Witness Name: Tom Wilkinson
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UK COVID-19 INQUIRY

WITNESS STATEMENT OF TOM WILKINSON

I, Professor Tom Wilkinson will say as follows: -

1. I have been asked to provide a statement pertaining to the role and conduct of the ACCORD clinical trial platform in evaluating new treatments for COVID-19. As a background I am a Professor of Respiratory Medicine, with over 2 decades of experience in respiratory infection research and the development of new treatments and vaccines and a specialist consultant in clinical respiratory medicine.

Roles and Responsibilities

2. I was Chief Investigator for the ACCORD trial and supported in that role by Professor Dave Singh, Professor of Respiratory Medicine and Clinical Pharmacology at the University of Manchester who was deputy Chief Investigator. We carried primary responsibility for the conduct of the trial overall, working closely with the trial sponsor University Hospitals Southampton NHS Foundation Trust and the Trial management and steering committees to ensure the safe and effective conduct of the study and adherence to good clinical practice. I was one of the initial team which conceived of the study concept and contributed to the design of the study, the oversight of the study conduct, the interpretation and publication of results.

3. The key figures in the trial management also included key experts in the trial management group:

    i. Professor Miles Carroll then Research Director of the Health Protection Agency research Unit at Porton Down, now Professor of Emerging Virsues the Pandemic Sciences Institute University of Oxford
    ii. Professor Clive Page Professor of Pharmacology and Director of the Pulmonary Pharmacology Unit Kings College London
    iii. Professor Gareth Griffiths Professor of Clinical Trials and Director of the Southampton Clinical Trials Unit- Statistical and trial design advice
    iv. Professor Robert Read – Professor of Infectious Diseases University of Southampton and Director of the NIHR BRC
    v. Professor Anthony DeSoyza University of Newcastle- expert respiratory infection researcher
    vi. Dr Karen Underwood Director of Research and Development Universities Hospital Southampton – Clinical Trial Sponsor
    vii. Professor Ashley Woodcock, Professor of Respiratory Medicine at the University of Manchester – Chair of the Trial Steering Committee
    viii. Professor Toby Maher – Professor of Clinical Medicine University of Southern California USA- Chair of the expert Independent Data Monitoring Committee

4. Other key contributors to the ACCORD programme were the two partner clinical research organizations (CROs) : IQVIA and the Medicine Evaluation Unit which coordinated the clinical sites.

5. The individual hospital site Principle Investigators (PIs) who were Respiratory or Infectious Diseases Consultants, present at every clinical site.

6. A key interface with the funders UKRI, the UK government and involved in the coordination of the four UK phase 2 clinical trials was Professor Patrick Chinnery, University of Cambridge and MRC Clinical Director.

7. Similarly Professor Ling Pei Ho- Professor of Respiratory Medicine University of Oxford Chair of the NIHR Respiratory Translational research Collaboration (RTRC) who facilitated the delivery of the trial by coordinating the involvement of key sites with Biomedical Research Centres (BRCs).

8. The three industry partners and their staff which facilitated access to the trial medications- AstraZeneca, Bergenbio and UCB. These were under contractual relationships with the sponsor UHS NHS FT to ensure independent conduct of the studies.

Genesis, Design and Set Up

9. In February 2020 I was made aware of the imminent threat of SARS COV2 through the media and through conversations with colleagues in Italy who were managing a deluge of clinical cases and I connected with existing respiratory infection research collaborators in the UK to discuss this threat. I connected with Professor Miles Carroll at the Health Protection Agency and with staff at the World Health Organisation to better understand the current status of the threat, the nature of any planned or existing trials our teams could support and to gain insights into the nature of the clinical disease now prevalent in China and Europe. There was no apparent organized active trial programme available to join in the UK and no hibernating drug development platform anyone could identify. Therefore, I reviewed the current opportunities from my own research portfolio that could contribute to developing potential treatments for COVID-19. At that time I was chief investigator on a clinical trial of inhaled interferon beta in acute respiratory viral infections in a lung condition called COPD. This was a drug in development by a University of Southampton spin out biotech company Synairgen. Recognising the potential for this anti-viral treatment in COVID-19 the company and collaborators on the original trial and I conceived of and designed a phase two study for this treatment in patients admitted to hospital with COVID-19. We sought regulatory approval form the Medicines & Healthcare products, Regulatory Agency (MHRA), the Health Research Authority (HRA) including their Research Ethics Committees and set up a phase 2 randomised double blind placebo controlled trial and recruited 101 patients across several UK hospital sites between March 30th and

May 30th 2020. The drug was shown to be safe and well tolerated and showed evidence of clinical benefit – improving recovery rates compared to placebo, the results were released in June 2020 and published formally in the Lancet Respiratory Medicine in Early 2021 see Monk et al The Lancet Respiratory Medicine, Volume 9, Issue 2, 196 – 206.

10. During this time the real impact of the pandemic in the NHS was becoming clear, I was working in my clinical role as a consultant managing hospitalised patients with severe COVID-19 – at this stage we had no evidenced based treatment to use and so care was supportive. Consequently, outcomes for patients were poor and it became apparent to myself and other colleagues that new treatments will be required to change this. At that time we became aware that a UK group, led by Professor Peter Horby, was planning a large phase 3 clinical trial - RECOVERY focusing on repurposing established drugs and testing this in COVID 19 - for example dexamethasone, but there were no plans at that stage to test early phase drugs. I met with my collaborators in March to discuss the need to trial new treatments in COVID 19 as it was likely that repurposed drugs would be of value but the use of phase three suitable drugs alone may not address the real clinical needs of the wide range of COVID-19 cases we were then managing in the NHS. My active experience of running the highly successful Interferon beta trial at that time gave me and colleagues real insights into the design and conduct of COVID-19 studies and so we formed a plan in March and April 2020 to develop a phase two trial platform: ACCORD - Accelerating Drug Development in COVID 19. The core team list above were central to this and became the original trial management group.

11. The aims of the project were to trial a number of therapies in a seamless, Phase 2, adaptive, randomised controlled platform study, designed to rapidly test candidate agents in the treatment of COVID-19. We designed a master protocol with each candidate agent being included via its own sub-protocol, randomising participants to a candidate drug or a single contemporaneous SoC arm. This would allow for the testing of a number of different drugs at the same time in relatively small numbers of patients whilst closely monitoring the safety and efficacy response to these as required in earlier phase drug development. The

design and rationale for the study platform was published in the Journal; Trials in July 2020 see Wilkinson et al: Trials 2020 Jul 31;21(1):691. doi: 10.1186/s13063-020-04584-9.

12. To clarify the name ACCORD-2 refers to the phase 2 nature of the trial platform and is synonymous with ACCORD. The original concept was of a seamless Phase 1 – into Phase 2 platform hence ACCORD 1 to ACCORD 2 however the Phase 1 activity for ACCORD was led by Professor Gareth Griffiths who partnered with another Phase 1 trial team in Liverpool (AGILE) and subsequently all the Phase 1 activity was delivered by that group (AGILE- ACCORD).

13. The ACCORD protocol was developed in collaboration with experts from the trial group and in collaboration with UHS NHS trust, the study sponsor. We discussed the concept with our NIHR research network in respiratory medicine (RTRC) and received endorsement and support and approached NIHR and UKRI for funding support. We received positive feedback in April 2020 and were introduced on a teleconference call to IQVIA, a large and established contract research delivery company (CRO) that had been asked to support COVID 19 trial activity. The funding award was to the partnership between ACCORD and IQVIA. The ACCORD collaboration was established with University Hospitals Southampton contracting with UKRI to sponsor the study. The funding therefore was provided by UKRI through the MRC to UHS NHS FT who managed the funds to partner sites and organisations, the funding decisions were rapid, 2-3 weeks compared to the usual practice of several months the initial award amount and conditions are detailed in the award letter provided as an exhibit. Exhibit TW01-ACCORD 01 [INQ000474540].

14. Professor Patrick Chinnery was appointed as the interface between the project team and the funders and attended and participated in ACCORD project meetings and steering committee meetings.

15. Our immediate tasks as a trial management group before the trial could commence were to establish the trial design, clinical trial protocol, trial governance and oversight processes, trial sites and PIs, identify candidate drugs and work with Research Ethics Committees and the MHRA to seek the necessary approvals to

conduct the study. The ACCORD team, UHS and IQVIA teams worked very hard to deliver this effectively, with many staff working in NHS posts and involved in complex clinical care of COVID-19 patients at this time. The trial achieved full regulatory approval on April 22nd 2020.

16. The approval process for the trial itself and the drugs selected for trial was the same rigorous process that is established practice in the UK- involving approval from the NHS sponsor, the HRA and the independent Research Ethics Committee and the MHRA. No steps were missed out and the full rigour of assessment and review was present. Involvement of the drug companies who owned the drugs in trial was also key as they provided the necessary detailed information on the drugs, their characteristics and safety data accrued to date. The key difference between this approval in the pandemic and usual practice was not that there was any departure from the completeness of usual practice but that it was accelerated. The HRA, Research Ethics Committees and MHRA were very responsive, the sponsor and regulatory teams focused specifically on expediting COVID 19-trial set up and helped to expedite the process in the context of the urgent public health need.

17. The specific ACCORD platform drugs, their selection and progress is described later in this statement.

18. Following these approvals the trial team sought to establish clinical trial sites in hospitals across the UK – we initially targeted establishing hospital sites to support patient recruitment. The hospitals approached for study set up were those that had responded to an initial enquiry from the IQVIA site team:

    i. Royal Oldham Hospital, Southend University Hospital, Basildon Hospital, Derriford Hospital Plymouth, Fairfield Hospital, Royal Devon and Exeter Hospital, Royal Brompton Hospital, University Hospitals Birmingham, Salford Hospital, Royal Hallamshire Hospital, North Manchester General, Hull Royal Infirmary, Aintree Hospital, Betsi Hospital Wales, UCLH, Newcastle University Hospital, Leicester University Hospital, Royyal Liverpool Hospital, Nottingham University Hospitals, Bradford Royal Infirmary, Leeds Teaching Hospitals, Morriston Hospital Swansea, Barts

Health, UHS NHS- Southampton, Belfast City Hospital, Wynthenshawe and Manchester Foundation Trust, Royal Gwent Hospital.

19. The number and location of active sites was dynamic and changed over the conduct of the study – as different sites experienced pressures of clinical care for COVID 19 patients or staff sickness they communicated their ongoing ability to recruit participants and site performance was constantly reviewed by the trial teams.

20. In total 166 subjects were recruited to the ACCORD trial platform in the UK. In addition, the ACCORD team supported the development of trials overseas where an additional 111 subjects were recruited to a Bergenbio sponsored study of the ACCORD selected drug Bemcentanib in India and South Africa in 2020 and a further 75 subjects were recruited in a trial of the ACCORD selected drug nebulized-heparin conducted in Brazil funded independently by the Jon Moulton Charity Trust.

21. The ACCORD study received Urgent Public Health Status in 2020, it was however not the top prioritized tier that the Phase 3 platforms Recovery and Remap CAP were. This meant that sites tended to prioritise delivery of the top tier studies and this impacted on ACCORD recruitment rates.

22. ACCORD was not involved in the RAPID C-19 programme to my knowledge, this was a collaboration with NICE, the MHRA and other agencies to explore how to rapidly implement recently tested drugs in COVID 19- as ACCORD was a phase 2 platform the next step for any promising drugs would be phase 3 trials rather than immediate use in clinical care.

23. ACCORD was one of a number of clinical trials platforms active in the pandemic in the UK. In June 2020 Professor Patrick Chinnery led an approach to coordinate the activities of the Phase 2 trials TACTIC, CATALYST, DEFINE and ACCORD. The trial leadership teams met regularly and discussed solutions to common problems and coordination of access to different clinical sites. The studies were never amalgamated into one trial as they differed in key design features such as end points and were trialing different drugs. The coordination took the form of regular online meetings, sharing of intelligence of sites active and available for

phase 2 studies and hence plans to optimize recruitment opportunities whilst minimizing competition at sites. This was helpful and did ensure that within the limits of the programmes opportunities were taken to enable subject recruitment. I understand the Phase 3 studies were appraised of the Phase 2 studies activity and drugs in trial by Professor Chinnery.

Oversight, Governance, organizational structure and decision- making in ACCORD

24. The ACCORD trial was governed using a conventional model of trial oversight in order to deliver the study to Good Clinical Practice -GCP and regulatory standards for drug development.

25. The study was sponsored by the University Hospitals Southampton - led by Dr Karen Underwood R&D Director and Professor Chris Kipps R&D Clinical Director, along with the myself as Chief Investigator we were responsible for the overall conduct of the trial.

26. A Steering Committee was responsible for the executive oversight and supervision of this ACCORD program. The Steering Committee served this role through regular scheduled meetings or teleconferences and, additional ad hoc meetings. I was the initial chair of the steering committee and once the project was established, we appointed an independent chair in Professor Ashley Woodcock.

27. The Steering Committee was responsible for:

    i. Evaluating interim analysis data to make decisions on further progression of the candidate agents within the study.
    ii. Providing guidance, advice, and recommendations to the ACCORD program on relevant clinical issues related to the strategy, implementation and conduct of the study. This may include, but not necessarily be limited to:
    iii. Advice on the strategy and design of the ACCORD Master Protocol and sub-protocols and any subsequent amendments or revisions.

iv. Advice on issues of study enrolment including patient accrual, number and location of investigator sites, recruitment goals, and patient eligibility/ineligibility issues.

v. Advice on issues relating to the clinical conduct of the protocol including protocol violations/deviations and investigative site or Research Ethics Committee/Institutional Review Board concerns/issues, and regulatory engagement.

vi. Advice on safety issues.

28. This committee initially met very frequently- every week whilst the study was in development and initial set up phase. This cadence then reduced as the trial was established.

29. The initial TSC membership was

i. Expert Members:
    i. Professor Lorcan McGarvey
    ii. Dr Timothy Felton
    iii. Professor Anthony De Soyza
    iv. Professor S. Dave Singh
    v. Dr Charlotte Summers
    vi. Professor Ling Pei Ho
    vii. Dr Manu Shankar-Hari
    viii. Professor Clive Page
    ix. Professor Miles Carroll
    x. Professor Robert Read
    xi. Professor Keir Lewis
    xii. Professor James Chalmers
ii. Statistician : Professor Gareth Griffiths
iii. BRCs Representative: Prof Matt Brown
iv. UKRI Representative: Professor Patrick Chinnery
v. Sponsors Representative: Dr Karen Underwood
vi. IQVIA: Dr Nuria Martinez-Alier, James Brook, Graeme Duncan

30. An independent IDMC was established for this study to assess safety on an ongoing basis throughout the study. The committee objectively monitored the safety data through scheduled meetings where formal assessment of clinical trial safety data was conducted. The IDMC members therefore performed ongoing safety surveillance and recommendations to the Steering Committee regarding study conduct. This IDMC was Chaired by Professor Toby Maher from the University of Southern California an expert in respiratory drug development and it included Professor Nihil Hirani (respiratory expert, Edinburgh University), Professor Emmanuel Lesaffre (expert biostatistician, Leuven), and Professor Elie Azoulay (medicine and critical care expert, Sorbonne France).

31. In addition to the IDMC – real-time review of drug safety data was conducted by the sponsor and CI or deputy and regular, initially weekly, safety review meetings were held with the individual drug company's safety experts.

32. Weekly sponsor meetings were held with UHS, the Chief investigator or deputy and representatives from the CRO- IQVIA then MEU to discuss trial conduct, any operational challenges or any emergent concerns and to plan for next steps in delivery.

33. The initial selection of candidate drugs was performed by a sub group steering committee members led by Professor Clive Page once the UKRI Therapeutics Prioritization Panel formed it reviewed and ratified the drugs selected. Detail on drug selection rationale and process is covered later in this statement.

34. The workforce for the conduct of the trial was provided by the expert group who supported the various committees, the dedicated R&D team for UHS NHS trust, the paid staff in IQVIA and the Medicines Evaluation Unit CROS, trial managers, site support staff, trial monitors and safety coordinators. The actual conduct of the study at the clinical sites was delivered by NHS clinical and research staff at the hospital sites. Each site was supervised by a suitably qualified medical expert, usually a Respiratory Consultant, who acted as Principle Investigator (PI) for that site and led a team of researchers there. The day-to-day trial coordination was led by the CRO supporting the trial, IQVIA in the first stage and the Medicines Evaluation Unit when the study restarted, this is explained in detail later in the

statement. Data curation and analysis was supported by the CROs and a statistical team in a company commissioned by the MEU – Veristat.

35. The greatest challenge for sites was manning the study with clinical teams, especially research nurses, as they were often being moved to clinical facing roles at a time of crisis in the NHS. This staffing issue was compounded by the fact that staff sickness levels were also high. Sites which had dedicated clinical research teams were more able to contribute to the study.

36. I have been asked to comment on the timeliness of the programme, obstacles to progress and oversight and governance:

37. The ACCORD programme was set up efficiently and effectively in response to an unprecedented challenge to health and to the NHS whilst adhering to the very best standards of practice and rigour of formal approval. It was set up in a very timely way, a process that would usually take many months took less than two. This was enabled by the incredible dedication of an expert and tireless team. The successful set up of the project was enabled by the support of the MHRA, HRA and the Research Ethics Committees in their focused attention and responsiveness, by the dedication of UHS team in coordinating the activity, support by the Universities of Southampton and Manchester for releasing Professor Singh and myself to focus when not busy clinically on the programme and by the time volunteered by committee members and experts. The NIHR respiratory TRC played a very supportive role in helping the project develop and involved sites and experts in support of this.

38. The key obstacles to progress were;

39. A break in funding: After our initial funding award and with our main sites open and actively recruiting, we were informed on the 27th of July by Professor Chinnery – our liaison with UKRI and then by letter from Dr Glenn Wells UKRI Director of Strategy and planning that our funding was being stopped, to quote form the letter which is supplied as a key document: Exhibit TW02-ACCORD 02 [INQ000474544].

40. " Following a Ministerial review of the COVID-19 Phase 2 activities … this letter represents formal notification of the intent of UKRI to terminate the grant funding

agreement. We would like to take the opportunity yo thank you for all your help, support and commitment in recent months to deliver this programme of work and appreciate the decision to terminate will be disappointing."

41. This came as a real shock to the ACCORD team and in the several hundred years of shared experience of the experts in team had never been experienced before. We had to convene rapidly and with the oversight of the sponsor team at UHS and the TSC formed a plan to pause new patient recruitment the studies immediately and to focus on the safe conduct and supervision of the subjects currently active in the trial. The MHRA, HRA and Research Ethics Committees were contacted immediately and the plan approved and all sites were informed. Professor Chinnery attended a number of meetings and explained that a central decision had been made to halt funding to all the Phase 2 platforms and that a centrally coordinated new phase 2 platform was intended. As ACCORD was funded for delivery on a rolling contract as our partner was a commercial company IQVIA and this was their way of working, therefore our funds would cease immediately and we had to pause the study to recruitment and focus on completing the monitoring of patients who were actively in the trial already. It was explained by Professor Chinnery that the other phase 2 studies TACTIC and CATALYST had received a block grant at the start of their projects and would continue until that was spent but no further funding would be provided. Exhibit TW03-ACCORD 03 [INQ000474542].

42. The ACCORD team formally expressed their concerns regarding withdrawal of funding through the sponsor. This decision had a dramatic effect on the ability to deliver the project. However, we were determined to take forward the programme as best we could and explored opportunities to continue to trial these promising drugs. We explored avenues for additional funding and working overseas. We were not aware who specifically made this decision only that this was communicated by the funder UKRI.

43. Bergenbio, a biotech which was part of the industry team, agreed to invest in a clinical trial of their drug Bemcentinib in an independent study in India and South Africa with IQVIA, based on the ACCORD trial design. Members of the ACCORD team explored routes to source additional funding from pharmaceutical industry

partners and charitable sources. This work eventually led to the award of support from the Moulton Charitable trust to fund a trial of one of our selected drugs, inhaled heparin, in a clinical study in Brazil the following year.

44. In august 2020 we were contacted by Professor Chinnery by email to state that after some reflection the funder UKRI/NIHR was willing to re-support the ACCORD platform to continue and we were asked to develop a restart plan. The centrally coordinated phase 2 platform had not been formed- I am not aware of why this was. It was not clear what the drivers to UKRI/NIHR changing their mind were. We were informed this award was contingent on finding a delivery solution that did not include IQVIA, which were deemed to be too expensive. The impact of the decision not to include IQVI meant that we had to find an alternative CRO partner to deliver the project. It therefore meant we had to rebuild several aspects of the trial platform delivery machinery such as computer and data systems as these were distinct for each CRO, this led to delays in restarting the platform.

45. Therefore the ACCORD team which was still actively monitoring the subjects in the study met to discuss the concept of a restart to be delivered in a different way. Various options were considered to enable the study supervision to work at scale and UHS as sponsor endorsed the selection of the Medicines Evaluation Unit at the University of Manchester as the CRO of choice, it is a world-renowned early phase drug development unit. The project was rescoped and costed and in discussions with the MHRA the position of individual drugs was agreed - see my comments later for individual drugs. Exhibit TW04-ACCORD 04 [INQ000474541].

46. The calculated budget required to support the next trial phase and complete the now 3 selected drugs only in a proof of concept phase (Stage 1 of the original protocol) was £1,233,413. After significant negotiation the UKRI stated it only had budget to award £750,000 and the ACCORD team negotiated with our industry partners for additional support. The remaining funds were then provided by the three industry partners AZ, Bergenbio and UCB.

47. The programme had to be recontracted, reapproved by the regulators and sites reactivated once these activities were complete. Therefore, approximately six months after the funding cessation announcement by UKRI, the study restarted

with a significantly reduced budget in comparison to the original plan in May 2020. This clearly had a major impact on the delivery of the study, the timeliness of the results and the morale of the teams and clinical sites who had worked tirelessly and at pace to set up the project. The rationale for this decision was never explained. Ultimately the limited funding led to an early end to the project and the infrastructure set up as the platform trial has now been lost. The decision to award funding and then within a few weeks was unusual as this is not the practice of funding organisations such as the MRC or UKRI which monitor trial performance at key milestones and work with investigators to ensure successful delivery. At the point the study funding was initially terminated we had just opened all our clinical sites and were primed to increase recruitment – hence the decision to withdraw at that stage was unusual. The suggested reason was that a centrally coordinated phase 2 platform was being planned.

48. To avoid these issues in future, a coordinated national effort from the outset involving all groups with established investigators and contracts in place waiting to be reactivated.

49. One additional factor impacting on trial delivery was access to patients at sites, and the capacity of research teams to recruit subjects and support more complex phase 2 studies. Where sites were prioritizing phase 2 work – largely in centres with BRCs the project went well. However, in many smaller clinical sites the phase 2 studies were being run alongside RECOVERY – this was a very large trial and the inclusion criteria (unlike phase 2) were very broad with a less intensive protocol compared to phase 2 studies with their focus on safety. Consequently, most sites reported that the default option for them was to recruit patients to RECOVERY as it was easier and that RECOVERY was prioritized above other trials by the Chief Medical Officer for England through direct communication to their hospitals. This impacted on ACCORD recruitment and was discussed with the other phase 2 studies which were similarly affected. To avoid this a co-prioritisation of phase 2 and 3 studies at sites would be key and local solutions to ensure that subjects willing and able to join phase 2 trials do so with close coordination between trial teams to enable this.

50. There were no particular issues with trial oversight or coordination only the impact of the issues in funding highlighted above and the effect this had on trial conduct.

51. I have been asked to comment on an excerpt from Kate Bingham's "The Long Shot". I can only say I was not party to the political discussions referred to in the quotation and not aware of where tensions around drug development plans lay. It is possible that the points I have made above regarding the unprecedented decision to halt and then re-award funding are perhaps evidence of these evolving opinions but I was not party to them.

52. Also I have been asked to respond to quotes and perceptions that 'Phase 3 UK studies were successful and Phase 2 COVID studies were not'. I would agree Phase 3 studies were successful and that success was by the nature of large, late phase studies which test drugs already widely used, was easy to understand by all including the more lay community. Drugs from phase 3 studies if positive can be immediately accepted into clinical practice and that attracts widespread public attention and quite rightly drives optimism and a change in practice. The successes of phase 2 studies are harder to spot and even undoubtedly positive outcomes are often not on the radar of the less expert decision maker or journalist. Firstly, they are smaller studies by design, carefully looking at safety signals and early signals of efficacy, so less headline grabbing. Secondly, they, even if positive, do not ever result in an immediate change in practice but to the development of the drug to the next stage a phase 3 study again this is less obviously headline news. They are far more complex in their design than phase 3 so that delivery requires highly trained individual teams to perform them – so at a difficult time in the NHS were not an easy proposition for local sites and PIs to take on. Considering all of this the performance of ACCORD and I suspect other studies was remarkably positive-establishing a safe and effective trial platform in weeks at the peak of the first wave of the pandemic was and is world leading and has never been done before, The drugs selected for ACCORD proved to be safe and well tolerated and many showed positive signals of potential efficacy, any expert in drug development would recognize the remarkable nature of this work. The portfolio approach used has led to a number of candidate drugs which may have utility in a range of viral infections and indeed in future pandemics. An example of this is Tozorakimab one of the ACCORD drugs tested in the platform. The robust safety data and evidence

of potential efficacy led to the decision by senior leaders at AstraZeneca to take this molecule forward into their own global phase 3 programme. This phase 3 trial called Tilia is actively recruiting in hospitals across the world currently and is seeking to impact on the outcomes of not only severe COVID 19 but other respiratory viral infections including influenza and RSV. This is a potential game changing programme that would not have occurred without ACCORD and a clear marker of success of phase 2. In addition to work in the UK, two of the ACCORD drugs were successfully trialed abroad (see above) using the ACCORD trial design and supported by the team both are planned for phase 3 studies an accomplishment that may not have been recognised.

53. Also I think that external expert opinion of phase 2 studies is different, Anthony Fauci himself highlighted ACCORD as an optimal approach to develop early phase drugs in the pandemic. Results presented internationally and in the UK have been commended and experts within the NIHR and elsewhere have championed its success. The issues with funding did impact on the overall delivery but despite this ACCORD was successful, we can only imagine its potential impact had it been fully supported.

Working with external organisations and individuals

54. The ACCORD team worked closely with the UK research networks including the NIHR CRN, the NIHR RTRC and multiple hospital sites. We developed a valuable and productive interaction with the MHRA, the HRA and the Research Ethics Committees. Our collaboration with industry partners led to free access to medications for trial and additional funding into the programme. This industry and charitable funding led to successful research overseas. We connected directly with the WHO pandemic team at the beginning of the programme and received advice on outcome selection and experience from previous pandemics. The HPA team at Porton Down led by Professor Miles Carroll were supportive and offered expert advice and insights which helped shape the programme. Our interactions with government bodies and the funders were conducted through the auspices of Professor Patrick Chinnery who was an active attendee at our meetings and interfaced with the decision-making processes held centrally in government and

funder organsiations. The ACCORD team recognize his energy and support and work to coordinate activities between different studies.

Participant Selection

55. The selection of participants, their clinical phenotype or nature of their condition and the care setting were defined by the clinical trial protocol which was developed by our expert team and approved by sponsor, MHRA, HRA and Research Ethics Committees. ACCORD selected to work with the population of patients admitted to hospital with COVID 19- at the early stage of the pandemic. This was a particularly important group of patients for whom treatment options were very limited, with a consequence of poor clinical outcomes, so it was apparent that new treatments were desperately needed. The exact nature of inclusion and exclusion criteria are detailed in the clinical trial protocol.

56. These participants were recruited by the clinical research teams present at the participating hospitals who reviewed patients admitted with COVID-19 daily and assessed their suitability and wish to participate in this and other clinical trials.

57. There was a concerted and energetic effort to optimize and increase recruitment rates throughout the project these included detailed education and support for clinical site teams, amendments to the clinical trial protocol and patient information sheets to ease study entry without compromising safety, innovations in the way informed consent was obtained and work to simplify the language and reduce the burden of information on patients so they could make an informed decision about trial involvement whilst they were unwell with COVID-19. All patients gave written informed consent for the study and this was obtained by expert members of the clinical trial team at each site. Any participant with the appropriate clinical criteria who wished to participate in the study and who gave informed consent was recruited.

58. The information sheets for the study were in English. We initially had planned to include information translated into the most commonly spoken (non-English) languages but with the halt in funding and reduced resource after refunding this

was not feasible. This could have potentially impacted on the diversity of trial participants.

59. The samples size for the study was decided upon by our expert steering group and calculated by our statistical team led by Professor Gareth Griffiths. At the time of the study design in early 2020 there was limited clinical data available from COVID-19 studies but we did use the data published form China, for example Cao et al 2020, to estimate the event rate in the standard of care arm. The primary endpoint was selected as the time taken to achieve a two-point improvement in a 9 point category (the OSCI) or hospital discharge. This approach had proven useful in previous infection studies and the OSCI had been recommended by a number of experts including the WHO trial team. The estimated sample size for each drug in the trial was therefore 54 participants this would provide enough statistical power (80%) to detect a hazard ratio of the primary outcome in the drug arm versus standard of care of 1.6. Put simply if the drug being tested was effective in increasing the rate of improvement by around one and a half times compared to usual medical treatments alone we would detect that in our trial in a sample of 54 patients. The original design was to deliver an initial stage of these 54 patients-recruiting up to 60 to allow for patients withdrawing, which is common in trials. The plan was then to expand the drug into a larger phase of 126 patients to provide information on other outcomes, to inform the design of phase 3 and to provide additional safety data. Because of the impact of funding limitations on delivery the trial platform plans for stage 2 expansion were shelved and a focus on completing the initial stage for the three drugs still in trial was made and approved by the MHRA, HRA and Research Ethics Committees. Full details of the sample size estimations are available in the clinical trial protocol.

Therapeutic Selection

60. The ACCORD platform initially planned to trial six drugs – the aim was to create a balanced portfolio of drugs, each with different mechanisms of action thereby increasing the chances of success as so little was know at the time about the mechanism underlying severe COVID-19. The initial long list of drugs for ACCORD was created by detailed work by members of the study group. The Health

Protection Agency at Porton Down in early 2020 had complied a list of potential therapies from the existing scientific literature on SARS and MERS studies, from expert insights into the nature of SARS COV2 infection and from any preclinical data available. From this long list the potential candidate drugs were shortlisted and presented to the UKRI Therapeutic Prioritization panel which met in April 2020. The approach taken to select drugs was: The need for a balanced portfolio with complementary mechanisms of action; Drugs with well-established safety/toxicity profile; to include generic, repurposed and early clinical agents; and to prioritise drugs not being trialed elsewhere.

61. The initially prioritized drugs all had a good safety profile from phase one studies, were available for trial i.e. the drug owners were willing to collaborate or in the case of heparin – a repurposed rather than new drug, it could be manufactured and supplied, that a suitable dose could be selected based on safety and other trial data and there was a strong scientific rationale for their potential benefit in COVID 19, summarized here for our first drugs:

    i. Acalbrutinib is a Brutons Kinase inhibitor- its was developed for cancer therapy particlulary non-Hodgkins lymphoma. Signaling in cells through this pathway impacts on important immune and inflammatory pathways active in COVID-19. Blockade of this enzyme had been shown to rescue mice form lethal influenza infection in experimental studies and patients on this drug for cancer trials showed less severe inflammatory profiles in response to other conditions.

    ii. Tozorakimab (MEDI 356) a monoclonal antibody targeting IL-33, a pleiotropic cytokine involved in various immune responses. Early evidence linking IL-33 with increased severity and worse outcomes in hospitalised COVID patients was emerging, highlighting its potential as a therapeutic target.

    iii. Bemcentinib, a small molecule inhibitor of the receptor tyrosine kinase AXL, offered a potential dual benefit. It was initially developed for cancer therapy but seen to have potential impacts on viral infections. Firstly, AXL activation suppresses immune responses, allowing viruses to evade detection and

dampen interferon signalling. Second, many enveloped viruses exploit tyrosine kinase receptors such as AXL to enter cells via a mechanism called apoptotic mimicry. Therefore blocking this target could deliver two benefits.

iv. Zilucoplan is a peptide inhibitor of the complement protein C5, preventing its cleavage into C5a and C5b18. Upregulation of complement is associated with increased inflammation, and respiratory failure in severe respiratory infections and in particular SARS and Avian influenza. Therefore, blocking C5 cleavage could improve outcomes in COVID-19.

v. Heparin was discovered back in 1916 as part of the clotting system. It has been trialed in a number of toxicology and then clinical studies and has been shown to reduce lung inflammation, lung injury and to be safe. The team collated data from over 20 studies involving over 500 patients and found that it also has an ability to bind and block the action of respiratory viruses and is widely available as it in manufactured for other indications.

62. The sixth drug slot on the programme was not finalised – we reviewed a number of candidates and infliximab an anti-TNF monoclonal antibody which had been proposed by the Prioritization group was a lead. This is a potent and well tested anti-inflammatory treatment for conditions such as rheumatoid arthritis. Early observational data suggested patients on this form of therapy were less likely to suffer from severe COVID 19 and TNF was highly expressed in cases of severe disease. We did not progress the sixth drug as we did not have the capacity initially to start all the drugs at once and the funding hiatus made us have to focus on the drugs which had commenced.

63. The platform was designed therefore to assess drugs already in development for other indications, e.g. Cancer, and yet to be licensed or for established drugs which were being used in COVID-19 for the first time but did not have a license for use in the way prescribed, e.g. heparin nebulized and inhaled rather than injected. Both types of drugs were treated in the same manner in the trial with a defined sub protocol and close monitoring of safety and efficacy.

64. I have been asked to reflect on these selections and the process and access. Our ACCORD expert group have subsequently discussed these drugs and their potential, and we have discussed the process and potential for these. Overall, the strong consensus was that these were excellent choices proving to be safe and in at least 4 cases - of potential clinical benefit. We were delayed by access to a suitable supply of unfractionated heparin as when we lost the UKRI initial funding in July we lost access to a particular batch that was being manufactured and labeled in Spain for the study – this led to a delay in getting the drug tested in Brazil.

65. The efficacy of the drugs was assessed by the drug effects on the trial outcomes in subjects receiving the drug and standard of care compared to these outcomes in the control arm subjects who received standard of care only.

66. The clinical trial efficacy assessment was improvement in the 9-point Ordinal scale. With the primary endpoint being time to a two-point improvement or hospital discharge.

67. Other efficacy assessment- are detailed in the trial protocol and include:

68. Overall mortality assessed on Days 15, 29, and 60, and, time from treatment (candidate agent) start date to death will be calculated.

69. The duration (days) of oxygen use and oxygen-free days (to Day 29)

70. The duration of mechanical ventilator-free days (to Day 29), as will be the incidence and duration (days) of new mechanical ventilation use.

71. The duration (days) of intensive care unit (ICU) and hospitalization

72. The National Early Warning Score 2 (NEWS2) assessed daily while hospitalised and on Days 15 and 29.

73. In addition to the clinical assessment additional samples were captured for scientific study, this led to a successful NIHR EME grant award and the mechanisms of action of bemcentanib, zilucoplan and tozorakimab have been

analysed with detailed maps of responder phenotypes and the key immune pathways identified.

Conduct of the Trial in Practice

74. The on the ground conduct of the study was performed by the clinical trial teams at each of the sites, supervised by their own PIs and working with the CROs coordinating the study – IQVIA May to July 2020 and MEU December 2020 to July 2021. As a trial team we worked closely with sites, all sites underwent a formal feasibility and capability assessment to ensure they had the necessary expertise and resources for the safe and effective conduct of the study. We conducted site training and performed remote site initiation visits. Sites were provided with all of the necessary paperwork and electronic tools for the collection of data. All sites received sampling consumables and were maintained with these for the study. Open communication with sites was maintained 7 days a week for expedited safety reporting and site PIs could contact the ACCORD CI or senior sub investigators for help or advice at any time. To facilitate this an senior investigator Professor Tony de Soyza (Newcastle) joined the core study team to support the acalbrutinib study arm.

75. We conducted regular web-based meetings with sites to update them on trial progress, address queries and share best practice around recruitment. These calls provided the opportunity to gain feedback from the sites and to consequently iterate trial processes and the protocol to improve the conduct of the study.

76. The key amendments made to the protocol and information sheet were to simplify the trial for sites to deliver, to focus on key outcomes and safety signals and to capture the change in CRO and team. These amendments included:

    i. Exploratory objective evaluating SARS-CoV-2 viral load in blood and saliva has been removed.
    ii. Requirement for all patients to be assessed for eligibility according to the master protocol and all ongoing sub-protocols added. This will allow the randomisation ratio to be adjusted automatically and ensure that the

number of subjects randomised to each sub-protocol is approximately equal to the number randomised to SoC.

iii. Removal of the Steering Committee, relevant responsibilities will be performed by the Sponsor, Chief Investigator and Sub-Chief Investigator. All references to the Steering Committee have been updated throughout the protocol.

iv. Reference to the multiple candidate agents being grouped into domains removed.

v. Clarification added to confirm that diagnostic imaging is only required if clinically indicated.

vi. Clarification added to confirm that the baseline 12-lead Electrocardiogram does not need to be repeated if results are already available from routine clinical care within 24 hours of Day 1.

vii. Targeted physical examination as clinically indicated removed.

viii. Frequency of blood sampling for exploratory soluble factors analysis, SARS-CoV-2 serology research (host response) and (PAXGENE) for transcriptome analysis (host genome) reduced.

ix. Blood sampling and analysis for optional PBMC cellular immunity assays removed.

x. Blood and saliva sampling and analysis for SARS-CoV-2 (qualitative and quantitative) removed.

xi. Mid turbinate nasal swab viral genome sampling and analysis removed.

xii. Criterion excluding patients that may transfer to another hospital that is not a study centre within 72 hours has been removed.

xiii. Electronically obtained informed consent has been replaced with paper informed consent.

xiv. Reference to the IQVIA medical monitor has been removed throughout the protocol. Responsibilities will be undertaken by the Sponsor, Chief Investigator, Sub-Chief Investigator, Principal Investigators and candidate agent Sponsors as appropriate.

xv. Appendix 3 'Clinical Laboratory Tests' updated to clarify that if sites/local laboratories are not able to test for certain parameters, this will not be deemed a protocol violation.

xvi. Reporting of SAEs will be completed using a paper report form, reference to electronic data collection reporting removed.

77. Because of the evolving nature of the study and of the limited resources available due to the funding cap the ACCORD committee made a number of specific decisions about the continuation of specific drugs in the study. All these decisions were ratified with the HRA, Research Ethics Committees and MHRA.

78. After the initial funding halt in July 2020 and during the replanning phase it was clear we would not have the resources to complete all 5 drugs through stage 2. Therefore, the decision was made to continue to stage one with Bemcentanib and to combine data with the overseas trials which were running to complete the phase 2 analysis of this drug. Also to continue with tozorakimab in the trial and to liaise closely with AZ to determine when they were able to make a decision about proceeding to a phase 3 study. To continue with recruitment into the zilucoplan arm – we became aware that another trial of this drug was being conducted in Belgium and we would monitor this closely. The inhaled Heparin arm had not started at that time, and we had no resources available to conduct it. Therefore, a plan to deliver a trial overseas was formed as there was the potential of charitable funding to deliver this in a lower- or middle-income country setting. Acalabrutinib which had been commenced in the initial phase in ACCORD was also tested in an open label study in the USA – this reported whilst we were planning for the next steps in the summer of 2020. This Calavi study reported that there was no benefit to COVID-19 recovery seen and so a decision was made to discontinue Acalabrutinib in the ACCORD study – a decision endorsed by the MHRA.

79. The eventual decision to stop the study in July 2021 was based on the falling number of hospital admissions impacting on trial recruitment combined with the limitation in funding availability. At that stage each of the drugs had a clear plan to continue or not and each of the drug companies had made decisions about next steps. We were alert to and responsive to the drugs in our platform being trialed elsewhere internationally and this enabled us to focus on drugs which were not trialed elsewhere.

80. Overall, we did not face any challenges to trial medication access thanks to our excellent relationships with the pharmaceutical teams. I have highlighted above the challenges associated with working alongside large scale priortised studies which did impact on phase 2 recruitment. The other 3 UK phase 2 platforms did coordinate their activity, there was no duplication of drugs in trials in the UK I am aware of and little or no competition at sites. Professor Chinnery facilitated a coordinated approach but having 4 seperate trial platforms clearly meant that each one platform had reduced access to the number of hospital sites, as they tended to deliver one platform only due to limited resources.

81. The main therapeutic effects of the drugs were:

    i. Acalabrutinib - Discontinued in ACCORD in July 2020 due to report of negative Calavi study in the USA. No safety concerns identified.

    ii. Bemcentanib - The drug was well tolerated with no safety concerns. A positive efiicacy signals seen in both ACCORD and when combined with sister trials in India and South Africa - time to improvement analysis HR 1.51 with a p value of <0.1 which was the prespecified level for the ACCORD primary analysis. These results were presented and were released by the company announcement as soon as topline data were available- May 2021. These data were formally presented at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) Conference April 2021 and with further analysis presented in 2022. Full publication in revision currently. I understand Bergenbio wish to proceed to phase 3 but, as a small biotech, need to raise the funding to do this.

    iii. Tozorakimab - was well tolerated, with no safety concerns identified. The primary outcome was not met – time to two-point improvement in OSCU was 8 days in the treatment arm vs 9.5 days standard of care but no significant difference. However the risk of death or respiratory failure was numerically lower in the treatment arm OR 0.55 but this was not statistically significant it was seen to be an even stronger effect in subjects with high IL 33 OR 0.33 meaning patients on the drug may be a third as likely to suffer a severe outcome than this not on it. The ACCORD trial data were provided

to senior management at Astra Zeneca by September 2021.They worked on the design of a potential phase 3 study and full resources were enabled to move to a Phase 3 study globally (TILIA) in August 2022. The Tilia Phase 3 study commenced in December 2022. The ACCORD trial data was presented at the European Respiratory Society Conference in September 2023. Results were published in European Respiratory Society Open Research in September 2023.

iv. Zilucoplan - was well tolerated with no safety concerns present. A positive signal of efficacy - a sustained clinical response in the treatment arm vs standard of care- p=0.069 was seen. The results were shared with the drug company UCB in September 2021. The results of the Belgian clinical trial were also assessed, please see de Leeuw et al Respiratory Research 2022. The company decided not to progress with the drug in further COVID trials. These results are part of the overall clinical trial report and of a summary paper which has been funded by an NIHR grant and is now in submission for publication.

v. Unfractionated inhaled heparin was not trialed in ACCORD but was trialed using a similar trial design in a collaborative study in Brazil funded by the Moulton trust. This trial showed no safety concerns and the drug was well tolerated, the study was published - de Nucci et al Pulmonary Pharmacology and Therapeutics in June 2023. Again, signals of efficacy were seen with numerical reductions in mortality, improvements in ordinal score and lower rates of mechanical ventilation in the treatment arm.

82. All study results were written up into a formal clinical study report this was shared with all drug company partners and the regulators and sponsor. Individual arms were reported as above. In addition, the ACCORD trial website was updated with trial progress and outcomes. Individual drug companies announced outcomes from their drugs in trial via formal company announcements to the public. ACCORD trial progress and results were shared with Professor Patrick Chinnery then CTAP chair who liaised with the phase 3 platforms to explore their interest in adopting any of the drugs for phase 3. I also understand that Astra Zeneca approached the RECOVERY study through this route in order for Tozorakimab to

be considered in phase 3. This drug was however declined which led to the decision for Astra Zeneca to deliver the phase 3 global study themselves. Study results were also shared with the NIHR and formed the basis of an NIHR EME grant application and award to extend the analysis of ACCORD trials data and use the biological dataset of gene expression and protein markers to better understand the nature of the drug effects and to refine approaches to select patients who may benefit from these drugs in COVID-19, severe non COVID viral infection or future pandemics.

83. The limited funding provided to the ACCORD platform after the restart of the study meant we had to focus all resources on completing the trials of the remaining 3 open drug arms and performing the topline safety and efficacy analyses. These were performed in a timely way within weeks of study data completion to enable clear decisions about progression of drugs until phase 3. However, there were delays, study sites struggled to lock down data and address queries as staff were moving into clinical roles as the pandemic changed. Our commissioned statistical supplier Veristat experienced significant delays as it was part of a corporate sale and a new team had to be brought in and trained on the project. Where there was pharma company interest in the drug progressing, e.g. Tozorakimab / AZ, there was additional resource found to support analysis and results were published more promptly. An additional grant from NIHR awarded to myself has enabled my University team to perform a complex analysis of the biological samples data which is now complete.

Impact

84. As stated above the impact of a phase 2 platform is to influence the conduct of phase 3 studies – promoting drugs for further study or halting their progress if there are concerns over safety or efficacy.

85. Here the impact of ACCORD has been significant. Tozorakimab is now the focus of a global phase 3 study which is recruiting almost 3000 subjects internationally. The indication for the drug is now broader including COVID-19, influenza and severe viral pneumonia. This design and indication is a direct result of the

ACCORD programme and if this is a positive phase 3 trial it will dramatically alter the treatment landscape for severe viral infection and for future pandemics.

86. Additional benefits include the promotion of evidence for the potential value for bemcentanib in a similar indication – Bergenbio is seeking funding to enter phase 3 and this too could become an important adjunct to treatment.

87. Inhaled heparin identified as a candidate therapy by ACCORD and supported in trial conduct abroad is now part of a global phase three meta trial in intensive care patients and the focus of planned studies in COPD.

88. Other studies have sought to replicate or augment the results of ACCORD or have delivered results in parallel and all of the assets chosen have had additional data produced which is aligned to the key findings of ACCORD, a testament to the rigour of the study.

Transparency and Public Engagement

89. The ACCORD study has always engaged the public and has had an open portal to trial design and progress via its own website and through the communications strategy of the NIHR and the University Hospital Southampton. See for example the UHS NHS and University of Southampton Health research web pages. In addition, the study was announced early in the pandemic by the health secretary on the daily COVID-19 updates, I have discussed the project and wider drug development progress with the media and we have presented the data at national and international meetings. Decisions about drugs in trial and conduct were updated via these channels.

90. Public communication was supported by these channels and particularly through the Southampton Center for Research Engagement and Impact (SCREI) the NIHR Southampton Biomedical Research Centre and the wider NIHR, I helped coordinate this with these expert groups.

Lesson Learning

91. The key lessons I think we can take forward form the experience of drug development in the pandemic and of ACCORD are:

    i. The need for pre-existing plans for trial set up and delivery and an established plan to coordinate delivery of studies of all phases effectively. This was lacking at the beginning of the pandemic and this could be addressed by establishing an extant capability. Rather than simply offering a mothballed platform this could keep limber by trialing drugs against common winter viruses each year which are major cause to hospitalization in the NHS and which would ensure sites and infrastructure is kept prepared.

    ii. Transparent and adequate funding for programmes in flight.

    iii. Coordination of phase 1 2 and 3 activity so a seamless transition of drugs could occur with minimal time and risk.

    iv. An international and fully searchable database of trials both planned and active and candidate drugs to ensure no overlap of activity.

    v. To increase diversity of inclusion - resources to translate all trials materials into the necessary languages to improve inclusivity. Active public engagement and support activity coordinated nationally, perhaps through NIHR.

92. We were able to develop strategies in ACCORD and at UHS NHS FT to aid the delivery of phase two studies whilst also continuing to support phase 3. The Southampton model is shared as a key document which explains how the more complex trials could be prioritized as they require few patients but a concerted effort to deliver them – this could significantly improve phase 2 trial delivery whilst not impacting on phase 3. Exhibit TW05-ACCORD 05 [INQ000236650].

93. It is now clear that a number of drugs targeting host immune and inflammatory responses could play a role in modulating the severity of this and future pandemics but also in a range of seasonal viral infection. An example of this is the extension

of the indication of Tozorakimab from ACCORD into severe viral infections more broadly in the Tilia study.

94. If this concept was extended – continued ongoing drug development of novel and repurposed compounds in phase 2 in respiratory viral infections in the UK could produce a repository of candidate drugs which could rapidly be rolled out into phase 3 in a pandemic and developed to tackle winter viral infections in the interim. Such a platform could be a permanent fixture and a world leading example of UK research in respiratory and infectious disease drug development.

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: _ **Personal Data** _____

Dated: ___19/11/2024_____