Understanding and tracking the impact of Long COVID in the United Kingdom

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To the Editor - There is now a rich body of knowledge on acute COVID-19, but much less is known about the risk factors, clinical presentation, duration, and management of persistent or new symptoms following recovery from initial infection, often termed Long COVID[1,2]. Post infection follow-up data shows that a significant proportion of hospitalised and non-hospitalised patients experience persistent symptoms and organ dysfunction[3-5].

The UK Office for National Statistics (ONS) estimates that the number of people in the UK self-reporting symptoms lasting more than 4 weeks currently stands at 1.1 million (1.7% of the population)[4], while the REal-time Assessment of Community Transmission (REACT) study in England estimated the overall number who reported at least one symptom lasting for 12 or more weeks at over 2 million by February 2021[6]. Patients globally have reported a range of new, returning, and/or ongoing symptoms, including but not limited to fatigue, shortness of breath, altered smell and taste, cough, myalgia, cognitive impairment and diarrhoea following COVID-19 infection[7]. Of great concern are data from imaging studies that report single or multiple organ impairment, even in non-hospitalised patients[8].

To build greater understanding of Long COVID a wide range of nationally funded studies have been launched in the UK (See Figure 1 and Table 1). The Post-HOSPitalisation COVID-19 study (PHOSP-COVID) was the first such study, securing £8.4 million in July 2020 from UK Research and Innovation (UKRI), and aims to understand and improve long-term outcomes for people who survive hospitalisation with COVID-19.

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Another study that begun early in the pandemic was the REACT programme, which was commissioned by the Department of Health and Social Care in April 2020. The REACT studies are nationally representative prevalence surveys of SARS-CoV-2 in the community in England. REACT was then extended to include REACT-Long COVID (REACT-LC) in February 2021 via NIHR and UKRI funding. REACT-LC aims to characterise the genetic, biological, social and environmental determinants, and their inter-relationships, that underpin progression to Long COVID, and to understand the natural history and long-term sequelae post-SARS-CoV-2 infection.

In early 2021 the NIHR and UKRI funded four research studies (totalling £18.5 million) to better understand and address longer-term effects of COVID-19 infection on physical and mental health. In summer 2021 NIHR funded a further 15 projects (totalling £19.6 million) to improve diagnosis of Long COVID, as well as treatment, rehabilitation and recovery.

From this cohort of funded projects, as well as other key national projects, nine major epidemiology focused Long COVID studies are currently running in the UK (See Figure 1 and Table 1). These studies cover population epidemiology, symptomatology, phenotyping, operational definition, health impacts post-hospitalisation, determinants, mechanisms and consequences of the long-term effects, and genetic, biological, social and environmental signatures and pathways. Researchers on these studies have formed the National Long COVID Research working group, to share key findings and promote rapid knowledge exchange and efficient timely research. Key outputs of the group are shared with the Chief

Medical Officer for England. An example of this is an Open Science repository platform[9] the National Long COVID working group has formed to collate and index the latest research on Long COVID.

There are a wide range of outstanding research priorities including defining Long COVID, identifying its pathogenesis, describing its clinical presentation and health impacts, characterising the longer term burden and predictive risk factors, and developing clinical interventions. The primary areas of knowledge that the studies outlined in Table 1 will advance are: the prevalence and phenotyping of symptom clusters (TLC, CIS, CONVALESCENCE, REACT-LC, PHOSP-COVID), identification of the short and long-term mental and physical health sequelae of Long COVID (TLC, CIS, CLoCk, PHOSP-COVID, CONVALESCENCE, REACT-LC, STIMULATE-ICP, OpenPROMPT), prevalence, phenotyping and operational research definition of Long COVID in children and young people (CLoCk), the immunological causes and consequences of Long COVID (TLC, REACT-LC), identifying mechanisms underpinning the development of Long COVID (TLC, CONVALESCENCE, REACT-LC), and identifying and trialling potential therapies and interventions to treat and manage Long COVID (TLC, PHOSP-COVID, STIMULATE-ICP). The CLoCk study is the largest study of Long COVID specifically in children we know of globally, uniquely uses child reported symptoms, has a control group, uses standardised measures, is longitudinal and is based on a national cohort.

A particular strength of a number of the studies (TLC, CLoCk, CONVALESCENCE and the REACT cohort follow-up), is the use of control groups which allows comparison of symptom profiles and burden in individuals with confirmed SARS-

CoV-2 infection compared to those without infection who may experience symptoms due to comorbidities, and because some reported Long COVID symptoms are non-specific and prevalent in the general population[10].

There is a huge burden of ill health from Long COVID in the UK and globally. People living with Long COVID were the first to identify and describe Long COVID[11]. The research community have joined patient-researchers in their efforts to improve understanding of Long COVID, including its symptoms, health impacts, pathophysiology, and treatments. Patient and public involvement is a feature of all the studies described above, with research teams working with patient partners from diverse backgrounds, as well as engaging with National Long COVID support groups. Multidisciplinary research collaboration with patients at the core, and co-producing the research as equal partners, is crucial for developing a comprehensive approach to unravelling the complexity and heterogeneity of Long COVID. This co-production will be fundamental in the development of targeted therapeutic approaches and to inform health service provision to meet the large unmet need from Long COVID.

Author Contributions

All authors conceived the idea for the article. AR, LOM and KK led on drafting,

editing and revising the content, and AR and LOM contributed equally. All other authors contributed to editing the content, and all authors approved the final version and are accountable for all aspects of this work.

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Table 1. Summary of major funded epidemiological studies on Long COVID in the UK

Study	Aim	Design/Cohort	Population	SARS-Cov-2 Serology	Place of Care for Acute COVID-19
Therapies for Long COVID in non-hospitalised individuals (TLC)	To develop a new Symptom Burden Questionnaire™ for Long COVID, phenotype symptom clusters with laboratory-confirmed SARS-CoV-2 infection compared to test-negative controls, identify potential therapies, develop a supportive, remotely-delivered intervention for patients with Long COVID in the community, and establish a trial platform for further intervention studies.	Using electronic GP records in partnership with the Clinical Practice Research Datalink (CPRD), the team will identify and recruit thousands of non-hospitalised patients with Long COVID who have had symptoms for 12 weeks or longer.	4000 patients with a positive SARS-CoV-2 RT-PCR result and 1000 matched controls recruited from primary care.	No	Non-Hospitalised
The COVID-19 Infection Survey (CIS)	To provide national estimates of SARS-CoV-2 prevalence and incidence over time.	Repeated cross-sectional surveys of representative households across the UK, identified either by one adult from the household having	Randomly sampled households (children and adults aged 2+) from all parts of the UK. Since the CIS began in April 2020, over	Yes	Hospitalised and Non-Hospitalised

		participated in existing surveys conducted by ONS or the Northern Ireland Statistics and Research Agency and providing consent for future contact regarding research, or by the household being randomly selected from a commercially available source such as AddressBase, or equivalent databases including in the Devolved Administrations.	476,000 individuals from over 236,000 households have participated.		
The Children & young people with Long COVID Study (CLoCk)	To describe the clinical phenotype of post-COVID symptomatology in Children and Young People (CYP) with laboratory-confirmed SARS-CoV-2 infection compared to test-negative controls, produce an operational research definition of Long COVID in CYP and establish the prevalence of Long COVID in CYP.	Second Generation Surveillance System; Patient Demographic Service. A longitudinal cohort of SARS-CoV-2 positives aged 11 to 17 years compared with age, sex and region matched SARS-CoV-2 test negative controls ('cohort-analytic' study), identified by Public Health England.	>17,000 11-17 years old (with 18-20 year old extension planned); half COVID-19 test positive and half matched controls, COVID-19 test negative.	No	Non-Hospitalised

Longitudinal Health and Wellbeing National Core Study	To understand the health, social and economic impacts of the COVID-19 pandemic by uniting established population cohorts and national anonymised electronic health records to inform policy.	Parallel and complementary analysis of national anonymized electronic health records (~59 million people), and 12 well established population cohort studies (~60 million).	Whole population (for anonymized electronic health records), geographically distributed population samples for cohorts.	Partial	Hospitalised and Non-Hospitalised
Coronavirus post acute long term effects: constructing an evidence base (CONVALESCENCE)	To define the sub-phenotypes of Long COVID, identify predictors and mechanisms, understand long term health (physical and mental) and socioeconomic consequences, and clarify and improve GP adherence to NICE diagnosis and management guidelines.	Linked to Longitudinal Health and Wellbeing National Core Study. In addition, a sub study of 800 participants (200 with Long COVID and evidence of SARS-CoV-2 infection (cases), 200 each of 3 groups of controls: 1) Symptoms of Long COVID but no evidence of infection, 2) Evidence of infection but no Long COVID, 3) Neither Long COVID nor history of COVID-19 infection) recruited for in depth phenotyping.	As above (National Core Study), the sub study participants recruited from population cohorts.	Yes for sub study	Hospitalised and Non-Hospitalised
REal-time Assessment of Community Transmission	To characterise the genetic, biological, social and environmental determinants, and their inter-relationships, that	Prospective study of 120,000+ (among over 2 million) participants in the REACT-1 and REACT-2 community	Random sample of the population in England aged 5 years and over. Subcohort of	Yes	Community-based

(REACT-Long COVID)	underpin progression to Long COVID, and to understand the natural history and long-term sequelae post-SARS-CoV-2 infection.	prevalence studies including detailed phenotyping and -omic profiles from >10,000 with prior SARS-CoV-2 infection. NHS record linkage follow-up of whole cohort (with consent). Nested qualitative study of patient experience and detailed symptom profiles.	>10,000 adults with prior SARS-CoV-2 infection, detailed phenotyping and whole genome sequencing. Survey follow-up and data linkage for 120,000+ aged 5 years and over.		
The Post-HOSPitalisation COVID-19 study (PHOSP-COVID)	To understand and improve long-term outcomes for survivors of a hospitalisation with COVID-19.	Prospective longitudinal cohort study recruiting patients aged over 18 years old who were discharged from one of 70+ National Health Service hospitals across England, Northern Ireland, Scotland and Wales following admission to a medical assessment or ward for confirmed or clinician-diagnosed COVID-19.	Aim to recruit 10, 000 adults discharged from hospital with COVID-19. 3000 to have careful in clinic phenotyping and samples for storage in a biobank for current use or for other studies/collaborators in future.	Yes	Hospitalised only
STIMULATE-ICP (Symptoms, trajectory, inequalities and management:	A programme of work focused on current long COVID care in the UK.	Mixed methods study of current long COVID care in UK to evaluate trajectory of illness, cost and effectiveness. A	Adults	Yes for those who had a test as part of	Non-hospitalised

		cluster randomized trial, recruiting >4,500 people with long COVID, testing effectiveness of repurposed drugs by measuring the effects of 3 months' treatment, including symptoms, mental health and outcomes such as returning to work. It will also assess the use of MRI scans to help diagnose potential organ damage, as well as enhanced rehabilitation through an app to track their symptoms.		routine care.	
understanding long COVID to address and transform existing integrated care pathways)					
OpenPROMPT (Quality-of-life in patients with long COVID: harnessing the scale of big data to quantify the health and economic costs)	To explore the health and economic impacts of Long COVID for those who are not hospitalised.	Cohort study of participants recruited though the Airmid smartphone app, and then submitting health-related quality of life data through the app. Data will be linked to the OpenSAFELY data platform.	Adults in primary care, recruited through a smartphone app.	Yes for those who had a test as part of routine care.	Non-hospitalised