The PHOSP-COVID Scientific Summit: Long-COVID research - the first 3 years and next steps

PHOSP-COVID Study Collaborative Group

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The severity of the acute SARS-CoV2 infection has decreased due to public health policies, vaccination, acute therapies and a degree of protective immunity in those who have survived past infection. However, in the wake of the pandemic post-acute sequelae of COVID-19, known as long-COVID, have emerged. Long-COVID is a chronic illness in people experiencing ongoing symptoms and disability beyond four weeks after infection[1].

Three years since the first UK national lockdown, the post-hospitalisation COVID-19 study (PHOSP-COVID)[2] held its Scientific Summit meeting in Leicester, UK (29-30 March 2023). PHOSP-COVID (PHOSP.org) is a UK consortium of leading multi-disciplinary researchers and clinicians, with patient, public and voluntary sector involvement (PPI), working together to understand and improve long-term health outcomes for adults who were discharged from hospital following COVID-19. The PHOSP-COVID consortium aims are: i) to describe the holistic impact of long-COVID on people that were hospitalised with COVID-19, ii) to identify the features associated either with good or poor recovery, iii) to investigate the underlying causes of long-COVID, iv) to determine whether long-COVID is altered by treatments given for the acute infection and v) to develop treatments for people with long-COVID to improve recovery.

The PHOSP-COVID consortium includes 83 hospitals, 25+ universities, 10+ patient groups and charities, and 1000+ researchers. We recruited adults discharged from hospital after COVID-19 between Feb 2020–March 2021 to three tiers of research: ‘Tier 1 which utilised use of routine health data, questionnaires, and a saliva sample for genetic testing; ‘Tier 2’ involving early (5 month) and later 12 month visits which included deep phenotyping with patient reported outcomes for symptoms (including a bespoke patient symptom questionnaire), mental health, health-related quality of life, and measures of cognitive impairment, device-measured

24h physical activity profiling, muscle strength, exercise capacity, frailty and organ impairment including clinical blood tests and lung function tests. A bioresource was collected sampling blood, urine, sputum and oral wash. For 'Tier 3' people from Tier 1 or Tier 2 were recalled for additional visits or procedures for more detailed immune tests and multi-organ magnetic resonance imaging (MRI). Recruitment across the four UK nations is now complete with 7935 participants enrolled (Tier 1: 5238, Tier 2: 2697).

A major strength of PHOSP-COVID is that patients, clinicians, and scientists worked together in 2020 to agree the priority research questions[3] and throughout the study, there has been close engagement between the consortium, patients involved in the study and the wider public. Although PHOSP-COVID did not study the impact of long-COVID in those not hospitalised during the acute infection, nor in children; it works closely with the other national long-COVID consortia[4] and internationally with professional societies such as the European Respiratory Society[5].

The early key findings were that at 5 months after hospital discharge from COVID-19, only about 30% of people self-reported that they had fully recovered[6]. The proportion was similar after 1 year with only marginal improvement from 5 months to 1 year[7]. Participants were less likely to have recovered if female, aged 35-65 years old, body mass index >30, or they had multiple long-term conditions prior to COVID-19 or required mechanical ventilation whilst hospitalised. These risk factors and the high proportion of persistent symptoms in those hospitalised for COVID-19 were very consistent with other studies[8]. We found that the treatments given for the acute infection such as corticosteroids did not affect the likelihood of recovery consistent with the 6-month follow-up of the REMAP-CAP study, which involved only critically-ill participants and identified only anti-IL6 and anti-platelet therapies as being

associated with greater improvements in health[9]. Through unsupervised cluster analysis, we identified the severity of physical and mental health largely grouped together whereas 'brain-fog' can occur on its own. Those with the most severe health impairments had evidence of persistent inflammation reflected by an elevated c-reactive protein[7]. Multi-organ, multi-modality MRI revealed changes in the brain, lungs and kidneys but no significant increase in cardiac or liver abnormalities compared to controls[10]. Patients with a higher burden of multi-organ injury were more likely to report poor physical and mental recovery. In the lungs, the prevalence of interstitial lung abnormalities on thoracic computed tomography was estimated at 8.5%[11]. We have found increased auto-antibodies and immunosenescence in people with long-COVID compared to controls. Despite the predominately working-age population of the study, exercise capacity was reduced with increased frailty indices[12]. Sleep pattern data derived from accelerometry showed decreased activity, increased sleep duration, but reduced quality with sleep regularity associated with breathlessness compared with non-COVID hospitalised patients[13]. PHOSP-COVID has evaluated clinical and cost effectiveness of clinical care pathways, and contributed to NICE and NHS-England long-COVID guidance.

Critically, in addition to the review of the progress to date, the Scientific Summit allowed for a discussion of 4 key questions described in **Table 1** which were subsequently reviewed with our PPI partners. ***Question 1*** considered lessons learned for the next pandemic, ***Question 2*** and ***Question 3*** identified knowledge gaps and next steps to extend the phenotypic characterisation and mechanistic understanding of long-COVID. ***Question 4*** illustrated the urgent need for new therapies delivered through comprehensive multi-disciplinary care pathways.

To date efficacy has been reported in an early phase trial for ant-oxidant therapy (AXA1125)[14]. PHOSP-COVID is undertaking 2 proof-of-concept randomised controlled trials in

rehabilitation (reviewed in[15]) and anti-IL6 therapy. Other platform trials are underway although there remains a need for further precision medicine trials that can specifically target the emerging mechanisms and phenotypes of long-COVID.

Overall, the PHOSP-COVID Scientific Summit highlighted that although we shared a collective relief that there has been a significant reduction in severe acute cases of SARS-CoV2 infection, long-COVID remains a major issue for the millions of people continuing to suffer with persistent morbidity, healthcare systems and economy through loss of work[1]. It is imperative that long-COVID remains a major healthcare and research priority. The planned ongoing work looking into mechanisms driving the effects on all organs will likely help to develop new tests, new treatments and improved outcomes for people living with long-COVID.

PHOSP-COVID Summit Key Questions and discussion highlights
Q1 - How should we approach future pandemic research for long term sequelae?
• maintain pandemic preparedness through 'sleeping studies' (large community and secondary care cohorts enabling detailed mechanistic studies) • requires early PPI, consideration of ethnicity, diversity and inclusivity, e-data capture tools, centralised biosampling, centralised knowledge platform, effective data linkage with health records, efficient, robust research governance and international collaboration • identify control groups matched for specific research questions utilising existing datasets, but also recruited as part of matched cohort studies and co-ordinated nationally • research for long term sequelae should be prioritised alongside the acute illness
Q2 - What are the main knowledge gaps in Imaging and Clinical phenotyping?
• the limitations of current definitions of long-COVID and the need to consider new taxonomy underpinned by biological, imaging and physiological biomarkers • how is phenotypic heterogeneity linked to specific mechanisms? (see Q3) • need for appropriate control groups for biomarkers (see Q1) • need to link to national and international consortia to ensure generalisability (see Q1) • the urgent need to translate phenotypes into precision medicine (see Q4)
Q3 - What are the main knowledge gaps in Mechanistic and Cellular biomarkers?
• hypotheses for the cause of long-COVID include persistent inflammation with immune activation, autoimmunity, microvasculopathy, viral reservoir, and altered microbiome, further evidence is required to test these hypotheses and to link to phenotype (see Q2) • PHOSP-COVID samples need to be utilised and combined with other studies, to develop predictive versus associative biomarkers, to link phenotype and precision medicine • risk factors for long Covid highlight the need to investigate possible mechanistic roles for adiposity and metabolic disease, sex hormones, immune aging, and deconditioning • need to understand the underlying mechanisms of the impacts on mental health alongside physical health • people with lived experience particularly highlighted the need to understand the effects of environmental factors and how to prevent reinfection
Q4 What are the main knowledge gaps in interventions and health service research?
• there is an urgent need for the platform and precision medicine trials to translate into patient care • rehabilitation strategies need testing to determine efficacy versus safety, and better management of postural orthostatic tachycardia syndrome (PoTS) and post-exertional symptom exacerbation are needed • need to test mental health interventions both pharmacological and non-pharmacological • existing sleep management strategies e.g. Sleepio, need to be tested • need to study weight management strategies both non-pharmacological and repurposing of existing pharmacological strategies • need to test integrated holistic clinical pathways to exclude co-morbidities, alternative diagnoses and management, precision medicine using biomarkers to direct therapy

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