Expert Report for the UK Covid-19 Public Inquiry

Module 2: Long Covid

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Author statement

I confirm that this is my own work and that the facts stated in the report are within my own knowledge. I understand my duty to provide independent evidence and have complied with that duty. I confirm that I have made clear which facts and matters referred to in this report are within my own knowledge and which are not. Those that are within my own knowledge I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.

Professor Chris Brightling	Dr Rachael Evans
26 September 2023	26 September 2023

About the authors

Professor Christopher E Brightling GMC reference number: Personal Data

Professor Chris Brightling is a Fellow of the Academy of Medical Sciences (AMS), National Institute for Health and Care Research (NIHR) Senior Investigator (Emeritus), Director for the Leicester Institute for Precision Health, Director Institute for Lung Health, Respiratory and Infection Theme Lead for Leicester NIHR Biomedical Research Centre and Honorary Consultant Respiratory Physician, Leicester, UK. He has been a consultant since 2004, and a professor since 2007. He is the former Science Council Chair of the European Respiratory Society (ERS) (2019-2022).

Beyond Covid-19, his main research focus is on improving the clinical management and understanding the immunopathogenesis of asthma, chronic cough and chronic obstructive pulmonary disease (COPD). He is Coordinator the MRC Molecular Pathology Node EMBER and Respiratory lead for the EU-IMI 3TR. He is a member of the Global INitiative for Asthma - GINA scientific committee. He has published over 560 peer-reviewed articles including more than 60 in either the New England Journal of Medicine or Lancet family of journals.

Of relevance to this report, Professor Brightling led the acute Covid-19 research for Leicester, with Leicester recruiting the largest number of patients for the national acute study platforms such as the RECOVERY study. Professor Brightling is the chief investigator for the UK Research and Innovation (UKRI) Post-Hospital COVID-19 study (PHOSP-COVID), and a co-investigator/collaborator for the UKRI funded studies OpenSAFELY, PHOSP-COVID, ISARIC collaboration and UK-ILD. He has co-authored 69 peer-reviewed scientific publications on Covid-19, of which 33 are focussed on Long Covid. During his tenure as ERS science council chair Professor Brightling led the ERS Long Covid scientific response and established the Long Covid clinical research collaboration END-COVID and co-authored the ERS COVID-19 guidelines.

Professor Brightling participated in the Secretary of State Roundtable Research into the long-term impacts of COVID-19 meeting 31st July chaired by the Department of Health and Social Care (DHSC) Secretary of State ahead of the formation of the SoS/ministerial-led (Lord Bethell or Matthew Hancock MP) Long Covid Roundtable meetings which were held between 13 Oct 2020 to 21 July 2021. He co-authored the AMS report published in July 2020 and gave evidence to the House of Lords Science and technology committee on the Science of COVID-19 in September 2020. He co-authored a report to SAGE, attended and presented on 22nd July 2021. He is a member of the National Long Covid Research Group chaired by Professor Kamlesh Khunti, University of Leicester.

Dr Rachael Andrea Evans GMC reference number Personal

Dr Rachael Evans is an Honorary Respiratory Consultant Physician at Glenfield Hospital, University Hospitals of Leicester NHS Trust and Associate Professor at University of Leicester. She has been a consultant since 2013, and an Associate Professor since 2016.

Beyond Covid-19, her research work focuses on symptom-based models of healthcare from diagnosis to interventions including exercise rehabilitation, using breathlessness as an exemplar symptom. She is the American Thoracic Society Pulmonary Rehabilitation Assembly Chair and the European Respiratory Society Pulmonary Rehabilitation and Chronic Care Chair. Her clinical work outside of Long Covid includes delivering healthcare for people with advanced chronic obstructive pulmonary disease (COPD), and people living with breathlessness.

Of relevance to this report, Dr RA Evans' clinical work includes being part of her local respiratory consultant Glenfield Hospital team working on the acute medical admissions unit outside of usual working hours on the 'on call' rota. She initiated, implemented and led the Leicester, Leicestershire, Rutland Long Covid service from June 2020 to present. The service has seen more than 6100 patients to date and over 1000 have been recruited to national research studies.

Dr RA Evans held an NIHR clinician scientist fellowship from 01 March 2017 to 30 Aug 2022. She is the lead clinical co-investigator for the UKRI Post-Hospital COVID-19 study (PHOSP-COVID), and a principal investigator/co-investigator for the NIHR LOng COvid Multidisciplinary consortium: Optimising Treatments and servIces acrOss the NHS (LOCOMOTION) study, NIHR Symptoms, Trajectory, Inequalities and Management: Understanding Long Covid to Address and Transform Existing Integrated Care Pathways (STIMULATE-ICP) study, UKRI HEAL-COVID study, NIHR Policy Research Programme PHOSP Health Services Research (PHOSP-HSR) and the Wolfson Foundation C-Fog study. She is part of the NIHR Therapies for Long Covid (TLC) study steering committee.

Dr RA Evans has been a member of the NHS England Long Covid Taskforce since inception to present and participated in the Lord Bethell Long Covid Roundtable meetings 13 Oct 2020 to 21 July 2021. She is a member of the National Long Covid Research Group and she co-authored a report to SAGE which was presented 22nd July 2021. She was part of the development of the Your COVID Recovery website and provided initial content.

Contents

1. The developing understanding of long-term sequelae arising from SARS-CoV-2 infection

1.1. At the start of the Coronavirus Disease 2019 (Covid-19) pandemic, understanding of the potential long-term sequelae from Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was extrapolated from existing knowledge of SARS-CoV, Middle East Respiratory Syndrome-CoV (MERS-CoV) [Peiris JS 2003, Chang YC 2005, Park WB 2018, WHO MERS 2019], other causes of acute respiratory distress syndrome (ARDS) and its consequences, and other post-viral syndromes. For example, post SARS-CoV abnormal diffusion capacity, a breathing test indicating possible underlying scarring in the lung, was identified in ~25% of people that had been hospitalised for the acute infection [Hui DS 2005, Ngai JC 2010]. Previous cohorts of survivors of ARDS report persistent physical function and psychological impairment five years post admission [Herridge MS 2011].

1.2. Attention was initially focussed on those hospitalised for acute Covid-19, in part because testing was only routinely undertaken in this group and because it was anticipated that long-term consequences would be more common in this group. Long-term consequences for some adults admitted to hospital with acute severe Covid-19 were predicted by clinicians and researchers to include breathlessness, fatigue, multi-organ impairment, physical inactivity and deconditioning, and impaired psychological and social well-being. These effects were anticipated to be partly the consequences of acute severe respiratory disease and the effects of prolonged hospital admission including intensive care unit (ICU) therapy. Post-ICU syndrome includes the multi-system/organ (whole body) effects of a severe illness where use of ventilation (breathing machine) and other organ support has been required. It was a well-recognised condition before the Covid-19 pandemic. The syndrome involves physical and mental health effects including post-traumatic stress disorder and can be supported by recovery and rehabilitation programmes [Brown SM 2019]. There are post-ICU clinics across the UK, typically run by intensivists (intensive care staff) to manage these 'after effects'.

1.3. There are known post-viral syndromes from other viruses, for example from Epstein-Barr virus, Coxsackie viruses and enteroviruses [Jenkins R 1991, Lorusso L 2008]. Post-viral syndromes are typically multi-system (may affect the whole body) and affect both physical and mental health. Of note, many of the acute illness due to these viruses do not require hospital admission for organ failure. Debilitating fatigue is a common symptom and some adults will subsequently develop Chronic Fatigue Syndrome (CFS) / Myalgic Encephalomyelitis (ME) [Hicki I 2006]. However, the extent and exact nature of post-viral effects appear to vary from virus to virus, and therefore for any viral pandemic it is challenging to anticipate the exact scale and precise sequelae.

1.4. The first national guidelines for follow-up of Covid-19 pneumonia were published by the British Thoracic Society in May 2020 [George PM 2020]. Whilst welcome, the guidance primarily focused on the respiratory system (lungs) and almost exclusively to adults admitted to hospital. The potential risk of long-term sequelae of Covid-19 in those hospitalised was recognised early on by some clinical teams. Healthcare pathways across the UK evolved differently across hospital NHS provider organisations in Spring to Autumn 2020 [Houchen-Wolloff L 2023] according to clinical enthusiasm or knowledge (situated resilience) and managerial support (structural resilience) [Overton C 2023]. More detail around the different healthcare pathways for Long Covid and how they developed is provided in the M3 section of this report.

1.5. The risk of long-term sequelae in those not hospitalised was recognised early by people with lived experience, and disseminated predominantly through social media with national and international reach. Long Covid is a public and patient derived term to describe ongoing symptoms after contracting SARS-CoV-2. In social media, the public were naming 'covid long haulers' amongst other terms. It was apparent that some adults who had experienced a relatively mild acute illness were at risk of ongoing symptoms and sequelae. The scale and extent of these issues was largely unclear during spring of 2020 other than to individuals living with Long Covid or their contacts. The Long Covid Support group was started on 2 May 2020 [Long Covid Support], and Long Covid SOS in June 2020 [Long Covid SOS] as patients and the public became aware of Long Covid. Long Covid SOS sent an open letter on 8 July 2020 with over 1,000 signatures to the Prime Minister and Secretary of State for Health and Social Care and others involved in health policy. Patients reported difficulty accessing healthcare and/or gaining knowledge about the symptoms they were experiencing [Ladds E 2020].

1.6. The National Institute for Health and Care Excellence (NICE) issued a themed review 'Living with Covid19' October 2020 (NICE 1 2020) issued a clinical knowledge summary on Long Covid including clinical case definitions to identify and diagnose the long-term effects of Covid-19 in December 2020 [NICE 2 2020] which remains active to date [NICE 2022]. Acute Covid-19 is defined as signs and symptoms of infection consistent with Covid-19 for up to four weeks. Ongoing symptomatic Covid-19 is defined by signs and symptoms of Covid-19 infection from four weeks up to 12 weeks. Post-Covid-19 syndrome is defined as signs and symptoms that develop during or after an infection consistent with Covid-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis. Long Covid usually presents with clusters of symptoms which may overlap, fluctuate, change over time, and affect any body system. The World Health Organisation has subsequently defined Post-Covid condition by a Delphi consensus as the continuation or development of new symptoms

three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least two months with no other explanation [WHO 2021].

1.7. It is important to consider the long-term consequences of SARS-CoV-2 in the UK within the context of availability of testing for SARS-CoV-2. In hospitals at the start of the pandemic, that is, February to April 2020, Covid-19 was diagnosed by clinicians based on: a typical history of acute symptoms e.g., fever, cough, fatigue, loss of taste and smell; risk of contact via travel to high-risk areas, for example China, Italy or cruise ships or known contact with someone with Covid-19. Any testing performed in hospital was confirmed later, often after the patient had been discharged from hospital [Department of Health and Social Care 2020]. The government released a five-pillar strategy to increase testing on 04 April 2020 [Gov UK 2020]: pillar 1 tests were those carried out in hospitals or as part of managing outbreaks and pillar 2 tests were those available to the wider public. By September 2020, rapid Covid-19 testing was available in UK hospitals, and thereafter Covid-19 was diagnosed in hospital by a combination of clinical criteria and SARS-CoV-2 test positivity (Polymerase Chain Reaction (PCR) or lateral flow). From 23 April 2020, SARS-CoV-2 testing was expanded for essential workers and their households, and by 18 May 2020 eligibility for pillar 2 tests extended to include anyone with symptoms. NHS Test and Trace was launched on 28 May 2020 and by Autumn 2020 achieved 180,000 tests per day in England (figure 1.).

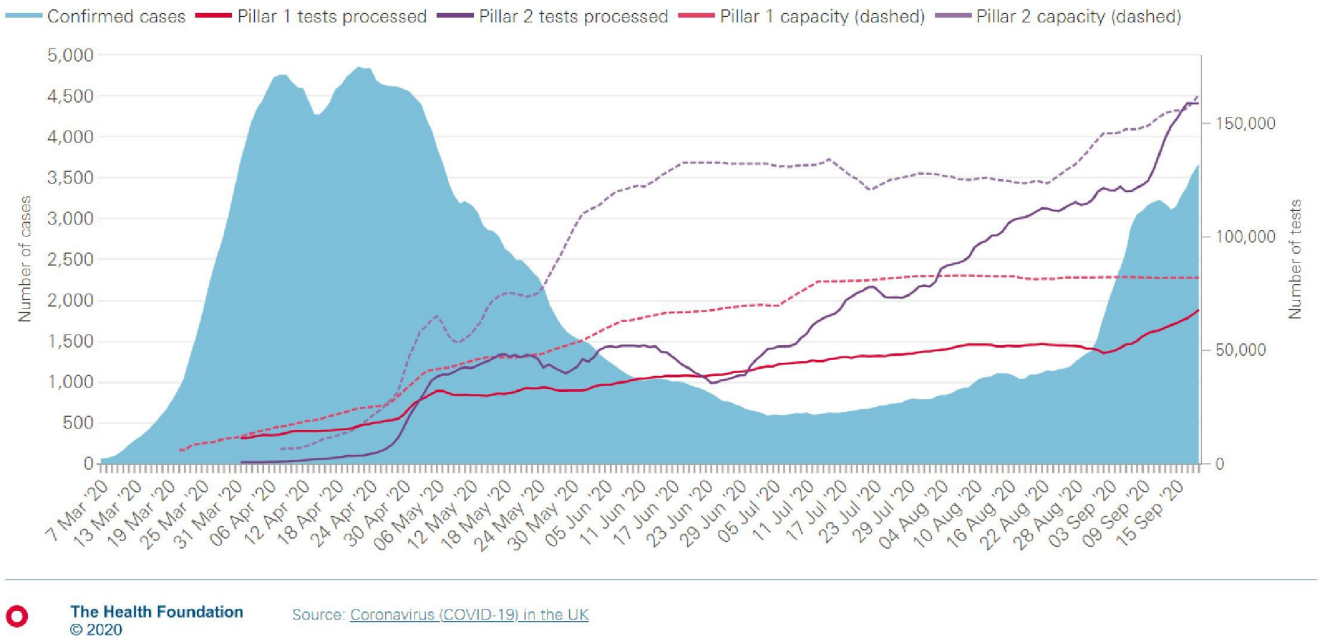

Figure 1. Daily number of COVID-19 tests and cases 7 March 2020 to 15 Sept 2020

Figure from: https://www.health.org.uk/publications/long-reads/nhs-test-and-trace-the-journey-so-far. Using data from https://coronavirus.data.gov.uk/

[Accessed 22 July 2023]

1.8. An important downstream effect of the lack of testing was that many people in the Spring/Summer of 2020 had undiagnosed Covid-19 in the community and many of these (approximately 10-30% of infections) developed unrecognised/undiagnosed prolonged symptoms i.e., what is now known as Long Covid. These sequelae were largely unknown to healthcare professionals or systems during this time. Qualitative research involving interviews with people with lived experience describes the anguish of not knowing what their prolonged symptoms were, difficulties seeking healthcare advice due to lockdown conditions, and many having unsatisfactory consults with healthcare professionals who were unaware of post-covid sequelae [Ladds E 2020].

1.9. In England, NHS England announced a five-point plan on 7 Oct 2020 [NHS England 2020]. To our knowledge a similar plan was not available in Northern Ireland, whereas Wales funded a recovery programme (£18.3 million to date) through the health boards aimed at primary and community care, and similarly Scotland invested £10 million to the Health Boards to support local services for Long Covid (https://www.gov.scot/publications/scotlands-long-covid-service/).

Further details about UK provision for Long Covid care are provided in M3. Although much of the Long Covid research occurred across the four nations, clinical care evolved differently with potential inequity which is further discussed in M3.

NHS England five-point plan
1) New guidance from NICE by the end of October on the medical 'case definition' of Long Covid including patients who had not been to hospital or had a previous test, 2) An online website of supported self-management called Your Covid Recovery https://www.yourcovidrecovery.nhs.uk/, 3) Designated Long Covid clinics to provide a physical, cognitive, and psychological assessment, 4) NIHR funded research on Long Covid which is working with 10,000 patients to better understand the condition and refine appropriate treatment. 5) The NHS-England support was to be overseen by the NHS-England Long Covid taskforce.

Summary of NHS England five-point plan, published 7 October 2020. Available from: https://www.england.nhs.uk/2020/10/nhs-to-offer-Long-Covid-help/ [Accessed 22 July 2023]

1.10. Lord Bethell, the Parliamentary Under-Secretary of State for Innovation at the Department of Health and Social Care at the time, chaired a monthly 'roundtable' hosted virtually with relevant stakeholders, including people with lived experience of Long Covid, to oversee the five-point plan from October 2020 to July 2021.

1.11. The Post-Hospitalisation COVID-19 (PHOSP-COVID) study (phosp.org) was the fourth point of the five-point NHS England plan and was already recruiting. PHOSP-COVID was the first UKRI/NIHR funded study investigating the long-term effects of Covid-19 and focused on survivors of a hospital admission. The UK wide team was established March and April 2020 utilising the NIHR infrastructures of Biomedical Research Centres and Translational Research Collaborations and a proposal including a full study protocol, patient information sheet and other necessary documents for ethical and regulatory approval were submitted for Urgent Public Health review on 05 May 2020, and was submitted to UKRI in early June 2020. The funding of £8.4 million was announced on 16 July 2020, ethical approval alongside the other necessary governance was gained on 14 July 2020, and the first patient was recruited at Glenfield Hospital, University Hospitals of Leicester NHS Trust on 14 Aug 2020. Professor Christopher Brightling is the Chief Investigator and Dr Rachael Evans is the lead Co-Investigator (clinical) (both authors of this report), and Professor Louise Wain is the lead Co-Investigator (non-clinical). PHOSP-COVID is a UK wide

study with 83 hospital sites across the four nations, (England = 61, Wales =12, Scotland n=9, Northern Ireland = 1). The aim was to recruit 10,000 participants, and to follow-up 2,500 participants at two research visits approximately six months and one-year post-discharge. The three main aims were 1) to determine the long-term sequelae, 2) to investigate the longer-term effects of acute and post-discharge treatments, 3) to provide a platform for future studies of emergent symptoms and worsening of pre-existing disease to improve care for current and future adult patients post-Covid-19.

The PHOSP-COVID study was completed by 31 March 2022, recruiting 7,935 participants with 2,697 participants attending in-person research visits.

1.12. The understanding of the long-term effects of SARS-CoV-2 internationally started with a focus on adults who had survived a hospital admission from Covid-19 (Figure 2). One of the early studies, published in July 2020, was from Rome, Italy, where they compared the symptoms experienced during the acute illness with symptoms experienced at two months after discharge from hospital in 143 adults [Carfi A 2020]. Only 18/143 (12.6%) were symptom free with 55% experiencing three or more symptoms. The most common symptoms were fatigue, breathlessness, joint pain, and chest pain. At three months after hospital discharge, data from Bristol, UK, showed 74% of 191 patients had ongoing symptoms [Arnold D 2021] and data from Paris, France, at four months after discharge highlighted 51% of 478 participants had ongoing symptoms [Comebac Study Group 2021]. The largest cohort reporting the first data at six months post-hospital discharge was from Wuhan, China [Huang C 2021], where 76% of 1,733 patients had persistent new symptoms, although the paper has since been retracted with a revised scientific paper of the same study published in June 2023 reporting 68% of 1,650 [Huang C 2023]. Data from the UK PHOSP-COVID study highlighted only 25% of 1,077 adults felt fully recovered by an average of five months after discharge [Evans R 2021]. By the end of 2020, it was apparent the majority of adults had persistent symptoms several months after hospital discharge for Covid-19. Data from Wuhan, China showed 55.5% (650/1190) of adults had at least one persistent sequelae two years after hospital discharge [Huang L 2022], and both clinical experience and reports from the Long Covid charity groups highlight that Long Covid can last for over three years and therefore could be conceptualised as a long-term condition.

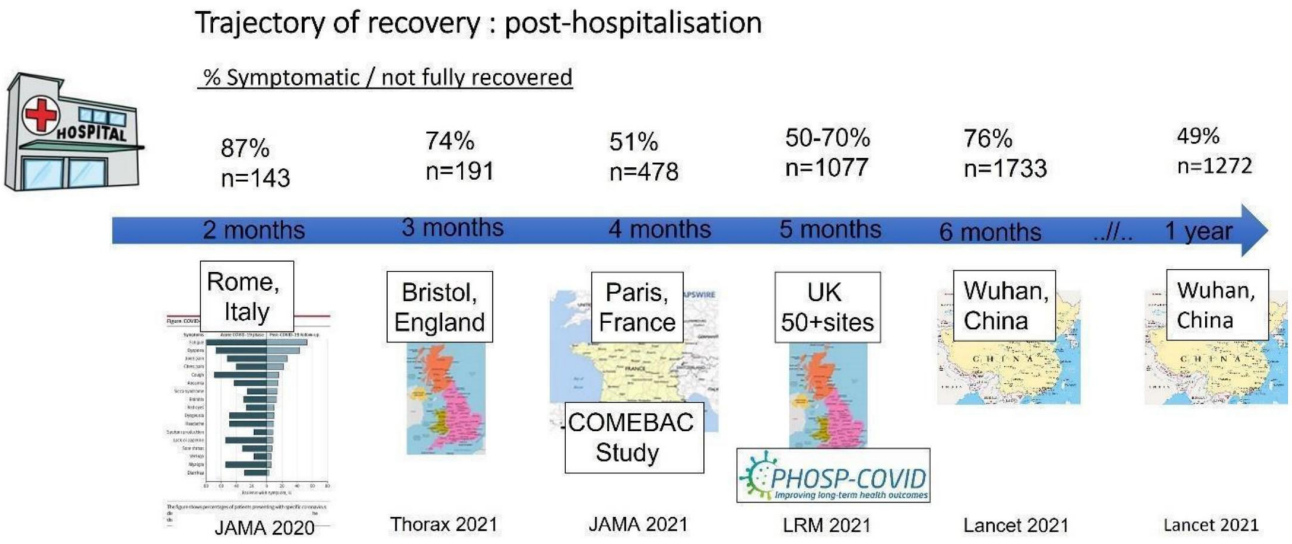

Figure 2. Trajectory of recovery from a hospital admission due to Covid-19

1.13. Research data describing the ongoing symptoms in adults who were non-hospitalised lagged behind the hospitalised data. The UK Office for National Statistics (ONS) developed a questionnaire: the 'Coronavirus (Covid-19) Infection Survey' (CIS), to be sent to private households along with testing kits and blood samples in a sub-sample. The CIS was delivered in partnership with the University of Oxford, the University of Manchester, the UK Health Security Agency (and its predecessor bodies based in Public Health England, DHSC, and NHS Test and Trace) and the Wellcome Trust, working with the University of Oxford and partner laboratories to collect and test samples. The initial CIS sample population was drawn from private households who had previously responded to official surveys and consented to be contacted for future studies. The first sample from 27 April to 10 May was reported on 14 May 2020 and included 10,705 people. The population was extended over time and included people over the age of two years old. The relevant Long Covid questions within the CIS were sent monthly. The CIS survey was piloted from May 2020 to Oct 2020 and started formally from 23 Oct 2020 [ONS 1 2020]. Data on prolonged symptoms were gathered from participants who tested positive from the beginning of the survey, and reported from December 2020 in an experimental dataset [ONS 2 2020], with regular publication from April 2021. The data was analysed and released monthly with cross-sectional estimates of the incidence of Covid-19 and Long Covid.

1.14. Long Covid is frequently characterised by symptoms of fatigue, breathlessness, brain-fog, joint and muscle pain, but over 200 symptoms have been reported

[Davis HE 2021]. The symptoms of Long Covid have a significant impact on both mental and physical function leading to disability and impaired health-related quality of life. Data from the PHOSP-COVID study showed an average quality adjusted life year of 0.71, where 1.0 is equal to one year of life spent in perfect health [PHOSP-COVID 2022]. This reduction is similar to some cancers and long-term conditions such as diabetes and epilepsy [Wilder L 2019]. In the same study, one in 10 people after hospital discharge were no longer working one year later and a fifth reported a change in work due to their health [PHOSP-COVID 2022]. Data from the CIS from ONS [ONS 2] highlighted the impact of Long Covid on work status compared with pre-infection. The peak impact was at 30-39 weeks post-infection with people reporting Long Covid being 45% more likely to no longer be working and the effect was greatest in those aged 50-64 who were 71% more likely not to be working. 21.4% of survey respondents who reported that they did not have Long Covid were not working and not looking for work compared with 23.3% for those with self-reported Long Covid. From July 2021 to July 2022, the inactivity rate among working-age people with self-reported long COVID grew by 3.8 percentage points, compared with 0.4 percentage points among working-age people without self-reported long COVID

1.15. One of the first attempts to describe distinct types of Long Covid was a qualitative assessment from patients, researchers, and doctors. The different syndromes suggested were post-intensive care syndrome, post-viral fatigue syndrome, and long term covid syndrome. In over 9,800 participants using the 'Covid Symptom Study smartphone app' (March 2020 to Dec 2021) with post-Covid-19 condition (and a related positive covid test), different clusters of symptoms were described across the different variants of SARS-CoV-2 including the original 'wild-type' virus (the naturally occurring, non-mutated strain), alpha, and delta variants [Canas LS 2022].

1.16. Data from the PHOSP-COVID study showed that the severity of on-going symptoms of fatigue, breathlessness, anxiety and depression, post-traumatic stress disorder (PTSD) and deficits of physical function largely tracked together, whereas there was a sub-group with moderate physical and mental health impairments but severe cognitive dysfunction (brain-fog) (Evans 2021, PHOSP 2022). In PHOSP-COVID sleep quality was also disturbed in those with Long Covid compared to people that were matched controls that participated in the UK-Biobank study [Jackson 2023].

2. Children and adolescents

Neither Professor Brightling nor Dr Evans have specific paediatric expertise and therefore our comments on the impact in children and adolescents are based upon the scientific literature, discussions throughout the pandemic with paediatric specialists leading Long Covid research, and consultation with Sir Professor Terence Stephenson (current Chair of the Health Research Authority; Chair of Child Health, University College London Great Ormond Street Institute of Child Health; and Honorary Consultant Paediatrician at UCL Hospitals NHS Foundation Trust & Great Ormond Street Hospital for Children NHS Foundation Trust) and Professor Roz Shafron (Professor of Translational Psychology at the UCL Great Ormond Street Institute of Child Health; Honorary Consultant Clinical Psychologist; member of the Health Professions Council; and Fellow of the British Association of Behavioural and Cognitive Psychotherapy.

2.1. The latest systematic review submitted to WHO in 2023 included a total of 60 studies involving a total of 333,472 children and young people. All 60 studies assessed outcomes at greater than 1 month after SARS-CoV-2 infection. The average length of follow-up was approximately three months and the longest follow-up was nearly two years after SARS-CoV-2 infection. Nearly half the studies were rated as having a low risk of bias (i.e the methodology of the study was more robust). Data from 12 studies where there was a comparator group were compared. Reporting three or more persistent symptoms was more common after SARS-CoV-2 infection than in control groups, but there were no differences between the two groups in reporting one to two symptoms. The data highlights the need for control groups as symptoms are prevalent in children and young people, and also highlights the importance of a higher total number of symptoms being more likely related to previous SARS-CoV-2 infection.

2.2. SARS-CoV-2 infection is predominantly a mild infection in children and adolescents and is often asymptomatic. Although severe Covid-19 and deaths are far fewer in children than in adults, data from the Max Planck Institute for Demographic Research (MPIDR) COVerAGE database (a global demographic database on Covid-19) reported over 17,400 deaths in children and adolescents under 20 years old, 0.4% of 4.4 million deaths reported [Unicef 2021]. There are some specific paediatric complications associated with Covid-19 such as Paediatric Inflammatory Multi-System Syndrome [Lawrensia S 2020] resulting in critical illness. However, this condition was mainly seen early in the pandemic [Munro A 2023]. The reduction of this complication over time might reflect changes in the spike protein with later variants or increase in immunity from previous infection or vaccination when available. Long Covid is not as prevalent in children compared with adults [ONS 3]. However, Long Covid symptoms are common at follow-up in children but only in a minority are these both very prolonged and severe. It is difficult to get a true prevalence or

incidence for Long Covid due to many children being asymptomatic with Covid-19, the cessation of national testing, and the absence of true, negative controls as by June 2022 just over 80% of primary school pupils and approximately 99% had SARS-CoV-2 antibody levels above the limit of detection [ONS 2 2022]. One of the largest studies to date is from the UK: the CLoCk study which recruited approximately 30,000 participants, half of whom had a proven positive PCR-test and half who had a negative PCR-test. At six months after infection when comparing children who have and have not tested positive, those who have tested positive are more likely to be symptomatic at six months [Stephenson T 2023]. However, it was also very notable that many children and adolescents develop new symptoms, measured at three and six months, regardless of test status and therefore control comparators are essential. To aid research, a modified Delphi (a method of achieving a consensus definition using online participation by clinicians, researchers, people with lived experience) was undertaken and defined Long Covid in children: 'post-Covid-19 condition occurs in young people with a history of confirmed SARS-CoV-2 infection, with at least one persisting physical symptom for a minimum duration of 12 weeks after initial testing that cannot be explained by an alternative diagnosis. The symptoms have an impact on everyday functioning, may continue or develop after SARS-CoV-2 infection, and may fluctuate or relapse over time' [Stephenson T 2022]. After 12 months of follow-up in 11-17 year olds, both PCR test-positives and negatives most commonly report tiredness and shortness of breath but with higher prevalence in previous test-positives. Older teenagers, females, those from an ethnic minority, and those with impaired health before the pandemic are more likely to have persisting symptoms. There was a large dropout with 5085 participants completing the 12 month questionnaire [Berg S 2023].

2.3. In summary, the CloCk study findings showed in children and young people:

- **Commonest persisting symptoms after Covid-19** are fatigue, headache, shortness of breath, persisting loss of smell
- **Many symptoms of Long Covid are** almost as common in negative controls – giving rise to the debate of Long Covid vs 'effects of living through the pandemic'?
- **Mental Health** scores using validated scales at follow-up were little different between test-positives and test-negatives and little different from pre-pandemic scores for adolescents.
- **Predictors of Long Covid are** age, sex, ethnicity and pre-Covid-19 health and wellbeing

2.4. **Symptoms decline with time in most young people** although at 12 months post infection, some teenagers report new symptoms, it is impossible to say whether these are causally related to previous SARS-CoV-2 infection. Although there was a delay in Long Covid in adults being recognised outside of those

living with it, in children and adolescents there was an even longer delay in Long Covid being recognised by general healthcare professionals, and the development of clinical care including specialist Long Covid services was slower. In response to these unmet needs, Long Covid Kids was established in 2021 and is a UK charity with international reach to support children and young adults living with Long Covid and their families. Similar to adults, perhaps some of this illness could have been anticipated, as post-viral syndromes have been described for decades, such as that associated after Epstein-Barr Virus, and with similar devastating impact for some with loss of schooling, loss of socialising and being very limited in physical function for prolonged periods of time. Similar to adults, the close interplay between physical health and mental health is described in Long Covid in children and adolescents. Often the prolonged impact of physical ill-health negatively affects mental health.

2.5. A key piece of shared learning and collaboration through the National Long Covid Research working group was around Long Covid in adults compared with children and adolescents. We presented early data from the various studies which highlighted the need for control groups and the presence of symptoms in the population and particularly children. The group are currently writing an article on control groups during a pandemic to summarise the challenges and to highlight future direction. The work group collaboration identified other studies involving children such as REACT-1 study and ONS for future collaborations. In 2023 there are plans to develop a similar bespoke 'symptom burden questionnaire' for children and young adults that was developed through the NIHR Therapies for Long Covid study in adults.

3. Diagnosis and pathophysiology of Long Covid

3.1. There is currently no diagnostic test of Long Covid. Long Covid is diagnosed as per the public, NICE and WHO definitions (described in paragraph 1.6). To diagnose Long Covid there needs to be an acute illness compatible with acute Covid-19 with or without an associated positive test (PCR or lateral flow) and prolonged symptoms for at least four weeks after the infection, not explained by an alternative diagnosis.

3.2. A positive PCR or lateral flow test at the time of the acute illness is useful in supporting the diagnosis, but testing was not routinely available especially in the community in the early stages of the pandemic, and community testing at test centres or at home is no longer routinely available. Before widespread vaccination, antibody testing in those where acute testing was not available had utility to confirm prior infection but with the variability in the magnitude and persistence of an antibody response following infection there was a risk of false negative results. When the prevalence of Covid is high, typical symptoms are sufficient to support a Long Covid diagnosis, however as prevalence decreases or becomes seasonal, testing is likely to regain value to support the diagnosis of Long Covid especially where there is diagnostic uncertainty.

3.3. The typical syndrome involves multiple symptoms with fatigue, breathlessness, and brain fog being amongst the most common. Other potential causes of the symptoms need to be excluded. The diagnosis is therefore made by a combination of a positive diagnosis of Long Covid (i.e., the symptoms fit) and exclusion of any other likely pathology. To ensure the symptoms of Long Covid are being correctly attributed, pre-existing health conditions such as diabetes, hypertension, and obesity, which are commonly associated with more severe disease, need to be optimally managed by the clinical team. Other pre-existing health conditions associated with pre-existing symptoms that have worsened since SARS-CoV-2 infection also need optimising, for example, commonly asthma, chronic obstructive pulmonary disease and other chronic respiratory conditions and worsening breathlessness.

3.4. The biology of SARS-CoV-2 and its variants, the mechanisms of acute COVID viral entry, the immune response and pathological changes from a molecular, cellular, and organ level and the beneficial effects of acute interventions are well described. In contrast, Long Covid is likely to be a consequence of multiple mechanisms interacting over time to lead to the various symptoms that have been described in the Long Covid phenotype.

3.5. Following an acute infection some individuals are asymptomatic or have acute symptoms for a few days. Others develop more severe symptoms that are driven by a hyperinflammatory state with the development of pneumonitis (pulmonary infiltrate in the small air pockets [alveoli] and the lung tissue

[interstitium]) which is often associated with thromboemboli and microthrombi [small clots]. The inflammation and microthrombi in severe illness can lead to respiratory failure needing high flow oxygen supplementation and sometimes respiratory support with non-invasive ventilatory support e.g., continuous positive airway pressure or invasive ventilation. In June 2020, the RECOVERY study team reported the beneficial effect of dexamethasone (corticosteroid) on short-term mortality. This finding has consistently been reported in other studies [Chalmers J 2021]. Benefit was also reported later for other anti-inflammatory therapies (tocilizumab [anti-IL6] in February 2021 and baricitinib in March 2022). Trial results for treatment dose anti-coagulation were less clear and NICE guidance currently recommends treatment dose dalteparin for patients requiring low-flow oxygen [NICE 2023]. The benefit of acute corticosteroids, and other anti-inflammatory therapies and, potential benefit of acute short-term anticoagulation support the mechanistic role of acute inflammation and thromboembolic disease in acute COVID-19.

3.6. In Long Covid, ongoing systemic (affecting the whole body) inflammation, autoimmune disease (the immune system attacking healthy tissue), micro-clotting, endothelial (lining of the blood vessels) dysfunction, dysautonomia (disruption to the autonomic nervous system leading to conditions such as Postural tachycardia syndrome [PoTS]), viral persistence of SARS-CoV2 or reactivation of other viruses such as Epstein-Barr virus leading to persistent immune activation have been proposed as underlying mechanisms [Davis HE 2023, Altmann D 2023]. These mechanisms are likely to lead to inflammation and sometimes damage in multiple organs which, together with physical deconditioning in those who were hospitalised, are likely to drive some of the symptoms, and physical and mental health impairments.

3.7. Some post-acute sequelae relate to the organ damage caused by the acute illness for example pneumonitis, myocarditis, kidney injury, the negative effects on both physical and mental health of a prolonged hospital stay, and post-intensive care syndrome. In an MRI study of 259 patients in the CMORE/PHOSP-COVID sub-study lung, brain and kidney MRI abnormalities were more common among patients compared to uninfected people [Raman B 2023]. The organ inflammation and damage were associated with impaired organ-specific blood markers and physiological tests. Multiorgan abnormalities were more frequent among patients and were independently associated with COVID-19 status, irrespective of comorbidity count and severity of acute infection. Multiorgan MRI abnormalities were associated with impaired patient recovery [Raman B 2023]. Data from the PHOSP-COVID study used by UKRI funded UK-ILD Post-COVID-19 study, estimated up to 11% of adults post-COVID-19 had residual lung abnormalities 240 days after hospital discharge [Stewart I 2023]. How generalisable these findings are to a broader population, whether these changes persist and to what extent they impact prognosis and

or treatment strategies is uncertain. Data from UK electronic healthcare records in over 47,000 patients discharged from hospital after COVID-19 matched to controls, supported an increased rate of respiratory disease, diabetes, cardiovascular disease [Ayoubkhani D 2021]. Over a mean follow-up of 140 days, nearly a third of patients with COVID-19 were readmitted and more than 1 in 10 died after discharge.

3.8. Estimates of the prevalence of new disease after COVID-19 must be interpreted with some caveats as many studies did not have comparative control groups and even where control groups are present, it is unknown whether some of the increased burden of disease/sequelae post-COVID-19 discovered during follow-up studies was pre-existing - either diagnosed or undiagnosed. Despite the caveats, there are ongoing organ impairments post-COVID-19. Using UK Biobank as a control group, one study reported brain imaging abnormalities in those post SARS-CoV-2 infection (n=401) compared to uninfected controls (n=384) at an average of 141 days post diagnosis [Douaud G 2022]. Although a smaller proportion of adults appear to have ongoing cardiac impairments than was initially thought [Raman C 2023, Morrow AJ 2022, Gluckman T 2022], data from large epidemiological studies consistently show an increased risk of cardiac events in the first year after SARS-CoV-2 [Raisi-Estabragh Z 2022, Xie Y 3033].

3.9. Similarly, Long Covid mechanistic studies must be interpreted with care and with particular attention to the population being studied including demographics, pre-existing disease, time since infection, severity and complications during the acute illness, particular definition used for Long Covid, and sample size. Most individual studies focus on one mechanism, so it is largely unknown how the different mechanisms interact in any one individual. However, it is very likely that there are different phenotypes (clinical expression) of Long Covid and therefore different underlying mechanisms in different individuals. The early success of interventions for acute COVID-19 helped to underscore the importance of inflammation and increased blood clotting as mechanistic drivers. To date there are no specific therapies for Long Covid but there are platform trials and precision medicine trials ongoing including drug and non-drug treatments. Importantly, these trials might translate into successful therapies as well as inform the underlying mechanisms.

4. Prevalence, incidence, and risk factors of Long Covid

4.1. During 2020, the prevalence of Long Covid was estimated between 20-50% of adults with COVID-19 [Whitaker M 2022, Blomberg B 2021]. However, research studies had limitations in study size, variable ways in assessing Long Covid, and variable time from infection. Large systematic reviews overall report a high prevalence of ongoing symptoms post SARS-CoV-2 (ranging from 45% at 4 months in >750,000 patients, to 75.0% at 8-12 months in 52 studies of >100 participants), but there are limitations in combining multiple studies with different definitions and methodology [O'Mahoney L 2023, Kelly JD 2023]. The largest retrospective nationwide cohort study was undertaken in Israel using electronic medical records from 1,913,234 people of all ages who did a polymerase chain reaction test for SARS-CoV-2 between March 2020 and October 2021 [Mizrahi B 2023]. From these people that underwent testing, data was available from approximately 300,000 infected individuals and the same number of matched controls were selected from the uninfected people. Over the 1-year follow-up those that had been infected had an increased risk of several symptoms and those that were aged 40-60 years had the greatest risk for disturbed smell and taste 3-fold increase, breathlessness 1.6-fold increase, brain fog 1.9-fold increase and weakness 1.4-fold. Even though the acute symptoms resolved in the majority of people over one year, and the increased risk in these symptoms was higher at six versus 12 months, there remained an increased risk of persistent symptoms for at least a year.

4.2. The World Health Organisation currently states that between 10 to 20% of people will develop post-covid condition after contracting SARS-CoV-2 infection. In people who were infected with Omicron virus and were triple vaccinated prior to infection the prevalence was just under 5% [ONS 4 2022] according to ONS data from the CIS published July 2022. Long Covid and post-Covid sequelae are more common in adults who were hospitalised compared to those who were not hospitalised, with an increased odds ratio of 3.45 (2.57 to 4.64) [Whitaker M 2022]. However, due to the volume of infections in the non-hospitalised population the absolute number with Long Covid is greater in the non-hospitalised population. From both research evidence and clinical experience, there are some noticeable differences in the pathology between those people hospitalised versus non-hospitalised due to the dominance of pneumonitis in those hospitalised. Therefore, as the pandemic progressed, and the number of hospital admissions reduced towards the end of 2022 these types of lung sequelae have reduced. Otherwise, the type and description of Long Covid has overall remained much the same throughout the first three years of the pandemic.

4.3. It is important to note that any adult is at risk of developing Long Covid after contracting SARS-CoV-2. Consistently, people of middle-age, female sex, obese, lower socioeconomic status and with pre-existing co-morbidities are

more likely to develop Long Covid and other post-covid complications [Whitaker M 2022, Evans R 2022, Subramanian A 2022]. The data around ethnicity is less consistent [PHOSP 2022, Subramanian 2022] and is difficult to interpret due to the influence of language and different health behaviours on what is almost entirely a patient reported condition. Nevertheless, ethnic minority background may have less of a role in the development of Long Covid compared to the association with worse outcomes during the acute illness [Evans 2021, PHOSP 2022, Subramanian 2022].

4.4. A less studied risk factor is occupational exposure of key workers who were more at risk of becoming infected and subsequently re-infected. It is unknown whether these groups were more at risk of Long Covid or more severe Long Covid. There are ongoing studies focusing on healthcare professionals as a subgroup of key workers including the UK Reach study which was set up to understand COVID-19 outcomes for ethnic minority healthcare workers [Al-Oraibi A 2023].

4.5. The ONS data suggests that vaccination prior to infection reduces the likelihood of developing Long Covid. Data from six studies included in a meta-analysis support the finding, where prior vaccination reduced the likelihood of developing Long Covid by half [Ceban F 2023]. The likelihood of developing Long Covid also reduces with the number of vaccinations with two vaccinations having a greater effect than one [Ceban 2023]. The effect of vaccination after the development of Long Covid is less clear. Overall to date the data appears to suggest a neutral effect, and importantly does not appear to be associated with harm overall and therefore people with Long Covid should be advised to adhere to the national recommendations for COVID vaccinations.

5. Scientific advice to government on Long Covid

5.1. The Secretary of State for Health and Social Care convened a roundtable to discuss research into the long-term impacts of SARS-CoV-2 (Covid-19) on patients. This was held on 31st July 2020. The objective of the roundtable was to identify what research is required to investigate and mitigate the long-term impacts of COVID-19 on survivors. The roundtable was to look at the current research landscape, the clinical issues faced by survivors of COVID-19 and the research needed to address these issues. This meeting was chaired by the Secretary of State for Health and Social Care (Matthew Hancock MP), and included the minister for health (Lord Bethell), the chief medical officer, senior clinical and non-clinical academics, and leadership from the research funders UKRI and NIHR. It is unclear if representatives from the devolved nations were invited. This meeting chronologically followed the publication of the Academy of Medical Sciences 'Preparing for a Challenging Winter' endorsed by SAGE at their meeting held 9th July, although we do not know whether the advice from that meeting specifically led to the Secretary of State-chaired meeting. On the 3rd and 7th September respectively 2020, the UKHSA document 'long term effects of Covid-19' (UKHSA 2020) and the Public Health England 'Guidance: Covid-19: Long-term health effects' (PHE 2020) were published. On the 7th October 2020, NHS England announced a five-point plan described above (NHS England 2020). Lord Bethell led the subsequent Long Covid roundtable meetings monthly hosted virtually with relevant stakeholders including people with lived experience of Long Covid to oversee the 5-point plan from October 2020 to July 2021. This 5-point plan evolved and was updated and extended to form 'Long COVID: the NHS plan for 2021/22' [NHS England 2021] with a renewed 10-point plan and additional funding.

5.2. Point five in the five-point plan was the establishment of the Long Covid task force. The NHS England Long Covid taskforce was set up Oct 2020, chaired by a General Practitioner with an agreed terms of reference and included three sub-groups for 'Clinics', 'Rehabilitation', and 'Research'. Each sub-group had a separate chair, met monthly virtually and included people with lived experience of Long Covid. In the taskforce DHSC specifically asked researchers for updates on the post-covid effects on different populations for example differences between sexes, ethnic backgrounds and socioeconomic status. Representatives from NICE and research studies were invited to present to the wider teams at DHSC to ensure they were familiar with the latest understanding on Long Covid.

5.3. In September 2021, NHS England appointed two National Specialty Advisors for Long Covid: Dr Melissa Heightman (Respiratory Consultant Physician, University College of London), and Dr Graham Burns (Respiratory Consultant Physician, Newcastle) who led the NHS England Service Specification. The

NHS England Long Covid Taskforce remains in operation and NHS England held the first Long Covid conference for clinicians in June 2023.

5.4. The House of Lords Science and technology committee held a public inquiry into the Science of COVID-19 in September 2020. The inquiry investigated the scientific and technological aspects of the COVID-19 pandemic, including the nature of the SARS-CoV-2 virus, its transmission and spread, the development of vaccines and treatments, and how digital technologies can be used for tracking and modelling. The 17th evidence session held on 15th September focussed on the long-term health impacts: respiratory, cardiovascular and diabetes and included questions related to Long Covid symptoms, risk factors, mechanisms and treatments.

5.5. The PHOSP-COVID study design and progress was also presented to NERVTAG on the 18th September 2020.

5.6. The National Research Long Covid group was set up by Professor Kamlesh Khunti to co-ordinate a collaboration between the principal investigators of the national research studies investigating the epidemiology of Long Covid. The meetings started April 2021 and met weekly and then fortnightly. The meetings facilitated learning in real time about study findings ahead of publications, support with interpretation of study findings, new joint research for example the largest systematic review on post-covid symptoms [O'Mahoney L 2023] and two reports mapping the work and the patient and public involvement [Routen A 2022, Routen A 2023]. A similar group was developed as a 'spin-out' for experts in qualitative work with collaborative outputs [Fang 2023].

5.7. The National Research Long Covid group involved research across the lifespan – children, adolescents, young and older adults, with different methodological expertise: statisticians, epidemiologists, clinical academics. The group fed back any new collaborations, for example with the NIH Recover team in the USA (reovercovid.org), and supported their study developments, discussed new published international research, and established a solid network. The group also met in person June 2022 with another event planned Nov 2023 to update on the latest findings and to plan next steps. All the activity for the National Research Long Covid Research Groups was voluntary. The minutes of all the virtual meetings were shared with NIHR, UKRI and DHSC.

5.8. A report on Long Covid was commissioned by SAGE and discussed at SAGE July 2021. The report included information from ongoing studies investigating long COVID including the COVID-19 Longitudinal Health and Wellbeing National Core Study-CONVALESCENCE Study, REACT-Long Covid (LC), PHOSP-COVID, CIS and the COVID Symptom Study App. The summary points of this report are listed later.

5.9. In our opinion, the communication between the Long Covid roundtable and Taskforce was effective. This underpinned the NHS England 2020 and 2021 plans for Long Covid. We were participants in these meetings and also presented to NERVTAG and the House of Lords. The research we led was reported directly at these meetings with regular formal reporting to UKRI, DHSC and NIHR. Other research projects reported to funders in a similar fashion. The chair of the National Research Long Covid group is a member of SAGE. However, it is not clear to us whether SAGE had additional communication beyond the AMS 2020 and 2021 reports [AMS 2020, AMS 2021] and the commissioned report from the Long Covid studies with the long-Covid roundtable and taskforce.

5.10. It is our opinion, shared with many of the participants of the National Long Covid research group, that there has been a lack of progression in research funding from mid-2021. Further discussion of current and future research, along with potential gaps are described in M3. Overall, there is no ongoing funding for longer term follow-up of the existing cohort studies [Routen A 2022], the CIS through ONS was stopped in March 2023, and no precision medicine studies were funded including no funding for mechanistic studies as part of Stimulate-ICP. The latter means that Stimulate-ICP may not be able to identify any variability in response to treatments that would inform next steps. There remains a substantial number of people suffering from Long Covid and there remain unanswered questions about causes, diagnostic tests and any specific treatments. In contrast, the UK's early response to Long Covid during the pandemic in terms of research was better than compared with other countries for example the National Institute of Health Recover initiative started in February 2021 (albeit a sizeable investment of over $1 billion) with awards being made in summer 2021 and 2022 [recovercovid.org] The crisis we faced due to acute Covid has subsided and correctly health priorities have been reset to address other acute and long-term conditions. However, Long Covid is now amongst these important long-term conditions and requires support commensurate to the scale of the problem i.e., research funding should be similar to other long-term conditions with a similar burden of symptoms and impact on quality of life.

6. The SAGE response to evolving understanding of Long Covid

6.1. We reviewed all the SAGE meeting minutes and searched the SAGE minutes for the following key words in the SAGE minutes: "post-Covid", "post-covid syndrome" (PCS), "post-acute covid sequelae" (PACS), "post-covid condition", "Long Covid" and "long-haulers". We found reference was made to uncertainty of duration of illness in February 2020 (meetings 4 and 9), the need for cohort studies of long-term effects in April 2020 (meeting 29) and a comment on funding plans in May (meeting 34). Long Covid was included in seven meetings (60th, 69th, 79th, 82nd, 85th, 93rd and 94th see relevant text boxes below) and was included in the AMS preparing for a challenging winter report July 2020 [AMS 2020] (49th SAGE meeting) and COVID-19 preparing for the future report July 2021 (94th SAGE meeting) which were discussed and endorsed by SAGE.

6.2. In February 2020 discussions in SAGE included the uncertainty of the duration of illness, particularly in relation to the acute event. At this time the terms Post-Covid syndrome and long-Covid had not been established.

4th SAGE meeting 4th February 2020

18. Duration of illness: median of 15 to 18 days, but great uncertainty around this. Longest time so far appears to be 41 days.

9th SAGE meeting 20th February 2020

6. Duration of illness: SAGE table should read "great variance" re. the median, rather than "great uncertainty".

6.3. In April 2020 the importance of studying long-term effects was highlighted with follow-up in the ISARIC cohort considered and in May reference was made to an agreed plan for funders to support longer-term cohort studies.

29th SAGE meeting 28th April 2020

14. SAGE reiterated the importance of cohort studies of Covid-19 survivors to understand longer-term effects.

ACTION: UKRI to review whether ISARIC cohort studies following discharged Covid-19 patients are sufficient and to identify any addition longitudinal research required, with input from **Calum Semple, NHS Medical Director, dCMO and UK Biobank.**

34th SAGE meeting 7th May 2020

20. SAGE also noted the existence of longer-term health sequelae (such as persistence of extreme tiredness and shortness of breath for several months) and the importance of monitoring these impacts through longer-term cohort studies (as agreed previously and being taken forward by funders).

6.4. The AMS report 'preparing for a challenging winter' report July 2020 [AMS 2020] included a description of the early understanding of post-Covid syndromes and estimated the likely magnitude of the long-term effects.

The term Long Covid was not yet adopted and was not used in this report. The AMS report highlighted potential impact on key workers and the consequent possible challenges on the workforce in the coming winter of 2020. By Summer 2020, it was clear that post-covid sequelae affected people irrespective of whether they needed to be managed in hospital or not. It affected adults and children and with multi-organ effects leading to impact on mental and physical health. Available data at the time was predominantly from studies reporting persistent symptoms via remote monitoring. Data from the Zoe App (Zoe Health Study) April 2020 estimated 1 in 10 infections would result in ongoing symptoms, and the next analysis in Oct 2020 estimated 1 in 20 people had ongoing symptoms eight weeks post-infection [Sudre C 2021]. Other studies reported higher incidence of approximately 20-50% of adults after COVID-19 [Whitaker M 2022, Blomberg B 2021] likely due to more extensive symptom profiling. The AMS report noted that understanding rates of recovery and long-term persistence of post-covid sequelae would be critical. It also underscored the need for multi-disciplinary clinics.

Specifically, the AMS report proposed a national registry to document post-Covid sequelae; expansion of post-ICU and post-hospital rehabilitation; review of capacity of those delivering covid follow-up services; acceleration of treatments and to tackle regional inequality of access to clinical services. With respect to multi-organ effects a series of post-covid syndromes were described including post-covid lung disease, pulmonary vascular disease in particular increased risk of thromboembolic events and non-pulmonary syndromes affecting the kidney, liver, skin, metabolic disease. A small proportion of children had been described as having inflammatory multisystem syndrome. The report was endorsed with minor amendments at the 49th SAGE meeting.

49th SAGE meeting 9th July 2020

Winter 28. SAGE endorsed the independent paper 'Preparing for a Challenging Winter' from the Academy of Medical Sciences, subject to minor amendments.

6.5. Reports of the proportion of individuals with Long Covid later included associations with the common variants identified at the same time. In later research Long Covid has been reported with all the COVID-19 variants and although some reports suggest that Long Covid is less likely and less severe following infection with later versus earlier variants it is difficult to be certain if this is related to the strain rather than later introduction of vaccination programmes and improved acute therapies.

6.6. The ONS's COVID-19 infection survey (CIS) together with other ongoing UK and non-UK research studies informed the ongoing knowledge base of the impact of Long Covid. It is unclear precisely when the ONS data was discussed at SAGE from the available meeting minutes, but the data was widely shared. Data from April 2021 onwards was shared publicly [ONS 5].

69th SAGE meeting 19th November 2020

37. Understanding of morbidity associated with COVID-19 has improved as further evidence has started to emerge on the longer-term impacts of the virus, both for those who initially self-isolate at home and those who are hospitalised. However, several important challenges remain when estimating the impact of Long Covid.

ACTION: ONS to follow up with Kamlesh Khunti on the potential impacts of Long Covid.

6.7. In early 2021, Long-Covid was described as a syndrome with recognition of the likely long-term effects on individuals and the health and care system.

79th SAGE meeting 4th February 2021

Long COVID and complications of COVID-19

43. Long COVID is likely to be a cluster of syndromes rather than a single one, and these syndromes may have different long-term outcomes. There are not currently internationally agreed case definitions, which are needed to help clinicians to understand and effectively treat these syndromes.
44. There are a wide range of symptoms associated with long COVID, with ONS survey data showing that 22% of respondents were still reporting at least one symptom at 5 weeks following COVID-19 infection, while 10% were still reporting symptoms at 12 weeks.
45. The most commonly reported symptoms at 5 weeks are fatigue (13%), cough (12%) headache (11%), loss of taste and/or smell (10%) and myalgia (9%), with females having a slightly higher 5-week prevalence than males (at 24% and 21%, respectively). Prevalence was greatest among those in the 35-49 years age group (27%), followed by 50-69 years (26%) and 25-34 years (25%).
46. It is not yet possible to estimate the prevalence of individual symptoms or age and sex breakdowns at 12 weeks due to insufficient sample sizes at longer follow-up times. ONS will continue collecting this data and will also launch a new CIS question on long COVID to improve understanding.
47. COVID-19 is a multi-system disease and patients in hospital who survive may experience complications. These complications are likely to have important short and long-term impacts for patients, healthcare utilisation, healthcare system preparedness, and society amidst the ongoing COVID-19 pandemic. These are different to the patients experiencing long COVID symptoms that were not hospitalised.
48. Disease severity at admission is a predictor of complications, so prevention likely requires a primary prevention strategy, i.e. vaccination. It is not yet clear to what extent vaccination will reduce complications, or the impact of long COVID. Existing comorbidities are also an indicator for complications post-admission.
49. Complications and worse functional outcomes are common even in younger, previously healthy patients. The impact may be greater on those patients who fall from a high functional baseline.
50. Complications are associated with reduced ability to self-care at discharge, with neurological complications being associated with the worst functional outcomes.
51. COVID-19 complications and long COVID are likely to cause significant challenges for individuals and for the health and social care system in the coming years.
52. Longitudinal studies, that include both people who have been hospitalised and those who have not, will be required to better understand these issues.

ACTION: NERVTAG to consider case definitions and to liaise with National Core Studies leads to ensure research questions are being considered.

6.8. The ISARIC study follow-up was reported and discussed at SAGE. A report on Long Covid to include other ongoing studies was commissioned by SAGE.

82nd SAGE meeting 25 February 2021

8. In an ISARIC study of the long-term effects of COVID-19 in those that survived hospital admission (based on self-reporting from 325 people), half of participants reported feeling not fully recovered from COVID-19 (median follow-up 7 months). The response rate was around 40% and, as with all such studies, there may be some responder bias as individuals who experienced symptoms (or more significant symptoms) may have been more likely to respond.
9. Fatigue was the most common symptom (77% of respondents), followed by shortness of breath (54% of respondents). Fatigue and breathlessness commonly occurred together, often along with other neurological and pain symptoms. Around a quarter reported a new disability in sight, walking, memory, self-care and/or communication.
10. Long COVID is likely to encompass a number of post-COVID syndromes rather than a single one, and these syndromes may have different outcomes. There may also be differences between those who were hospitalised compared to those who had infection that did not become severe. There are not currently any internationally agreed case definitions. The ISARIC analysis shows that symptoms commonly occur in related clusters, which may provide some preliminary indications about sets of symptoms that define these syndromes.
    a. The first of these clusters includes fatigue, being breathless on exertion, headache, dizziness, muscle pain, joint pain, disturbance of balance and limb weakness.
    b. The second is nested within the first and includes muscle pain, joint pain, disturbance of balance and limb weakness.
    c. The third includes loss of smell, taste, difficulty passing urine, weight loss and disturbance of appetite.
11. Overall, participants reported a drop in quality of life including greater difficulty doing their usual activities and increases in anxiety, depression and pain.
12. Outcomes were worse in working age females than males. Females under 50 were over five times more likely to report incomplete recovery, over five times more likely to report a new disability, more likely to have severe fatigue, and more than six times more likely to report increased breathlessness than males under 50. The long-term impact of post-COVID syndromes on the working age population is not well understood but is may be very significant.
13. Participants who had required invasive ventilation were four times more likely to report an incomplete recovery compared to those who had not required supplementary oxygen.
14. The most effective way to reduce prevalence of these syndromes is to reduce the prevalence of COVID-19 (high confidence). The impact of vaccination on reducing prevalence of these syndromes is not yet known; post-COVID syndromes can occur after mild disease and the impact of vaccination on mild disease is not yet entirely clear.
15. Further work is underway including studies in people who have not been hospitalised and work to bring together different studies to better understand the overall impact of these syndromes. It will be important to have a better understanding of physiology including oxygen levels, lung function and evidence of scarring.

ACTION: National Core Studies (Nishi Chaturvedi) to provide an overview of the work being done on post-COVID syndromes, including evidence on workforce impacts, and to share insights as they emerge with GCSA, CMO and Senior Clinicians Group.

6.9. The possible impact of the vaccination programme upon Long-Covid was discussed at SAGE in March 2021.

85th SAGE meeting 31 March 2021

7. The vaccination programme means that high numbers of infections will not lead to as high a number of hospitalisations and deaths as it would previously have done. However, there will be other health impacts, including post-Covid syndromes ("Long Covid"). The overall prevalence and impact of these syndromes is not well understood, and nor is the potential role in vaccination in preventing them. This needs to be considered when assessing the impact of difference levels of prevalence.

6.10. Increased infections leading to more Long-Covid was included in Meeting 93.

93rd SAGE meeting 7th July 2021 Held via Video Teleconference

6. There are four major risks associated with high numbers of infections. These are an increase in hospitalisations and deaths, more "Long-COVID"; workforce absences (including in the NHS); and the increased risk of new variants emerging.

The combination of high prevalence and high levels of vaccination creates the conditions in which an immune escape variant is most likely to emerge. The likelihood of this happening is unknown, but such a variant would present a significant risk both in the UK and internationally.

6.11. The commissioned report on Long Covid by SAGE was presented and discussed at SAGE July 2021. The report included information from ongoing studies investigating Long Covid including the COVID-19 Longitudinal Health and Wellbeing National Core Study-CONVALESCENCE Study, REACT-LC, PHOSP-COVID, CIS and the COVID Symptom Study App. The summary points from this report were included in the SAGE meeting minutes and are described in the box below. At the same SAGE meeting the AMS COVID-19 preparing for the future report [AMS 2021] was endorsed. Together these reports at the SAGE July 2021 meeting included the diagnosis of Long Covid, estimates of the proportion of people infected that develop Long Covid including early evidence of impact of vaccination, risk factors, and the need for better mechanistic understanding, diagnostic tests, treatments and holistic healthcare pathways.

94th SAGE meeting on COVID-19, 22 July 2021

Situation Update

12. SAGE welcomed the publication of a report by the Academy of Medical Sciences on preparing for winter 2021-22, and a report from the Royal Academy of Engineering on infection resilient environments. Both of these reports have recommendations that should be considered by a number of government departments.

ACTION: SAGE Secretariat to share AcMedSci and RAEng reports across government.

Long COVID

23. The prevalence of prolonged symptoms at 12 weeks post SARS-CoV-2 infection (long COVID) is uncertain and estimates vary by study design, ranging from 2.3% to 37% of those infected. Those reporting symptoms that limit their daily living range from 1.2% in young adults to 4.8% in middle age. Fatigue is the most commonly reported persistent symptom.

24. No clear individual syndromes have yet been identified, but it appears that there are likely to be at least four distinct syndromes. There are similarities in the symptoms for those who have been hospitalised and those who have not, and it is not yet clear how syndromes or symptom clusters link to severity of initial disease.

25. Rates of medium-long term multi-organ sequelae (respiratory disease, major adverse cardiovascular event, diabetes, renal failure, and liver disease) are elevated in patients hospitalised with COVID-19 compared with matched general population and are similar to those hospitalised with pneumonia; however, estimates of the incidence of post-infection adverse events in non-hospitalised COVID-19 cases are lacking.

26. Consistent risk factors across studies include increasing age, female sex, being overweight/obesity, pre-existing asthma, pre-pandemic poor physical and mental health, and severity of the initial illness.

27. There are limited data available for children, but the data which are available suggest that long illness duration after SARS-CoV-2 infection in school-aged children is uncommon, with around 2% experiencing symptoms at 8 weeks post infection (low confidence). For those children who do suffer long illness duration, there may be a need for guidance to parents, carers and schools on how to support them.

28. The limited data available on the impact of vaccination suggest that prevalence of symptoms may be substantially reduced in individuals who become infected after double vaccination compared to those who are not vaccinated (low confidence).

29. Data from studies which are underway should help answer some of the outstanding questions. Research into treatments will be important and these studies may also have relevance to other similar syndromes. Studies have given insight into some of the biological changes that occur with long term symptoms.

30. Data from the UK on long COVID are broadly consistent with international comparators.

7. Was the risk of long-term sequelae from Covid-19 reasonably foreseeable?

7.1. As noted in the first section long-term sequelae following acute respiratory viral infections are well recognised. It was therefore predictable that there would be long-term sequelae following a pandemic of a respiratory infection. Indeed, this is the reason why studies such as PHOSP-COVID were established to assess the long-term consequences following hospitalisation for Covid-19, as well as later studies of the consequences in those with community managed Covid-19.

7.2. The key factors in predicting the impact of the long-term sequelae are the proportion of the people that have the infection getting long-term sequelae, the severity of these sequelae and the overall incidence of the viral infection.

7.3. Following a respiratory viral infection, the proportion of people that would have chronic symptoms is uncertain and is variable in those infected with the same virus and moreover is different between viral infections. Insights from SARS-CoV and MERS-CoV were limited as follow-up studies were small. However, the available evidence suggested that the post-viral sequelae following these infections were common and ranged from mild-to-severe. Lessons from research of survivors of ARDS and intensive care also provided evidence of substantial persistent symptoms in many for at least five years [Herridge M 2011].

7.4. Thus, it was foreseeable that there were going to be long-term sequelae from COVID-19 extrapolated from previous coronavirus pandemics and previous knowledge of post-viral syndromes. Even though the scale of these consequences was unknown if long-term sequelae followed a similar trajectory to SARS-CoV and MERS-CoV it was likely that post-infection sequelae would be common and could in some cases be severe. Unlike SARS-CoV and MERS-CoV the rapid transmission of SARS-CoV2 identified early in the pandemic predicted the incidence of infection would be very high and consequently the incidence of the Long Covid was also likely to be high.

7.5. Prior to a pandemic, estimates of the incidence and severity of post-viral sequelae would have an enormous uncertainty as the likelihood of long-term sequelae, their severity and the transmission rate would be all unknown and would need to be considered and modelled for different possible pathogens. However, early identification of SARS-CoV2, the severity of the infection and rate of transmission gave valuable information that could have been used to predict the likely incidence and severity of Long Covid.

8. How the risk of long-term sequelae altered or impacted the approach taken by SAGE in its provision of advice to core decision-makers.

8.1. As described above, DHSC and the NHS established taskforces and working groups that included broad stakeholder groups to provide advice on the risks of long-term sequelae following Covid-19 independently of SAGE.

8.2. SAGE endorsed the AMS preparing for a challenging winter report in July 2020. The report summarised the current knowledge of post-Covid syndrome. It described the risks on capacity of the workforce particularly key workers e.g., healthcare, and the risk on individuals in terms of physical and mental health impact. The report suggested that the number of people likely to be affected by post-covid long-term sequelae was likely to be large and potentially persistent. Even though the focus of SAGE was to mitigate the risk of overall infection rates with attention on public health measures, testing and acceleration of vaccine strategies, the long-term effects and the emergence of long-Covid was an issue under discussion at SAGE as detailed above.

8.3. A report on Long Covid was provided at the request of SAGE and discussed at SAGE July 2021. The report included information from ongoing studies investigating Long Covid including the COVID-19 Longitudinal Health and Wellbeing National Core Study-CONVALESCENCE Study, REACT-LC, PHOSP-COVID, ONS's COVID-19 Infection Survey (CIS) and the COVID Symptom Study App. The summary points from this report were included in the SAGE meeting minutes that are in the box above. At the same SAGE meeting the AMS COVID-19 preparing for the future report was endorsed.

8.4. Together these reports at the SAGE July 2021 meeting included the diagnosis of Long Covid, estimates of the proportion of people infected that develop Long Covid including early evidence of impact of vaccination, risk factors, and the need for better mechanistic understanding, diagnostic tests, treatments and holistic care pathways.

8.5. It is unclear from the SAGE meeting minutes whether the emerging evidence of the impact of Long Covid throughout the pandemic affected the advice provided by SAGE to core decision-makers. Indeed, there are few actions related to Long Covid recorded in the SAGE meeting minutes beyond commissioning and endorsement of reports. Notwithstanding this limitation, as noted throughout this report the impact of Long Covid follows the impact of the acute disease. Therefore, any advice provided by SAGE to minimise the risk of the acute infection (priority was to prevent Covid-19 through public health measures and vaccination programmes) would in turn reduce the impact of Long Covid.

9. Capturing of data on long-term sequelae and limitations of that data.

9.1. The International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) study was a 'hibernating' observational study of people hospitalised for an acute infection that was 'trial-ready' to undertake intervention trials able to respond quickly with protocols, agreements and governance in place across England, Wales and Scotland for activation at the onset of the pandemic [ISARIC 2020]. This included early post-hospitalisation follow-up and later included longer-term follow-up. Unlike the ISARIC study for acute care, there were no planned studies or plan to capture data from clinical care regarding post-COVID-19 sequelae. Therefore, studies had to be set up at scale and pace at the start of the pandemic (Figure 3). Clinicians were key to provide clinical input to these studies, yet were also delivering essential clinical care.

9.2. One of the first studies to be set up was the Covid Symptom Tracker App (Zoe Health Study) which started in March 2020 in collaboration between ZOE Global Limited, Kings College London, Guy's and St Thomas' Hospitals and with funding from the UK government. The study was set up to track the symptoms of SARS-CoV-2 infection and was subsequently adapted to capture persistent symptoms. The ONS CIS (described in para 1.13) collected data on prolonged symptoms alongside testing. The population targeted were from private households so data on nursing homes, residential care, other long-term institutions and people from lower socioeconomic backgrounds were not captured. In Feb 2021, the REACT study amended their acute study to follow-up participants with and without infection – REACT- Long Covid. In the first few months of the pandemic data on prolonged symptoms after SARS-CoV-2 particularly in those non-hospitalised was developed opportunistically from existing studies. The timelines for many of the early nationally funded studies are shown in Figure 3.

9.3. Not having 'hibernating' studies or planned follow-up in clinical care with embedded research meant there was significant delay in starting the research studies during the first wave of the pandemic (despite studies being designed, protocols written, and governance approved at unprecedented speed). The first study with in-person objective testing was the PHOSP-COVID study which started recruiting 14 Aug 2020, six months after the start of the pandemic in the UK. A range of hibernating studies are needed to include surveys or remote monitoring of patient reported outcomes including symptoms (such as the ONS CIS and REACT-LC) which can involve larger number of participants and therefore more accurate information about incidence and prevalence of persisting symptoms. Other study designs need to include in-person research

visits to include measures which cannot be performed remotely such as breathing tests, exercise capacity, frailty, and blood sampling.

10. Requested summary of the paper 'Understanding and tracking the impact of Long Covid in the United Kingdom' dated 22nd November 2021.

9.4. This paper was written by the National Research Long Covid group described in paragraphs 5.6 and 5.7. The group published papers focussed on the epidemiology of Long Covid. The first was to describe for an international audience the UK effort to investigate the prevalence and risk factors for Long Covid. The main studies, predominantly funded through the two large NIHR Long Covid focussed calls for £39.2 million (studies starting March 2021 and August 2021) ([NIHR 1, NIHR 2], were highlighted alongside the study timelines [Figure 3] and study designs. The interaction and collaborative venture to answer the research questions together was highlighted. The paper aimed to highlight the depth, success and some challenges of public and patient involvement within the studies at the time of a global pandemic [Routen A 2023].

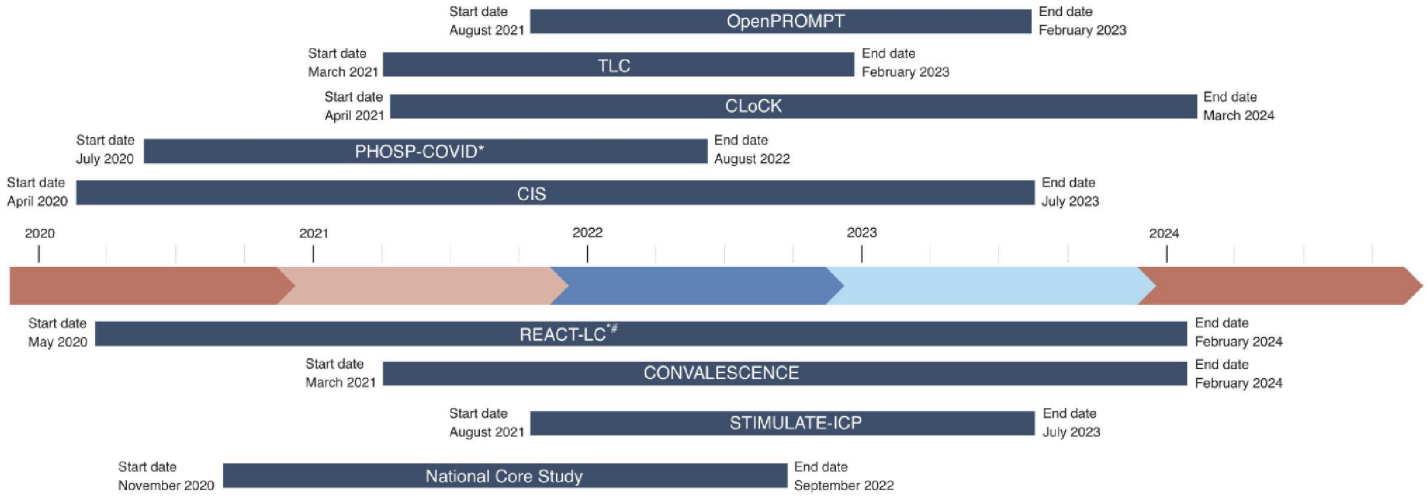

Figure 3. Timeline of major funded epidemiological studies on long COVID in the UK.

11. Current and future interventions against Long Covid, and recommendations for addressing long-term sequelae of infection in future pandemics

11.1. Long Covid is a consequence of acute SARS-CoV-2 infection. Therefore, strategies to reduce transmission (public health measures), improved host immunity to protect people from the consequences of the infection (vaccination) or reduce viral load during the acute phase of infection (antivirals including specific biological therapies) will in turn reduce the incidence of Long Covid [Ayoubkhani D 2022, Xie Y 2023]. The overall effect of COVID vaccination on symptoms in people with Long Covid prior to vaccination is uncertain, but from a systematic review small reports do not suggest harm [Byambasuren O 2023].

11.2. Notwithstanding the high priority in a pandemic to prevent viral infection and reduce the severity of the acute infection, Long Covid was foreseeable and remains a major health problem. More focus on long-term consequences as part of pandemic preparedness is important and greater attention to the cause, diagnostics and treatment of Long Covid is critical [Gov UK 3].

11.3. Keys issues to consider include:

- Pandemic preparedness is currently focussed on reducing the impact of future pandemics by making diagnostics, therapeutics and vaccines available early such as the 100 days mission. However, there is minimal focus on preparedness for long-term consequences.

- There was not enough surveillance for Long Covid planned at the outset of the Covid-19 pandemic, highlighting the need for future 'hibernating' pandemic studies. These studies need to have ethical approval, funding, and sites ready to implement including contracting.

- There was no pre-existing broad plan for how to deal with the consequences of a viral pandemic and no research plan to embed into clinical care. Within the first six-months of the Covid-19 pandemic, studies such as PHOSP-COVID needed to help drive the development of a clinical service and the service specifications as no clinical service existed to manage Long Covid. Earlier development of the clinical service with a clear ambition to embed research into the clinical care might have led to earlier recognition of Long Covid. The reality was clinical care followed the research. Similar to the 'hibernating pandemic studies' there should be a 'hibernating clinical plan' around follow-up care to include agreed lead sites with hub and spoke models across regions. How to embed the research studies into these clinical care models needs to be pre-established.

- There remain a number of important research questions for Long Covid which require further clarity including prevalence, ongoing severity and duration over

many years to decades including children and young adults, further understanding the mechanisms behind the risk factors for Long Covid, and the need for further research in high-risk groups such as key workers. There is a clear need to further investigate the potential effects of ethnicity on Long Covid including the effect of culture and language in describing ongoing symptoms underpinned with biological mechanisms. Understandably a large proportion of the public and funders want to move on from the pandemic and try to re-establish 'business-as-usual'. Everyone has been adversely affected by Covid to varying degrees and it is natural to wish the problem is over. However, Long Covid remains. Not sufficiently investigating the causes and necessary treatments not only means people living with the consequences of Covid are under-served but also threatens the opportunity to be better prepared for future pandemics.

- There is an urgent need for more therapeutic trials conducted safely, rapidly, with underlying mechanistic work. The mechanisms of Long Covid are complex as described above, without experimental medicine outcomes embedded into intervention trials it will be difficult to interpret the findings (e.g., in trials of anti-inflammatory medication understanding which patients had ongoing relevant inflammation).

- More national (including all four UK nations and building on national infrastructure e.g., NIHR translational research collaborations) and international trials are required to ensure generalisability.

- In contrast to the longstanding knowledge base for other chronic diseases / long-term conditions Long Covid research is in its infancy. Therefore, funders need to recognise that the pilot data and evidence base often required to be successful for UKRI grant funding will not have the same foundations. Prioritisation still needs to be given to tackle Long Covid to overcome the problems.

- Charities focussed on other diseases that are impacted by Long Covid and Long Covid specific charities have played an incredibly important role in underpinning the early patient and public involvement (PPI) in research. For example, in the PHOSP-COVID study Asthma and Lung UK co-ordinated over ten different disease-based charities embedded within the working group infrastructure alongside Long Covid Support. Long COVID SOS, Long Covid Support and Long Covid Kids supported high quality PPI in a number of the NIHR funded studies. The Long Covid specific charities remain very engaged and strong advocates for improved healthcare and research. However, they do not have the resources to fund research whilst the other disease/organ-specific charities are retreating to fund and support the much-needed research in their own domains. This means that at the same time as Long Covid research is considered alongside established disease areas there is very limited funding

support from other charities. The net effect is at the point when Long Covid research needs to accelerate it is being stifled.

- It is becoming harder to definitively diagnose Long Covid since routine testing for COVID-19 stopped – soon it will be unclear who did and did not have COVID-19. This is more critical now than during the height of the pandemic as the likelihood that symptoms consistent with acute Covid were due to Covid was very high whereas now there is an increased possibility of an alternative diagnosis and thus persistent symptoms might be due to an alternative diagnosis than Long Covid with an increased risk of mis-diagnosis and uncertainty for patients and clinicians.

- There is a need to continue Long Covid services including clinics and rehabilitation where appropriate with specialist staff who have accrued valuable experience in managing Long Covid over the last three years. Long Covid clinics have typically developed in addition to the usual workload of healthcare providers. With the reactivation of other services and the need to clear backlogs in the NHS there is pressure on the specialist clinics. This is the time to have dedicated sustainable funding for Long Covid specialist clinics that build on current knowledge and experience and are equitable and accessible. The rationale for Long Covid treatments and healthcare services will be further discussed in M3.

- There is well documented loss in the workforce associated with long-term conditions including Long Covid particularly in those of middle age. To address this problem there needs to be strategies to engage with employers to work with people to provide opportunities to return to work by understanding and adapting to the particular challenges someone with Long Covid experiences.

- There are good examples of co-development of research programmes with people with lived-experience and continued public involvement in future research and clinical service is important. It is essential that Long Covid research and access to clinics are inclusive and accessible to diverse groups of people.

- Communication of the science of Long Covid needs to continue to be appropriate, balanced and accessible. There are good examples of public dissemination through the NHS website, charities, professional medical societies, and research consortia. Throughout the pandemic the science media centre played an important role in hosting presentations by academic groups on key findings to a broad group of major media outlets including broadcasters and newspapers. This allowed early and effective dissemination of scientific discoveries to the wider public. Consistent, clear, informative and trustworthy communication is needed to continue to raise awareness of long Covid, highlight the unmet needs and disseminate new findings.

- Pandemic planning for research needs to include but not limited to: how to recruit patients as early as possible (and we suggest embedding research into clinical care), pre-planned use of control groups specific to the research question, promote efficiencies using existing controls where possible and avoiding duplication, embed collection and storage of biological samples in observational studies and clinical trials, improve data linkage with routine health records and between studies, and improve the ability to nest intervention studies within the observational study framework.
- Whilst the next pandemic pathogen is unknown there are broad principles and learning from the COVID pandemic that should be in place to reduce the long-term effects to individuals, the healthcare system and the economy.

12. SECTIONS TO FOLLOW:

- Treatment of Long Covid (M3)
- Research, long term management (M3), and lessons learned (M2 and M3)

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