatment guidelines Living Guidance 2-Sept-2020 to "a strong recommendation for systemic (intravenous or oral) corticosteroid therapy in patients with severe and critical COVID-19".

31. Immune modulation drugs: between November 2020 and June 2021; in critically ill patients with COVID-19 receiving organ support in ICUs, treatment with the interleukin-6 receptor antagonists, tocilizumab and sarilumab, both improved outcomes, including survival and were similarly effective. Anakinra was not effective in this population. This had immediate UK impact with three MHRA CAS alerts.
    a. CEM/CMO/2020/038 "a UK wide position statement has been agreed to support off-label prescribing and access to tocilizumab, administered intravenously, for eligible COVID positive patients in the intensive care setting".
    b. CEM/CMO/2021/001 "Organisations are encouraged to consider prescribing either tocilizumab or sarilumab in the treatment of patients admitted to intensive care with COVID-19 pneumonia."
    c. CEM/CMO/2021/004 "UK Interim Clinical Commissioning Policies have now been published, recommending that two Interleukin-6 (IL-6) inhibitors - tocilizumab and sarilumab - are made available as a treatment option for critically ill adult patients (aged 18 years and older) hospitalised with COVID-19 in accordance with the agreed criteria. The REMAP-CAP trial has reported a finding of survival and time to recovery benefits for tocilizumab or sarilumab, over and above current standard of care (including corticosteroids), in the immune modulation therapy domain of the REMAP-CAP platform trial. Mortality was reported as 35.8% in the standard of care group, compared to 27.3% in the treatment group, an overall reduction in the relative risk of death of 24%. The treatment also reduced the time patients spent in the intensive care unit (ICU) by more than a week on average."

Later the WHO Therapeutics and COVID-19 - Living Guidance was updated on 6-July-2021 "In this update, the panel makes a strong recommendation to use IL-6

receptor blockers (tocilizumab or sarilumab) in patients with severe or critical COVID-19. Publication of the … REMAP-CAP trial addressing IL-6 receptor blockers as a potential treatment for COVID-19 triggered this recommendation."

32. Antiviral drugs – November 2020; Among critically ill patients with COVID-19, treatment with lopinavir-ritonavir, hydroxychloroquine, or combination therapy resulted in worse outcomes compared to no COVID-19 antiviral therapy.
33. Therapeutic dose heparin (anti-coagulation) – December 2020, January 2021, May 2023; In non-critically ill patients with COVID-19, therapeutic-dose anticoagulation with heparin increased the probability of hospital survival with reduced use of organ support. In contrast, in critically ill patients, therapeutic-dose anticoagulation with heparin did not improve hospital survival and may have led to worse outcomes. Subsequent analyses showed that among patients hospitalised for COVID-19, the effect of therapeutic-dose heparin was heterogeneous (varied between individuals). In three different approaches to assessing heterogeneity of treatment effect, heparin was more likely to be beneficial in those who were less severely ill at presentation or had lower body mass index (BMI) and more likely to be harmful in sicker patients and those with more obesity. These findings illustrate the importance of considering variation in treatment effect between individuals in the design and analysis of clinical trials.
34. Convalescent plasma - January 2021; among an unselected group of critically ill adults with confirmed COVID-19, treatment with two units of high-titre, convalescent plasma had a low likelihood of improving outcomes. In the pre-specified subgroup of patients with immunodeficiency, convalescent plasma demonstrated potential benefit (probability of superiority of 89.8%). This intervention in this subgroup of patients continues to be evaluated in REMAP-CAP in both ward and ICU patients. This had impact through an updated MHRA CAS alert CEM/CMO/2021/010 "The REMAP-CAP trial, an international randomised, embedded, multifactorial, adaptive platform trial has also announced that no significant benefit was seen from treatment with convalescent plasma (up to two ABO-compatible units administered over 48 hours) in patients requiring organ support in an intensive care setting. It is therefore now recommended that convalescent plasma is NOT used in the management of hospitalised patients with confirmed or suspected SARS-CoV-2 infection."

35. Anti-platelet drugs (aspirin and clopidogrel, both anti-clotting drugs) – June 2021; Among critically ill patients with COVID-19, treatment with an antiplatelet agent, compared with no antiplatelet agent, had a low likelihood of improving short term outcomes. The effects of aspirin and clopidogrel were similar.
36. Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) – March 2023; Among critically ill adults with COVID-19, initiation of an ACE inhibitor or ARB did not improve, and likely worsened, clinical outcomes.
37. Intravenous vitamin C – October 2023; In hospitalized patients with COVID-19, vitamin C had low probability of improving outcomes and may be associated with worse outcomes.
38. Simvastatin – October 2023; In critically ill patients with COVID-19 simvastatin had a high probability (96%) of improving outcomes but this didn't reach the pre-defined threshold for superiority (99%).
39. Up to March 2023, each of these results were sent to the DHSC Therapeutics Taskforce and the CMO's office, as soon as the results were available to the investigator team before publication. It was understood these would be shared with the RAPID C-19 committee. As soon as publications were submitted to journals for peer review these draft manuscripts were also sent to DHSC. To date there have been four primary result publications in the New England Journal of Medicine, six in the Journal of the American Medical Association and two in the Intensive Care Medicine journal. All are internationally leading peer-reviewed journals and are open access, so available free for public access. We have disseminated trial results through online podcasts, videos and other social media platforms. We also worked closely with the Science Media Centre, holding webinars and Q&A sessions through them to present results to the invited journalists, to ensure prompt and accurate reporting in the media.
40. For the steroid, tocilizumab, and sarilumab results there were several meetings with various NHS, MHRA and NICE groups to ensure rapid dissemination of results and rapid incorporation into clinical guidelines. I was invited to join the panel of the Covid-19 Therapeutics Access and Policy group so that we could ensure that clinical guidelines were consistent with the trial results.
41. It is difficult to quantify the exact impact that REMAP-CAP had during the pandemic. As an example at the end of 2022, Roche / Genentech announced "Since the beginning of the pandemic, more than one million people hospitalized

with COVID-19 have been treated with Actemra [tocilizumab] worldwide". REMAP-CAP was the first trial to report that tocilizumab saved lives in this group of patients. Based on the results seen in REMAP-CAP (~24% relative / ~8% absolute mortality reduction, i.e. 1 life saved for every 12 patients treated) this could equate to close to 100 thousand lives saved.

Data from the UK ICNARC COVID-19 report from 17-Feb 2023, showed that mortality rates for critically ill patients admitted to intensive care in the UK improved by one third since the beginning of the pandemic. There will be many reasons for this but undoubtedly the robust evidence about which treatments did or did not work from large randomised controlled trials, including REMAP-CAP, contributed to this mortality reduction.

42. In order to ensure the validity of our findings we shared our results with other groups to combine multiple trials in meta-analyses to provide the most comprehensive evidence to aid guideline development and treatment decisions. In particular this was done in conjunction with the WHO to ensure that results from around the world could be shared to provide the fullest evidence to guide ongoing care. Evidence from REMAP-CAP was combined with other trial results as part of WHO living guidelines for drugs for COVID-19.

Transparency and public engagement

43. To ensure transparency was maintained throughout the trial, we posted all our trial protocols, analysis plans, amendments and outputs on our trial website, as soon as they were finalised. Therefore it is possible to see all the signed, dated prospective plans for the trial and compare them to the published trial results. Our manuscripts have all been published as open-access, so are readable for free by anyone. The main text of published manuscripts usually has strict word limits, so we have provided large online supplements (usually many 100's of pages) to ensure full transparency of all results, including sensitivity analyses that incorporate alternative analytical assumptions to demonstrate robustness of the results.
44. REMAP-CAP undertook major public engagement prior to the pandemic about general principles about the trial and how it would work during a pandemic. This engagement helped shape many of the design and operational characteristics of the trial. During the pandemic, ongoing public engagement was mainly limited to

lay reviewers within the NIHR UPH committee who oversaw the introduction of new interventions and the ongoing trial progress. As results have become available, we have worked with our Patient & Public Involvement (PPI) group to ensure we have suitable public-facing summaries of the trial results, e.g. visual abstracts. We are also working with this PPI group to ensure we learn lessons of the pandemic, as the REMAP-CAP trial progresses.

Lesson Learning

45. Conducting clinical research during a pandemic is crucial to learn how best to treat the disease. No matter how well intentioned, opinion-only based guidelines will often turn out to be wrong, particularly for a new disease. These opinion-based guidelines sometimes conflicted with each other which was unhelpful and confusing for clinical teams. Also, when clinicians see a guideline suggesting a treatment, this can mislead them to think there is already a known best treatment option (i.e. incorrectly reduces the uncertainty). Clinicians may then be less willing to enrol patients into trials of alternative options that would provide this missing evidence and reduce uncertainty. Robust evidence from randomised controlled trials is vital to generate the highest quality evidence to guide patient management, ensuring best outcomes for patients, using limited resources appropriately and generating new scientific knowledge to develop novel therapies.
46. Outside of a pandemic, long term outcomes are usually the most important endpoints in clinical trials. However, in a pandemic, results are needed quickly and other outcomes in addition to mortality are also vitally important for healthcare planning.
47. Even when clinical services are under great pressure it is vital to ensure clinical trials and other research activity can be maintained. We must "learn while we do". Having research support already embedded in NHS hospitals through the NIHR Clinical Research Network was key to the UK being a global leader in clinical trial activity during the pandemic. It is vital that clinical research is core business within the NHS, at all times. This has the dual benefit of improving all healthcare and ensuring adequate resources are in place to conduct vital time-sensitive research in a pandemic.
48. Clinical research activity must be coordinated during a pandemic. The NIHR UPH system ensured that limited research resources were used to deliver clinical trials

that would provide actionable evidence during the pandemic. Without co-ordination there was a risk that multiple small, competing studies would have produced very few useful results. Research should be coordinated nationally and internationally. It is important to have independent replication of science to ensure validity and generalisability, but unnecessary duplication is wasteful.

49. NIHR UPH coordinated delivery of research, but other aspects of research activity need similar levels of coordination. This includes funders to avoid different trial groups competing against each other after funding is approved. The selection of drugs for evaluation requires independent oversight and coordination, through a prioritisation committee. Many proponents for possible interventions are conflicted academically or financially and a large team is required to objectively assess the rationale for each proposal. UK-CTAP did this well but was required earlier in the pandemic.
50. Similarly drug supply for trials (and clinical use) needs to be managed centrally. Early in the pandemic some individual hospitals tried to place large orders for drugs to stockpile, that would have prevented national evaluation in trials and later national use. In other countries within REMAP-CAP, drug supply to recruiting hospitals was a major obstacle to recruitment.
51. Responding and adapting in a pandemic are crucial to successful delivery of research. Although sleeping / hibernating pre-approved protocols that can be activated in a pandemic may have some benefit, protocol writing and regulatory approval are only small parts of delivering research. The REC, MHRA and HRA all provided rapid review of new trial documents for UPH studies anyway. There are many other operational and logistics issues that are also required and these are probably best provided by using existing ongoing research infrastructure and systems that can be scaled up or adapted to deal with new pandemic issues.
52. Large scale trial platforms are an effective way to provide such infrastructure and provide results quickly and efficiently in a pandemic for multiple interventions, as we were able to do. They do require time to set-up, i.e. to put in place all the necessary tangible components of a trial but also require time for individual investigators and groups to establish effective working relationships and trust.
53. Trial platforms require funding over long periods of time and this may need to be coordinated with overseas funders for international platforms which are vital to tackle global pandemics. Such large platforms may dominate the research

landscape for a long period of time. Therefore, there must be ways to ensure such platforms are open to new investigators and new ideas.

54. The REC, MHRA and HRA all provided excellent support by adapting their processes to help UPH trials deliver in a timely manner. Some aspects can't be maintained outside of a pandemic emergency, e.g. 48-hour review of submission, and is not required. However, many other adaptions could help reduce unnecessary bureaucracy and thus facilitate research in and outside of a pandemic. For example, not requiring a new formal substantial amendment submission for adding new sites and investigators, accepting queries to be asked before submitting documents for formal approval and allowing more data sharing between NHS organisations to aid data collection when patients move hospital. There was also a more collaborative approach to trial regulation and oversight during the pandemic. Rather than simply rejecting an application due to an issue and stating resubmission was required, alternative solutions were provided that helped investigators achieve their goals more quickly, while still complying with regulations and maintaining trial integrity and safety.

55. Although the UPH trials in the UK recruited very well when compared with most other countries, we still only recruited a minority (maybe between 10-20%) of possible patients in hospital into COVID-19 trials. Barriers to recruitment should be explored. When hospitals are overrun with clinical cases it can be hard to find staff to carry out research specific tasks, such as long discussions about individual trial consent. In the emergency situation of a pandemic research could be embedded more in everyday clinical activity. Rather than individual hospitals and clinicians making individual decisions based on limited information, important research methods such as randomisation could be built into hospital prescribing systems to aid more rapid evidence generation. Routine samples and clinical data could be used more easily for analysis, without requiring additional research-specific processes to be set-up and undertaken by over-stretched clinical teams. This may also help inclusion and diversity as a broader population would be included in such trials and this would make any evidence generated more generalisable to the whole population. Such processes would require careful set-up in advance and require working with communities, especially minority groups so that transparency and trust are maintained.

56. We were not set-up to collect biological samples in REMAP-CAP. Collecting such samples in a clinical trial can help understand mechanisms of disease and the mechanism of action of interventions. Adding such sample collection in clinical trials, even if only in select sites, should be considered in future pandemic trials.
57. We will continue to run REMAP-CAP in the UK and internationally, investigating treatment for other causes of pneumonia, such as influenza and bacteria, as long as we can secure financial support to continue to do so. We have expanded the trial to include a broader population of patients in hospital, not just in intensive care, and we now also include children, as well as adults. We would be able to adapt REMAP-CAP for a future pandemic.
58. The most effective platforms during the COVID-19 pandemic were phase 3 trials, testing existing interventions. The phase 2 trial space, evaluating more novel interventions earlier in the development process was less effective. There were multiple phase 2 trials that lacked coordination of the therapeutic interventions tested, and in which populations to conduct the trials. It was also difficult in a new disease to rapidly design a trial that could clearly show preliminary proof of benefit in a small number of patients (phase 2 trial) that was then ready for testing in a much larger phase 3 trial. With other colleagues both in the UK and internationally we are setting up an adaptive platform for phase 2 trials (PANTHER - Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failure) to evaluate more novel therapies for acute lung injury (like that seen in COVID-19) using a precision medicine approach, i.e. using biomarkers to test therapeutics in more select groups of patients more likely to respond to different treatments. We know that not all patients respond the same way to treatment and so as new therapies are developed, we need to tailor them to specific groups of patients (precision medicine). This platform would provide a pipeline of novel therapeutics for larger scale testing in other platforms, such as REMAP-CAP. By setting up in advance we have designed methods to detect early signals of potential benefit, in which case therapies could then proceed to larger scale testing in phase 3 platforms. And at the same we can identify treatments that appear not be working and replace them earlier with alternative treatments.

Statement of Truth

I believe that the facts stated in this witness statement are true. I understand that proceedings may be brought against anyone who makes, or causes to be made, a false statement in a document verified by a statement of truth without an honest belief of its truth.

Signed: PD

Dated: 09-Oct-2024