UNIVERSITY OF DERBY

UNDERSTANDING LONG COVID, THE IMPACT UPON QUALITY OF LIFE AND FUNCTIONAL STATUS AND THE NEED TO DEVELOP BESPOKE INTERVENTIONS TO IMPROVE RECOVERY.

Rebecca Mai Owen-Toon

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List of abbreviations

6MWT: 6 Minute-Walk-Test

ADL: Activities of daily life

AU: Arbitrary Unit

CFS: Chronic Fatigue Syndrome

COVID-19:

EBV: Epstein-Barr Virus

FAS: Fatigue Assessment Scale

FEV1: Forced Expiratory Volume in 1 second

FVC: Forced Vital Capacity

GET: Graded Exercise Therapy

GPs: General Practitioners

HRQoL: Health Related Quality of Life

HCPs: Healthcare Professionals

ICU: Intensive Care Unit

ME: Myalgic Encephalomyelitis

MEP: Maximum Expiratory Pressure

MFIS: Modified Fatigue Impact Scale

MIP: Maximum Inspiratory Pressure

MoCA: Montreal Cognitive Assessment

MRC: Medical Research Council

PCFS: Post-COVID-19 Functional Status Scale

PEF: Peak Expiratory Volume

PEM: Post Exertional Malaise

PESE: Post Exertional Symptom Exacerbation

PPE: Personal Protective Equipment

PPIE: Patient and Public Involvement and Engagement

PROMs: Patient Reported Outcome Measures

QoL: Quality of Life

RNA: Ribonucleic Acid

UK: United Kingdom

Preface

I declare that the work contained in this thesis is my own, and where research has been undertaken as part of a wider project, I made significant contribution in conceptualisation, data collection, analysis and writing. All research within this thesis has been ethically approved, evidenced in Appendices 1a, 1b and 1c.

I declare that the word count of this thesis is: 20,043.

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2) Owen, R., Ashton, R., Ferraro, F., Phillips, B., Skipper, L., and Faghy, M. (2023). Acute COVID-19, the Lived Experience, and Lessons to Learn for Future Pandemics. *Disaster Medicine Public Health Preparedness. (22)*;17:e534. doi: 10.1017/dmp.2023.197. PMID: 37990549.
3) Owen, R., Ashton, R., Ferraro, F., Skipper, L., Bewick, T., Leighton, P., Phillips, B., and Faghy, M. (2023). Forming a consensus opinion to inform Long COVID support mechanisms and interventions: a modified Delphi approach. *The Lancet EClinicalMedicine. 9;*(62):102145. doi: 10.1016/j.eclinm.2023.102145. PMID: 37599906; PMCID: PMC10432807.

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3) Faghy, M, A**.,** Owen, R., Thomas, C., Yates, J., Ferraro, FV., Skipper, L., Barley McMullen, Brown, D., Arena, R., Ashton, REM., (2022), Is Long COVID the next global health crisis? *Journal of Global Health. DOI:* 10.7189/jogh.12.03067
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5) Faghy, M, A., Maden-Wilkinson, T, M., Arena, R., Copeland, R, J., Owen, R. Hodgkins, H, M, J., Willmott, A, G, B., (2022)., COVID-19 patients require multi-disciplinary rehabilitation approaches to address persisting symptom profiles and restore pre-COVID

quality of life. *Expert Reviews in Respiratory Medicine*, **DOI:** https://doi.org/10.1080/17476348.2022.2063843

Conference Proceedings:

1) Owen, R., Ferraro, F., Ashton, R., Thomas, C. Phillips, B., Faghy, M. (2024). Time to re-define 'normal' for Post-Acute COVID-19 biomarkers in the assessment of patient outcomes? *American Physiological Society Summit, Long Beach, California.* April 2024. Poster Presentation.
2) Owen, R., Ferraro, F., Ashton, R., Phillips, B., Faghy, M. (2024). Understanding the episodic nature of symptom profiles and functional status in individuals with Long COVID. *American College of Sports Medicine.* May 2024. Boston, Massachusetts. May 2024. Presentation.
3) Owen, R., Faghy, M., Ashton, REM, Ferraro, F., Thomas, C., Yates, J., Haggan, K., Bewick, T., Phillips, B. The impact of living with Long COVID on quality of life and daily activities: the lived experience. *University Professorial Council Research Showcase,* University of Derby, September 2022.
4) Owen, R., Faghy, M., Ashton, REM, Ferraro, F., Thomas, C., Yates, J., Haggan, K., Bewick, T., Phillips, B. (2023). Forming a consensus opinion to inform long COVID support mechanisms and interventions: a modified Delphi approach. *University Professorial Council Research Showcase,* University of Derby, September 2023.
5) Owen, R., Ashton, R., Ferraro, F., Skipper, L., Bewick, T., Leighton, P., Phillips, B., & Faghy, M. (2023). Forming a consensus opinion to inform long COVID support mechanisms and interventions: A Modified Delphi Approach. *MyResearchMyReach,* University of Derby. Presentation.
6) Owen, R., Ashton, R., Ferraro, F., Skipper, L., Bewick, T., Leighton, P., Phillips, B., Faghy, M. (2023). Long COVID Experiences and Support Mechanisms. *Biomedical and Clinical Science Research Theme,* University of Derby. Presentation.
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8) Owen, R., Ashton, R, E, M., Yates, J., Ferraro, F., Thomas, C., Idris, R., Faghy, M, A., (2022). Pre-COVID physical activity status does not protect against developing

Long COVID symptoms. *Physiological Society Long COVID: Mechanisms, Risk Factors, and Recovery*. Flash Talk.

9) Owen, R., Ashton, R., Ferraro, F., & Faghy, M. (2024). Long COVID Research and Clinical Exercise Sciences. *BASES Webinar* – Respiratory Physiology and Training: Application for Health.

10) Faghy, M., Owen, R., and Ashton, R., (2022). Reduced respiratory muscle strength, lung function, and functional status and symptomology in patients referred to Long COVID clinics, an observational cohort analysis. *British Thoracic Society.* London, UK, December 2022.

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12) Yates, J., Faghy, M, A., Owen, R., Thomas, C., Idris, R., Ferraro, F., Ashton n, R, E, M., (2022). Comparing the profiles of individuals hospitalised with COVID-19 with those referred to Long Covid services, *Physiological Society Long COVID: Mechanisms, Risk Factors, and Recovery*. Flash Talk.

Abstract

Long COVID is a patient made term defined as the continuation or development of new symptoms 3 months following COVID-19 infection, with symptoms lasting at least 2 months, amid no alternative diagnosis. Long COVID arises following at least 10% of COVID-19 infections with an estimated 65 million individuals believed to have Long COVID, a number steadily increasing. Biomedical research has made progress in hypothesising the underlying pathophysiological mechanisms and risk factors of Long COVID. However, knowledge surrounding the variable onset of symptoms, the impact on functional status and quality of life and current diagnostic and treatment options incorporating the lived experience remain scarce. The complexity of long COVID and its diverse profile of over 200 symptoms affecting multiple organ systems contributes to unprecedented challenges for patients, clinicians and healthcare services.

The significant long-term impairment caused by Long COVID in the months and years following acute infection has been evidenced, however there is limited empirical data highlighting the frequency and severity of fluctuating and disabling symptom profiles. As public health messaging of Long COVID is overlooked, research centred around the voices and lived experience of those with the debilitating long-lasting effects of COVID-19 is key. Accordingly, the overarching aim of this thesis is to understand Long COVID, considering the impact upon quality of life, and functional status and the need to develop bespoke mechanisms and interventions to support recovery.

Individuals are being severely impacted by their symptoms and are unable to or limited in participating in their daily activities, or live life fully subsequently reducing quality of life (Study 1). Furthermore, patients report varying healthcare experiences, with reports of medical gaslighting, barriers to support and inadequate care. Data from this thesis highlights the episodic and relapsing nature, which can be used to characterise Long COVID disability and inform the development of bespoke guidelines and support services to respond to the reduction in functional status (Study 2). This thesis presents consensus achieved by key stakeholders including patients and medical professionals regarding the appropriate support mechanisms and interventions for long COVID (Study 3). The outcomes of this thesis can be used to guide the design and implementation of efficient and effective services to address the broad challenges of living with Long COVID.

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Chapter 1

General Introduction and Literature Review

1.1 SARS-CoV-2 and COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly contagious and pathogenic coronavirus that emerged in late 2019, resulting in a global pandemic of acute respiratory illness known as 'Coronavirus Disease 2019' (COVID-19)(11). Throughout this thesis, 'SARS-CoV-2' will be used when discussing the virus itself, such as the virology and transmission, and 'COVID-19' will be used to describe the illness caused by the virus, such as symptoms, clinical manifestations, public health measures and the pandemic. The widespread and global transmission of SARS-CoV-2, also known as the COVID-19 pandemic, has undoubtedly posed the biggest threat to global health and well-being in living memory (12, 13) resulting in global health systems being placed under an insurmountable pressure due to a surge in demand for inpatient care (14). During 2020, approximately 20% of confirmed COVID-19 cases resulted in hospitalisation due to the high transmission rate and virulence (15, 16) forcing health services globally into a shortage of resources including staff, supplies, equipment, and bed space (17). Within the United Kingdom (UK) and globally, the healthcare crisis provoked governments to introduce public health measures, including lockdowns, quarantining, social distancing, and mandatory mask-wearing to control the spread of the virus, in line with World Health Organisation guidelines (18, 19). Figure 1 displays the timeline of COVID-19 guidelines, including a visual representation of the tightening and easing of restrictions that took place in the UK (1-10).

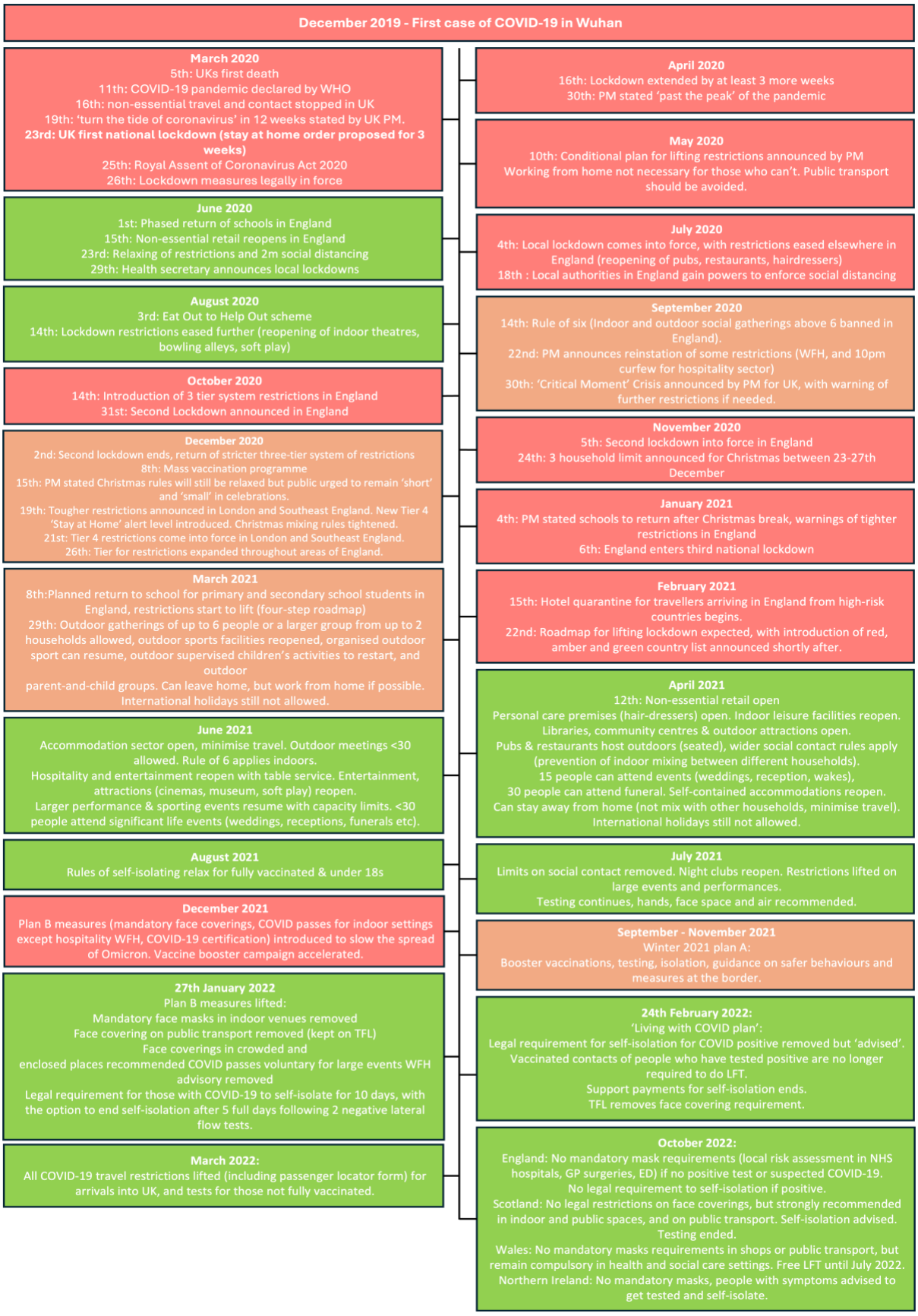

Figure 1.1: Timeline of COVID-19 prevention measures from the first reported case until ease of measures in the UK in line with the UK government guidelines (1-10).

COVID-19 is not unique in its ability to result in post-acute sequelae and reduced patient outcomes (20). Symptoms of acute viral infections that persist in the weeks, months and even years post-infection are collectively referred to as post-viral syndromes (21). Arguably, the most devastating epidemic in modern/recorded history is the Spanish Flu epidemic in 1918 which had an estimated global mortality between 24-50 million people and occurred over three distinct waves of infection (22). Of particular interest was the high prevalence of reported complications and impaired recovery, with physical exertion and fatigue being documented as important limiting factors. More recent epidemics, including SARS-CoV or SARS-CoV-1 (2002-2004) have also demonstrated persistent symptoms that impact functional status and quality of life (QoL) directly with evidence showing sustained impact at 12 months post-infection (23). Initially, these epidemics were considered controlled due to the plateau in acute infections after June 2003, however, a cohort of post-SARS patients remained disabled and unable to return to work one year later with persistent debilitating symptoms including dyspnoea, musculoskeletal pain, weakness and fatigue (24). This narrative is consistent with the COVID-19 virus that arose in 2019. As of March 2024, global transmission of COVID-19 has led to over 704 million cases and more than 7 million deaths worldwide following infection (25). Despite initial suggestions that recovery following COVID-19 would occur within a matter of weeks, it is estimated that over 3 million people are living with long-term consequences of COVID-19 in the United Kingdom (26, 27). These figures are likely to be much higher due to the time required to develop and provide access to testing at the start of the pandemic, the absence of testing measures which have subsequently been removed as part of the world's approach to living with COVID-19, and an inconsistency in definitions and reporting mechanisms (28). The risk of long-standing issues following acute COVID-19 was anticipated, but the extent and clinical features of this was not. Despite being well established, there has been little attention paid to the post-acute sequalae of viral infections, which has often resulted in chronic illnesses and complex symptom profiles, impacting functional status and QoL. Furthermore, viral proliferation due to SARS-CoV-2's use of ribonucleic acid (RNA) and its transmission via airborne particles (29) coupled with the removal of all mitigation strategies, has resulted in highly mutated variants being allowed to circulate globally and remains an important threat to global health and wellbeing (13). SARS-CoV-2 is known to evolve at an approximate rate of 1.1×10^{-3} substitutions per site per year, equivalent to a single substitution approximately every 11 days (30). Whilst recognised that not all mutations pose a threat to public health, previous variants including Omicron (B.1.1.529, BA.1, BA.1.1, BA.2

[including BA.2.86]), BA.3, BA.4 and BA.5 lineages) and Delta (B.1.617.2 and AY lineages) are widely regarded as variants of concern (31), due to several mutations that affect the spike protein, thus increasing transmissibility (32).

1.2 Long COVID/Post-Acute-COVID-19

1.2.1 Prevalence and risk factors

Long COVID is an umbrella term encompassing a heterogeneous group of pathophysiological processes triggered to varying degrees in different individuals, following a SARS-CoV-2 infection (33). Also referred to as Post-COVID-Condition, the term Long COVID is patient made and describes the continuation or development of new symptoms 3 months following COVID-19 infection, with symptoms lasting at least 2 months, amid no alternative diagnosis (34). The global impact of COVID-19 and Long COVID has been profound, with global trends estimating that 65-150 million people worldwide (35) and ~3.3 million people in the UK are living with Long COVID (27). In England and Scotland, the day-to-day lives of 1.5 million people have been adversely affected by their symptoms (27) and one in ten people experiencing persistent symptoms that are not resolved at 12 months (35, 36). Prevalence is greatest amongst individuals aged 35-49 years, females, and living in low socio-economic areas however anyone who becomes infected with COVID-19 can go on to develop Long COVID (37). People who are not vaccinated against COVID-19 may be at an increased risk of developing Long COVID compared to vaccinated counterparts (38) and the risk of developing Long COVID increases with every infection (38, 39). Various biological risk factors may be detected during the initial phase of infection, including pre-existing type 2 diabetes, assessments of SARS-CoV-2 RNAemia, EBV, and present autoantibodies (40). However, these findings are based on patients 2-3 months post-infection, and may not be transferable to more chronic cases (41).

1.2.2 Morbidity and Impact

The health burden of Long COVID is becoming more evident as research highlights that a high proportion of people living with the condition experience moderate-poor self-reported health (83.3%, n=1005), moderate-to-extreme problems with daily activities (62%) and moderate-to-severe pain or discomfort (49%) (42). Approximately 30% of the COVID-19 related health burden is due to long-lasting morbidity following COVID-19 impacting functional status and

QoL, rather than mortality (43), creating major economic implications. The annual global economic impact of Long COVID is estimated at $1 trillion, equivalent to approximately 1% of the global economy (44). Moreover, an economic analysis by Cambridge Econometrics reports that Long COVID may have wider economic ramifications for the UK, by burdening economic growth and NHS pressures with no long-term healthcare funding commitment (45). Consistent with the estimations by Cambridge Econometrics of 138,000 jobs becoming vacant (45), 86.2% of Long COVID patients have felt mildly to severely unable to work, and 45% have required ongoing accommodations because of their symptoms. Only 27.3% of participants were working their pre-COVID-19 hours and 23.3% were unable to work at all (46). As a result of patients reduced ability to work contributing to lower household incomes and economic growth overall, it is estimated that the GDP is likely to reduce by £1.5bn (45).

Furthermore, the burden of Long COVID drastically impacts the global burden of disease, health, and wellbeing, and significantly impacts healthcare services, which are chronically underfunded and under-resourced (47, 48). Alarmingly, this has led to a substantial unmet clinical need, with a backlog of waiting lists for routine treatments and procedures and a reduction in non-elective surgery diagnoses affecting around 7 million people which is prominent in the most deprived areas of the UK (55% in low social-economic areas, compared to 36% in the least deprived areas) (49, 50). There has also been a decline in cancer screening and diagnoses, resulting in missed opportunities for early detection, preventive care visits and diagnostic procedures which will have further detrimental consequences on survival, mortality and quality of life among these people with cancer (51). The COVID-19 pandemic will continue to place significant strain on healthcare systems globally and has undoubtedly increased health inequality gaps. Of further concern is that health and social care workers are more severely affected as a result of increased exposure to COVID-19, with media reports suggesting that 199,000 UK frontline healthcare professionals (HCPs) are currently living with Long COVID, and many have lost jobs due to related health challenges (52). A major survey by the British Medical Association found that for 60% of doctors, post-acute COVID ill health has impacted the ability to carry out daily tasks on a regular basis and 1 in 5 respondents unable to work at all (53). These figures are increasingly alarming considering the insurmountable strain on healthcare services, the existing issues of workforce capacity and service delivery NHS as vacancy statistics estimate of 100,000 vacancies in the NHS (50, 54).

1.3 Long COVID pathophysiology and manifestations

The persistent and episodic symptom profile of Long COVID is underpinned by a complex and interacting pathology (46, 55). Over 200 diverse symptoms have been identified, affecting cardiovascular, pulmonary, neurological, and autonomic systems shown in figure 1.2 (46, 56).

People with Long COVID experience a unique manifestation of the condition, which can be described as an umbrella term encompassing fluctuating symptoms, periods of remission and sudden, severe unexpected exacerbation, often associated with preceding over-exertion (57, 58). The causes and subsequent impacts of Long COVID remain an important area of research to increase the knowledge of proposed mechanisms underpinning pathological changes, and there are several current hypotheses for the pathogenesis of Long COVID. Determining the underlying pathophysiology of Long COVID is beyond the scope of this thesis, but a brief summary of the current understanding is presented in below.

Figure 1.2 redacted due to copyright.

Figure 1.2: Long COVID symptoms and the impacts on numerous organs with differing pathology from a review by Davis et al., (2023) (59).

1.2.3.1 Endothelial cell damage, clotting disorders, and platelet hyperactivation

Endothelial damage promotes platelet adhesion and coagulation, impairing organ function and sustaining platelet hyperactivation through increased expression of inflammatory and adhesion molecules (60). Persistent endothelial inflammation, micro clots, and platelet hyperactivation, along with their link to the chronic symptoms of Long COVID, have been central to previous research (59, 61-66). These studies have consistently reported coagulation abnormalities in Long COVID, which may account for prolonged symptom persistence (67-71).

1.2.3.2 Mitochondrial dysfunction

Mitochondria play a crucial role in cellular energy production, and is essential for maintaining cellular and systemic homeostasis (72, 73). Mitochondrial dysfunction may play an integral role in the clinical presentation of PEM, as impaired mitochondrial function has a widespread impact on body functions (73-75). Skeletal muscle mitochondrial respiration, biomarkers of

mitochondrial function, content, and biogenesis, and loss of cytochrome c oxidase activity, subsarcolemmal mitochondrial accumulation, and abnormal cristae, have all been found to be significantly lower in patients with Long COVID (76, 77). Decreased energy production, initiation of inflammatory pathways and increased production of reactive oxygen species caused by mitochondrial dysfunction may explain the reduced exercise capacity and excessive fatigue in Long COVID patients (72).

1.2.3.3 Immunology: immune dysregulation, viral persistence or remnants in tissues and reactivation of latent viruses

Persistent SARS-CoV2- viral antigens, reactivation of latent herpesvirus and chronic inflammation may all contribute to Long COVID, but data is less consistent with an autoantibody-dominated disease process which requires further investigation (78, 79). Significant immunological differences have been identified between people with Long COVID and matched populations, one-year post-acute infection (80). Exploratory analyses revealed significant alterations in immune cell populations, with increases observed in non-conventional monocytes, double-negative B cells and IL-4/IL-6 secreting CD4+ T cells and decreases in conventional DC1 and central memory CD4+T cells. Residual RNA has been present in tissues in the months and years following infection in other single-stranded RNA viruses such as Ebola and Zika virus (81-83), and may be responsible for the persistent and chronic disease presentation (84, 85). Furthermore, Epstein-Barr virus (EBV) status has been linked to an enhanced risk of various autoimmune diseases, and Long COVID cohorts have exhibited elevated levels of antibodies targeting SARS-CoV-2, and EBV (61, 80, 86). The relationship between Long COVID and EBV reactivation is merely correlative but offers one mechanism that may potentially contribute to Long COVID immunopathogenesis (61).

SARS-CoV-2 RNA and protein have been observed in a range of tissue types (brain regions, lymph nodes, thorax, sciatic nerve, ocular tissue, central nervous system [cervical spinal cord, brainstem, olfactory nerve]) collected weeks or months after acute infection (81, 87). Further detail on the research identifying SARS-COV-2 RNA proteins in tissue biopsies, autopsy and stool samples can be found in reviews by Altmann et al (61) and Proal et al (81). Evidence also suggests that autoimmunity triggered by COVID-19 may exacerbate or prolong mitochondrial dysfunction, by leading to a continuous immune-mediated damage to mitochondria, maintaining a state of inflammation and mitochondrial impairment (72).

Autoimmunity including efforts to screen identified autoantibodies for sequency homology to microbiome/virome-derived proteins/metabolites must be a focus for further Long COVID research (88).

1.2.3.4 Dysautonomia

Autonomic nervous system (ANS) symptoms are described by a proportion of Long COVID patients, including palpitations, orthostatic intolerance, severe fatigue, temperature dysregulation, cognitive dysfunction and headaches. Long COVID patients may not meet the diagnostic criteria for postural orthostatic tachycardia syndrome (POTS) or inappropriate sinus tachycardia (IST), they often demonstrate an altered haemodynamic profile consistent with a neurocardiovascular dysautonomia response and symptoms of orthostatic intolerance.

1.2.3.5 ME/CFS, Post-exertional malaise (PEM) and post-exertional symptom exacerbation (PESE)

An estimated 13-45% of people with persistent and debilitating symptoms following acute COVID-19 meet the case definition for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) (89-93). Often, ME/CFS follows an 'infectious-like illness' marked by respiratory and gastrointestinal symptoms, fatigue, myalgia, and fever (94). The overlap of the pathophysiology of Long COVID and ME/CFS has been extensively reviewed, establishing considerable similarities of the two conditions (95). Around 90% of Long COVID patients experience post-exertional malaise (PEM) or post-exertional symptom exacerbation (PESE), the cardinal symptom of ME/CFS (46), defined as a worsening of symptoms following exertion above a personal and variable threshold (96). PEM can be brought on by varying stressors, including exercise, cognitive and emotional upset, and prolonged upright position, and is associated with a reduced functional status and QoL in Long COVID and ME/CFS cohorts (46, 97). Some symptoms differ between the two conditions, with anosmia, dysgeusia/ageusia, rash, and hair loss more commonly reported in Long COVID, and tinnitus, painful lymph nodes and chemical sensitivities more frequently reported in ME/CFS (95). A review by Komaroff and Lipkin, (2023) summarise that both conditions share several biological abnormalities including the central and autonomic nervous system, the immune system, reactivation of latent viruses, energy metabolism and cardiac, pulmonary, and vascular abnormalities (95). Similarly to ME/CFS, the cyclical, multisystemic nature and heterogeneity

of Long COVID coupled with the scarcity of biological screening tools has resulted in a lack of pharmacological treatments, and rehabilitative interventions for both conditions.

1.4 Long COVID management and services

The complexity of Long COVID is reflected in the absence of established (curative) treatments for patients with Long COVID, and whilst some clinician-initiated treatments show promise, they have not been rigorously assessed in controlled clinical trials. The dearth of evidence to inform practitioners on how to support those living with Long COVID presents an unprecedented challenge for patients, their families and healthcare professionals. Understandably, concern has been expressed by people living with Long COVID on medical professionals lack of knowledge and understanding, as well as barriers to accessing healthcare, unhelpful messaging and difficult to navigate processes and inconsistent and conflicting guidance (98). Current diagnostic tools for Long COVID have been repurposed from existing conditions such as tilt table tests for POTS, and MRI scans for cardiovascular impairment, but methods specific to Long COVID require further development such as imaging to detect micro clots and validating appropriate biomarkers (59). Furthermore, multidisciplinary teams have been encouraged in the development and delivery for Long COVID support services, however this may hinder consideration and interaction between disciplines for a heterogeneous condition that requires broad expertise working in unison with each other. Long COVID requires bespoke services informed by novel and integrated approaches, making interdisciplinary working the better solution (13). Understanding patient needs using the lived experience of patients is also crucial in the development and delivery of support mechanisms (13). The personal knowledge gained through direct, first-hand involvement when living with a condition provides an additional dimension to research, and ensures that the patient's needs are central to outcomes (99).

It is clear from the existing literature that people are experiencing debilitating symptoms for months and years (35, 39, 41, 56, 100-108), and key research has conceptualised disability as a result of the episodic and unpredictable nature of Long COVID and highlights the health challenges associated with this (109, 110). However, one study concluded that Long COVID symptoms in patients with mild COVID-19 infections resolve within a year (111). The study was a retrospective nationwide cohort study, and used the electronic health records of 300,000 people who had mild COVID-19. The findings show that patients with mild COVID-19 are at

risk for a small number of health outcomes, most of which resolved within a year, however the cohort was not representative of people living Long COVID. The sample is also limited to members of a single healthcare organisation in Israel, which may contribute to bias relating to healthcare access, socioeconomic determinants and ethnic diversity. Using electronic health records for a condition which has likely been unrecognised by health care professionals, will also result in clear underrepresentation of the condition. The study did not consider different manifestations of the condition nor include PEM or POTS, which are 2 key symptoms of Long COVID. The retrospective design also carries inherent limitations that may affect the reliability of results. Therefore, the interpretation of the results requires careful consideration of the study's limitations, particularly regarding data quality, potential biases, and the generalisability of findings. Future research is required to build on these findings by exploring the mechanisms behind Long COVID symptoms and developing targeted interventions to mitigate their impact. Research shows that COVID-19 survivors have a remarkably lower health status than the general population 2 years post infection (112), however periodic observations quantifying the day-to-day impacts reflecting the episodic and relapsing nature of Long COVID are also scarce within Long COVID research.

The Centre for Disease Control and Prevention recognises that despite funding, the complexities of Long COVID results in challenges for healthcare professionals, hindering diagnosis, care and treatment (38). The dearth of knowledge surrounding the underlying pathophysiology of Long COVID highlights the need for deeper understanding to inform the design and development of bespoke services allowing the provision of tailored and individualised support to patients. It is also key to understand whether the plans and guidance set out by healthcare systems translates adequately to the lived experience.

1.5 Thesis Aims and Objectives

Accordingly, the knowledge and need for Long COVID support mechanisms have been used to formulate the aims and objectives of the thesis:

- To understand the need for, and inform bespoke interventions to improve recovery, QoL, and functional status following Long COVID through the following chapters:
- To understand the lived experience of COVID-19 considering healthcare experiences and QoL using a mixed methods approach.

- To describe, quantify and critically evaluate the clinical, physiological, biochemical, and psychological domains of the recovery following a COVID-19 infection.
- To engage with established patient support groups, clinicians, and allied health professionals to inform rehabilitative interventions to improve recovery outcomes including QoL and functional status following a COVID-19 infection.
- To use evidence-based approaches to consider bespoke support mechanisms, promoting patient-led care during recovery, in line with National Institute for Health and Care Excellence and global healthcare priorities.

Chapter 2

Understanding the lived experience of COVID-19, considering healthcare experiences and quality of life using a mixed method online survey.

Peer-reviewed Papers from this Chapter:

Owen, R., Ashton, REM., Ferraro, F, Phillips, BE., Skipper., L, Faghy, MA., (2023)., Acute COVID-19, the lived experience, and lessons to learn for future pandemics. *Disaster Medicine and Public Health Preparedness*. *17*(e534). DOI: https://doi.org/10.1017/dmp.2023.197. IF: 2.7.

Owen, R., Ashton, REM., Yates, J., Thomas, C., Ferraro, F, Bewick, T., Haggan, K., Faghy, MA., (2023)., The impact of living with Long COVID on quality of life and daily activities: the lived experience. *Qualitative Health Research*. *4*(p133-134). DOI: doi.org/10.1007/s11136-023-03513-y. IF: 4.233

Conference Proceedings:

Owen, R., Faghy, M., Ashton, R., Ferraro, F., Thomas, C., Yates, J., Haggan, K., Bewick, T., Phillips, B. The impact of living with Long COVID on quality of life and daily activities: the lived experience. *University Professorial Council Research Showcase,* University of Derby, September 2022.

Owen, R., Ashton, R., Ferraro, F., Skipper, L., Bewick, T., Leighton, P., Phillips, B., Faghy, M. (2023). Long COVID Experiences and Support Mechanisms. *Biomedical and Clinical Science Research Theme,* University of Derby. Presentation.

2.1 Introduction

Clinical manifestation and features of acute COVID-19 presentation, including pathophysiology, diagnosis and symptom profiling have been extensively investigated to inform the response to treatment and intervention strategies (113, 114). However, there is a lack of research that truly delves into the first-hand experiences of COVID-19 infection from the perspective of patients, and the broader impact of the pandemic. The available literature explores the experiences of COVID-19 patients who were hospitalised (115, 116), however, the perspective of those who were not hospitalised are less studied. Missel and colleagues (113) identified three themes relating to the meaning of COVID-19 from 5 hospitalised and 10 not hospitalised individuals during the first phase of the pandemic. Within this study, participants perceived COVID-19 as a threat to existence, threat to bodily perception, and an interference in ordinary social relationships. Importantly, participants shared their feelings of threat from the novel virus, including existential thoughts and death. Due to the inaccessibility and limitations of testing methods throughout the pandemic, the perception of those without a confirmed COVID-19 diagnosis is unknown. The need to document and understand the lived experience of patients is pivotal to increasing holistic preparedness for future health pandemics (117).

The profile, awareness, and management of Long COVID and the lived experience remains overlooked by governments, the media and public health messaging (118). In addition to determining the mechanisms of Long COVID, there is a demand for health care practitioners (HCPs) and patients to work together to facilitate multidisciplinary approaches within research to develop support mechanisms, incorporating the lived experience (119-121). Medical professionals and academics often facilitate research and decide on hypotheses and outcomes in clinical areas (122) however a movement from the National Institute of Health Research and Funding Councils in the UK recognises the importance of involving patients throughout the research process (123). Patient and public involvement and engagement (PPIE) should be included in all stages of healthcare design (119, 124-126) as it provides an opportunity to embed the lived experience within research, enabling those living with illnesses to identify questions and issues that matter to them (99, 122, 127). Inclusivity of PPIE representatives in Long COVID research allows those with lived experience to have a central role within shaping the research question and study design (118, 122). The debilitating symptom profile associated with Long COVID including PEM and fatigue is important to consider when fostering

collaborations and integrating PPIE representatives in Long COVID research. To encourage meaningful and inconsequential contributions from Long COVID representatives, individuals should be supported through governance documents and structures, such as flexibility at meetings, breaks, reduced screen time, documents and agendas sent in advance, key summary documents, and adjustments necessary based on individual needs (128). Forming partnerships with patients ensures that their interests are central to the research, while also embedding and prioritising the patient voice and their health (122).

Of those with persisting symptoms following COVID-19 infection, one survey quantifying Long COVID as a debilitating multisystem illness found that 83.3% (n=1005) experience moderate-to-poor self-reported health, moderate-to-extreme problems with daily activities (62%) and moderate-to-severe pain or discomfort (49%) (42). The impact of Long COVID on functional status has resulted in a reduction of individuals' ability to continue with domestic chores (84.3%), leisure (84.8%), social activities (77.1%), work (74.9%), self-care (50%), childcare (35.8%) and mental health (63.7%) (100). Furthermore, 32.3% of individuals report being unable to live alone without any assistance, and 34.5% experience moderate to functional limitations (100).

Accordingly, the current study aimed to use the patient voice to capture the lived experience of those with a history of COVID-19 during the acute phase of COVID-19 infection, considering testing, diagnosis, clinical status, and care; and to capture the impact of Long COVID on QoL and seek recommendations for healthcare services through an exploratory online questionnaire.

2.2 Method

Following institutional ethics approval by the Human Sciences Research Ethics Committee at the University of Derby (ETH2021-4335), a web-based survey (Qualtrics) was distributed from 18th October 2021 to 31st January 2022 via social media (X and LinkedIn), word-of-mouth and PPIE. Participants read the participant information sheet (available in appendix 2a) and provided informed consent (available in appendix 2b) before completing the survey. All responses were anonymised by participants creating a unique identification code using the last two letters of their postcode and last two numbers of their mobile phone number.

Due to the shortage and limitations of COVID-19 testing, participant inclusion criteria included those who had tested positive and those who suspect that they had COVID-19 through NHS recognised symptoms at the time of the survey, and having Long COVID symptoms (symptoms consistent with the WHO Long COVID definition) (34, 129). Patients had to understand written English and be >18 years old. Participants were excluded if they were uncertain of the survey requirements and their answers provided in the informed consent form did not meet the required criteria.

The survey covered the lived experience during the acute phase of infection and long-term implications following COVID-19. There were 6 sections, for a total of 65 questions including demographics (9 questions: age, sex, ethnicity, disability, region, relationship status, employment/occupation status), COVID-19 in the acute phase of infection (15 questions: testing, diagnosis, and clinical status [hospital admission, management of condition, impact of testing on treatment]), and adequacy of care, pre- and post-COVID-19 health (3 questions: pre-COVID-19 QoL and health, post-COVID-19 QoL and health [5-point Likert Scale; very good, good, average, below average, poor, with an open text box for further information], history of auto-immune conditions), activities of daily life (ADL) (10 questions: returning to previous activities, importance of activities, barriers) and Long COVID (28 questions: care experience, obstacles to care, medical gaslighting, living with Long COVID, impact on daily living, and advice for HCPs). The survey consisted of open and closed ended questions, and participants were encouraged to provide detail surrounding their response to closed ended questions. The full survey can be found in appendix 2c.

2.2.1 PPIE

PPIE was used throughout the research process when developing the research question, and during the creation and design of the survey through roundtable discussions. The PPIE network are established partners in the Long COVID research group and Long COVID physiotherapy network, external from the research group. PPIE representatives assessed the survey using their lived experience to determine survey length, content, terminology, and format prior to distribution. PPIE representatives supported the circulation of the survey by sharing it within their Long COVID networks and support in disseminating the results, by sharing findings into these support groups and forums.

2.2.2 Data Analysis

Closed ended questions were analysed according to frequency counts. Normal distribution was assessed for statistical data using the Kolmogorov-Smirnov test of normality (IBM SPSS Statistics v27), with Likert responses treated as interval data. Wilcoxon signed-rank tests were used to analyse within groups data, with statistical significance set to $P<0.05$. Statistical data are presented as mean ± standard deviation (SD), with confidence interval (CI; 95%). QoL Likert scale responses were labelled as very good (1), good (2), average (3), below average (4), and poor (5) in SPSS.

The analysis of open-ended questions was guided by Braun and Clarke's thematic analysis framework (130). Open responses were uploaded to NVivo 12 pro (Version 12.7 QSR International, Doncaster, Australia). Following familiarisation of the data, initial codes were generated within NVivo and data were organised into groups. During this process, the findings were organised into the acute stage of infection and the long-term implications following acute infection. Codes were analysed, and initial themes were identified, and then reviewed and defined. The aim of the thematic analysis was to provide a narrative of the patient voice and are presented with quotes in verbatim. Word frequency count was also analysed within NVivo. Enhancing trustworthiness was done by using a team approach using confirmation from multiple members of the research team throughout analysis and interpretation (131).

2.3 Results

2.3.1 Demographics

There were 132 complete responses (85.6% female), with 32.6% of participants aged 18-40 years, 65.9% aged 41-65 years, and 1.5% >65 years. An additional 54 responses were not included in the analysis due to participants not progressing further than the demographics section. Sample size was adjusted for missing responses when calculating frequencies. Sample size of 132 was accepted in line with saturation of open responses (132). Of the 132 responses, 77.3% of participants were white British, 12.9% from other white backgrounds, 5.3% white Irish and 0.8% were either mixed white and black Caribbean, other Black, African, or Caribbean background, Indian, Pakistani, Bangladeshi, or other mixed or multiple ethnic backgrounds. Within the sample, 16.7% had a pre-existing auto-immune condition. Full participant demographic information is presented in Table 2.1.

Table 2.1: Participant characteristics of those who completed the lived experience survey showing age, sex, ethnicity and geographical location

	Demographics	N= (%)
AGE	18-40 years	n = 43 (32.6%)
	41-65 years:	n = 87 (65.9%)
	65+ years:	n = 2 (1.5%)
SEX	Female	n = 113 (85.6%)
	Male	n = 17 (12.9%)
	Transgender	n = 1 (0.8%)
	Gender variant / non-conforming	n = 1 (0.8%)
ETHNICITY	White British	n = 102 (77.3%)
	White Irish	n = 7 (5.3%)
	Other White Background	n = 17 (12.9%)
	White and Black Caribbean	n = 1 (0.8%)
	Other Mixed or Multiple Ethnic Background	n = 1 (0.8%)
	Indian	n = 1 (0.8%)
	Pakistani	n = 1 (0.8%)
	Bangladeshi	n = 1 (0.8%)
	Other Black, African or Caribbean Background	n = 1 (0.8%)
GEOGRAPHICAL LOCATON	Scotland	n = 13 (9.8%)
	Northern Ireland	n = 2 (1.5%)
	Wales	n = 5 (3.8%)
	Northeast England	n = 3 (2.3%)
	Northwest England	n = 11 (8.3%)
	Yorkshire and Humber	n = 11 (8.3%)
	West Midlands	n = 5 (3.8%)
	East Midlands	n = 28 (21.2%)
	Southwest England	n = 12 (9.1%)
	Southeast England	n = 17 (12.9%)
	East of England	n = 3 (2.3%)
	Greater London	n = 15 (11.4%)
	Missing responses	n = 7 (5.3%)

Within the sample, 59.1% of participants had tested positive for COVID-19, and 40.2% had not, but had symptoms consistent with COVID-19. Median time from acute infection to completion of the survey was 11.3 months and the median month of positive infection was December 2020. During the acute COVID-19 infection phase, 87.9% recovered in community settings, 9% were admitted to hospital (length of stay: 4.5% <7 days and 4.5% >7 days), and 3% did not respond to this question. A further 3.8% of those admitted to hospital were admitted to an Intensive Care Unit (ICU). Within this sample, 76.5% of participants had been diagnosed with Long COVID, 17.4% had not but report suspected Long COVID and 6.1% did not disclose this information.

2.3.2 Word frequency count

Word frequency count and weighted percentage was analysed in NVivo for open text responses, with covid (count 253, weighted percentage 1.25%), long (count 239, weighted percentage 1.18), work (count 210, weighted percentage 1.04), symptoms (count 169, weighted percentage 0.85) and fatigue (count 152, weighted percentage 0.75) being the most commonly used words throughout. This data was used to inform and substantiate the development of resulting themes and to further evidence the impact on QoL and functional status.

2.3.3 Descriptive statistics

QoL was perceived to be higher pre-COVID-19 infection than post-COVID-19 infection ($P<0.01$; pre-COVID-19 QoL mean 1.50 ± 0.73, 95% CI; 1.36, 1.64, post-COVID-19 QoL mean 4.40 ± 0.97, 95% CI 4.23, 4.59), shown in box plot data in Figure 2.1. Pre-COVID QoL and health status were reported as ‘very good’ by 52%, and 2% post-COVID-19. No participants reported ‘poor’ QoL and health status pre-COVID-19, but this was reported by 54% post-COVID-19. Furthermore, 43% (n=50) were unable to return to their pre-COVID-19 activities, 38% (n=44) had made a partial return to their ‘typical’ activities but symptoms still impacted their ability to engage with these activities, and 4% (n=5) reported making a full return but had limitations undertaking these. Additionally, 73.5% (n=97) of participants reported difficulties engaging with friends, family, or colleagues and 73% (n=33) of parents within this sample reported that they can no longer undertake parental responsibilities fully.

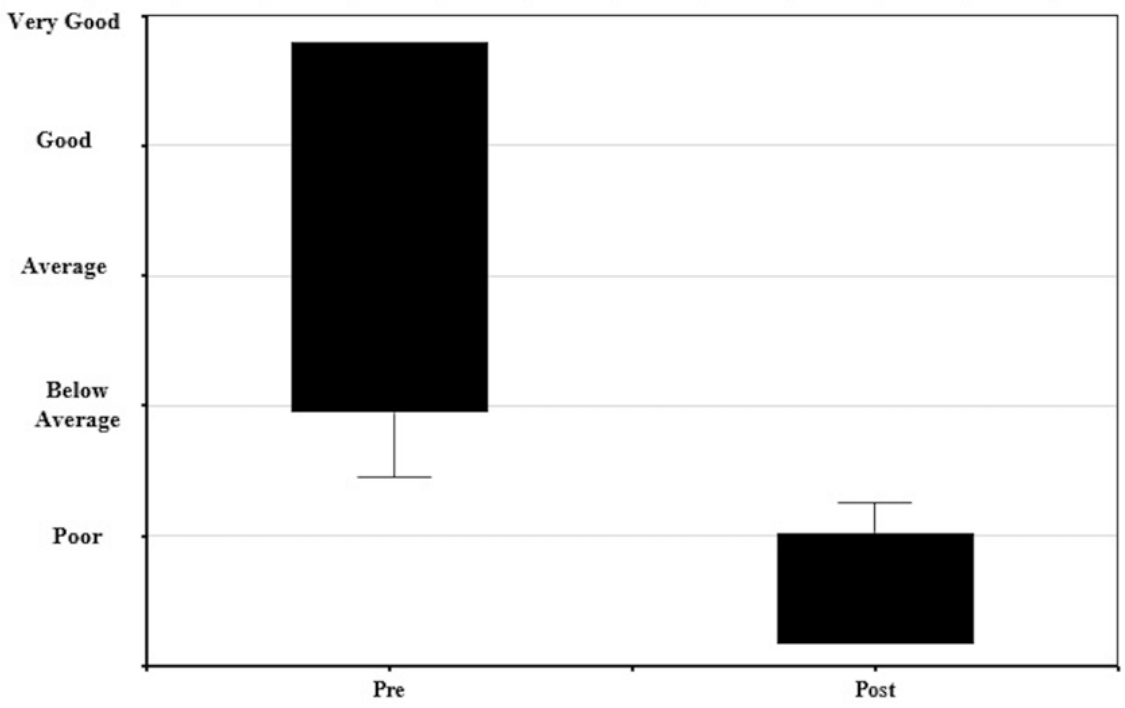

Figure 2.1: Box plot showing change in quality-of-life pre -and post-COVID-19 infection.

2.3.4 Thematic Analysis

2.3.4.1 Acute Lived Experience

The thematic analysis of the lived experience during the acute phase of COVID-19 resulted in 5 themes and 3 sub-themes shown in figure 2.2. Participants described how they managed their condition during their infection, which was often accompanied by a description of the symptoms they were experiencing, their need for medical support, and how they felt during this time.

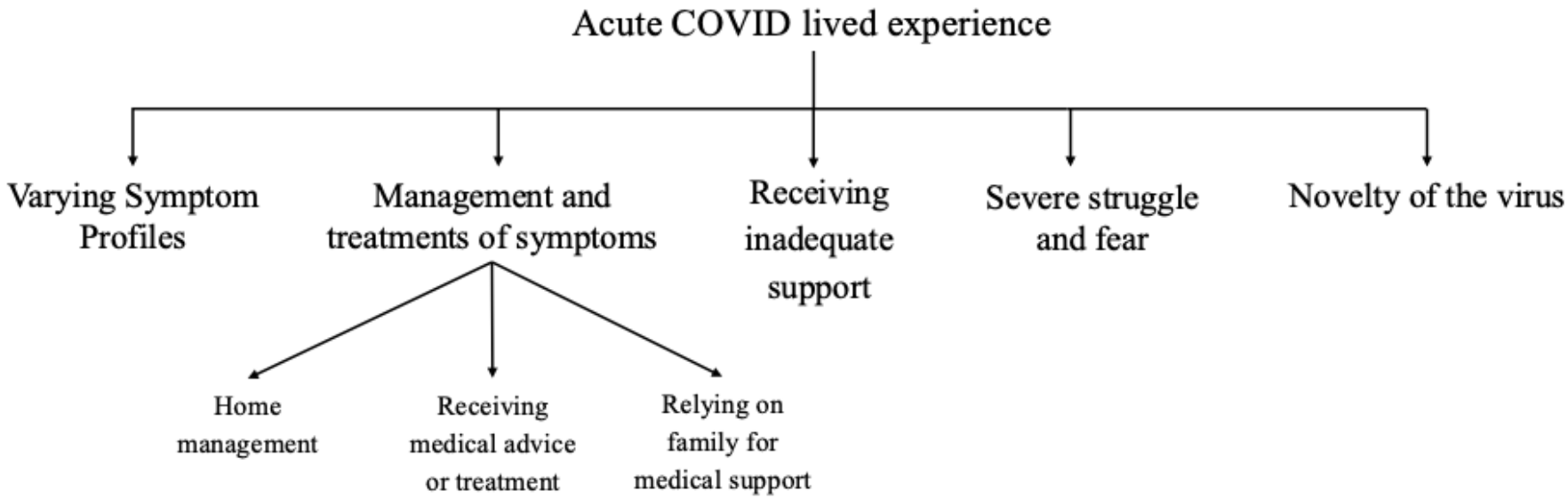

Figure 2.2: Schematic of Acute COVID experience themes from the lived experience survey.

Theme 1: Varying symptom profiles

Participants in the study reported varying symptom profiles at the acute stage, ranging from mild, to moderate and severe. The term 'symptoms' had the highest weighted percentage (1.28%, count 113), followed by covid (1.25%, count 110), pain (1.18%, count 104), and rest (1.13%, count 100). When including stemmed words, the term 'breathing' (breath, breathe, breathing) had the highest weighted percentage (1.61%, count 142), followed by 'rest' (rest, resting, rested;1.48%, count 130), and 'pains' (pain, painful, pains;1.45%, count 128). When stemmed, 'symptoms' had a weighted percentage of 1.36% (count 120). The term 'mild' had a weighted percentage of 0.16% (count 14), with participants describing:

'Very mild, no fever, no respiratory symptoms.'

'Very mild initial illness with some fatigue.'

Comparatively, the term 'severe' had a weighted percentage of 0.48% (word count 42), as well as further descriptions of:

'I thought I died at one point'

'It was so horrific with racing heartbeats, breathlessness that felt like I'd suffocate, pain in my abdomen that felt like I must be dying, fever, hallucinations, GI symptoms of diarrhoea and acid reflux with swelling in abdomen…'.

Theme 2: Management and treatment of symptoms

Participants described how they managed their condition regarding symptom severity, which ranged from home management to requiring medical support (calling 111, an ambulance or a GP) due to the varying symptom profiles. The term 'hospital' (stemmed) had a weighted percentage of 0.51% (word count 45), with 111 services having a weighted percentage of 0.40% (word count 35).

Sub-theme 1: Home management of symptoms

Participants with mild-moderate symptom profiles described managing their symptoms independently with the use of over-the-counter medications which predominantly included 'painkillers' such as paracetamol (weighted percentage 0.57%, count 50). Other self-management methods were described which included resting, taking time off work, and staying hydrated:

'I took 2 weeks off sick initially and then worked from home but struggled. I slept between meetings. I had lower back pain and tinnitus, my body aches all over. I could barely keep my eyes open sometimes'.

'Lay still. Drink lots of liquid. Rest near an open window. Vitamin D. Raise head of bed.'

In more moderate-severe cases, participants described how their symptoms left them *'bedbound'* or on *'bed rest'*. The term 'bed' had a weighted percentage of 0.68% (word frequency 60):

'Didn't leave bed for first 2 days'

'Bed bound for 3 months'.

Additionally, one participant described that they felt '*completely debilitated'*, and another stated that:

'At the height of it I could not get out of bed. If I got up, I struggled to keep upright or walk and got dizzy'.

Sub-theme 2: Receiving medical advice or treatment

For more moderate-severe-critical cases, participants report requiring medical assistance, and receiving support and intervention from nurses and General Practitioners (GPs):

'Regular discussion with asthma nurse by phone'

'Managed by GP who knew me well, medication to help breathing, bring down fever, coughing etc, inhaler for a time, referrals made to specialist departments like ENT.'

Other participants reported receiving advice from 111 and NHS services:

'Had to call ambulance 2 times due to breathing and chest pains. Called 111 due to migraine pains being unbearable.'

'I called 111, and they advised me to come to A&E but I felt too ill and didn't want to spread it… looked on the NHS website (there was little to no info at the time)...kept warm, took Lemsip, ate and was in an elevated position.'

However, one participant reported:

'Hospital full so advised to recover at home and call 111 if oxygen dropped… antibiotics for pneumonia, high dose vitamin c, d, b'.

Theme 3: Receiving inadequate support

Whilst 88% (n=116) of participants recovered in community settings and 9% (n=12) were admitted to hospital, 55% (n=73) of all participants report that they do not believe they received adequate care during the acute phase of infection. Inadequate experiences were described by participants, where they felt they had to '*beg'* for support. Furthermore, participants felt like they were disbelieved, and/or not taken seriously.

One participant described:

'I felt I had to beg to be seen and felt disbelieved …I felt as though I had been left to die at home despite seeking care. Nobody took over my care medically to look after me… It was some weeks before I saw someone or had any tests, likely more than 6 weeks.'

Similar experiences were described by other participants:

'I feel as though I was not believed. I was struggling to function at home and despite calls to 111 and my GP I could not gain medical help...'

'Sought emergency care but was denied as I could speak a whole sentence and could get myself outside of my front door if needed, although with difficulty and unable to do anything once there'.

'had minimal medical help, 111 did not answer and GPs were overwhelmed.'

Additionally, experiences of being sent home after seeking care were reported:

'Paramedics ... tried to take me to hospital but they wouldn't let me in so they had to take me back home.'

'I called 111… mostly on hold for 3 hours ... no help told me to call "when you are struggling to breathe or speak". Next time my husband called them … I was struggling to breathe and speak. After several hours ... they directed me to A&E, but — opposite to what they said they would do — did not inform the A&E, who did not expect me. I got sent back from A&E, who told me I had Covid, without help. Back home I passed out, and I can't remember much of the days afterwards, except that I expected to die and didn't.'

Negative experiences with GP services were also described:

'Only contact with a GP was when I phoned, seemed little interest in what I was experiencing.'

'GP literally hung up on me.'

'Struggled to speak to the same GP.'

However, it seemed this was dependent on the GP as one participant described:

'GP's did not care about my symptoms despite how much I was struggling and did not examine me... Only when I moved back home was I then seen at a different practice when things were worse and I then received excellent care as well as at A&E.'

Sub-theme 3: Relying on family for medical support

Due to the lack of care received by healthcare services, participants described the importance of relying on family to support them:

'If he (husband) hadn't been there ... don't think I would have survived. I should not have been left without treatment or care to develop pneumonia and manage that at home without help for weeks.'

'Family had to care for me.'

'My husband cared for me during this period.'

Theme 4: Severe struggle and fear

Throughout the acute phase, participants with severe symptoms made references to death and planning their funeral. The term 'struggling' had a weighted percentage of 0.31% (count 27), and 'extreme' 0.19%, (count 17):

'I really thought my kids were going to find me dead by morning.'

'Decide to relax and accept death gently.''

'I thought I was going to die and planned my funeral.'

Participants also described their feelings of fear and being scared:

'Never been as scared in my life and at times felt like I would not make it through'.

'I was very scared'.

Theme 5: Novelty of the virus

Although participants described receiving inadequate support, they also referred to the novelty of the virus, and the potential impact this had on why they may have received insufficient medical care.

'Nobody knew what we were dealing with then'

'GPs were overwhelmed'

'I was told I would be safer at home than in hospital'

'They advised me that under normal circumstances they would have taken me to hospital'

2.3.4.2 Long COVID Lived Experience

A schematic of the Long COVID lived experience themes are presented in figure 2.3. There were two distinct areas encompassing the lived experience of Long COVID: 1) the impact and challenges of Long COVID on QoL and 2) the healthcare experiences of those living with Long COVID.

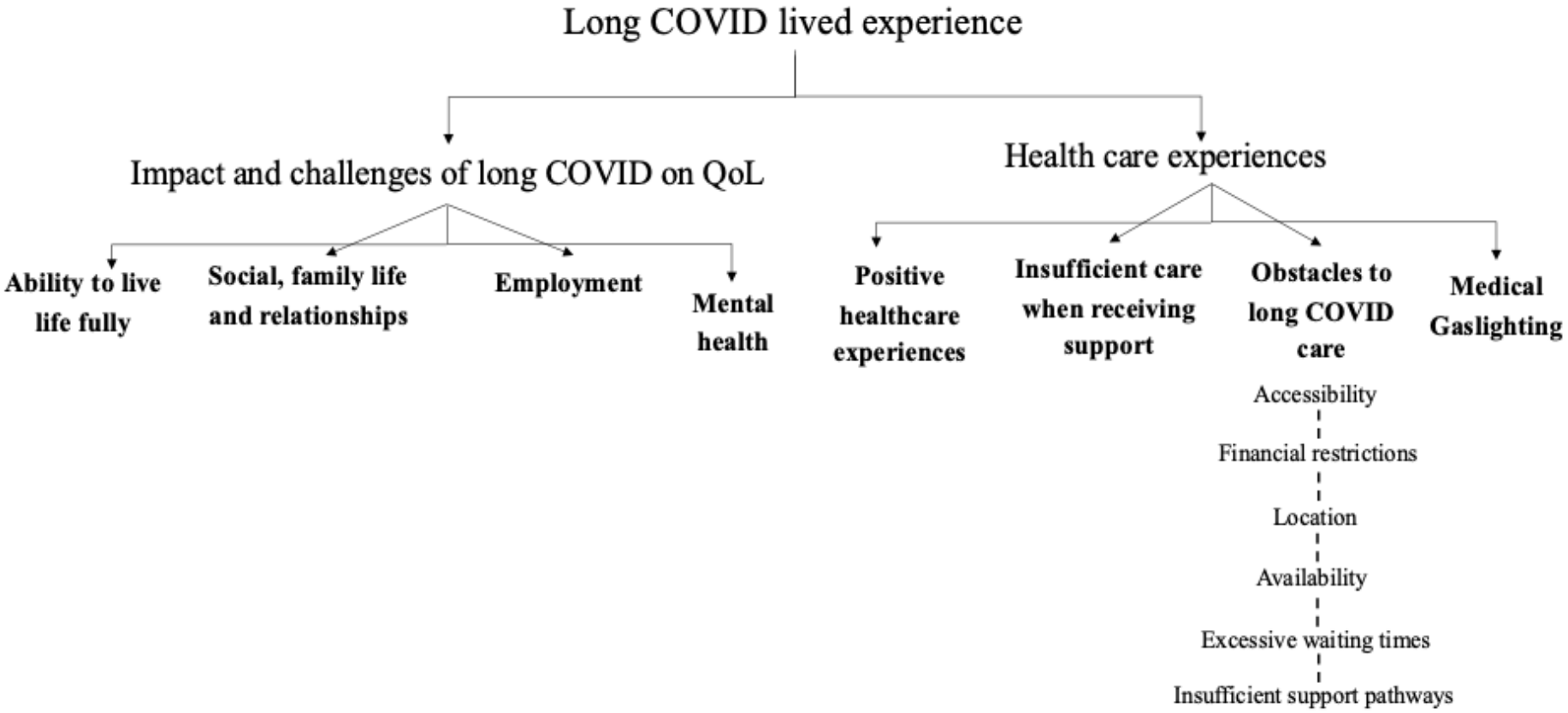

Figure 2.3: Schematic of Long COVID QoL and healthcare experiences themes from the lived experience survey.

Theme 6: The impact and challenges of Long COVID symptoms on QoL

As highlighted in the descriptive statistics, QoL was significantly reduced as a result of Long COVID symptoms ($P<0.01$), and the impact and challenges associated with this were derived into 4 sub-themes: the ability to live life fully, social, family life and relationships, employment, and mental health.

Sub-theme 7: Ability to live life fully

'Completely changed lifestyle, which is depressing, can't live usual life, no energy for anything.'

Symptoms result in severe limitations of participating in daily life, with individuals having to change their lifestyle and sacrifice participating in their normal level of activities. When individuals do return to their typical activities, they still suffer limitations and consequences following participation. Inability to live life fully includes the ability to work, socialise, exercise, and complete their previous everyday tasks.

Sub-theme 8: Social, family life and relationships

'I feel like people are fed up hearing me complain about symptoms which has made me feel isolated from friends and family. Pressure of living with reduced capabilities has impacted relationships'

Symptoms impacting the ability to participate in life have consequently impacted social and family life, and damaged relationships. People with Long COVID also worry that they are burdening those around them due to changes in family roles, resulting in feelings of isolation.

Sub-theme 9: The impact on employment

'Missing work, feeling guilty about missing work'

Those with Long COVID who are unable to work or have reduced schedules experience feelings of guilt, financial concerns, and lack interaction with colleagues.

Sub-theme 10: Mental health

'If I didn't have children, I'd have taken my own life a long time ago'

As a result of Long COVID symptoms, people experience reduced mental health with feelings of isolation, hopelessness, loss of identity and suicidal ideation.

Theme 7: Long COVID health care experiences

Referral to a Long COVID clinic was reported by 56% (n=63) of participants, and 48% of participants had a practitioner over-seeing Long COVID care (GP or Long COVID clinic [n=29]), multidisciplinary team or specialist services (physiotherapist, immunologist, respiratory, occupational therapist [n=8]). The type of care that participants received varied from commonly reported telephone appointments to a range of testing such as x-rays, blood tests, echocardiogram, and magnetic resonance imaging.

Healthcare experience themes include positive experiences, insufficient care when receiving support, obstacles to Long COVID care (sub-themes; accessibility, financial restrictions, location, waiting times, availability, and insufficient support pathways), and medical gaslighting.

Sub-theme 11: Positive healthcare experiences

'2 phone calls with a (very good) OT. Provision of useful written materials, and request for GP to refer me to the local ME/CFS [myalgic encephalomyelitis/chronic fatigue syndrome] service'.

Those who describe positive healthcare experiences received mental health support, symptom management and referral to specialised routes of care. HCPs considering fatigue was also important, with 62% reporting their fatigue was considered and 38% did not.

Sub-theme 12: Insufficient care when receiving support

'After a lot of struggle to access it and having been initially discharged without treatment, I have not been seen by a post-Covid clinic.'

When receiving insufficient support for Long COVID care, experiences consisted of no effective interventions or treatments to support their symptoms, treatment worsening their condition such as experiencing PEM or PESE, and solely telephone calls.

Sub-theme 13: Obstacles to Long COVID care

Obstacles to accessing and receiving Long COVID care were reported by 72.7% (n=96) of participants. Participants reported accessibility, financial restrictions, location, excessive waiting times, availability, and insufficient support pathways as obstacles to receiving Long COVID care.

Sub-theme 14: Accessibility

'My husband has to take me to most appointments because I can't walk far.'

The severe impact of symptoms on functional status such as fatigue, and cognitive dysfunction, impact the ability to access support, such as getting to appointments, booking appointments and advocation.

Sub-theme 15: Financial restrictions

'Too expensive and already paying to see PoTS consultant privately.'

Private healthcare settings may have the capacity to offer testing and support for people with Long COVID, however financial restrictions are a barrier to attain this.

Sub-theme 16: Location

'Long COVID research and treatments just don't seem to exist in Northwest England.'

It also appears that there are discrepancies between services dependent on location, with Long COVID clinics available in some areas of the UK and not others.

Sub-theme 17: Excessive waiting times

'Very long delay.'

After initially seeking care, patients reported extended waiting times for appointments with their GP and Long COVID clinics, as well as long waits for further referrals following this.

Sub-theme 18: Availability

'They (support mechanisms and treatments) are not available on NHS.'

Long COVID care was deemed unavailable, including a lack of services, clinicians, and appointments suggesting that testing and treatment options may exist but are not readily available.

Sub-theme 19: Insufficient support pathways

'Lack of commissioning of services. Lack of knowledge of who GP can refer to. Lack of understanding. Being completely pushed from pillar to post and getting nowhere.'

When accessing and receiving support, a lack of medical investigation, support and treatment, referral pathways and communication between medical professionals were described.

Sub-theme 20: Medical gaslighting

'The neurologist told me I was lying and purposely exaggerating my reflexes, also implied I was lying about other symptoms.'

Medical gaslighting was experienced by 46% (n=60) of participants. People with Long COVID felt dismissed, disbelieved, and not taken seriously by HCPs as well as being misdiagnosed and prescribed anti-depressants to resolve their physiological symptoms.

2.3.5 Patient recommendations for Long COVID care and support

As a result of the current offering of support and medical gaslighting, participants shared feedback and recommendations on how care can be improved to enhance health related quality of life (HRQoL). These recommendations can be considered in 4 sections; (1) patients feelings, (2) consideration of symptoms, (3) awareness of living with Long COVID, and (4) acknowledging the challenges of Long COVID as shown in figure 2.4.

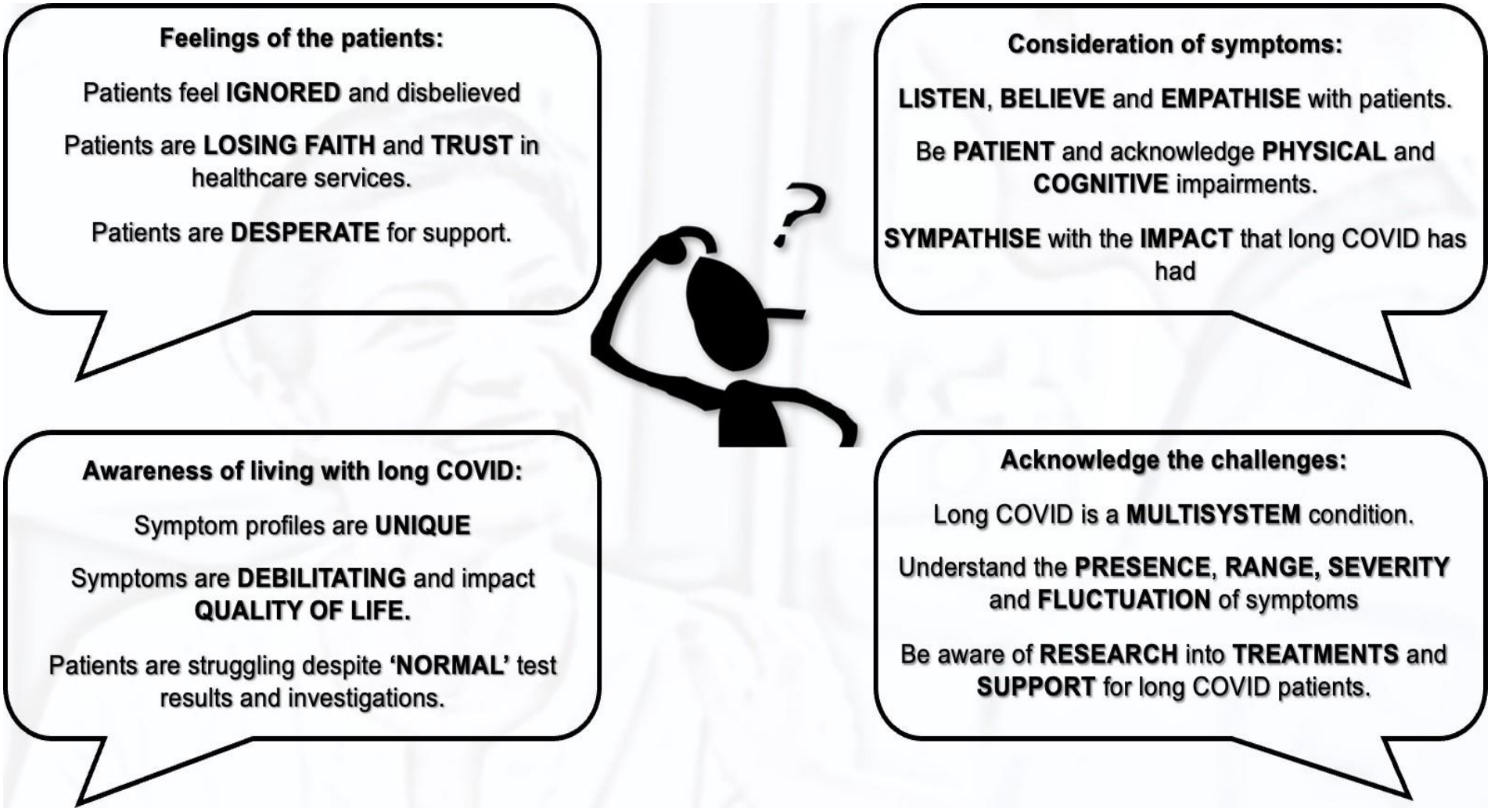

Figure 2.4: Patient recommendations for health care professionals helping people with Long COVID to enhance health related quality of life from the lived experience survey.

2.4 Discussion

To our knowledge, this study is the first to highlight the lived experience of individuals with confirmed or suspected COVID-19, during the acute phase of infection. Varying symptom profiles and a lack of knowledge and evidence of effective treatment strategies meant that some patients were left to convalesce in community settings with an apparent lack of access to medical care and support services. It is acknowledged that health services were placed under unprecedented strain at various times throughout the pandemic which resulted in patients being left feeling stranded and even worrying if they were going to survive (133, 134). Whilst the circumstances were unprecedented, this study highlights the perceived inadequacy of management and support when requiring medical assistance and reassurance during the heights of the COVID-19 pandemic.

Over half of the participants in this study felt that they did not receive adequate care in the acute phase of infection, with patients being sent home from the hospital and in some cases not being able to be admitted to the hospital due to services being overburdened. Data here provides a novel insight into the patient perspective which adds a different dimension to the findings that have been published by those working in frontline healthcare settings (135, 136). The sample of the current study is made up of 88% of individuals who were not hospitalised, however open text responses such as '*Hospital full so advised to recover at home',* '*advised that under normal circumstances they would have taken me to hospital' and 'I was told I would be safer at home than in hospital'* suggest that this may not be because all individuals had mild symptoms, but because medical services were not available due to capacity issues. Although participants referred to the 'novelty' of the virus, existing research states that the nature of pandemics makes them unpredictable, and sufficient planning and preparation can support their management (137). When considering these findings, it is important to be mindful of the pressure on frontline healthcare workforces who worked tirelessly out of routine, often with inadequate personal protective equipment (PPE) were commonly redeployed and suffered mentally (52, 135, 136). To be clear, the question of preparedness is not solely aimed at healthcare organisations and their staff as this must include a whole-systems viewpoint and consider the relevant and necessary stakeholders that are involved in the decision-making relating to planning, funding, and organisation.

Furthermore, the Independent Panel for Pandemic Preparedness and Response reported that the global COVID-19 pandemic *'was a preventable disaster, with weak links at every point in the chain of preparedness and response'* (138). Specifically, the panel reports that years of warnings highlighting an inevitable pandemic that threatened public health were ignored, and when the Public Health Emergency of International Concern was declared, a 'wait and see' approach was widely adopted, compounding the inevitable global health disaster that unfolded. An aggressive containment strategy that may have prevented the global pandemic (138) could have resulted in improved patient outcomes and healthcare experiences for all patients. The continued disregard and absence of political leadership had a major impact on the global response to the pandemic (138), in addition to several other factors contributing specifically to the UK's response (139, 140). These factors include the decision to delay the implementation of lockdown procedures; shortages of PPE for frontline workers; an insufficient number of ventilators; confusion in communications to the general public; and an improper track and trace system, all undoubtedly contributing to the experience described by the participants in this study.

This is reinforced by public health-related decisions that have seen access to free testing removed despite widespread community transmission which continues to result in hospital admissions. There are also no planned clinical assessments or follow-ups for patients with COVID-19 (141), which is partly caused by deep and systemic backlogs across the healthcare system. As of April 2024, it is estimated that 7.6 million people are waiting for routine treatments from the UK NHS with those living in the most deprived areas adversely impacted by these waiting list (50). Additionally, the lowest level of patient satisfaction with health services in the UK has been recorded, with 51% of respondents to the Kings Fund survey dissatisfied with their experience and/or treatment (142). Furthermore, the strain on staff from responding to the pandemic is alarming and has resulted in greater sickness absences than before the pandemic (143) as well as ~110,000 job vacancies across the healthcare sector, with thousands more in primary care (144). Subsequently, only 27% of staff within the healthcare services feel that they can do their jobs properly (144), which is concerning for patients receiving care. This may be represented in the drop in public satisfaction with the healthcare service (142, 145) and is further evidenced in our findings. As understood amongst the participants in the present study, a novel virus allows for a reasonable understanding of restricted access to healthcare during a pandemic, however, the continuation of the UK's

healthcare restrictions is alarming, and unknown future variants (146) and Long COVID pose a further threat to the healthcare sector.

Our findings are consistent with previous research demonstrating that people with Long COVID are convalescing in community settings with persistent symptoms and long-standing morbidity that primarily affects physical and mental well-being, ADL and QoL (26, 42, 100, 147). Data here provides a deeper insight and demonstrates the broader impact that this has on social and economic determinants, that as a result further impact health and wellbeing. This study presents evidence of the adverse effect on personal and professional relationships (inclusive of relationships with healthcare professionals), an increasing reliance on friends and family for support, and psychological and emotional functioning alongside financial challenges. Evidence from other chronic conditions has outlined the broad impacts previously, however, this is not adequality considered in conditions that are underpinned by multi-dimensional and episodic characteristics that are observed in Long COVID (148-151).

The detrimental impact on mental health and wellbeing has been previously articulated and includes increased, isolation, loneliness, and suicidal ideation (152). This data further explores the detriments and impact that inconsistencies and a lack of support and treatment received when accessing Long COVID care services and the effect this has on mental and physical well-being. Specifically, patients express frustration and concern at a lack of specific and efficacious treatments and support services to eradicate and manage the condition that broadly impacts their lifestyle. Feelings of anger and frustration are possibly intensified by limited progress in the development, implementation and consistent access to efficacious support and treatments which is coupled with the manifestation and increasing reporting of isolation and loss of self-identity. The term ‘medical gaslighting’ has been widely associated with Long COVID patients (153), and is a form of psychological abuse that can be intentional or unintentional and used to make victims appear or feel ‘crazy’ (154). The term gaslighting should not be used lightly due to its critical and established use to describe both violent and non-violent abuse by an intimate partner (155). However, medical gaslighting is an established concept with consideration to power structures within medicine separated by age, gender, social class, and race (155). Medical gaslighting has been used by HCPs most commonly to dismiss, invalidate, and provide inadequate healthcare for women’s health concerns due to the century-old stereotype that women are irrational (155). As females are more likely to develop Long COVID (156), it should not be a surprise that medical gaslighting is commonly reported

by participants here when 86% of respondents are female (157). Other Long COVID cohorts report similar experiences where HCPs did not recognise the condition, believe it existed, refused to offer testing or referral to existing services and dismissed concerns as mental health struggles (102, 158-160).

Chronic and disabling conditions with poor diagnostic and prognostic procedures, have been known to challenge medical knowledge and approaches (161, 162), and can sometimes lead to confrontation and a disconnect between patients and HCPs (163). With complex multi-dimensional chronic diseases when HCPs are not able to explain fully explain or resolve patient issues, patients may feel as they are not being taken seriously or believed due to perceived scepticism (164-166). It must be acknowledged that HCPs find it difficult to support patients with these conditions (167), and when HCPs are unable to provide a resolution to symptoms, feelings of helplessness may challenge their professional identity, resulting in victim blaming to allow the HCP to escape feelings of shame (161). Furthermore, a lack of appropriate laboratory tests when investigating Long COVID contributes to HCPs scepticism that Long COVID symptoms have a physiological basis (159). However, with the threat Long COVID poses on individuals mental health and QoL, it is vital that those living with the debilitating condition receive the appropriate support. For context, whilst Long COVID shares overlap with other chronic conditions such as ME/CFS, there remains a dearth of understanding about the causal mechanisms that result in a broad and debilitating symptom profile that impacts health and well-being.

Existing research shows commonalities in the clinical features and pathophysiology of Long COVID and ME (89). Whilst the aetiology of Long COVID is considered multifaceted with research ongoing, the links to the inflammatory state and dysregulated immune response of both conditions are similar (168, 169). Data here demonstrates that participants report receiving treatment and care that was not helpful to their condition, with some even harmful causing PEM, such as advocating graded exercise and cognitive behavioural therapies. Importantly, research suggests that PEM must be carefully considered for Long COVID, with rehabilitation and interventions incorporating pacing and strategies to minimise PEM (170). Similarly, graded exercise therapy (GET) has been posed to cause harm in instances of ME (171-173), with the National Institute for Health and Care Excellence cautioning the use of GET for patients recovering from COVID-19 (174). The appropriate interventions and support mechanisms are required to restore functional capacity and QoL, and these should be created

considering the recommendations of the patients suffering. As Long COVID is a multifaceted, complex condition presenting with a range of physical, cognitive, and psychological symptoms, a multidisciplinary approach utilising pharmacological and rehabilitative approaches to restore functional status and QoL adopting physiatry is needed (175).

The burden of Long COVID drastically impacts the global burden of disease, health, and wellbeing, but it also significantly impacts healthcare services, which are already chronically underfunded and under-resourced (47, 48). Alarmingly, waiting lists for routine treatments and procedures is affecting around 6 million people which is prominent in the most deprived areas of the UK (55% in low social-economic areas, compared to 36% in the least deprived areas) (49). The COVID-19 pandemic has undoubtedly increased health inequality gaps and will continue to place significant strain on healthcare systems globally. Recent reports indicate that 125,000> HCPs are unable to work due to Long COVID (176) adding to existing issues with workforce capacity, and service delivery (54) at a time when the NHS is attempting to clear a backlog of over 6 million elective treatments (177). To support the delivery of Long COVID support, a collaborative approach is needed, to bring together medicine and clinical services alongside those parallel with disciplines such as exercise sciences, digital technologists, and engineering (175). The lived experience is invaluable in enriching the understanding of Long COVID and plays a key role within research (122, 127). Research and the future design and development of Long COVID services must engage patients as active stakeholders in co-creation approaches to ensure that the resultant approaches are enriched with the lived experience to ensure that patient needs are prioritised (118, 122).

This study highlights the impact on individuals suffering from varying symptom profiles during the early stages of the COVID-19 pandemic and raises alarm about the response to the pandemic within the UK, much of which was mirrored globally. Although this survey took place in the UK, the relevance of this data and the contextualisation in terms of pandemic preparedness and long-term impacts is likely relevant globally. Future pandemics are inevitable and expected to occur more frequently (178). Thus, health services must be able to prepare for well-timed action and mitigation strategies to prevent the catastrophes that have occurred following the outbreak of COVID-19, and to ensure medical intervention and care are available when needed, even in less critical cases. Furthermore, Coccolini and colleagues (179) state that resilient health systems must be built as part of pandemic preparedness, to promptly detect, assess, report, and respond to novel outbreaks. Pandemics cannot be

controlled by science alone, with management requiring an integrated approach coordinating science, public outreach, and policymakers to improve the control of public health emergencies (137).

The epistemic injustice of those living with Long COVID is evident, however further research is required to better understand the dynamics of the relationship with people with Long COVID and HCPs. HCPs are subject to a lack of knowledge and understanding of Long COVID. This may be partially responsible for the negative therapeutic relationship between people with Long COVID and HCPs (180).However the repeated reporting and evidence of gaslighting is damaging to patients and the prospective future treatments and interventions that could be beneficial to QoL. Therefore, increasing the understanding and improving relationships between HCPs and those living with Long COVID is vital to foster collaboration for Long COVID research, intervention development and implementation to restore HRQoL and functional status.

2.5 Limitations

Whilst the survey received national responses throughout the UK, 85.6% of respondents were female and 95.5% of respondents reported their ethnicity as being white. Additionally, by using an online survey circulated through social media, it is likely that older participants may not have had the opportunity to participate. Further research is required to understand demographic differences that are representative of society. The survey consisted of 65 questions, all designed by those living with Long COVID to ensure the lived experience would be heard. However, participants were required to recall experiences which may have been challenging due to Long COVID symptoms such as cognitive dysfunction and fatigue, potentially impacting the recall of information and data entry. The survey was developed and tested using patient representatives to ensure it was suitable for those living with Long COVID, and participants were able to save the survey and complete it at a later date. Finally, within this sample, 40.2% of participants did not have a positive COVID-19 test. However, our study is in line with the World Health Organisation definition of Long COVID which includes both probable and confirmed COVID-19 infection (34), and due to the issues regarding accuracy, accessibility and affordability of testing (124), those without a positive test have not been excluded.

2.6 Conclusion

The lived experience of Long COVID indicates that individuals are living with a severe reduction in physical and mental well-being which broadly impacts their QoL and ADL. In response to the challenges highlighted in this study, it is clear that existing support mechanisms are ineffective, sporadic, and disproportionate and there is a clear need for bespoke services that address the complex and multifaceted nature of the disease.

Chapter 3

Profiling the determinants of recovery to improve clinically relevant and patient-reported outcomes in the post-COVID-19 period: a prospective cohort study.

Peer-reviewed papers from this Chapter:

In Press in the Journal of Global Health - 2024

Conference Proceedings:

Owen, R., Ferraro, F., Ashton, R., Thomas, C. Phillips, B., Faghy, M. (2024). Time to re-define 'normal' for Post-Acute COVID-19 biomarkers in the assessment of patient outcomes? American Physiological Society Summit, Long Beach, California. April 2024. Poster Presentation.

Owen, R., Ferraro, F., Ashton, R., Phillips, B., Faghy, M. (2024). Understanding the episodic nature of symptom profiles and functional status in individuals with Long COVID. American College of Sports Medicine. May 2024. Boston, Massachusetts. May 2024. Rapid Fire Presentation

3.1 Introduction

In the context of post-viral complications following an acute infection with COVID-19, Long COVID is associated with persistent, episodic, and often disabling symptom profiles that broadly affect QoL and functional status (55). Consistency in clinical definitions and implementation of appropriate reporting methods, together with a dearth of pathophysiological and mechanistic understanding, make it difficult to accurately estimate those living with Long COVID. In response to the emerging narrative of persistent and debilitating symptoms in Long COVID, a series of studies were established to quantify patient outcomes and pathophysiologic function over time. Cohort observation study designs are commonplace in clinical research settings and are used to identify and evaluate causes, risks or changes in diseases or health-related events (181). Within their very nature, cohort observations can take a prospective or retrospective approach. Retrospective cohort designs have been widely implemented and make use of existing data sets that are recorded as part of and reporting in clinical settings to determine the long-term outcomes for patients in specific clinical areas. In the context of Long COVID, Taquet *et al,* (2021), conducted a retrospective cohort study via electronic health records data from >81 million patients including 273,618 COVID-19 survivors (41). The data revealed that 57% had at least one feature of Long COVID during the 6-month study period, defined as the acute phase and which were not resolved at 12 months in 37% of cases. The most reported symptoms included abnormal breathing (18%), fatigue/PEM (13%), chest/throat pain (13%;), headache (9%), other pain (12%), abdominal symptoms (16%), myalgia (3%), cognitive symptoms (7%), and anxiety/depression (23%). The use of electronic health records to perform detailed investigations do not generalize to patients who have had COVID-19 but were asymptomatic at the point of infection and/or not admitted to hospital or acute care settings. Whilst it is recognised that these approaches allow fast analysis of large data sets and allow conclusions to be derived quickly and from large data sets, these approaches are limited and cannot be used to establish definitive causality in chronic disease. Additionally, retrospective approaches are not designed to support closer inspection and determination of regular fluctuations in symptom profiles and the ongoing persistence of clinical features that affect everyday life.

The use of prospective cohort observations has also produced data that has been intentionally designed and used to increase knowledge of risk factors and patient outcomes over a period of time following an infection with COVID-19. Most notably in the UK, the Post-Hospitalisation

COVID-19 study (PHOSP) was established to increase the understanding of why some recover more quickly than others, why patients develop other health problems and to determine which treatments received in hospital or afterwards that were helpful, collectively seeking to improve the care of patients after they have been discharged from hospital. In a tiered approach, PHOSP recruited ~10,000 patients over a two-year period and have reported widespread sequelae across a range of health domains in hospitalised COVID-19 patients that remained substantial 12 months after discharge with only a minority reporting feeling fully recovered (182). Further exploration within this consortium have also reported widespread physical, cognitive, and mental health impacts (183), models of predicting reduced patient outcomes using bio-marker analysis (184) and extensive multiorgan abnormalities (185). The nature and design of prospective projects permit insight to be obtained over prolonged periods of time and from a clinical perspective, and data can be collected and analysed in relation to significant health and wellbeing outcomes in relation to prognosis and to test the efficacy of interventions. Evidence to date demonstrates significant impairment and a long disease course (<12 months) but there remains little insight into the episodic and debilitating nature of Long COVID which is prone to exacerbation and captures the lived experience as part of a prospective study that quantifies the impact upon health and wellbeing, patient reported outcomes, functional status, and QoL. Accordingly, this study aimed to describe, quantify and critically evaluate the clinical, physiological, biochemical, and psychological domains of the recovery following a COVID-19 infection.

3.2 Method

Following institutional and NHS ethical approval (IRS 292920), a 16-week prospective cohort observation study took place at the University of Derby using a mixed-method approach. Data collection started on 26th June 2020 and finished on 15th May 2023.

3.2.1 Recruitment, screening, and eligibility

Long COVID patients were assessed according to the eligibility criteria and were recruited following referral or contact with a Long COVID clinic or having suspected or confirmed Long COVID. Social media (twitter, Long COVID community Facebook groups and LinkedIn) and targeted recruitment from established Long COVID groups were used to

advertise the opportunity to engage with the trial for those within travelling distance to Derby University.

Inclusion criteria consisted of participants scoring 2> on the Post-COVID-19 Functional Status Scale (186), (PCFS) being admitted to hospital for treatment for COVID-19 or persistent symptoms consistent with a Long COVID diagnosis, being >18 years and being able to understand verbal or written information in English. Exclusion criteria consisted of individuals <18 years, with no confirmed or suspected diagnosis of COVID-19, who did not achieve >2 on the PCFS, were not admitted to hospital for COVID-1 or referred to a Long COVID clinic, and/or had reduced or lack of mental capacity.

3.2.2 Experimental Protocol:

The determinants of recovery were profiled using a mixed method approach. Participants attended a total of 5 face to face visits each occurring ~4 weeks, interspersed by bi-weekly telephone calls, shown in table 3.1. Data collection took place in the physiology lab at Derby University, Kedleston Road (DE22 1GB) by at least 1 of 3 research assistants who had been extensively trained in the protocol, using the same technique for each measure. This was ensured by each research assistant attending training days on the protocol, signed off by the Principal Investigator, Professor Mark Faghy. On each face-to-face visit, physiological variables, patient reported outcome measures (PROMs), functional status tests (6-Minute Walk Test [6MWT], Timed Up and Go [TUG]), and respiratory function tests were complete. During telephone consultations, PROMs and symptom profiling were completed, and details of contact with healthcare services were taken.

Table 3.1: The 16 week cohort observation protocol to profile the determinants of recovery.

	Study Enrolment:
Week 0	**Visit 1 (Baseline):** Background & medical history (occupation, pre Covid-19 health, route into study, smoking history), Blood sampling, Anthropometry, Symptom reporting, Physiological measures (respiratory & cardiovascular), Mobility, and PROMs. **Approximately 120 mins.**
Week 2	**Telephone consultation 1:** Healthcare contact, Symptom reporting, and PROMs (exc. MOCA). **Approximately 20-30 mins.**
Week 4	**Visit 2:** Symptom reporting, Physiological measures (respiratory & cardiovascular), Mobility, and PROMs. **Approximately 90 mins.**
Week 6	**Telephone consultation 2:** Healthcare contact, Symptom reporting, and PROMs (exc. MOCA). **Approximately 20-30 mins.**
Week 8	**Visit 3:** Symptom reporting, Physiological measures (respiratory & cardiovascular), Mobility, and PROMs. **Approximately 90 mins.**
Week 10	**Telephone consultation 3:** Healthcare contact, Symptom reporting, and PROMs (exc. MOCA). **Approximately 20-30 mins.**
Week 12	**Visit 4:** Symptom reporting, Physiological measures (respiratory & cardiovascular), Mobility, and PROMs. **Approximately 90 mins.**
Week 14	**Telephone consultation 4:** Healthcare contact, Symptom reporting, and PROMs (exc. MOCA). **Approximately 20-30 mins.**
	Study Completion
Week 16	**Visit 5:** Symptom reporting, Physiological measures (respiratory & cardiovascular), Mobility, and Questionnaires. **Approximately 90 mins.**

Initial screening was complete via telephone prior to the baseline visit and patients were sent the Participant Information Sheet for the study. Once screening had taken place and consent was provided, anthropometric data was assessed, including height and weight, and date of birth, sex, past medical history, smoking history, and occupational status. For those who had been admitted to hospital due to either acute or Long COVID related symptoms, data regarding admission and contact with primary and secondary care was taken. Five levels of performance status were defined as Asymptomatic (0), Symptomatic but completely ambulatory (1), Symptomatic, <50% in bed during the day (2), Symptomatic, >50% in bed, but not bedbound (3), Bedbound (4). For those admitted to hospital, performance status was taken at time of admission and baseline (1 month prior to admission), as well as date and time of discharge, length of stay and mechanical or non-invasive ventilation details. For those referred from a Long COVID clinic, performance status at baseline (1 month prior to infection), at the point of infection, at the point of referral to a Long COVID clinic and present day were taken, as well as date and route of referral, date of COVID-19 infection and details of acute infection including severity and duration of symptoms, contact with primary/secondary care and impact since infection were taken. A blood sample was taken from the antecubital fossa region of the arm using a butterfly needle and BD vacutainer system (BD Vacutainer, Becton, Dickinson and Company, Franklin Lakes USA) measuring inflammatory and metabolic markers (Full blood count [FBC], Ferritin, D-Dimer, C-reactive protein [CRP], Lactate dehydrogenase [LDH], Neutrophil leukocyte ratio [NLR], Polymorph lymphocyte ratio [PLR]).

3.2.4 Patient reported outcome measures (PROMs)

Patient reported outcome measures (post-COVID-19 functional status scale (PCFS), EQ-5D-5L, Medical Research Council Dyspnoea Scale (MRC Dyspnoea Scale), Fatigue Assessment Scale (FAS), Modified Fatigue Impact Scale (MFIS), symptom score and profiling) were completed during phone calls, and face to face visits.

3.2.4.1 PCFS

The PCFS was developed to assess recovery following COVID-19 infection covering the entire range of functional limitations, such as changes in lifestyle and social activities (available in appendix 3d) (186). The PCFS determines how much an individual is affected in their everyday life by COVID-19, from having no limitations (0), to suffering from severe limitations in everyday life, without being able to care of themselves and being dependent on

nursing care and/or assistance from another person due to symptoms, pain, depression, and anxiety (5).

3.2.4.2 EQ-5D-5L

The EQ-5D-5L is a commonly used assessment for QoL within health research comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (available in appendix 3e) (187). Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The UK value set and scoring algorithm was used and potential values ranged from -0.281 to 1, where values <0 represents a health status considered worse than death (188). A visual analogue scale is used to record the patient's self-rated health on a vertical scale, with endpoints 'the best health you can imagine' and 'the worst health you can imagine'.

3.2.4.3 MRC Dyspnoea Scale

The MRC Dyspnoea Scale is a simple and valid method used to assess the degree to which dyspnoea affects functional ability (189). The scale measures perceived respiratory disability, allowing patients to indicate the extent of breathlessness on their mobility (available in appendix 3f).

3.2.4.4 FAS

The FAS is a 10-item self-report scale evaluating symptoms of fatigue (available in appendix 3g) . The FAS treats fatigue as a unidimensional construct, measuring both physical and mental symptoms (190). The total score ranges from 10-50, with a higher score accounting for more severe fatigue. A total score of <22 indicates a healthy level of fatigue, 22-34 indicates mild-to-moderate fatigue, and 35+ indicates severe fatigue.

3.2.4.5 MFIS

The MFIS is a 20-item self-reported questionnaire assessing fatigue, consisting of 9 'physical', 10 'cognitive' and 2 'psychosocial' items (available in appendix 3h) (191). Higher scores indicate a greater impact of fatigue on QoL and are calculated for each subscale (physical; 0-36, cognitive; 0-40, psychosocial; 0-8) with a maximum total score of 84 (191).

3.2.4.6 Symptom profile

The symptom score measure was completed, detailing the severity of symptoms for the previous 24 hours. Patients reported symptoms and the extent of these on a scale of 0-5.

3.2.5 Functional Status and Physiological Tests:

Functional tests (6-minute walk test, timed up and go, Montreal cognitive assessment) and physiological measures (heart rate, pulse oximetry, temperature, blood pressure, lung function test, and mouth pressure meter) were completed on each face-to-face visit.

3.2.5.1 6-minute Walk Test (6MWT)

The 6MWT is a standardised and widely used measure of functional status within clinical populations as well as assessing responses to interventions and predicting morbidity and mortality (192-194). The 6MWT was conducted in accordance with published guidelines from the 2002 American Thoracic Society (195) utilising a 15m corridor marked with 3m intervals. The participant was instructed to walk up and down the corridor, covering the greatest distance they could over a 6-minute period with no encouragement provided.

3.2.5.2 Timed Up and Go (TUG)

The TUG is a reliable measure accepted for use across multiple clinical populations and is validated as a predictor of frailty and risk of falls in elderly adults (196). Participants were instructed to stand from a seated chair with armrests, walk toward to and from a three-meter marker where they were required to tap the practitioner's hand and sit back down (197). No encouragement was provided, and a total of three attempts were timed using a stopwatch, with the quickest recorded as the best effort.

3.2.5.3 Montreal Cognitive Assessment (MoCA)

The MoCA is a widely used assessment in clinical settings and research. It is a validated, highly sensitive measure used for early detection of mild cognitive impairment, assessing short term memory, visuospatial abilities, executive functions, attention concentration and working memory, language and orientation of time and place (198). Two distinct versions of the MoCA

were used as recommended by developers to reduce the impact of learning effect (available in appendix 3j and 3k).

3.2.5.4 Physiological Measures:

All physiological variables were measured on each face-to-face visit. Vital signs such as blood oxygen saturation (Nonin Medical Pulse Oximeter [Model 2500, Nonin Medical, INC., Plymouth, MN, USA]), resting heart rate and blood pressure (automatic blood pressure monitor [Omron M2, Omron Healthcare Co Ltd., Kyoto Japan]) and core body temperature (tympanic reading [Braun thermoscan model 6022, Germany]) were measured at the start of each visit.

3.2.5.5 Lung and Respiratory Muscle function:

Measurements of Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP) were conducted during face-to-face visits. These assessments were performed with the patient seated, in accordance with published guidelines and with verbal encouragement provided throughout (199). MIP was assessed using a hand-held respiratory pressure meter (RP Check, MD Diagnostics Ltd., Maidstone, UK) with an occluded nasal pathway. Manoeuvres were initiated from residual volume and a maximal inspiratory effort was maintained for 3 seconds. Similarly, MEP was assessed using the same hand-held device, however participants initiated the manoeuvre from total lung capacity followed by a maximal expiration maintained for 3 seconds. The best of three consecutive values within 10% was taken as the values for MIP and MEP. However, if this condition was not met, the average of the three highest values from 10 efforts was taken as the values (199).

A hand-held, electronic spirometer (Spiro Connect, MedChip Solutions Ltd., Kent, UK) was used to measure Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV_1), FEV_1/FVC ratio, and Peak Expiratory Flow (PEF) with an occluded nasal pathway while seated. Manoeuvres were taken in accordance with appropriate guidelines (200) and were initiated from total lung capacity. A maximal expiratory effort was maintained for 5 seconds; a minimum of three attempts were performed with an acceptability criterion being when there was a $\leq$0.15 L differences between the largest and next largest FVC and FEV_1 measurements, within a maximum of 5 attempts (201). Breathing rate was assessed while

seated at rest by observing participants chest rise and fall over a 10-second period, which was then extrapolated to provide a one-minute breathing rate.

3.2.6 Data analysis

Raw data from the case report form (CRF) was transferred to and organised in Microsoft Excel. Data was then imported into to Python (Version 3.11.5) through the Pandas package (Version 2.0.3), where time-plot and heat map figures were created using both seaborn (version 0.12.2) and matplotlib (Version 3.7.2). Data was also imported into SPSS (Version, 29.0.1.1), which was used for the analysis of descriptive statistics (mean ± standard deviation, median, interquartile range), box plots, normal distribution, Mauchly's sphericity test, repeated measures analysis of variance (RMANOVA) and post-hoc analysis. A RMANOVA was conducted to analyse outcome measures over a series of time points (0-16 weeks)(202). Where normality was violated but the assumption of sphericity was met, RMANOVA was still used due to the robustness of the test in relation to Type 1 error and power (203). In line with the literature, where 5-10% of data were missing (204) multiple imputation was used. The multiple imputation model in SPSS was used to replicate the incomplete dataset 5 times and replace the missing data in each replicate with plausible values. Single multiple imputation was calculated by combing the estimates obtained from each completed dataset and pooling the data according to Rubin's Rules (205, 206). Multiple imputation was used for missing data for those who did not reach the end of the study but had completed >2 face to face visits [n=65] (204, 207). For those who were unable to complete the 6MWT test during a visit due to worsening symptoms and reduced functional capacity (week 4; n=3, week 8; n=6, week 12; n=4, and week 16; n=3), data was recorded as 0m covered and used for analysis. For missing data that was due to worsening symptomology resulting in a participant being unable to perform a measure (LFT, MIP/MEP, TUG), multiple imputation was not used. Where less than 5% of data were missing, multiple imputation was not used (204, 205). Frequencies, normative data and expected values were used for comparison to this cohort.

3.3 Results

3.3.1 Participant Characteristics

Sixty-five participants (75% females) aged 51 ± 11 years completed >6 weeks of the study and were therefore used for data analysis. The median date of infection was December 2020,

and the mean time from infection to date of participation was 467 ± 254 days [1 year and 3 months] (median: 446 days, minimum time from infection to participation 62 days [2 months], maximum 936 days [30 months/ 2.5 years]). At the time of their baseline visit, 64/65 were vaccinated (1 dose: n=5 [7.6%], 2 doses: n=17 [25.8%], 3: n=36 [54.5%], 4: n=6 [9.1%]. Within the study, 58.5% (N=59) received their vaccination after their initial COVID-19 infection that had caused Long COVID, 27.7% (n=18) had their vaccination before the infection, and 1.5% (n=1) got infected the day they received the vaccine. In total, N=45 (68.2%) of participants were non-smokers, and n=19 (28.8%) had smoked previously but did not at the time of participation.

Table 3.2: Participant characteristics for individuals who completed more than 6 weeks of the 16-week cohort observation study and used for analysis.

Demographics (%)	**Time since infection**	**Vaccination Status (%)**	**Underlying health conditions (n)**
Females: 75	Mean: 1 year 3 months	Vaccinated: 99	Endocrine: 8
Age: 51 ± 11 years	Median: 425 days	1 dose: 8	Renal: 6
Non-smoker: 68.2	Min: 14 days	2 doses: 26	Cardiovascular: 20
Previous smoker: 28.8	Max: 1158 days	3 doses: 55	Gastrointestinal: 34
		4 doses: 9	Neurological/Cerebrovascular: 20
		Pre-LC: 53	Malignancy: 8
		Post-LC: 35	Other: 54
			None: 4
			1 comorbidity: 12
			2+ comorbidity: 49

3.3.2 Key findings

3.3.2.1 Long COVID Symptoms

Cumulative symptoms score relative to severity was 29 ± 14 arbitrary unit (AU) at baseline [max 90 AU], and post-hoc analysis determined statistically significant differences between week 6 (31 ± 14 AU) and week 16 (26 ± 14 AU, $p=.007$), and week 14 (32 ± 16 AU) and week 16 ($p=<.001$) shown in Figure 3.1. Fatigue, concentration problems, and memory loss were the most reported symptoms across the 16 weeks. The most reported symptoms are displayed in Figure 3.2.

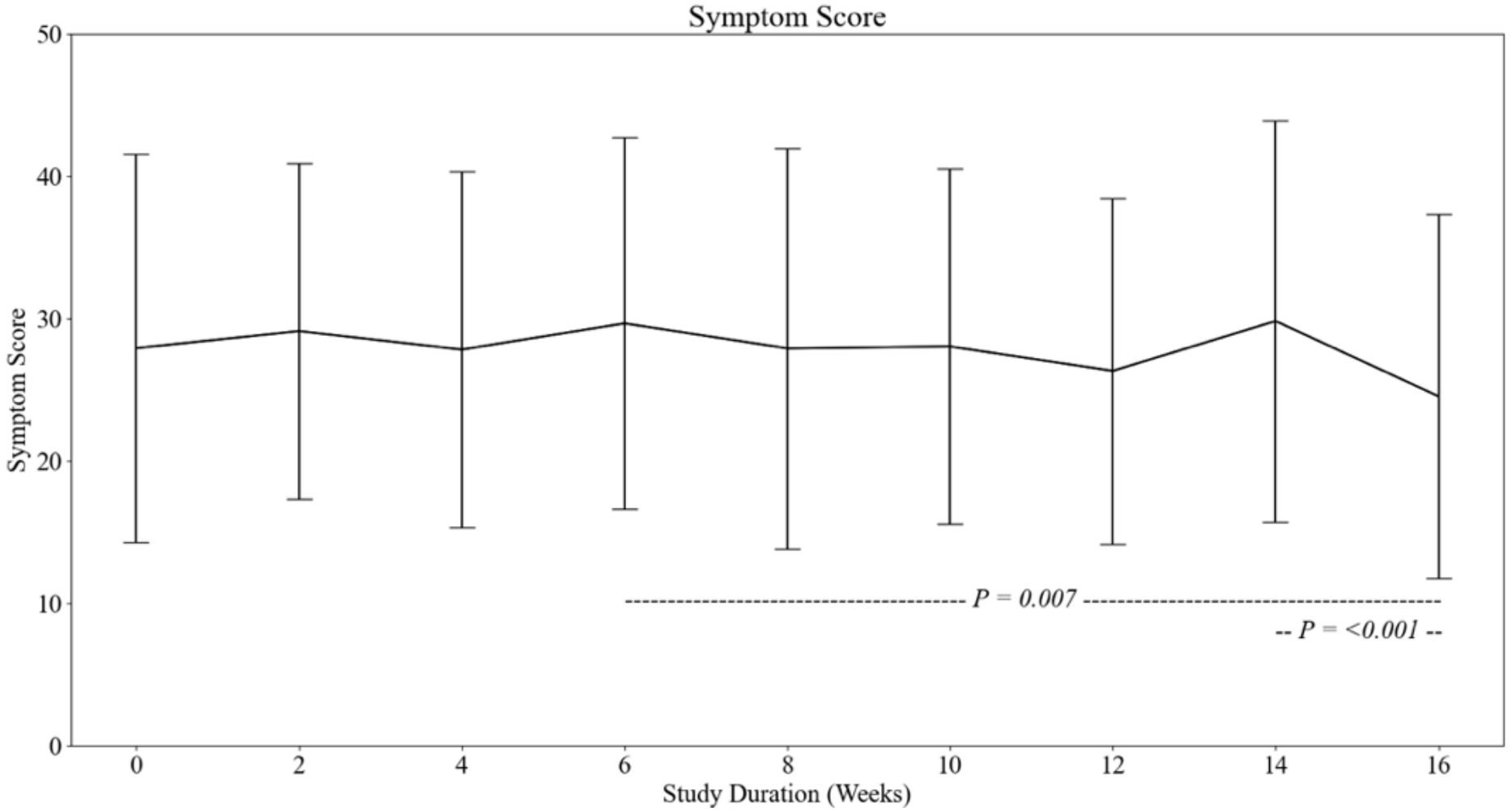

Figure 3.1: The mean symptom score over 16 weeks with standard deviation bars. Dashed lines showing where significant differences lie (P<0.05). Possible maximum of 90 AU (higher score reflects worse symptomology).

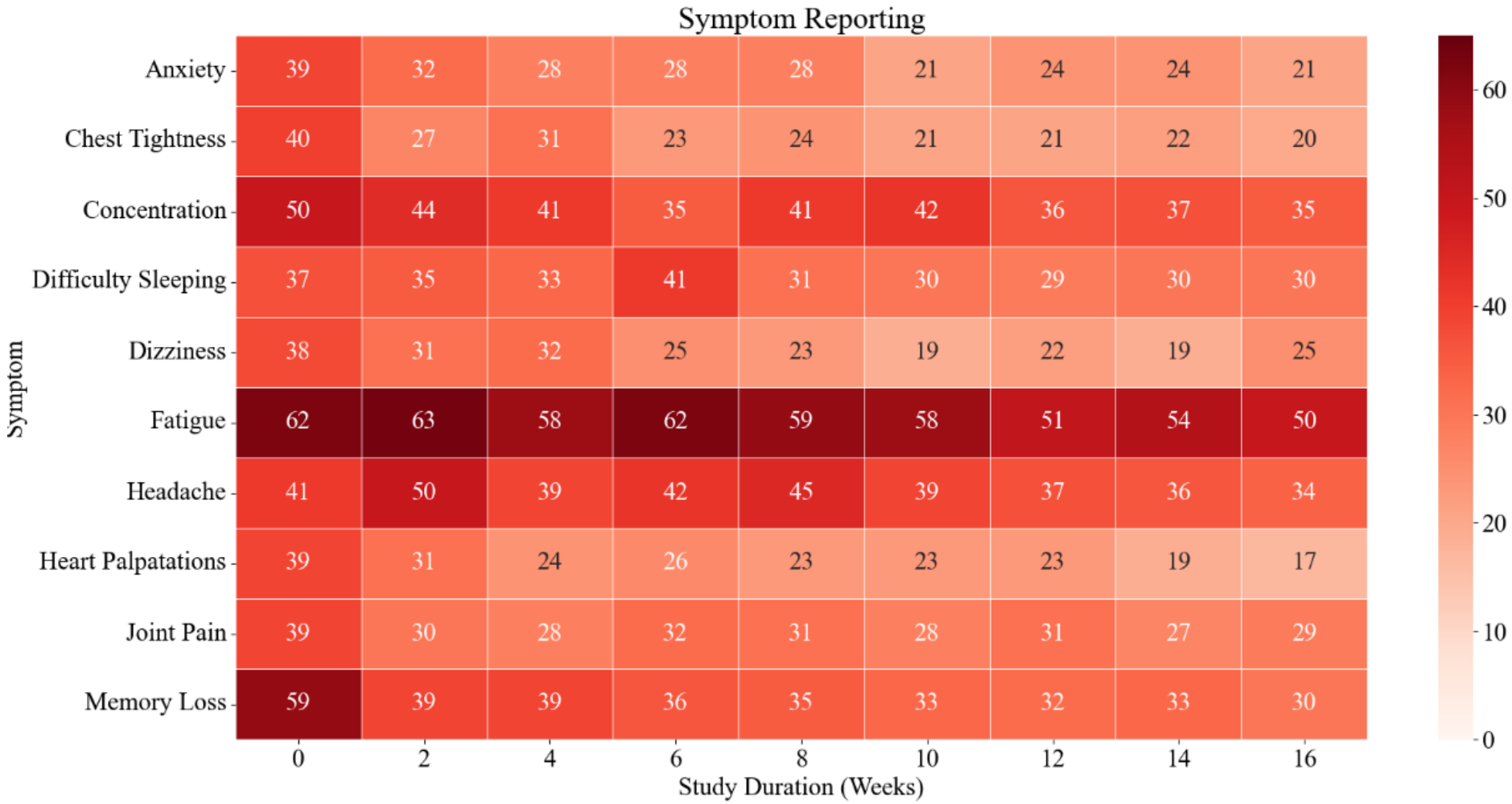

Figure 3.2: Symptom prevalence heat map showing the number of participants experiencing each symptom across 16 weeks (n=65).

3.3.2.2 Patient Reported Outcomes

PCFS at baseline was 2.8 ± 0.5 AU and was improved relative to week 16 (2.4 ± 0.9 AU, *p*=.028, Figure 3.3). Post hoc analysis determined between trial differences from week 8 (2.6 ± 1.0 AU, *p=.031*) and week 16. Dyspnoea was 3 ± 1 AU (Arbitrary Unit) at baseline and was unchanged at any timepoint. Cognitive function was 26 ± 3 AU at baseline and improved for week 4 (27 ± 2 AU, *p=.038*), week 8 (28 ± 2 AU, *p>.001*), week 12 (28 ± 2 AU, *p=<.001*) and week 16 (28± 2 AU, *p=<.001*). Post-hoc analysis demonstrated improvements between week 4 and week 12 (*p=.040*) and finally between week 4 and week 16 (*p*=.010). FAS indicates severe fatigue at baseline (35 ± 7 AU), which was unchanged at all follow-up time points (See Figure 3.3) except for between weeks 14 (34 ± 9 AU) and week 16, where a nominal improvement was observed (32 ± 9 AU, *p=.021*) classified as moderate-severe fatigue. Fatigue was further assessed with the MFIS, the cumulative score at baseline was 61 ± 13 AU which was improved at week 4 (56 ± 15 AU, *p*=.002) and was improved again at weeks 8 (54 ± 17 AU, *p=.004*), week 10 (56 ± 15 AU, *p=.002),* week 12 (53 ± 18 AU, *p=.004),* week 14 (54 ± 18 AU, *p=.017)* and week 16 (52± 19 AU, *p=<.001)*. When analysed for each subsection of the MFIS, physical fatigue (Figure 3.4) was 28 ± 5 AU at baseline and was improved at week 4 (26 ± 6 AU, *p=.034*) and again at week 16 (25 ± 8 AU, *p=.009*). Cognitive fatigue was 27 ± 8 AU at baseline and was improved at weeks 8 (24 ± 9 AU, *p=.005*), 14 (24 ± 10 AU, *p=.049*), and week 16 (23 ± 10 AU, *p=.002*) and was unchanged at all other time points. Psychosocial fatigue (Figure 3.4) was 6 ± 2 AU at baseline and was improved at week 4 (5 ± 2 AU, *p=.009*) but worsened between week 8 (5 ± 2 AU) and 10 (6 ± 2 AU, *p=.044*) and was improved between week 10 and 16 (5 ± 2 AU, *p=.005*).

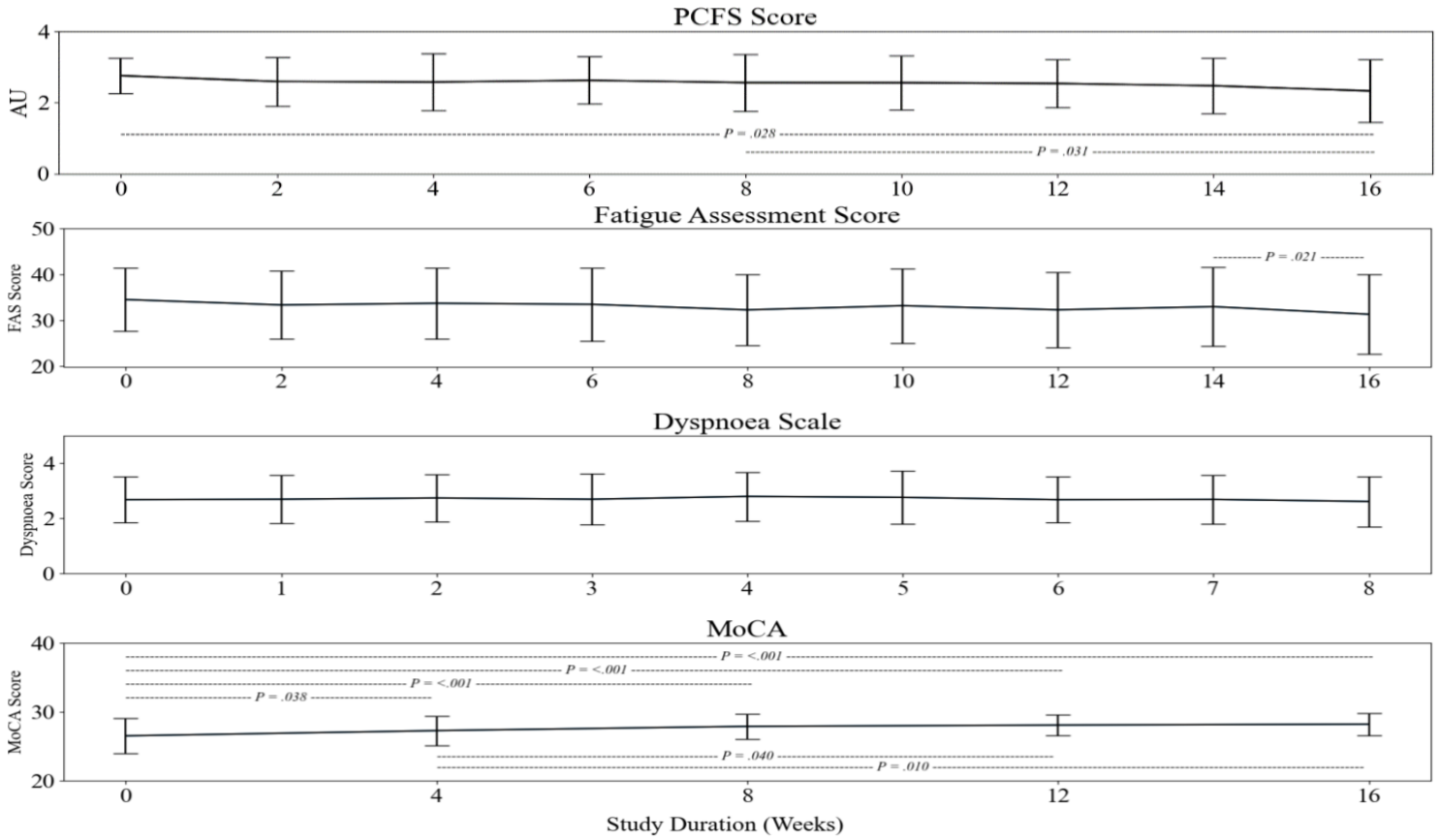

Figure 3.3: Panel plot showing the mean PCFS, FAS, Dyspnoea, MoCA over 16 weeks with standard deviation bars. Possible maximum scores: PCFS: 4, FAS: 63, Dyspnoea Scale: 4 (higher value reflects a worse symptomology), MoCA: 30 (higher value reflects higher cognitive function). Dashed lines showing where significant differences lie (P<0.05).

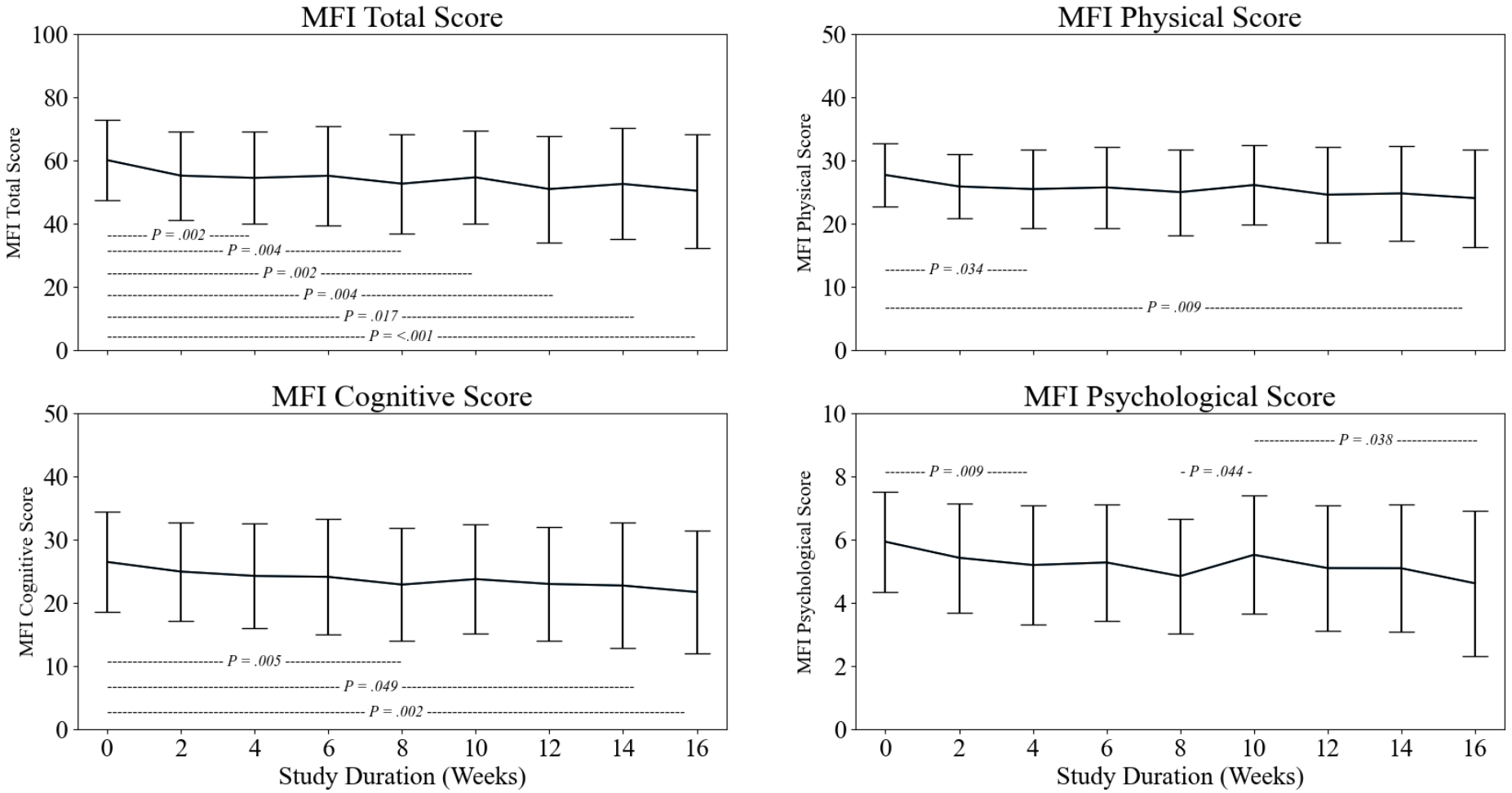

Figure 3.4: Panel plot showing the mean MFIS total, physical, cognitive, psychosocial across 16 weeks with standard deviation bars. Possible maximum scores: MFIS total: 84, physical: 36, cognitive: 40, psychosocial: 8 (higher value reflects increased fatigue). Dashed lines showing where significant differences lie (P<0.05).

3.3.2.3 Quality of Life (QoL)

Across the 16 weeks, the mean utility index score for the EQ-5D-5L ranged from 0.01-1 but did not significantly change between time points (p=.242), as shown in Figure 3.5. EQ visual analogue scale improved between week 6 (50 + 20 AU) and week 16 (57 ± 20 AU p=.009), week 10 (50 ± 21 AU) and week 16 (p=.003), and week 14 (50 ± 21 AU) to week 16 (p=.003).

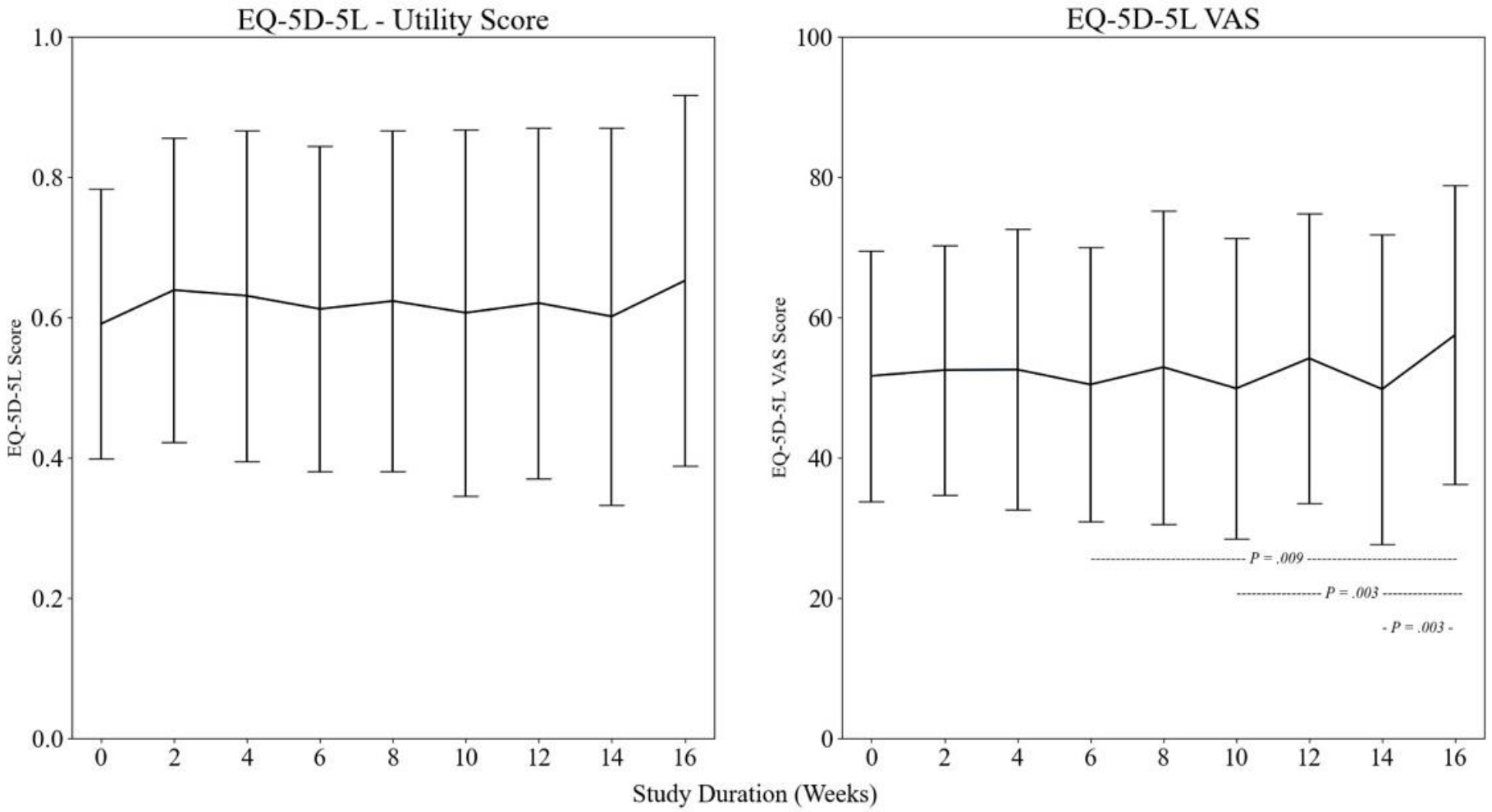

Figure 3.5: Panel plot showing mean EQ5D5L utility score and visual analogue scale (VAS) score across 16 weeks with standard deviation bars. Possible maximum scores: utility score: 1 and VAS: 100 (closer to maximum reflects higher quality of life. Dashed lines showing where significant differences lie (P<0.05).

3.3.2.4 Functional Status

6MWD at baseline was 375 ± 13m and was subsequently improved between baseline and weeks 12 (413 ± 12 *p*=.002, Figure 3.6), and week 16 (426 ± 13 *p*=<.001). Post-hoc analysis also demonstrated further improvements between week 4 (392 ± 13 m) and week 12 (*p*=<.001), week 4 and week 16 (*p*=<*.001)*; and finally, week 8 and week 16 (*p*=.008). TUG was improved between baseline (6.7 ± 2.7 s) and week 4 (6.3 ± 2.6, *p=.007)* and baseline to week 8 (6.1 ± 2.7, *p=.022*) between baseline and week 12 (5.9 ± 2.8, *p*=<*.001*) and between baseline and week 16 (5.8 ± 2.4, *p*=<*.001*). There were no other between timepoint changes (Figure 3.6). Table 3.3 shows the number of participants who were unable to complete the functional measure due to worsening symptoms. For those who were unable to complete the 6MWT, there distance was recorded as 0m, and those who were unable to complete the TUG were excluded from analysis.

Table 3.3: The number of participants who were unable to complete the functional tests over the 16 weeks due to worsening symptoms

	Week 0	**Week 4**	**Week 8**	**Week 12**	**Week 16**
6MWT		N=3	N=4	N=4	N=3
TUG			N=3	N=2	N=1

Participants unable to complete the functional measure.

***6MWT was recorded as 0m travelled and TUG was removed from analysis.**

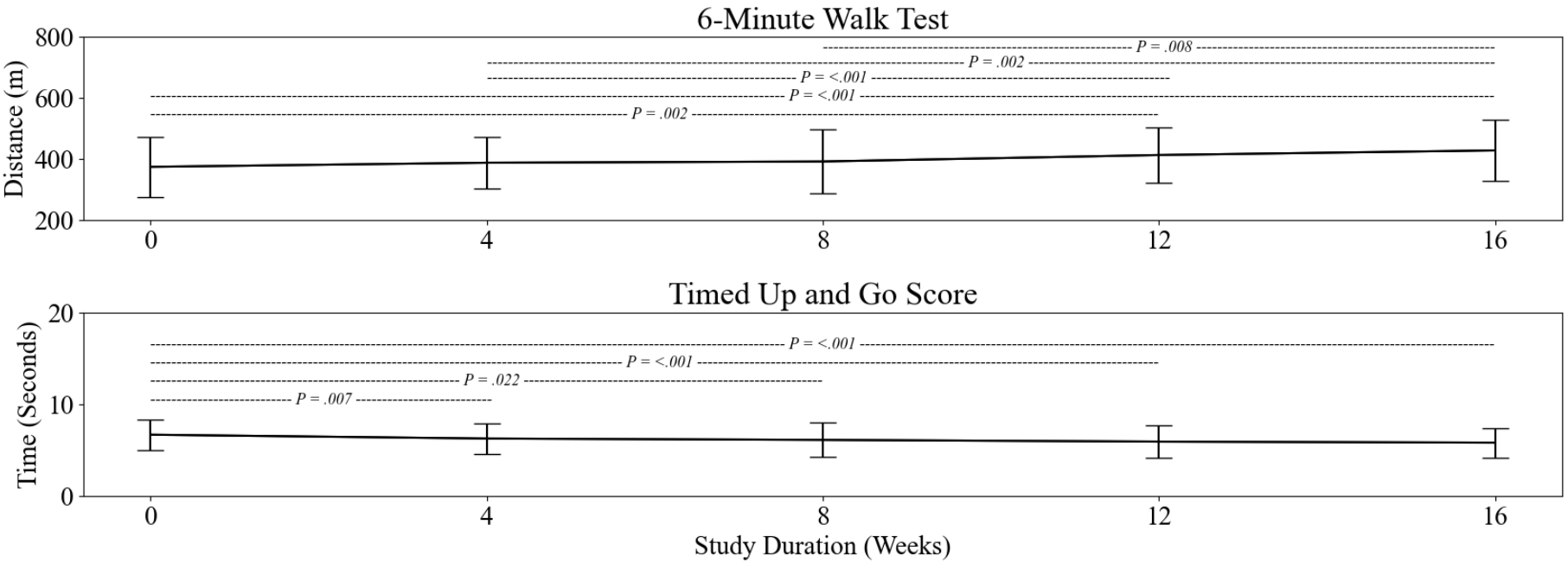

Figure 3.6: Panel plot showing mean 6-Minute-Walk-Test & Timed-Up-and-Go time across 16 weeks with standard deviation bars. Dashed lines showing where significant differences lie (P<0.05).

3.3.2.5 Physiology

MIP at baseline was 72 ± 3 cmH2O and was improved between baseline and week 16 (83 ± 3 cmH_2O, p=.001), week 4 (74 ± 4 cmH_2O) and week 16 (p=.032) and between week 8 (72 ± 4 cmH_2O) and week 16 (p=.021, Figure 3.7). MEP at baseline was 108 ± 5, cmH_2O and was improved between baseline and week 16 (120 ± 6 cmH_2O, p=.012, Figure 3.7). There was no change between any other time points for MIP or MEP**.** Global effect was significant for FEV1 (p=.006), FEV1/FVC (p=.024), FVC (p<.001, Figure 3.7), however post-hoc analysis showed no significance within pairwise comparisons. There was no significant difference for PEF. Table 3.4 shows the number of participants who were unable to complete the respective manoeuvre due to worsening symptoms, and were therefore excluded from analysis.

Table 3.4: The number of participants who did not complete each respiratory measurement due to worsening symptoms over the 16 weeks.

	Week 0	**Week 4**	**Week 8**	**Week 12**	**Week 16**
MIP	N=1	N=6	N=7	N=5	N=2
MEP	N=1	N=2	N=4	N=6	N=3
LFT		N=1	N=4	N=3	N=3
Participants unable to complete the manoeuvre and excluded from analysis.					

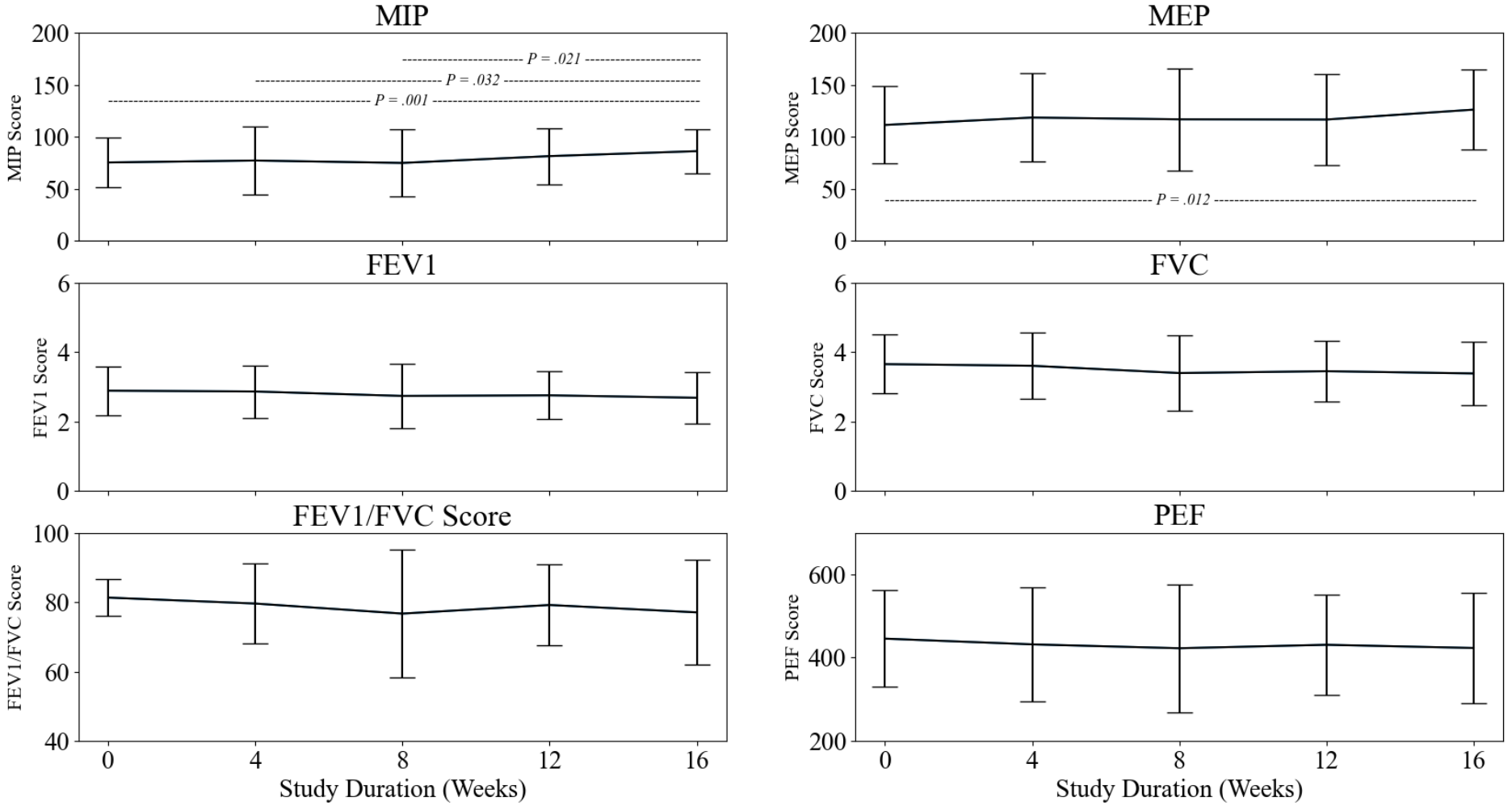

Figure 3.7: Panel plot showing mean lung function (FEV1 [l], FVC [l], FEV1/FVC [%], PEF l/min) and mouth pressure meter [cmH_2O] across 16 weeks with standard deviation bars. Dashed lines showing where significant differences lie ($P<0.05$).

Table 3.5: Blood panel from 34 participants on their baseline visit showing mean ± standard deviation, minimum and maximum value for each marker.

N=34	Mean ± SD	Min	Max
WBC (x10^9/L) Expected: 4.3-11(208)	7.03 ± 1.83	**4.10***	**11.70***
RBC (x10^12/L) Expected: 4.2-6.9 (208)	4.71 ± 0.51	3.88	5.77
Haemoglobin (g-L) Expected: Males: 130-180 Females: 120-160(208)	138.24 ± 12.53	114.00	169.00
Haematocrit (%) Expected: Males 40-50, females 36-48(209)	42 ± 3	35	50
MCV (fL) Expected: 80-100(208)	88.89 ± 6.60	**65.10***	**102.40***
MCH (pG) Expected: 27-32(208)	29.32 ± 2.59	**19.80***	**33.70***
MCHC (g-L) Expected: 320-360(208)	331.88 ± 10.49	**304.00***	352.00
RDW (%) Expected: 11.5-14.5%(210)	13.01 ± 1.30	11.70	**17.80***

Platelets (x10^9/L) Expected: 150-400. (208)	290.29 ± 56.35	200.00	**428.00***
Neutrophils (x10^9/L) Expected: 1.8-7.8(208) **%**	4.36 ± 1.47 61.13 ± 7.44	2.35 45.30	**8.38*** 76.80
Lymphocytes (x10^9/L) Expected: 0.7-4.5(208) **%**	1.97 ± 0.62 28.57 ± 6.84	1.15 15.20	4.42 42.40
Eosinophils (x10^9/L) Expected: 0-0.4(208) **%**	0.11 ± 0.06 1.16 ± 0.88	0.02 0.1	0.23 4.2
Monocytes (x10^9/L) Expected: 0.1-1.0(208) **%**	0.56 ± 0.15 8.23 ± 1.97	0.33 5	**1.09*** 13.3
Basophils (x10^9/L) Expected: 0-0.2(208) **%**	0.03 ± 0.01 0.40 ± 0.24	0.01 0.10	0.07 1.30
Ferritin (ug-L) Expected: Males 30-300, females 10-200 (211)	111.32 ± 105.89	**0.98***	**430.00***
D-Dimers (ug-mL) Expected: 0.0-0.5(212)	0.37 ± 0.32	0.00	1.85*

CRP (mg L) Expected: <0.3(213)	2.62 ± 3.95	<0.01	19.0
LDH (IU-L) Expected: 140-280(214)	177.95 ± 20.90	**121.00***	207.00

Means, minimum and maximum values are presented with expected/standardised values. *

Data with a maximum or minimum value outside of expected values.

WBC (White Blood Cells), RBC (Red Blood Cells), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Haemoglobin), (MCHC (Mean Corpuscular Haemoglobin Concentration), RDW (Red Cell Distribution Width), CRP (C-reactive protein), LDH (Lactate Dehydrogenase)

3.4 Discussion

The key findings of this prospective cohort observation meet the study's aims by describing, quantifying and evaluating the clinical, physiological, biochemical, and psychological domains of the recovery following a COVID-19 infection. These findings highlight the severity and frequency of Long COVID symptom profiles that impair QoL and functional status by assessing clinically relevant PROMs. Furthermore, the data demonstrates little/no improvement over sixteen weeks and the regular contact with patients also highlights the episodic and relapsing nature of Long COVID as a condition. Data presented here should be used to help characterise Long COVID disability and to inform the development of Long COVID-specific guidelines and support services that can adequately respond to the observed reductions in all areas of patient wellbeing. From the authors knowledge, this is the first study to objectively collect biological, physiological, psychological, and cognitive parameters with regular frequency (bi-weekly) and intensity over sixteen weeks. It is evident from the data across the patient profile that performance in all areas of the study was well below expected clinically relevant ranges when compared to existing clinical and normative data sets. Here, we provide a multi-dimensional insight into the characteristics/presentation of Long COVID that contains frequency and intensity in the data, where previous data has been separated by prolonged periods where multiple remissions and changes in patient presentation are reported but not captured. There is also evidence within the data to specifically highlight the episodic nature of Long COVID, which has been postulated and hypothesised in numerous patients' testimonies and accounts (55) but until now has not been demonstrated empirically via cross-sectional methodologies in Long COVID patients. The undulating/relapsing nature of fatigue, dyspnoea, and symptom profiles includes frequent and intense changes in symptom profiles. There is a high level of heterogeneity regarding symptom profiles and reporting of PROMs across the study, thus providing further evidence and a need for a distinct characterisation of Long COVID patients and their symptoms.

Importantly, the data here also demonstrates little/no progress towards pre-COVID-19 levels, although it is important again to highlight within-sample differences/heterogeneity across the measures/data. Throughout research on Long COVID, reports demonstrate that some, but not all patients improve over time, and it is not clear why some improve and others do not (215). Still, there remains a level of uncertainty about whether those who are adversely affected by Long COVID expect a full recovery and return to pre-Long COVID status. This is important

when considering the severity of reported disability and organ damage/insults that occur following infection with previous SARS-COV infections (216) and SARs-COV-2 . In the context of Long COVID, a longitudinal cohort study conducted over 2 years found that only 7.6% (n=26) of participants fully recovered, most of which presented with less severe symptoms (217). The authors did not explicitly state the age and gender of these patients who recovered, but stated that recovery was more likely in male subjects. Additionally, a multicentre, prospective cohort approach found that of 1170 patients hospitalised with COVID-19, only 29% (n=239) of individuals felt fully recovered and 20% (n=158) had a new disability 6 months later (183). Again, the authors did not state participant demographics of those who had recovered, but factors associated with not recovering were female sex of middle age, with 2+ comorbidities and more severe acute illness. Furthermore, it is reported that 59.8% of respondents (n=79) experienced one or more Long COVID symptoms in 6 months following the onset of acute COVID-19, decreasing to 53% at 12 months and increasing to 71.2% at 24 months (218). At twenty-four months the most frequent symptoms were fatigue (34.8%), amnesia (30.3%) and concentration difficulties (24.2%), which is similar to our findings where fatigue, concentration problems and memory loss were most prevalent across the 16 weeks. These studies highlight the importance of recognising the long-standing nature of Long COVID, as the knowledge gap of how patients present with high levels of variation demonstrates the need to understand various time points. A nationwide retrospective cohort study conducted by Mizrahi et al., (2023) concluded that mild COVID-19 cases lead to a small number of health issues which are resolved within a year of diagnosis (111). Their findings demonstrate that ‘mild’ cases do not lead to serious or chronic illness for the majority of patients and therefore add only a minor continuous burden to the healthcare system (111). They matched patients infected with COVID-19 to uninfected people, and used hazard ratios to compare risks during the early period of infection, and 180-360 days post-infection. A Long COVID cohort was not solely used, therefore the suggestion that individuals will not still be suffering at 12 months is not generalisable to Long COVID patients. Long COVID has been labelled the biggest mass-disabling event in history (219) and this study fails to acknowledge the struggles of those disabled by their Long COVID symptoms. The study discussed the frequently reported symptoms associated with Long COVID-19, but also used ‘seriousness’ to quantify risk, and does not consider the impact of moderate-severe symptoms on an individual's QoL.

In line with our findings, previous research has conceptualised Long COVID as an episodic illness, that is both multidimensional and unpredictable (55). Several longitudinal studies adopt methodologies to demonstrate the changes in symptom profiles and functional status from baseline to an end time point (3, 6, 12, 24 months) (41, 42, 111, 183, 184, 218, 220-222). However, to date methodologies that specifically observe and detail what happens between these time points are limited; therefore, research regarding the high variation of symptoms beyond one point in time to better understand the episodic nature of Long COVID is vital to shaping support services that address the day-to-day challenges that patients experience. The fluctuating symptoms, relapse-remission cycles and reporting bias may overestimate recovery from Long COVID, particularly in studies with shorter follow-up periods or increased time lapses between assessments. The data here supports existing literature that highlights the severity, magnitude, and undulating nature, of symptoms that can considerably reduce the QoL (26, 152, 170, 223, 224). Findings of HRQoL in patients 2 years post severe COVID-19 infection demonstrate a persistent worsened health status measured by the EQ-5D-5L (225). In agreement with existing literature (225), the mean utility index score for the EQ-5D-5L for our study was lower compared to population norms at baseline showing a reduced QoL (226). Despite this and other variables significantly improving by week 16, we cannot conclude that this signifies recovery due to the non-linear trajectory and relapsing and remitting nature of Long COVID.

The highly cyclical symptom profiles and functional status of Long COVID further burden individuals and complicate their ability to plan and engage with typical life such as reducing individuals' work participation and social activities (227). Furthermore, the lingering and unpredictable nature of symptoms heavily impacts emotional state and challenges with emotional regulation, increases anxiety, hopelessness and depression as well as limiting daily functioning (228). Justified by the episodic nature of Long COVID considering the variation of symptom characteristics and severity, which is often exacerbated by periods of physical, mental and/or emotional exertion (152, 229, 230), uncertainty is a key theme across the Long COVID lived experience literature (35, 55, 109, 231, 232). The multidimensional nature of disability and fluctuations of episodic symptoms may vary over a day, and this unpredictability results in participants living and planning for one hour to the next (109).

What is clear is that it remains a big challenge to address the broad and debilitating symptom profile. The research and findings here align with previous research that has identified the most

prevalent symptom profiles associated with Long COVID and adds greater insight and evidence that characterises Long COVID as an episodic and disabling condition by demonstrating the frequent and intense changes that occur in the symptom profile and performance of patients. However, data here further outlines the integration of the symptoms with factors such as QoL status, and comparisons with healthy others and previous self, rather than considering these in isolation. For many participants, symptoms were managed by rest or sleep, which impacts their ability to undertake ADL (i.e., completing the school run or engaging in social activities). It was reported that when participants did attempt activities that are deemed low intensity this would exacerbate symptoms and lead to an extended period of convalescence. Accordingly, attempting to live with Long COVID requires considered support mechanisms that aim to help individuals understand changes in their physical, mental, and emotional health which is in line with an episodic symptom profile that is prone to exacerbation. A further consideration is to understand the episodic nature of Long COVID. In a study using patient diaries across 16 weeks participants reported improvements in symptom severity, and referred to 'turning a corner' (152). However, the exact number of patients who reported this is unclear, and this could change instantaneously and without any provocation in some cases, a finding that has been recognised in other studies (41, 109, 170, 223). It has been suggested that patients with chronic diseases will increase their activities when they feel able but with little consideration of the consequences (35). However, this does not align with our data which is better associated with the findings of Humphreys et al. (233) who report that Long COVID patients prioritise a sense of normality and control over relapse. Our findings indicate that pacing advice of activities seems to have become more widespread and useful through Long COVID clinics and television programmes since this work, yet specific guidelines are still scarce. As such, further research is required to document changes in symptom profiles relative to increased volume and intensity of activity.

There are many hypotheses for the underlying pathophysiology and mechanisms of Long COVIDs episodic nature. Still, there remains a dearth of literature that demonstrates efficacy in the form of pharmacological treatments that can be used to treat and address the complex and debilitating long-term outcomes that broadly impact people's lives (59). Cross-disciplinary conversations amongst relevant specialists commonly take place to discuss complex Long COVID cases, however despite this well-recognised approach, research suggests that its practicality in terms of service utilisation, patient outcomes (234) and patient experience (235) remains equivocal. Furthermore, there are currently no unified strategies in place to support

patients with their uncertainties, or their daily struggles and reduced QoL from undulating symptoms. Many patients will benefit from a complex tailored treatment approach, however, identifying patient profiles or phenotyping patients according to their symptom clusters may also present an additional challenge. Symptom clusters have been well-researched and generally accepted, however, there is limited research regarding the underlying mechanisms behind phenotypes (104, 116, 236-238). Symptom trajectory is highly variable within Long COVID, with symptoms sensitive to change and external factors. Instead of varying pathogenically independent sub-syndromes, research observing sub phenotypes suggests additive severity of a single, multisystemic, multifaceted post-viral illness (217). Subsequently, there is a demand to develop approaches to phenotype relative to the underlying pathology and pathophysiology and clustering of symptoms rather than by the symptom presentation. Due to the broad, multi-system and complex profile of Long COVID, assessment and support services have been established which are underpinned by multi-disciplinary and integrated care approaches. Considering the evidence of adopting multi-disciplinary and integrated care, there is a need to devise substantive pathways that utilise coordinated, integrated whole-system thinking approaches (239). Further assessment tools, for example cardiorespiratory exercise testing (CPET)(240) and protocols are required urgently to inform the development of targeted, patient-centred, interdisciplinary support pathways, to restore functional capacity and QoL.

3.5 Limitations

A limitation of this research is that the heterogeneity in the sample is limited with the majority of participants in this study Caucasian females. Within COVID-19 research, there is a lack of ethnic diversity, and representation of males, and young people (152). Although the prevalence of self-reported Long COVID is greatest amongst females aged 35-69 years, ethnic minorities have been adversely affected by the COVID-19 pandemic (241-244), and there is a need for more representation within COVID-19 research. Additionally, the sample consists of individuals from a range of functional status identified using the PCFS tool. Whilst some participants corresponded to 4 on the PCFS, those with the most severe symptoms, such as being house/bed bound, would have been unable to complete the study therefore limiting the generalisability of the results.

3.6 Conclusion

The findings demonstrate the long-term and broad range of issues affecting people living with Long COVID and show as a result of increased frequency and intensity of patient contact, the variable and episodic nature of Long COVID and the impact that this has on QoL and functional status. Further research and sustained investment are needed to develop detailed Long COVID assessments that can inform targeted, patient-centred, interdisciplinary support pathways, that can be used alongside medicinal interventions to restore functional capacity and QoL.

Chapter 4

Forming a consensus opinion on Long COVID support mechanisms and interventions using a modified Delphi approach.

Peer-reviewed papers from this Chapter:

Owen, R., Ashton, REM., Ferraro, F., Skipper, L., Bewick, T., Leighton, P., Phillips., B., Faghy, M. A. Forming a Consensus Opinion on Long COVID Support Mechanisms and interventions Using a Modified Delphi Approach. *EClinicalMedicine 9*(62)102145. https://dx.doi.org/10.2139/ssrn.4420775 **IF: 17.033**

Conference Proceedings:

Owen, R., Faghy, M., Ashton, REM, Ferraro, F., Thomas, C., Yates, J., Haggan, K., Bewick, T., Phillips, B. (2023). Forming a consensus opinion to inform long COVID support mechanisms and interventions: a modified Delphi approach.

University Professorial Council Research Showcase, University of Derby, September 2023.

4.1 Introduction

As COVID-19 and Long COVID affect multiple organ systems, treatment and management pathways will be complex and require input from varying healthcare specialties (general, vascular, respiratory, neurology, immunology (245, 246). Due to high demand, there is pressure to develop efficacious support pathways to assist those living with long-standing morbidity caused by Long COVID, which will undoubtedly strain healthcare services for many years to come (247). Management of Long COVID is currently the only approach being offered to patients whilst treatment options are devised (248) and a lack of continuity and guidance remains across healthcare services, despite global efforts being directed at creating multi-disciplinary support pathways (249). These issues have led to people living with Long COVID reporting self-prescription, turning to a range of over-the-counter medicines, supplements, various therapies, and dietary changes in an attempt to self-manage their symptoms (58).

To date, the lack of definitive insight and understanding of Long COVID pathophysiology and aetiology (58) propels this to being an emergent threat to global public health (13). In light of this urgency, there is a need to determine consensus and consistency in the components of Long COVID support pathways to ensure patients receive adequate assistance. Accordingly, the following aimed to establish an expert consensus among medical professionals, people with Long COVID, and Long COVID academic researchers on the appropriate support mechanisms and potential interventions needed for those living with Long COVID.

4.2 Methodology

4.2.1 Delphi process

When there is limited evidence and guidance for a clinical issue, a consensus development technique, such as the Delphi method, can support decision making and further guidance (250). The Delphi process is an acclaimed method to achieve consensus of a clinical issue using an expert-based judgement, assuming the group of experts and varying perspectives will provide a more valid result than an individual expert (251, 252). The process involves repeated communication of statements, which are either accepted or revised/rejected depending on the panel of expert's responses, until consensus is achieved (253).

Modifying the Delphi method is appropriate to ensure the methodology is suitable for the study aims, instead of configuring the study aims to fit the methodology (254). The first round of a traditional Delphi typically uses open questioning to identify the focus, however the present study modified this by the study management group including PPIE representatives reviewing the existing literature and generating and discussing structured statements. Free open text boxes were provided, and experts had the option of commenting on each item in the first round and were analysed by the research team.

4.2.2 Expert Panel Selection

The experts panel consisted of GP's, physicians, physiotherapists, HCPs, academic/researchers in the area of Long COVID, HCPs living with Long COVID and those living with Long COVID. The first round of the Delphi study was circulated via social media, word of mouth to Long COVID forums, and physician and healthcare worker networks using established links within the research team and project partners. On completion of the first round, participants disclosed which expert they were participating as, and provided an email address to be contacted on for the subsequent rounds.

In line with institutional ethics approval (ETH2122-0658) from the Human Sciences Research Ethics Committee at the University of Derby, participants were required to confirm they had read the participant information sheet provided, they understood the requirements of the study and provided informed consent before progressing onto the survey. The surveys were complete between February 2022 and August 2022, and experts were given ~4 weeks to complete each round.

4.2.3 Delphi Data Collection

4.2.3.1 Round one

Initial identification of items for round one was completed by the research team which consisted of 5 clinical researchers with experience in Long COVID and 1 patient representative. Statements were generated considering the existing Long COVID research, and patient and professional experience. The first round consisted of 65 statements over 6 sections (Long COVID, Long COVID needs, Long COVID support, specific rehabilitation

interventions for Long COVID, Long COVID interventions focus and Long COVID rehabilitation inclusion).

Using a Likert Scale, experts selected to what degree they agreed with a statement, or how important a statement was. The scale consisted of '*strongly agree', 'agree', 'neither agree nor disagree', 'disagree', 'strongly disagree', 'unsure'*, for the first 4 sections, and '*very important', 'important', 'moderately important', 'slightly important', 'not at all important', 'neither',* and *'unsure'*, for the last 2 sections. Results were downloaded from JISC with responses anonymised, and items were reviewed. Items with a response greater of 80% for *'strongly agree'* and *'agree'* were taken as achieving consensus, with all other items revised and recirculated following analysis of the open text responses for round two.

4.3.2.2 Round two and three

Following analysis of the open responses within round one, key terms were defined (rehabilitation, ME, PEM, PESE, GET). Additionally, the option of '*unsure'* and *'neither'* were removed from the Likert scale. The use of the term 'Rehabilitation Interventions' was also adapted to 'Support Mechanisms and Rehabilitation Interventions'.

The survey link with the revised statements was sent to the previous round respondents via email, along with the results of whole group responses without identifying individual responses for each round of the survey.

4.3 Results

4.3.1 Response rate

After an appeal for participants was sent via social media (twitter) and via research network groups for the first round, there were 273 responses. Round two received 186 responses (drop-out rate of 31% from round 1), and round three received 138 responses (drop-out rate 25% from round 2).

4.3.2 Expert Characteristics

Across the three rounds, the expert panel consisted of 60-62% of Long COVID patients [LCPs], with the remainder of the panel being made up of HCPs living with Long COVID

[HCP/LCP] (12-16%), HCPs (5%), Physiotherapists (5-8%), Physician (4-7%), GPs (1%), and Academics / Researchers in the area of Long COVID [A/Rs] (7-8%). Physiotherapists, Physicians, GPs, and HCPs responses were combined to make one group when analysing intergroup responses, labelled HCPs. Throughout the three rounds, participants represented every region within England, including the midlands (25.3-27.4-%), South England (26.5-29.7%), North England (13.7-14.3%) and East of England (4-4.8%). Participants also represented Scotland (7.7-10.2%) and Wales (0.5%-1.8%), and a further 15-17% of participants resided outside of the UK.

4.3.3 Summary of rounds

The summary of responses for each round are presented in Table 4.1, showing the aim of the round, the total number of statements included, the number of statements that reached consensus and were accepted, the number of statements that were modified and included in the following round, and the number of statements that were removed or rejected.

Table 4.1: Summary of responses for each Delphi round.

	Number of statements	**Round aim**	**Statements that reached consensus (<80%)**	**Statements modified for the next round**	**Statements removed or rejected**
Round 1	65	Exploratory	33	32	0
Round 2	32	Clarifying	17	15	0
Round 3	15	Clarifying and confirmatory	5	0	10

In round one, 33 statements were accepted, and 32 were revised by the research group, using the qualitative free text responses, and were modified for round two. In round two, 17

statements were accepted, and 15 statements were modified. In round three, 5 statements were accepted 10 were rejected.

4.3.4 Summary of results

Consensus was reached on 55 statements. For ease of understanding and improved comprehension, statements were merged where relevant from 55 to a final list of 44 and are displayed in table 4.2. These statements can be considered in four domains: Long COVID as a condition (n=6), clinical assessments for Long COVID (n=3), current support and care available for Long COVID (n=3), Long COVID support mechanisms and rehabilitation interventions (n=13), and three sub-domains: what these should consider (n=4), include (n=9), and focus (n=6) on. Full response breakdown including % agreement, and when consensus was achieved for each round is available within appendices.

Table 4.2: Accepted statements across the three Delphi Survey rounds.

Long COVID as a condition	Long COVID is a public health concern.
	Long COVID is a condition that will require support for patients' long term (6+ months).
	Long COVID is a condition that affects multiple systems of the body, presenting itself through several symptoms.
	Long COVID is a condition that affects individuals of good health prior to contracting COVID-19.
	Long COVID cannot be predicted by the severity of symptoms during the acute phase (first 2 weeks) of COVID-19 infection.
	It is unknown whether individuals living with Long COVID will make a full recovery.
Current support and care available	There is inadequate and inconsistent support amongst all healthcare services for individuals living with Long COVID.
	There is a lack of clear referral pathways to support patients living with Long COVID throughout all healthcare settings.
	There is a lack of understanding from healthcare professionals on how to support Long COVID patients.
Clinical assessment for Long COVID	People living with Long COVID require detailed clinical assessments, medical investigations, and appropriate laboratory tests and functional screening assessments which should be considered when diagnosing and treating patients.
	Respiratory function should be assessed to establish rehabilitation needs for patients living with Long COVID.

	Long COVID patients should complete a formal assessment of physical and emotional functioning to identify rehabilitation needs.
Support mechanisms and rehabilitation interventions for Long COVID	Long COVID requires specialised and comprehensive rehabilitation interventions, that should be guided by the needs of the patient, and created with patient input.
	Long COVID rehabilitation and support mechanisms should be dependent on each individuals' symptoms.
	Long COVID support and rehabilitation should be individualised to the patient's needs.
	Patients completing Long COVID rehabilitation and support interventions should have regular communication and monitoring with care providers.
	Long COVID services should offer psychological well-being support for patients who require it.
	Patients living with Long COVID should receive adequate support from their GP.
	Long COVID support should adopt a multidisciplinary approach (e.g., including physiotherapists, clinicians, rehabilitation specialists, exercise scientists working together).
	Long COVID rehabilitation intervention should be personalised according to age and comorbidities (i.e., pre-existing medical conditions).
	Patients undergoing Long COVID rehabilitation should be closely monitored to establish whether their condition is improving deteriorating or neither.
	Long COVID rehabilitation might be different for each patient.
	Improving quality of life and physical function is a key aim of Long COVID rehabilitation.
	Patients in hospital with COVID-19 should receive tailored rehabilitation and support before being discharged.

	Individuals experiencing symptoms consistent with ME/CFS and PEM should be carefully supported before participating in physical activity.
Long COVID rehabilitation should <u>focus</u> on:	Breathlessness
	Cognitive dysfunction (thinking, remembering, learning, attention confusion)
	Fatigue
	Respiratory function
	Restoring functional capacity
	Sleep disturbance
Long COVID rehabilitation and support mechanisms should <u>include:</u>	Advice on modifying/adapting daily activities such as using aids to allow greater functional ability. Self-management of daily living
	Cognitive (regulating energy use for activities that involve mental capacity e.g., thinking, understanding, learning, remembering) and physical (regulating energy use for physical activity or tasks) pacing of activities.
	Support returning to work
	Support returning to normal activities of daily living
	Breathing techniques and relaxation techniques (meditation, mindfulness)
	Fatigue management
	Patient preference on how they attend their interventions and support, and what is most suitable for them at the time.
	A model that contains face to face and virtual sessions.
	The mental impact of living with Long COVID
	Tolerance to physical activity

Long COVID rehabilitation and support mechanisms should <u>consider</u>:	Emotional distress and wellbeing
	Research of pre-existing conditions with similar symptoms e.g., myalgic encephalomyelitis / chronic fatigue syndrome.

Following analysis, all statements that did not reach consensus in the first 2 rounds were revised, and included in the third and final rounds. However, 10 statements did not reach consensus by the end of this Delphi study, and were rejected. Rejected statements are presented in table 4.3.

Table 4.3: Rejected statements from 3 Delphi Survey rounds.

Long COVID as a condition	If regular physical activities do not provoke symptoms or post exertional symptom exacerbation, then Long COVID patients can participate in their regular physical activities.
Support mechanisms and rehabilitation interventions for Long COVID	Those designing support mechanisms for Long COVID can learn lessons from other acute respiratory infections (e.g., pneumonia).
	Those designing support mechanisms for Long COVID can learn lessons from other chronic respiratory diseases (e.g., asthma and COPD).
Long COVID rehabilitation and support mechanisms should <u>include:</u>	Low level physical activities (e.g., walking) that results in moderate increases in heart rate.
	Activities incorporating muscle use.
	Support to increase flexibility and functional movement proficiency.
	Advice on nutrition and diet to support recovery.
	Interventions should be delivered face to face and make use of specialist facilities and personnel.
	Interventions that can be completed remotely and away from clinical settings.

4.3.5 Between group discrepancies

Across the three rounds, there were 11 statements that reached consensus but had discrepancy between expert group responses presented in table 4.4. Furthermore, the expert panel consisted of 15-17% of participants not residing in the UK throughout the 3 rounds. When excluding international responses, one statement would not have reached consensus in round three: ‘Long COVID support mechanisms and rehabilitation interventions should include a model that contains face to face and virtual sessions’.

Table 4.4: Discrepancies between expert groups for each Delphi round.

Round 1 (reached overall consensus)	**Overall**	**HCPs N=55**	**LCPs N=164**	**HCPS/LCP N=33**	**A/Rs N=21**
Long COVID is an illness that requires specialised rehabilitation interventions.	86%	84%	89%	91%	62%
Respiratory function should be assessed to establish rehabilitation needs for patients living with Long COVID.	81%	69.1%	84%	91%	71%
Long COVID patients should complete a formal assessment of physical and emotional functioning to identify rehabilitation needs.	88%	91%	88%	91%	72%
Patients living with Long COVID should receive adequate support from their GP.	87%	81.8%	90%	91%	71%
Patients living with Long COVID should receive a comprehensive rehabilitation programme.	88%	85.1%	91%	85%	72%
How Important is it for Long COVID rehab to focus on Respiratory function	86%	75%	87%	85%	85%
How Important is it for Long COVID rehab to include breathing techniques	85%	78%	87%	91%	91%
Round 2 (reached overall consensus)	**Overall**	**N=55**	**N=164**	**N=33**	**N=21**
There is a lack of clear referral pathways to support patients living with Long COVID throughout all healthcare settings.	87%	69%	85%	100%	100%

How Important is it for Long COVID support and rehabilitation interventions to include relaxation techniques and breathing techniques (e.g., meditation, mindfulness)	81%	81%	85%	77%	60%
Round 3 (reached overall consensus)	**Overall**	**N=20**	**N=83**	**N=25**	**N=10**
Long COVID cannot be predicted by the severity of symptoms during the acute phase (first 2 weeks) of COVID-19 infection.	88%	75%	90%	96%	80%
How important is it for Long COVID support and rehabilitation interventions to include a model that contains both face to face and virtual sessions?	80%	85%	79%	84%	70%

4.4 Discussion

The present study used a modified Delphi method to inform the future development of bespoke interventions and support mechanisms for those living with Long COVID. Fifty-five statements received consensus by a panel of experts relating to Long COVID; Long COVID as a condition, care and support available for Long COVID, clinical assessment for Long COVID, and support mechanisms and rehabilitation interventions for Long COVID (focus, inclusion, and considerations). Whilst there are no proven pharmacological treatments for Long COVID to date, this study has clinical value in supporting the development of support mechanisms and rehabilitation interventions, based on consensus by healthcare professionals and those living with Long COVID.

The consensus reached agrees with existing literature that it is likely that Long COVID will have a substantial impact on public health (255). Consistent with other research, the panel agreed that Long COVID is a condition that affects multiple systems of the body, presenting itself through several symptoms, and those living with Long COVID will require long term support (59). Experts within this study also agreed that it is unknown whether individuals will make a full recovery (59). When diagnosing and treating Long COVID, a detailed clinical assessment, medical investigations, laboratory testing and functional screening should be complete. These should include formal assessments of respiratory, physical, and emotional functioning. A review by Davis and colleagues, (2023) suggests that further research is required to build on the existing knowledge of the appropriate tests for Long COVID, such as neuroimaging, metabolic profiling and nanoneedle diagnostic testing. Furthermore, the outputs from this study suggest that the current offering of Long COVID support is inconsistent across health care settings, with a lack of clear referral pathways and understanding from HCPs on how to support those living with Long COVID. This Delphi proposes potential guidelines on what support mechanisms and interventions should include, focus on, and consider in order to improve QoL and physical function.

One key finding of the Delphi and consistency with existing research is the established link and considerations between symptoms of ME/CFS, PEM, and Long COVID (89). The panel agreed that individuals experiencing symptoms consistent with ME/CFS and PEM should be carefully supported before participating in physical activity, and if PESE is not provoked by physical activities, then those living with Long COVID still should not participate in regular

physical activities. In line with existing research that exercise is detrimental for patients with Long COVID and ME/CFS, or PEM (256, 257), the panel disagreed that Long COVID support mechanisms should include low level physical activities that results in moderate increases in heart rate, activities incorporating muscle use, and support to increase flexibility and functional movement proficiency. PEM, or PESE is commonly experienced by those with Long COVID (174) and presents a significant challenge such as reduced capacity to work and reduced physical and social functioning (170). Furthermore, experts agreed that there should be consideration of the research of pre-existing conditions with similar symptoms such as ME/CFS, but not respiratory conditions such as chronic obstructive pulmonary disease, asthma, and pneumonia.

According to this modified Delphi study, support mechanisms and interventions might be different for each patient, and should be specialised, comprehensive, personalised (according to age and comorbidities), guided by the needs of each patient and made with patient input. Where appropriate for the patient, interventions should include advice on modifying/adapting daily activities such as using aids to allow greater functional ability, self-management of daily living such as support returning to work and normal ADL, cognitive and physical pacing of activities, fatigue management and breathing and relaxation techniques. Experts agreed that breathlessness, cognitive dysfunction, fatigue, respiratory function, restoring functional capacity and sleep disturbance should be some of the focuses of the support and interventions, with psychological well-being support available for those who require it. This is in line with the existing literature suggesting that exhaustion, cognitive dysfunction, chest pressure and/or tightness, and dyspnoea are the most common symptoms of Long COVID (100). Additionally, the mental impact of living with Long COVID, tolerance to physical activity and emotional distress and wellbeing should be considered.

This Delphi study concludes that Long COVID support should adopt a multidisplinary approach utilising physiotherapists, clinicians, rehabilitation specialists exercise scientists, as well as patients receiving adequate support from their GP. The use of adopting a multidisplinary approach is beneficial in supporting an already strained NHS (258). A multidisciplinary and collaborative approach encompassing medicine and clinical services can extend the knowledge base and utilise space and facilities to conduct physiological assessments such as respiratory function and cardiopulmonary testing (121, 175). Support mechanisms should be delivered via a model that contains face to face and virtual sessions,

with patient preference on how they attend their interventions and support, and what is most suitable for them at the time. When completing interventions, patients should have regular communication with HCPs, with adequate monitoring to establish improvements, deterioration or neither.

4.6 Limitations

The Delphi method is a flexible approach, with anonymity being a key feature of the method. However, due to the need of identifying respondents and non-respondents for participation in consecutive rounds, quasi-anonymity was used for the present study (259). Therefore within the current study, respondents were known to the researcher, but their judgements and responses remained anonymous.

One consideration for the current study is that 11 statements that reached overall consensus did not reach consensus within every group. Specifically, 7 of these statements did not reach consensus amongst the academics and researchers, potentially explained by the smaller sample size (n=21) compared to other groups, meaning averages and values are more susceptible to fluctuate. Additionally, 5 of these statements did not achieve consensus by HCPs, 1 by LCPs and 1 by HCPs/LCPs. These statements should be considered with caution.

4.7 Conclusion

Accordingly, this study established an expert consensus among medical professionals, people with Long COVID, and Long COVID academic researchers on the appropriate support mechanisms and potential interventions needed for those living with Long COVID. This consensus will aid the development of bespoke interventions, to support those living with Long COVID.

Chapter 5:

General Discussion

5.1 Overview

The research presented in this thesis aimed to document and understand the lived experience of people in the aftermath of the COVID-19 pandemic and the broad impacts of Long COVID upon people's quality and activities of daily life (Chapter 2). Capturing this information alongside diagnostic clinical details that profile patients' symptoms and physiological status (Chapter 3) is important to support the development of bespoke Long COVID support mechanisms (Chapter 4) to improve patient outcomes, QoL and functional status.

5.2 Key findings

The lived experience survey in Chapter 2 highlighted the severe impact of Long COVID symptoms on patients QoL and functional status. The data highlights a broadly debilitating symptom profile that affects the physical and mental wellbeing of patients which when viewed in totality affects all aspects of a patient's life and includes, but is not limited to, impaired ability to engage with employment, family roles and social activities. Whilst Long COVID is recognised as a threat to global health, the design and implementation of support services is largely fragmented and has been labelled by patients as being 'unfit for purpose', with a high prevalence of gaslighting and a lack of understanding and support from medical professionals being highlighted as key barriers to the services that are so desperately needed.

A 16 week cohort observation study (Chapter 3) was conducted to describe, quantify and critically evaluate the clinical, physiological, biochemical, and psychological domains of the recovery following a COVID-19 infection. This study demonstrated a non-linear trajectory of recovery, with outcomes improving from baseline to week 16, but frequency and severity of symptoms and patient reported outcome measures fluctuating between visits. This study further highlights the reduction in QoL and functional status, determined by the complexity of Long COVID. Furthermore, this data accentuates the episodic and relapsing nature of symptoms and can be used to characterise Long COVID disability in the development of guidelines and support services for patients.

A modified Delphi Consensus (chapter 4) methodology was conducted using key stakeholders, including patients and medical professionals, to provide an outline to inform the design and implementation of bespoke Long COVID support mechanisms. The study reached a consensus on 55 statements in the areas of Long COVID as a condition, the current support and care

available, clinical assessments and support mechanisms and rehabilitation interventions going forward for Long COVID. Stakeholders concluded that Long COVID support services should adopt an interdisciplinary approach that brings together medical professionals, rehabilitation experts, and exercise specialists. It was determined that support mechanisms should be personalised for each patient, focusing on individual symptom profiles, including detailed specialist input.

The over-arching aim of this thesis was to understand the need for bespoke support mechanisms and what these should consist of for Long COVID. The thesis met this aim by exploring the lived experience of COVID-19 and Long COVID, demonstrating the impact of Long COVID on QoL and experiences within existing healthcare services. The lived experience highlighted an urgent need for bespoke support mechanisms and interventions to improve recovery outcomes including QoL and functional status for Long COVID. Furthermore, the thesis increased understanding of the physiological, biochemical, and psychological domains of the recovery following a COVID-19 infection. To better inform the development of Long COVID support services, this thesis utilised engagement with established patient support groups, clinicians, and allied health professionals to inform rehabilitative interventions, emphasising the need for patient-led care and incorporating the lived experience during recovery, in line with National Institute for Health and Care Excellence and global healthcare priorities.

5.3 Novel contribution to the area

The findings from this thesis provides deep insight to the broad impact of Long COVID on quality of life and functional status, as a result of its episodic and relapsing disabling symptom profile shown through a mixed methods approach. The lived experience demonstrates the increased reliance on friends and family for support and psychological and emotional functioning, and the consequences of inconsistencies and lack of support and treatment available when accessing Long COVID care services, further impacting mental and physical well-being. Furthermore, this thesis provides recommendations made by those living with Long COVID to provide recommendations to those supporting people with Long COVID, including acknowledging the patients feelings, the complex symptom profile and the challenges these come with, and an overall awareness of Long COVID. Consensus achieved within this thesis also provides comprehensive guidance for tangible support mechanisms and

interventions, including personalisation of care and adopting an interdisciplinary approach. In the absence of pharmacological intervention, patients should be provided with support on modifying daily activities to allow greater functional ability, self-management of daily living, pacing, fatigue management, and symptom tailored care.

5.4 Limitations

The UK has made progress in recognising Long COVID as a serious condition, and effort has been made to establish specialist clinics, develop guidelines and dedicate resources to manage the condition and fund research. However, when using clinical coding of Long COVID within primary care, a recent study analysing the health records of over 19 million adults in England reported low rates of Long COVID diagnoses and referrals recorded by GPs, with rates steadily declining from 2021-2022(260). Records were substantially less than the number of people estimated to be living with Long COVID by the Office for National Statistics(27), and this under-reporting will undoubtedly result in a lack of appropriate referrals and care for those living with Long COVID. The existing lived experience research highlights an urgent need for improved healthcare services and support structures for managing Long COVID within primary care. As highlighted in this thesis (Chapter 2), the NHS has established Long COVID clinics attempting to offer multidisciplinary care, however inconsistencies between services have resulted in inadequate care, patients facing extensive delays in diagnosis and care, and geographical disparities in service availability. This has been further confounded by the funding constraints and pressure on healthcare systems post-pandemic, and services have limited capacity to meet the growing demand for Long COVID care. Furthermore, a more coordinated, resource intensive, and patient-centred approach is crucial to addressing the ongoing and long-term challenges posed by Long COVID. As evidence and diagnostic criteria continue to develop, it may be prudent to update referral guidelines for specialist services to ensure resources are allocated most efficiently.

To date, most Long COVID research, including this thesis, represents adult populations, limiting the external validity of the findings specifically to children and young people. Research involving children and young people is scarce and heterogeneous, restricting definitive conclusions surrounding the pathophysiology, symptom profile and lived experience in these patients. Moreover, the inclusion of Black, Asian and minority ethnic groups in Long COVID research must be advocated for to address health inequalities. The few

studies that do include data on ethnic minority groups suggest that they are disproportionately impacted by Long COVID, with varying symptom profiles to white individuals. Therefore when it comes to creating and implementing the appropriate pharmacological interventions and support mechanisms, these must be appropriate for the relevant population considering age and ethnic groups.

5.5 Areas for future research

The removal of COVID-19 restrictions is complex, multifaceted and often critiqued due to morbidity risks, the continuation of community transmission periodically surging, and the existing increased risk of certain sub-groups (older adults, infants, people with comorbidities) (261). However, the decision was based on several factors, including vaccination success, reduction of infection rates, hospital capacity, and assessment of future variants of concern. Public health authorities, scientific advisory groups and medical professionals have expressed concerns about relaxing these measures, emphasising the need for caution in the ongoing pandemic response. It is well reported that Long COVID is associated with all acute phase disease severities, with the highest percentage of diagnoses predominantly in non-hospitalised patients with mild acute illness (59). Removing preventative measures such as social distancing, face mask mandates, and access to free testing in an effort to restore pre-pandemic economic and social activities has continued to result in sustained COVID-19 transmission and a subsequent increase in Long COVID diagnoses. Without effective pharmacological treatments and support mechanisms to address the disabling effects of Long COVID, the burden on public health and healthcare services will continue to grow.

Efforts have been made to strengthen diagnostics, treatment, and rehabilitation with the expansion of Long COVID services to post-COVID assessment clinics, with services introducing multifaceted rehabilitation pathways to provide physical and mental health support (262). However, recently in the UK, post-COVID services have been established following the framework of an integrated care system, with the aim of fostering collaboration among providers within the integrated care system to deliver coordinated, multidisciplinary integrated care (NHS) (263). These services are said to include multi-disciplinary teams, symptom/needs-based rehabilitation, referral into and from specialist services, provision of a self-management plan, in person and virtual support, peer support and social prescribing (262). However, the findings of this thesis has highlighted a need for interdisciplinary care, and the lived experience demonstrates that the current level of support is not consistent or adequate. Additionally,

whilst some of this sample have previous healthcare experience and/or medical training, research highlighting the healthcare practitioners' perspective of services and support is important to ensure congruence between patients and healthcare professionals.

Building on previous methods, there is a need to develop and implement substantial pathways supported by whole system thinking approaches, enhanced with interdisciplinary consideration and practice. It is appropriate to ensure relevant specialists have the capacity to discuss the mechanistic and integrated issues affecting Long COVID patients. Using established models such as the Medical Research Council Complex Intervention Tool is needed to implement, test and evaluate a bespoke service development plan for Long COVID. Moving forward, the adopted model and research must be flexible to adapt to the constantly developing field when informing the learning and knowledge of support mechanisms. Given the broad challenges of Long COVID, it may be prudent to develop assessment services incorporating objective triaging and monitoring to ensure support is bespoke. Adopting such approaches will undoubtedly improve patient outcomes and experiences but will come with significant logistical challenges. Further work is required to inform the understanding and collaboration of these approaches and test their efficacy against important outcome measures such as quality of life, which may lead to coordinated and integrated methods. More broadly, this may lead to the design and implementation of efficient and effective services to address a growing and significant burden on healthcare services, potentially serving as a model for managing long-term and post-acute-viral conditions.

5.6 Implications

Long COVID is a challenge to traditional models of illness, recovery and healthcare delivery due to the complex multi-system pathology that interacts across several of the bodies systems. This thesis highlights the importance of the lived experience and public awareness and understanding of the long-term consequences of viral infections on all aspects of health status and quality of life. The findings within this thesis carries far-reaching implications for patients, healthcare services, public health and policy makers as it provides detailed accounts of the quantitative and qualitative impacts of Long COVID upon those affected. This insight is important in the context of raising the profile and awareness of Long COVID but also in the design and development of intervention and management approaches that are required to support a chronic and multisystem condition that is a global public health concern.

Data from this thesis can be used to provide recommendations for healthcare professionals helping people with Long COVID to enhance HRQoL (Figure 2.4) and to inform clinical practice and guide healthcare policies. Additionally, statements which reached consensus to inform Long COVID support mechanisms and interventions (Table 4.2) by key stakeholders can be used to contribute to the development of care approaches and resources, and form the foundation of intervention strategies and support structures. Furthermore, the implications of increased frequency and intensity of patient contact within this thesis (Chapter 3) highlights the variable and episodic nature of Long COVID, which must be considered by medical professionals, and when informing bespoke support mechanisms, rehabilitations and interventions. Future research should focus on designing and assessing targeted, patient-centred, interdisciplinary support pathways, that can be used alongside medicinal interventions to restore functional capacity and QoL. By integrating these insights, the healthcare experience for Long COVID patients can be improved, and the appropriate support mechanisms in place will allow for more effective care subsequently improving QoL and functional status.

5.7 Conclusion

This thesis highlights the severe reduction in QoL and functional status, insufficient healthcare support and treatment, and the need for bespoke interdisciplinary mechanisms for people living with Long COVID. From March 2022, all restrictions, including the legal obligation to test and self-isolate, were removed as part of the UK Government's plans to 'live with' COVID-19 (9), an approach which has since been replicated worldwide. This decision was contentious, as there is no doubt that sustained transmissions, future variants of concern and the disabling impacts of post-COVID-19 syndrome or Long COVID, continue to affect public and global health and well-being and will likely do so for years to come (143). Whilst clinical services have somewhat been restored, the aftermath of the pandemic is still being felt, including a backlog of patients requiring routine procedures coupled with over 10 million patients with undiagnosed or untreated health needs that occurred during the pandemic (143, 177). Confounded by prior years of investment cuts (264), the COVID-19 pandemic left the UK NHS and other global healthcare systems inadequately prepared to address this unforeseen and global threat to public health, which likely indirectly contributed to adverse patient outcomes and mortality. This thesis concludes that bespoke support mechanisms and interventions are needed alongside pharmacological treatments to restore functional capacity and quality of life in Long COVID patients.

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7.0 List of Appendices

Appendix 1 – Ethical Approvals

a) Chapter 1 Institutional Ethical Approval
b) Chapter 2 Institutional Ethical Approval
c) Chapter 3 IRAS Ethical Approval

Appendix 2 – Chapter 2

a) Participant Information Sheet, Informed Consent with Full Survey

Appendix 3 – Chapter 3

a) Participant Information Sheet and Informed Consent
b) GP Letter
c) Patient reported outcome measures
    a. Post-COVID-19 Functional Status Scale
    b. EQ-5D-5L
    c. MRC Dyspnoea Scale
    d. Fatigue Assessment Scale
    e. Modified Fatigue Impact Scale
    f. Symptom Score
    g. MoCA

Appendix 4 – Chapter 4

a) Participant Information Sheet
b) Invitation letter to GP's, Respiratory Physicians, Physiotherapists, Healthcare Professionals, Long COVID Researchers
c) Invitation letter to Long COVID patients.
d) Full response breakdown including % agreement and when consensus was achieved for each round.

Appendix 1a. *Chapter 1 Institutional Ethical Approval*

Kedleston Road, Derby
DE22 1GB, UK

T: +44 (0)1332 591060
E: researchoffice@derby.ac.uk
Sponsor License No: QGN14R294

Dear Rebecca

ETH2122-0658

Thank you for submitting your application to the College of Science and Engineering Research Ethics Committee, which has now been reviewed and considered.

The outcome of your application is:

approved.

If any changes to the study described in the application are necessary, you must notify the Committee and may be required to make a resubmission of the application.

On behalf of the Committee, we wish you the best of luck with your study.

Yours sincerely

Charlotte Dakin

Appendix 1b. *Chapter 2 Institutional Ethical Approval*

Kedleston Road, Derby
DE22 1GB, UK

T: +44 (0)1332 591060
E: researchoffice@derby.ac.uk
Sponsor License No: QGN14R294

Dear Rebecca

ETH2021-4335

Thank you for submitting your application to the College of Science and Engineering Research Ethics Committee, which has now been reviewed and considered.

The outcome of your application is:

approved.

If any changes to the study described in the application are necessary, you must notify the Committee and may be required to make a resubmission of the application.

On behalf of the Committee, we wish you the best of luck with your study.

Yours sincerely

Charlotte Dakin

Appendix 1c *Chapter 3 IRAS Ethical Approval*

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Mark Faghy
Senior Lecturer in Exercise Physiology
University of Derby
Kedleston Rd
Derby
Derby
DE22 1GB

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

25 February 2021

Dear Dr Faghy

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Profiling the determinants of recovery to establish novel rehabilitation guidelines to improve clinically relevant and patient-reported outcomes in the post-COVID-19 period.**
IRAS project ID:	**292920**
Protocol number:	**COVID-19-UoD&RDH20/21**
REC reference:	**21/SW/0006**
Sponsor	**University of Derby**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **292920**. Please quote this on all correspondence.

Yours sincerely,
Sharon Northey

Approvals Manager

Email: approvals@hra.nhs.uk

Copy to: *Professor Sue Dyson*

IRAS project ID	292920

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
The study involves Participant Identification Centres (PICs).	PIC activities should not commence until a PIC Agreement is in place. HRA and HCRW recommend use of the standard Participating NHS Organisation to PIC agreement available here.	HRA and HCRW recommend use of the standard Participating NHS Organisation to PIC agreement, available here.	Funding has been secured.	Neither a Principal Investigator or Local Collaborator is expected to be in place at the NHS site.	No HR arrangements are expected.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated they intend to apply for inclusion on the NIHR CRN Portfolio.

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [University Insurance Doc]		01 August 2020
GP/consultant information sheets or letters [GP letter]	1.1	02 February 2021
IRAS Application Form [IRAS_Form_10122020]		10 December 2020
Letter from funder		11 January 2021
Participant consent form [Consent Form]	1.1	02 February 2021
Participant information sheet (PIS) [PIS]	1.1	02 February 2021
Research protocol or project proposal [Protocol]	1.1	02 February 2021
Summary CV for Chief Investigator (CI) [CI-CV]		08 December 2020

Appendix 2a. *Chapter 2 Participant Information Sheet, Informed Consent and Full Survey*

Living with COVID-19, please hear what we have to say?

Start of Block: Participant Information Sheet

Participant Information Sheet:

Living with COVID-19, please hear what we have to say.

The aim of this study is to capture and increase understanding of patient experiences of a COVID-19 infection in the areas of COVID-19 diagnosis, acute COVID-19 and long COVID to help inform the development of bespoke COVID-19 interventions.

Before you decide whether you want to participate, it is important for you to understand why the research is being conducted and what it will involve. Please read the information below carefully, and contact m.faghy@derby.ac.uk or r.owen@derby.ac.uk for any queries.

Am I eligible to take part?

You have been asked if you would like to volunteer and participate in the research study as you fit the criteria for participant inclusion, which are;

· You have tested positive for COVID-19, or have shown symptoms of COVID-19 and suspect you have had COVID-19.

· You are over the age of 18 years.

· You are able to understand written English.

You will be excluded from this research if:

· You are uncertain of the survey requirements.

· Your answers provided on the informed consent form do not meet the required criteria.

You are under no obligation to participate, and you have the right to withdraw from the study at any point by simply exiting from the browser window prior to submitting.

What will taking part in the study involve?

This study requires you to complete an online questionnaire which will take approximately 20 minutes. You will complete the questionnaire once and we ask that you do this honestly. Following consent, you will be asked whether you would like to be contacted regarding participation in future research, which is optional. If you would like to be contacted, please specify your email address in the next section of the survey. If you do not want to be involved in further research, please choose this option. When the study is concluded, you will be able to read the findings on request.

What are the possible risks of taking part?

There are no perceived risks of taking part in this study. If anything transpires, please contact the research team for advice and support using the contact details provided.

What are the possible benefits of taking part?

The main benefit of participating is that you will be helping to further the existing research within the area of long COVID. This is beneficial as the COVID-19 pandemic is a global concern, and the results of this study will help further the existing knowledge on the effects of COVID-19.

What will happen to the results of the study?

All data collected will be kept confidential, and any data presented will be done anonymously alongside the applicable laws and regulations such as not being made publicly available. Only data relevant to the study will be collected and used and secured safely where no-one else will be able to get to. Data may be analysed by any member of the research team, under the supervision of the project leaders. All data will be destroyed within 7 years, but if you withdraw from the study, your data will be immediately destroyed. The results of the study will be available within a University of Derby press release and may be used as part of a PhD thesis, and if the results of this study are published, participants identity will remain confidential and anonymous.

Who is conducting and funding the research?

The study is being completed by the University of Derby.

What if I have any questions?

Please use the contact details below for any questions or queries.

Contact details

Dr Mark Faghy: m.faghy@derby.ac.uk

Rebecca Owen: r.owen@derby.ac.uk

Further guidance on the use of your data and your rights:

Researchers will be collecting data from your participation in this study. We need these data to understand patient experiences of a COVID-19 infection in the areas of COVID-19 diagnosis, acute COVID-19 and long COVID to help inform the development of bespoke COVID-19 interventions. This is the legal basis on which we are collecting your data and while this allows us to use your data, it also means we have obligations towards you to:

• Not seek more information from you than what is essential and necessary for the study.

• Make sure that you are not identified by the data by anonymising it, using ID codes.

• Use your anonymised data only for the purposes of this study and for any relevant publications that arise from it.

• Store data safely in password-protected databases to which only the named researchers have access.

• Not keep your information for longer than is necessary (usually for five years).

• Safely destroy your data by shredding or permanently deleting them.

You have a right to withdraw from the study at any point up to 2 weeks after data collection has been completed. Should you wish to withdraw during this timeframe, you can do so by contacting Mark or Rebecca as lead researchers via email using the contact details available at the end of the form. Within this email, you should quote your 5-character unique identification code and all data associated with this code will then be destroyed immediately by the researcher.

To protect your right to confidentiality and anonymity, your data will not be stored against your name. Your data will be stored against a 5-character unique identification code based on the 2 digits reflecting the day of the month you were born (01-31) followed by the last 3 characters of your postcode. You can generate this code and write it at the top of this sheet for your own records. Your data and electronically signed consent form will be stored on a

password protected computer to which only the lead researcher has access. Anonymised raw data will be shared in a read-only file with the co-researchers for the purpose of analysis. At no point in the research will you be named, and any identifying information provided in the survey will not be included in the study. The data collected is for research purposes only and may be stored for a period suitable for the aims of the research, according to Article 89 of the GDPR regulations relating to scientific research, enforced in May 2018. Your data will be kept for a minimum of 7 years and then destroyed. Data will only be accessible to the named researcher.

Researchers on the project with access to the data are highly qualified and experienced staff and have been very careful to ensure the security of your data. The study was approved for its ethical standards by The University of Derby Human Sciences Research Ethics Committee. Further information about the project can be obtained from Dr Mark Faghy, m.faghy@derby.ac.uk or Rebecca Owen, r.owen@derby.ac.uk at University of Derby, Kedleston Road, Derby DE22 1GB.

○ I have read and understood the participant information sheet (1)

Appendix 2b. *Chapter 2 Informed Consent*

Start of Block: Informed consent

Unique Identification Code

Please use the 2 digits reflecting the day of the month you were born (01-31) followed by the last 3 characters of your postcode. This will create a 5-character unique identification code allowing us to access your data whilst keeping you anonymous.

Display This Question:

If Living with COVID-19, please hear what we have to say. The aim of this study is to capture and... = I have read and understood the participant information sheet

Informed consent Statement of Consent:

1) I agree to partake as a participant in the above study.

2) I understand from the participant information sheet, which I have read in full, that this study will involve me completing one questionnaire.

3) It has also been explained to me that the risks of participation are minimal.

4) I am aware that I can withdraw my consent to participate in the procedure at any time up to two weeks after participation and for any reason, without having to explain my withdrawal and that my personal data will be destroyed and that my medical care or legal rights will not be affected.

5) I understand that any personal information regarding me, gained through my participation in this study, will be treated as confidential and only handled by individuals relevant to the performance of the study and the storing of information thereafter. Where information concerning myself appears within published material, my identity will be kept anonymous.

6) I understand that my data will be held for a maximum duration of 7 years from the commencement of the study and will be destroyed by the following date: January 6th, 2027.

7) I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers.

Please remember that you have the right to withdraw your participation. To withdraw from

the study following participation, please contact m.faghy@derby.ac.uk or r.owen@derby.ac.uk providing your unique ID code.

○ I consent to participating in this study and I am happy to be contacted regarding participation in future research. Please provide your email address in the text box below. (1) _____

○ I consent to participating in this study but do not want to be contacted regarding participation in future research (2)

○ I do not consent to participate in this study (3)

Skip To: End of Survey If Participant Statement of Consent to Participate in the Investigation Entitled:Living with COVID-19, = I do not consent to participate in this study

End of Block: Informed consent

Appendix 2a. *Chapter 2 Lived experience survey*

Q1 Age

- 18-40 (1)
- 41-65 (2)
- 65+ (3)

Q2 To which gender identity do you most identify?

- Female (1)
- Male (2)
- Transgender female (3)
- Transgender male (4)
- Gender variant/non-conforming (5)
- Not listed (6) _____
- Prefer not to say (7)

Q3 Please select your ethnicity/nationality:

- White British (1)
- White Irish (2)
- White Gypsy or Irish Traveller (3)
- Any other White background (4)
- White and Black Caribbean (5)
- White and Black African (6)
- White and Asian (7)
- Any other Mixed or Multiple Ethnic background (8)
- Indian (9)
- Pakistani (10)
- Bangladeshi (11)
- Chinese (12)
- Any other Asian background (13)
- African (14)
- Caribbean (15)
- Any other Black, African or Caribbean background (16)
- Arab (17)

- Any other ethnic group (18)

  _____

Q4, Are you registered as having a disability?

- Yes, if so was this pre-existing or since COVID-19 infection? (1)

  _____

- No (2)
- Prefer not to say (3)

Q5 Which region of the UK do you live in?

- Scotland (1)
- Northern Ireland (2)
- Wales (3)
- Northeast (4)
- Northwest (5)
- Yorkshire and Humber (6)
- West Midlands (7)
- East Midlands (8)
- Southwest (9)
- Southeast (10)
- East of England (11)
- Greater London (12)

Q83 Which region of the UK do you live in?

- Scotland (1)
- Northern Ireland (2)
- Wales (3)
- Northeast (4)
- Northwest (5)
- Yorkshire and Humber (6)
- West Midlands (7)
- East Midlands (8)
- Southwest (9)
- Southeast (10)
- East of England (11)
- Greater London (12)

Q6 What is your current relationship status?

- Single (1)
- Living with partner (2)
- Married (3)
- Separated (4)

- Divorced (5)
- Widowed (6)

Q7 Which of these best describes your current employment status?

- Employed part time (1)
- Employed full time (2)
- Self-employed (3)
- Employed but currently off sick due to COVID-19 related symptoms (7)
- Employed but currently off sick for other reasons (8)
- Unemployed (4)
- Retired (5)

Q8 What is your current occupation? If this has changed since COVID-19 please detail

_____

End of Block: Section 1: Demographics

Start of Block: Section 2: Your COVID Diagnosis

Q1 Have you tested positive for COVID-19?

- Yes (Please indicate when in the text box provided) (1)

  _____

- No, but I had symptoms consistent with COVID-19 (2)

Q2 What was your COVID-19 status:

- Recovered in a community setting (1)
- Admitted to hospital for less than a week (2)
- Admitted to hospital for more than a week (3)

Q3 If you were admitted to hospital, were you admitted to ICU?

- No (1)
- Yes, if so for how long (2)

  _____

Q4 Has a clinician diagnosed you with Long COVID?

- Yes, if so which clinician and when was this (date) (1)

  _____

- If you haven't had a diagnosis but you suspect you have Long COVID, please select here (2)
- Prefer not to say (4)

End of Block: Section 2: Your COVID Diagnosis

Start of Block: Section 3: General Questions about your pre COVID-19 and post COVID-19 state

Q1 How would you describe your quality of life and general health before you were diagnosed or believe you contracted COVID-19? Please feel free to tell us why you selected this answer

- Very good (1) _____
- Good (2) _____
- Average (3) _____
- Below average (4) _____
- Poor (5) _____

Q2 How would you describe your quality of life and general health since you were diagnosed or believe you contracted COVID-19? Please feel free to tell us why you selected this answer

- Very good (1) _____
- Good (2) _____
- Average (3) _____
- Below average (4) _____
- Poor (5) _____

Q3 3. Do you have a history of other auto-immune issues prior to being diagnosed or believe you contracted COVID-19? Please feel free to tell us why you selected this answer

- Yes (1) _____
- No (2) _____
- Prefer not to say (3)

  _____

End of Block: Section 3: General Questions about your pre COVID-19 and post COVID-19 state

---

Start of Block: Section 4: Acute COVID-19

Q1 Did you get a test for COVID-19 in the first few days of symptoms?

- Yes (1)
- No (2)

Display This Question:

If Did you get a test for COVID-19 in the first few days of symptoms? = No

Q1a If you did not get a test for COVID-19 in the first few days of symptoms, please tell us why not?

_____

Display This Question:

If Did you get a test for COVID-19 in the first few days of symptoms? = No

Q1b Do you believe that not having a test in the first few days of symptoms impacted upon you getting medical help? Please feel free to tell us why you selected this answer

- Yes (1) _____
- No (2) _____
- Prefer not to say (3)

Q2 Can you describe your experience during the acute phase (i.e., the first 6 weeks) of COVID-19 infection?

_____

Q2a Can you describe how you were managed during the acute phase, considering medical management (i.e., the first 6 weeks) of COVID-19 infection?

_____

Q2b Can you describe what you did to manage your symptoms during the acute phase (i.e., the first 6 weeks) of COVID-19 infection?

_____

Q3 Do you believe you had adequate care during the acute phase (i.e., the first 6 weeks) of COVID-19 infection?

- o Yes (1)
- o No (2)

Display This Question:

If Do you believe you had adequate care during the acute phase (i.e., the first 6 weeks) of COVID-19... = No

Q3a If you did not receive adequate care during the acute phase (i.e., the first 6 weeks) of COVID-19 infection, please tell us why not?

_____

Q4 What do you wish you had known about the acute phase to help with your recovery?

_____

Q5 Are there any 'safety' issues or developing symptoms/pathologies that people who have acute COVID-19 need to look out for?

_____

Q6 What symptoms should alert clinicians or patients to seek urgent medical help?

_____

End of Block: Section 4: Acute COVID-19

Start of Block: Section 6: Activities of daily life

Q1 Have you experienced any difficulties engaging with friends, family, or colleagues regarding your symptoms? Please feel free to tell us why you selected this answer

- Yes (1) _____
- No (2) _____
- Unsure (3) _____

Q2 Since your COVID-19 infection, have you been able to return to your usual activities of daily life? This could include social and leisure activities. Please can you provide some details on this

- Yes (1) _____
- Partially (2) _____
- No (3) _____

Q3 What leisure activities do you like to engage in? (i.e., hobbies, favourite past times, recreational activity)

_____

Display This Question:

If Since your COVID-19 infection, have you been able to return to your usual activities of daily life... = Yes

And Since your COVID-19 infection, have you been able to return to your usual activities of daily life... = Partially

Q4 If you have been able to return to your leisure activities, how long after your COVID-19 was this?

- In a matter of weeks (1)
- After a month or more (between 1-3 months) (2)
- After a several months (>3months) (3)
- I've not been able to return to these activities (4)

Q5 How important are these activities to you? We'd like to hear more about how important these activities are to you, please can you provide some details on this

- Very important to me (1)

  _____

- Somewhat important to me (2)

  _____

- Not at all important to me (3)

  _____

Display This Question:

If Since your COVID-19 infection, have you been able to return to your usual activities of daily life... = Yes

And Since your COVID-19 infection, have you been able to return to your usual activities of daily life... = Partially

Q6 What support if any do you need to undertake these activities?

_____

Display This Question:

If Since your COVID-19 infection, have you been able to return to your usual activities of daily life... = No

Q7 If you have not been able to return to these activities, what would you say is the biggest barrier for you?

_____

Q8 Are you a parent with childcare responsibilities?

- Yes (1)
- No (2)

Display This Question:

If Are you a parent with childcare responsibilities? = Yes

Q9 Do you feel you are able to undertake these responsibilities fully? We'd like to hear more about this, please can you provide some details on this.

- Yes (1) _____
- No (2) _____

Display This Question:

If Are you a parent with childcare responsibilities? = Yes

Q80 Are you experiencing any difficulties fulfilling your childcare responsibilities? If so, please state what these are and how they are being impacted.

- Yes, always (1) _____
- Sometimes (2) _____
- No, not at all (3)

End of Block: Section 6: Activities of daily life

Start of Block: Section 7: Long COVID

Q1 Do you have anyone over-seeing your long COVID care?

- Yes (1)
- No (2)

Display This Question:

If Do you have anyone over-seeing your long COVID care? = Yes

Q1a If someone is over-seeing your long COVID care, please provide details of who or where you receive this care from?

_____

Q2 Have you been referred to a long COVID clinic?

- Yes (1)
- No (2)

Display This Question:

If Have you been referred to a long COVID clinic? = Yes

Q2a If you have been referred to a long COVID clinic, how long did you wait to see someone after you had caught COVID-19?

Display This Question:

If Have you been referred to a long COVID clinic? = Yes

Q2b If you have been referred to a long COVID clinic, what did your care consist of?

_____

Q3 If you have accessed long COVID care, have these services taken into account your fatigue when assessing you? Please give details on how they have or have not

- Yes (1) _____
- No (2) _____

Q4 Have you experienced any obstacles to receiving care for your long COVID?

- Yes, if so please give details (1)

  _____
- No (2)

Q5 5. Have you experienced any medical gaslighting i.e. where someone has blamed your symptoms on psychological factors such as anxiety?

- Yes, if so can you describe this? (1)

  _____

- No (2)

Q6 What have been your main difficulties in living with long COVID?

_____

Q6a How have these impacted upon your activities of daily living?

_____

Q7 Have you experienced or are you receiving support for mental health issues because of COVID-19 related symptoms?

- Yes (1)
- No (2)
- Prefer not to say (3)

Display This Question:

If Have you experienced or are you receiving support for mental health issues because of COVID-19 re... = Yes

Q7a If you experienced mental health issues or are receiving support for mental health issues because of your COVID-19 experience, would you be willing to tell us more about this?

- Yes, please detail below (1)

  _____

- No, I'd prefer not to (2)

Q8 Has long covid affected your cognitive abilities? (E.g. thinking, knowing, remembering, judging, and problem-solving)

- Yes, if so how? (please detail) (1)

  _____

- No (2)

Q9 How do you think long COVID has affected you emotionally i.e. your ability to deal with different emotions such as stress, happiness, worry etc?

_____

Q10 How does exercise or activities impact upon your symptoms?

- Not at all (1)
- Very mildly (2)
- Mild (3)
- Moderately (4)
- Severely (5)

Q11 How do your exercise levels compare between now and pre-covid?

- Far below pre-covid (1)
- Below pre-covid (2)
- The same as pre-covid (3)
- Above pre-covid (4)
- Far above pre-covid (5)

Q12 What systems in your body do you feel have been affected by Long Covid?

- Skeletal (bones) (1)
- Muscular (muscle) (2)
- Nervous (brain) (3)
- Endocrine (hormonal) (4)
- Cardiovascular (heart) (5)
- Lymphatic (immune function) (6)
- Respiratory (lungs, airways) (7)
- Digestive (8)
- Urinary (9)
- Reproductive (10)
- Other (please detail) (11)

  _____

Q13a What treatments have you received for long COVID that have been the most helpful?

_____

Q13b What lifestyle changes have you made that have been helpful in managing your long COVID?

_____

Q13c What treatments/ lifestyle changes do you feel would help you but you may not have access to them?

_____

Q13d Why can you not access the treatments/ lifestyle changes you feel would help you?

_____

Q14 What do health care professionals need to know when assessing and treating someone with long COVID?

_____

Q15 What has been positive or negative about being unwell with an unknown/novel virus?

_____

Q16 Have you been taking any supplements or medication for long COVID?

- Yes, if so please detail (1)

  _____

- No (2)

Display This Question:

If Have you been taking any supplements or medication for long COVID? = Yes, if so please detail

Q17 Have the supplements or medication you have been taking for long COVID been helpful or made symptoms worse? Please give us more details on this

- Helpful (1) _____
- Made symptoms worse (2)

  _____

- Neither helpful nor made symptoms worse (3)

  _____

Q18 Have you had any cardiac symptoms? (Heart palpitations, increase heart rate, blood pressure)

- Yes, if so how have they been dealt with? (please detail) (1)

  _____

- No (2)

Q19 Have you noticed any changes in weight?

- Yes, if so have these been associated with gut symptoms? (please detail) (1)

  _____

- No (2)

Q20 Have you had to change what you eat since having long COVID?

- Yes, if so why and how (1) _____
- No (2)

End of Block: Section 7: Long COVID

Appendix 3a. *Chapter 3 Participant Information Sheet*

Participant Information Sheet

Profiling the determinants of recovery to establish novel rehabilitation guidelines to improve clinically relevant and patient-reported outcomes in the post-COVID-19 period.

IRAS Number: 292920

Chief Investigator: Dr Mark Faghy
Principal Investigator: Dr Thomas Bewick

Part 1: Invitation

You have been invited to take part in a research study. Before you decide whether to take part or not, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

PART 1: Tells you the purpose of this study and what will happen to you if you take part.

PART 2: Gives you more detailed information about the conduct of the study.

Ask us if anything is unclear, or if you would like more information. Take time to decide whether you wish to take part.

1. What is the purpose of the study?

Few studies are looking to understand the important factors that lead to recovery following a COVID-19 infection. The knowledge obtained from this project will increase our understanding of recovery and allow us to develop COVID-19 specific rehabilitation and patient support services which can be implemented to help patients and restore wellbeing, physical capacity, and functional status.

2. Why have I been chosen?

You have been asked to take part in the study because you are:

- Aged 18 years or older
- Have been admitted to hospital for treatment for a COVID-19 infection, referred to an established long-COVID clinic or have persistent symptoms consistent with a long COVID diagnosis.
- Identified as a grade 2, 3 or 4 using the post-COVID functional status scale.
- Chest radiograph/CT scan consistent with COVID-19 infection if previously hospitalised with COVID-19.
- You can understand verbal or written information in English.

3. Do I have to take part in this study?

No, your participation is completely voluntary, and it is up to you to decide whether or not to take part. If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form to confirm that you understand what is involved when taking part in this study. If you decide to take part, you are free to leave the study at any time and without giving a reason.

4. What will happen to me if I take part in the study?

This study is a 16-week cohort observational study. This means that once you have been discharged from hospital or referred to a long-COVID clinic, we would like to test some important markers that we know are associated with recovery to see how these change over time. If we can increase our understanding of recovery, we may be able to develop approaches that can support other patients in the future with their recovery. If you agree to take part, you will be invited to the University of Derby (Kedleston Road, Derby, DE22 1GB) in the first few days following discharge to conduct some baseline tests and again on four more occasions, each session lasting approximately 60 minutes. In between face-to-face visits, we will also phone you to ask you some questions about your recovery.

The specific details about the activities that you will be asked to complete can be found on the next page.

What do I have to do?

Study duration:

Study duration will be approximately 16 weeks, but it could be between 15-17 weeks as there is some flexibility with your visits to the University to suit your schedule.

Your Participation Involves:

1) A post-discharge visit to the University of Derby, within three days of your discharge, to conduct a baseline assessment.

   In this visit we will capture the following information:

   - We will take a blood sample from your arm to assess important biomarkers that are associated with COVID-19 severity and recovery.
   - Assess your lung and respiratory muscle function to determine how well your lungs and respiratory muscles are working.
   - Ask you questions to understand the severity of your symptoms.
   - Gather information about your functional status, quality of life and physical capacity.
   - Ask you questions relating to your cognition and your sleep performance.

2) Every four-weeks, until you have completed four visits you will be invited back to the University to complete these measurements again, however, there will be no blood samples taken in any follow-up visit.

3) In between each face-to-face visit, we will also phone you to ask you about your symptoms and more generally about your recovery. This will last approximately 15 minutes.

4) We will also provide you with a diary for the duration of the study where you can record your experiences of your recovery.

Study Flow Chart

Week 0	**Study Enrolment** **Visit 1:** At the University of Derby (Kedleston Road Campus) following your discharge from hospital to conduct all baseline measures. **Approximately 120 mins.**
Week 2	Telephone consultation to ask you about symptoms and more generally about your recovery. **Approximately 15 mins.**
Week 4	**Visit 2:** At the University of Derby for your first follow up visit and to repeat all baseline measures (except blood samples). **Approximately 60 mins.**
Week 6	Telephone consultation to ask you about symptoms and more generally about your recovery. **Approximately 15 mins.**
Week 8	**Visit 3:** At the University of Derby for your first follow up visit and to repeat all baseline measures (except blood samples). **Approximately 60 mins.**
Week 10	Telephone consultation to ask you about symptoms and more generally about your recovery. **Approximately 15 mins.**
Week 12	**Visit 4:** At the University of Derby for your first follow up visit and to repeat all baseline measures (except blood samples). **Approximately 60 mins.**
Week 14	Telephone consultation to ask you about symptoms and more generally about your recovery. **Approximately 15 mins.**
Week 16	**Study Completion** **Visit 5:** At the University of Derby for your first follow up visit and to repeat all baseline measures (except blood samples). **Approximately 60 mins.**

5. What are the alternatives for diagnosis or treatment?

This study does not involve a diagnosis or a treatment. We want to see how your symptoms change throughout your recovery.

6. What are the side effects of any treatment received when taking part?

There are no treatments involved in this research and we do not anticipate that you will experience any side effects from taking part in this research.

7. What are other possible disadvantages and risks of taking part?

There are no identified risks of taking part in this research. We are looking to profile your symptoms once you have been discharged from hospital and monitor how these change in the 16 weeks post your discharge.

Should you experience any problems or have any questions relating to the research then we encourage you to contact the research team using the details provided at the end of the document.

8. What are the possible benefits of taking part?

Your participation in this study is completely voluntary and you can withdraw your participation at any time. There will be no tangible benefits of taking part in the research, but we will be able to cover the cost of your expenses for attending all face-to-face sessions at the University of Derby.

Your participation will also contribute to the development of new knowledge into the recovery of patients following a COVID-19 infection. This will allow researchers to understand how your symptoms change and develop approaches to support patients in their recovery in the future.

9. What happens when the research study stops?

Once your participation has been confirmed, your data will be completely anonymized and analyzed by our trial statistician to determine the important areas that we must consider when supporting patients with their recovery.

10. What happens if there is a problem during the study?

If you have a concern about any aspect of this study, you should ask to speak with the trial researchers who will do their best to answer your question.

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital or you can contact PALS (Patient Advice and Liaison Service) telephone 0800 183 0204.

Insurance and indemnity for this study will be provided via the University of Derby's role as sponsor. If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

11. Will my taking part in the study be kept confidential?

All data collected will remain confidential under the regulations of the GDPR Act (2018). Only the research team and research partners will have access to the data and all data will remain strictly confidential and stored in a secure location.

All data collection spreadsheets will not link data directly to individuals and will be encrypted by a password for storage. Individual participants will be unidentifiable in the analysis and write up.

12. Contact Details

Research Associates: Rebecca Owen - R.Owen@derby.ac.uk or 01332 591086

James Yates – J.Yates@derby.ac.uk

Callum Thomas: C.Thomas@derby.ac.uk

Chief Investigator: Dr Mark Faghy – M.Faghy@Derby.ac.uk or 01332 592109

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2:

13. What if new information becomes available?

Various COVID-19 research projects are happening around the world in an attempt to better understand the challenges provided by this novel virus. The research team are actively tracking the state of the research in this area and should any new and important information be made available relating to the recovery, the research team will inform you and discuss with you whether you want to or should continue with the study. On receiving new information, we might consider it to be in your best interests to withdraw you from the study, but all details and decisions will be discussed with you first.

14. What will happen if I do not want to carry on with the study?

To withdraw from the study please just contact any of the research team. You can withdraw at any time, for any reason without having to explain your reasons for withdrawing. You can withdraw from participation up to 1 month after your participation in the study has finished. Once this time has passed, it will not be possible to withdraw your data from the research as your data will be anonymised.

15. Will my participation in this study be kept confidential?

If you consent to take part in this study, your data obtained during the study will remain strictly confidential at all times. The information will be held securely on paper and electronically by the research team at the University of Derby under the provisions of the 1998 Data Protection Act. Your name will not be passed to anyone else outside of the trial research team or the sponsor.

Your name will appear on your consent form. For the telephone identification, we will keep your surname (study ID) on your record form whilst data is being collected, but this will be removed when the data is entered into the electronic record. All other records will have your name removed and will only feature your initials and date of birth. Please note that for this study we will not be using hospital numbers, we will have a subject enrolment log that will contain the personal details of subjects and their study ID. This will be used to contact you, but all other study documentation will only contain your subject ID.

Your data will be available to people authorised to work on the trial but may also need to be made available to people authorised by the Research Sponsor, which is the organisation responsible for ensuring that the study is carried out correctly. A copy of your consent form may be sent to the Research Sponsor during the study. By signing the consent form you agree to this access for the current study and any further research that may be conducted, even if you withdraw from the current study.

The information collected about you may also be shown to authorised people from the UK Regulatory Authority and Independent Ethics Committee; this is to ensure that the study is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you as a research participant.

If you withdraw consent from further study treatment, unless you object, your data will remain on file and will be included in the final study analysis.

In line with the Good Clinical Practice guidelines, at the end of the study, your data will be securely archived for fifteen years. Arrangements for confidential destruction will then be made.

16. Use of your personal data in research

The University of Derby is the sponsor for this study based in the United Kingdom. We will be using information from you to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The research team at the University of Derby will keep identifiable information about you for 7 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use minimal identifiable information as possible. You can find out more about how we use your information using the following link (https://www.nuh.nhs.uk/gdpr) or by contacting the Information Commissioners Office on 0303 123 1113.

17. Informing your General Practitioner (GP)

We will contact your GP to inform them via a letter about your participation in this study. We inform them of your participation just in case they see you during your involvement in the study.

18. What will happen to any samples that I give?

During your baseline visit, we will collect a blood sample from your arm to investigate some important biomarkers following discharge. These samples will be analysed at the University of Derby and destroyed in line with University guidelines for sample disposable. No samples collected as part of this research will be stored following analysis or used in future research.

19. Will any genetic testing be done?

Genetic testing will not be carried out in this study.

20. What will happen to the results of this clinical trial?

Once the study has been completed all data will be anonymised and used for analysis by researchers at the University of Derby. Upon completion of the analysis, all raw data will be disposed of according to appropriate governing bodies. The anonymised results of the evaluation will be shared with the project partners and the company who developed the device.

All participants will be eligible to receive a summary of the project findings which will be available upon completion of the study (anticipated December 2021). Should you wish to receive a summary please contact the Chief Investigator on the contact details provided on page 6 or 10.

If deemed appropriate, the findings may also be published in a peer-reviewed academic journal. In this instance, all your data will be completely anonymous and not contain any information that will identify you.

21. Who is organising and funding this clinical trial?

The University of Derby will act as the sponsor for the research and Dr Mark Faghy will act as the Chief Investigator. Dr Thomas Bewick from the Royal Derby and Burton Hospital will act as the study's Principal Investigator.

The research has been funded by the GILEAD Sciences COVID-19 RFP Program: COMMIT.

22. Who has reviewed this study?

The research protocol and all study documentation have been reviewed by an independent group of people called a Research Ethics Committee, to protect your safety, rights, well-being, and dignity. This study has been reviewed and given a favourable opinion by the Research Ethics Committee (Ethics approval number 292920) and also by the University of Derby Human Sciences Research Ethics Committee (REC number: ETH2021-3135).

The trial will be monitored by a trial steering group that consists of researchers from the University and its research partners who will regularly review the progress of the study and check study documents for accuracy.

23. Contact information and further information?

If you have read the above information and you are still interested in taking part in this study, then please inform a member of the clinical team whilst in hospital and we will make arrangements for you to attend your first session. If you are at all unsure, you may have more time to think this through.

Thank you for taking the time to read this information sheet and to consider this study.

Please contact the Research Associates below to ask questions and take part in the study:

Rebecca Owen: R.Owen@derby.ac.uk

James Yates: J.Yates@derby.ac.uk

Callum Thomas: C.Thomas@derby.ac.uk

01332 591086

Chief Investigator: Dr Mark Faghy

M.Faghy@Derby.ac.uk or 01332 592 109

Appendix 3b. *Chapter 3 Informed Consent*

UNIVERSITY OF DERBY

NHS University Hospitals of Derby and Burton NHS Foundation Trust

Participant Consent Form

Version: 1.1 Date: 2nd February 2021 IRAS Number: 292920

Profiling the determinants of recovery to establish novel rehabilitation guidelines to improve clinically relevant and patient-reported outcomes in the post-COVID-19 period.

Chief Investigator: Dr Mark Faghy

Participant Study ID: …..…….. Initials: ……

Participant initial each box

1. I _____ (insert name) confirm that I have read and understood the participant information sheet for the above study. ☐
2. I confirm that I have had the opportunity to consider the information, ask questions and I have received satisfactory answers. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. ☐
4. I consent to the storage including electronic, of personal information for the purposes of this study. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication. I agree to take part in the above evaluation. ☐
5. I consent for my GP to be informed that I am taking part in this study. ☐
6. I give permission for my contact details to be kept on University of Derby's database for future research participation. *(Please circle Y=Yes or N=No)* Y / N
7. I agree to take part in the above study. ☐

_____	_____	_____
Name of the participant *(Print)*	Date	Participant signature
_____	_____	_____
Name of person taking consent *(Print)*	Date	Signature

Original to be retained and filed in the site file and 1 copy to patient

Appendix 3c. *Chapter 3 GP Letter*

University of Derby
Kedleston Road
Derby
DE22 1GB
Direct Dial: 01332592109
Email: m.faghy@derby.ac.uk

Date:……

GP name:……

GP address: ……

……

Dear Dr ……..

The following person has agreed to participate in the clinical study detailed below and has given their consent for me to inform you of this.

Patient Name: ……

Date of birth: ……

Address: ……

Study Title: Profiling the determinants of recovery to establish novel rehabilitation guidelines to improve clinically relevant and patient-reported outcomes in the post-COVID-19 period.

Protocol no: COVID-19-UoD&RDH20/21.

Sponsor: University of Derby

Please find enclosed a copy of the patient information sheet for your records.

We have approval from the relevant regulatory committees (IRAS Number: 292920) to carry out this study.

Yours sincerely

Signature redacted for data protection

Dr Mark Faghy

Chief Investigator

Appendix 3d. *Post-COVID-19 Functional Status Scale Patient Reported Outcome Measure*

Post-COVID-19 Functional Status Scale

How much are you currently affected in your everyday life by COVID-19? **Please indicate which one of the following statements applies to you most.** *Please tick only one box at a time*		**Corresponding PCFS scale grade if the box is ticked**
I have no limitations in my everyday life and no symptoms, pain, depression, or anxiety.	☐	0
I have negligible limitations in my everyday life as I can perform all usual duties/activities, although I still have persistent symptoms, pain, depression, or anxiety.	☐	1
I suffer from limitations in my everyday life as I occasionally need to avoid or reduce usual duties/activities or need to spread these over time due to symptoms, pain, depression or anxiety. I am, however, able to perform all activities without any assistance.	☐	2
I suffer from limitations in my everyday life as I am not able to perform all usual duties/activities due to symptoms, pain, depression, or anxiety. I am, however, able to take care of myself without any assistance.	☐	3
I suffer from severe limitations in my everyday life: I am not able to take care of myself and therefore I am dependent on nursing care and/or assistance from another person due to symptoms, pain, depression, or anxiety.	☐	4

Appendix 3e. *EQ5D5L*

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Appendix 3f. *MRC Dyspnoea Scale*

Used with permission of the Medical Research Council.

MRC Dyspnoea Scale

1	Breathless only with strenuous exercise.
2	Short of breath when hurrying on the level or up a slight hill.
3	Slower than most people of the same age on a level surface OR Have to stop when walking at my own pace on the level.
4	Stop for breath walking 100 meters OR After a walking few minutes at my own pace on the level.
5	Too breathless to leave the house.

Appendix 3g. *Fatigue Assessment Scale*

Fatigue Assessment Scale (FAS)

The following ten statements refer to how you usually feel. Per statement you can choose one out of five answer categories, varying from Never to Always. Please circle the answer to each question that is applicable to you. Please give an answer to each question, even if you do not have any complaints at the moment.

1 = Never, 2 = Sometimes; 3 = Regularly; 4 = Often and 5 = Always.

	Never	Sometimes	Regularly	Often	Always
1. I am bothered by fatigue	1	2	3	4	5
2. I get tired very quickly	1	2	3	4	5
3. I don't do much during the day	1	2	3	4	5
4. I have enough energy for everyday life	5	4	3	2	1
5. Physically, I feel exhausted	1	2	3	4	5
6. I have problems to start things	1	2	3	4	5
7. I have problems to think clearly	1	2	3	4	5
8. I feel no desire to do anything	1	2	3	4	5
9. Mentally, I feel exhausted	1	2	3	4	5
10. When I am doing something, I can concentrate quite well	5	4	3	2	1

Appendix 3h. *Modified Fatigue Impact Scale (MFIS)*

Modified Fatigue Impact Scale (MFIS)

Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. But people who have medical conditions like MS experience stronger feelings of fatigue more often and with greater impact than others.

Following is a list of statements that describe the effects of fatigue. Please read each statement carefully, the circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks.

Because of my fatigue during the past 4 weeks

		Never	Rarely	Sometimes	Often	Almost Always
1.	I have been less alert.	0	1	2	3	4
2.	I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3.	I have been unable to think clearly.	0	1	2	3	4
4.	I have been clumsy and uncoordinated.	0	1	2	3	4
5.	I have been forgetful.	0	1	2	3	4
6.	I have had to pace myself in my physical activities.	0	1	2	3	4
7.	I have been less motivated to do anything that requires physical effort.	0	1	2	3	4
8.	I have been less motivated to participate in social activities.	0	1	2	3	4
9.	I have been limited in my ability to do things away from home.	0	1	2	3	4
10.	I have trouble maintaining physical effort for long periods.	0	1	2	3	4
11.	I have had difficulty making decisions.	0	1	2	3	4
12.	I have been less motivated to do anything that requires thinking	0	1	2	3	4
13.	My muscles have felt weak	0	1	2	3	4
14.	I have been physically uncomfortable.	0	1	2	3	4
15.	I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16.	I have had difficulty organizing my thoughts when doing things at home or at work.	0	1	2	3	4
17.	I have been less able to complete tasks that require physical effort.	0	1	2	3	4
18.	My thinking has been slowed down.	0	1	2	3	4
19.	I have had trouble concentrating.	0	1	2	3	4
20.	I have limited my physical activities.	0	1	2	3	4
21.	I have needed to rest more often or for longer periods.	0	1	2	3	4

Instructions for Scoring the MFIS

Items on the MFIS can be aggregated into three subscales (physical, cognitive, and psychosocial), as well as into a total MFIS score. All items are scaled so that higher scores indicate a greater impact of fatigue on a person's activities.

Physical Subscale

This scale can range from 0 to 36. It is computed by adding raw scores on the following items: 4+6+7+10+13+14+17+20+21.

Cognitive Subscale

This scale can range from 0 to 40. It is computed by adding raw scores on the following items: 1+2+3+5+11+12+15+16+18+19.

Psychosocial Subscale

This scale can range from 0 to 8. It is computed by adding raw scores on the following items: 8+9.

Total MFIS Score

The total MFIS score can range from 0 to 84. It is computed by adding scores on the physical, cognitive, and psychosocial subscales.

Appendix 3i. *Symptom Score*

Symptom Score

In the past 24 hours, how much have you been bothered by:						
Symptom	Patient did not have symptom / problem	Patient had symptom/problem and it bothered them;				
		Not at all	A little	Moderately	Quite a bit	Extremely
1. Coughing	0	1	2	3	4	5
2. Coughing up phlegm / sputum	0	1	2	3	4	5
3. Coughing up blood	0	1	2	3	4	5
4. Chest pain	0	1	2	3	4	5
5. Shortness of breath	0	1	2	3	4	5
6. Sweating	0	1	2	3	4	5
7. Chills	0	1	2	3	4	5
8. Headache	0	1	2	3	4	5
9. Nausea	0	1	2	3	4	5
10. Vomiting	0	1	2	3	4	5
11. Diarrhoea	0	1	2	3	4	5
12. Stomach pain	0	1	2	3	4	5
13. Muscle pain	0	1	2	3	4	5
14. Lack of appetite	0	1	2	3	4	5
15. Trouble concentrating	0	1	2	3	4	5
16. Trouble thinking	0	1	2	3	4	5
17. Trouble sleeping	0	1	2	3	4	5
18. Fatigue	0	1	2	3	4	5

Appendix 3j. *Montreal Cognitive Assessment (1)*

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Appendix 3k: *Montreal Cognitive Assessment (2)*

Content removed due to copyright restrictions.

Appendix 4a: *Delphi Study Invitation Letter to GP's, Respiratory Physicians, Physiotherapists, Healthcare Professionals, Long COVID Researchers*

DELPHI STUDY INVITATION LETTER (GP's, Respiratory Physicians, Physiotherapists, HCP etc)

Dear Sir or Madam,

I am writing to invite you to participate in a Delphi study to support a research project regarding bespoke rehabilitation interventions for patients with Long Covid. The aim of the study is to provide expert guidance for GP's and long COVID clinical services, and inform interventions to improve recovery, quality of life and functional status following a long COVID diagnosis. As an established expert in the field, we are keen to gain your views and construct an expert consensus to inform rehabilitation interventions for Long Covid.

The Delphi process will consist of 3 rounds and will involve you completing an online survey. You will be required to state the extent to which you agree or disagree with several proposed statements, with the opportunity to provide context and further information on your answer using a free text box. All statements will be revised according to the data we collect.

If you are interested in participating in this research project or you have any further questions, please email r.owen@derby.ac.uk or m.faghy@derby.ac.uk and you will be sent a full Participant Information Sheet.

Yours faithfully,

Rebecca Owen
University of Derby

Appendix 4b: *Delphi Study Invitation Letter to Long COVID Patients*

DELPHI STUDY INVITATION LETTER (Long Covid Patients)

Dear Sir or Madam,

I am emailing regarding your interest in participating in Long COVID research, following the 'Living with COVID-19: Please hear what we have to say' survey you have previously completed. We are currently recruiting for participants to be involved in a Delphi study to inform bespoke rehabilitation interventions for patients with Long Covid. The aim of the study is to provide expert guidance for GP's and long COVID clinical services, to inform interventions to improve recovery, quality of life and functional status following a long COVID diagnosis. As an individual living with Long Covid, we are keen to gain your views to help construct an expert consensus to inform rehabilitation interventions for Long Covid.

The Delphi process will consist of 3 rounds and will involve you completing an online survey. You will be required to state the extent to which you agree or disagree with several proposed statements, with the opportunity to provide context and further information on your answer using a free text box. Please be aware that some statements may seem controversial to you as someone living with long COVID, but your response and feedback will be used to reach consensus on these issues.

If you are interested in participating in this research project or have any further questions, please email r.owen@derby.ac.uk or m.faghy@derby.ac.uk and you will be sent a full Participant Information Sheet.

Yours faithfully,

Rebecca Owen
University of Derby

Appendix 4c: *Chapter 4 Participant Information Sheet*

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Participant Information Sheet:

Using a Delphi Consensus approach to inform bespoke rehabilitation interventions for long COVID.

We would like to invite you to participate in our research study. Before you decide whether you would like to participate, it is important for you to understand why the research is being conducted and what it will involve for you. Please read the information below carefully and contact **r.owen@derby.ac.uk** or **m.faghy@derby.ac.uk** for any enquiries.

What is the purpose of the study?

The aim of the study is to consult expert groups, including GP's, long COVID clinical services, and those living with long COVID, to develop a consensus statement that can be used to inform the development of bespoke interventions to improve recovery, quality of life and functional status for patients recovering from long COVID.

Why have I been invited?

We are looking for people who have experience, expertise and contact with those with COVID-19, or a lived experience with long COVID. As an expert within one or more of these areas, we are keen to gain your views to construct an expert consensus on long COVID rehabilitation.

Do I have to take part?

Participation in this research is completely voluntary and it is up to you to decide whether or not you would like to participate. You are under no obligation to take part in the study, but if you would like to take part, you will be given this information sheet to keep and will provide digital consent before completing the survey. You are free to withdraw from the study at any time without jeopardy.

What will happen to me if I take part?

If you agree to participate, you will be sent a link to the online survey. This survey will involve you scoring each statement using a Likert scale, such as strongly agree, agree, disagree, strongly disagree or unsure. Once the results of this round are collected and analysed, you will then be sent a second survey including the results of the first round. The second survey will be

shorter due to items being revised. A total of three forms will be sent out over a time frame of 6-8 months.

What will happen if I do not want to continue with the study?

Your participation is voluntary, and you are free to withdraw at any time, without reason. If you decide to withdraw, we will no longer collect any further information from you, but we will keep the data we have already obtained if it has already been analysed. This is because we are unable to tamper with study records, and this information may have been used in analyses or revision of the Delphi piece. Any personal information, such as your email address, will be deleted permanently on withdrawal.

Expenses and payments:

There will be no payments for inconvenience allowance for the current study, and no travel expenses due to the nature of the online survey.

What are the possible benefits in taking part?

There are no certain benefits to this study, but this study may help improve the quality of life for patients living with long COVID due to the rehabilitation interventions informed by your response.

What are the possible risks of taking part?

There are no perceived risks of taking part in this study, but if you have any concerns, please contact **r.owen@derby.ac.uk** or **m.faghy@derby.ac.uk**.

Who is conducting and funding the research?

This study is being conducted as part of a PhD thesis and as part of wider research in the Human Sciences Research Centre at the University of Derby. There are also research partners involved from The University of Nottingham and University Hospitals of Derby and Burton NHS Foundation Trust.

Further guidance on the use of your data and your rights.

Researchers will be collecting data from your participation in this study. We need these data to inform bespoke interventions for those living with persisting symptoms of COVID-19. This is

the legal basis on which we are collecting your data and while this allows us to use your data, it also means we have obligations towards you to:

- Not seek more information from you than what is essential and necessary for the study.
- Make sure that you are not identified by the data by anonymising it, using ID codes.
- Use your anonymised data only for the purposes of this study and for any relevant publications that arise from it.
- Store data safely in password-protected databases to which only the named researchers have access.
- Not keep your information for longer than is necessary (usually for a maximum of seven years).
- Safely destroy your data by shredding or permanently deleting them.

You have a right to withdraw from the study at any point, however any data that has already been collected from you will be unable to be withdrawn. Should you wish to withdraw during this timeframe, you can do so by contacting Rebecca Owen via email using the contact details available at the end of the form. Within this email, you should quote your 6-character unique identification code and you will no longer be contacted as part of this research. Your personal data will be permanently deleted on withdrawal.

To protect your right to confidentiality and anonymity, your data will not be stored against your name. Your data will be stored against a 6-character unique identification code based on the first 4 digits of your postcode items, followed by the 2 digits reflecting the day you were born (e.g., if you were born the 1st of June, please use 01). You will generate this code within the survey, so please keep note of this for your own records. Your data and electronically signed consent form will be stored on a password protected computer to which only the lead researcher has access. Anonymised raw data will be shared in a read-only file with the co-researchers for the purpose of analysis. At no point in the research will you be named, and any identifying information provided in the survey will not be included in the study. The data collected is for research purposes only and may be stored for a period suitable for the aims of the research, according to Article 89 of the GDPR regulations relating to scientific research, enforced in May 2018. Your data will be kept for a maximum of 7 years and then destroyed. Data will only be accessible to the named researcher.

Researchers on the project with access to the data are supervised by highly qualified and experienced staff and have been very careful to ensure the security of your data. The study was

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approved for its ethical standards by The University of Derby Human Sciences Research Ethics Committee. Further information about the project can be obtained from Rebecca Owen, **r.owen@derby.ac.uk** or Dr Mark Faghy, **m.faghy@derby.ac.uk** at University of Derby, Kedleston Road, Derby DE22 1GB.

Further Information and Contact Details:

Rebecca Owen
PhD Student at the University of Derby
r.owen@derby.ac.uk

Dr Mark Faghy
Associate Professor in Respiratory Physiology
m.faghy@derby.ac.uk

Appendix 4d: Full response breakdown including % agreement and when consensus was achieved for each round.

Percentage agreement for statements that achieved consensus (>80%) following Round 1 (N=33).

	Agree	Neither	Disagree	Unsure
Long COVID is a condition that will require support for patients' long term (6+ months).	96.7%	2.6%	0.7%	0.7%
Long COVID is a public health concern.	96.6%	0.7%	1.8%	0.7%
Long COVID is a condition that affects multiple systems of the body.	99.3%	0.0%	0.8%	0.4%
Long COVID is a condition that affects individuals of good health prior to contracting COVID-19.	91.6%	5.1%	2.5%	1.1%
Long COVID is an illness that presents itself through several symptoms.	98.2%	1.1%	1.1%	0.4%
Long COVID is a condition that requires specialised rehabilitation interventions.	86.1%	5.90%	3%	4.40%
People living with long COVID require clinical assessments and medical investigations.	95.2%	2.6%	0.8%	1.5%
Respiratory function should be assessed to establish rehabilitation needs for people living with long COVID.	81%	7.7%	7.4%	4%
People living with long COVID should complete a formal assessment of physical and emotional functioning to identify rehabilitation needs.	88%	6.2%	4%	1.8%
Long COVID intervention should be implemented as early as possible.	92.3%	3.7%	1.9%	2.2%
People living with long COVID should receive adequate support from their GP.	87.2%	3.3%	7.7%	1.8%
People living with long COVID should receive a comprehensive rehabilitation programme.	87.5%	5.5%	3.3%	3.7%
Long COVID support should adopt A multidisciplinary approach.	94.1%	1.8%	2.6%	1.5%
Long COVID rehabilitation plans should be made with patient input.	98.5%	0.0%	1.5%	0.0%
Early implementation of rehabilitation interventions should be encouraged for those with long COVID.	87.6%	2.6%	4.8%	5.1%
Long COVID rehabilitation intervention should be personalised according to age and comorbidities.	91.1%	2.6%	1.4%	4.8%
Those undergoing long COVID rehabilitation should be closely monitored to establish whether their condition is improving deteriorating or neither.	93.4%	3.3%	1.6%	0.7%
Long COVID rehabilitation might be different for each patient.	98.40%	1.1%	1.1%	0.4%

Improving quality of life and physical function is a key aim of long COVID rehabilitation.	94.60%	3.3%	1.5%	0.7%
Long COVID rehabilitation interventions should be guided by the needs of the patient.	97.1%	1.1%	1.1%	0.7%
How important is it for long COVID rehabilitation to focus on the following…	**Important**	**Neither**	**Not Important**	**Unsure**
Breathlessness	97.2%	1.9%	0.0%	1.5%
Cognitive dysfunction	96.4%	1.8%	0.4%	1.5%
Fatigue	97.4%	1.8%	0.0%	0.7%
Respiratory function	96.3%	1.8%	0.7%	1.1%
Restoring functional capacity	97.2%	1.5%	0%	1.5%
Sleep disturbance	96.7%	1.5%	0.7%	1.1%
How important is it for long COVID rehabilitation to include the following…	**Important**	**Neither**	**Not Important**	**Unsure**
Self-management of daily living	96.3%	1.1%	0.4%	2.2%
Cognitive pacing	96.3%	0.7%	0%	3%
Physical pacing of activities	95.6%	1.5%	0.7%	2.2%
Support returning to work	96.3%	1.1%	0.4%	2.2%
Support returning to normal activities of daily living	96.4.%	1.1%	0.7%	1.8%
Breathing techniques	96.5%	1.1%	0.4%	2.9%
Fatigue management	97.4%	1.1%	0.0%	1.5%

Categories collapsed: Strongly agree+agree, strongly disagree+disagree; very important+important.

Percentage agreement for statements that did not achieve consensus (>80%) following Round 1 (N=32).

	Agree	Neither	Disagree	Unsure
Long COVID is mainly experienced by those who had severe symptoms when they contracted COVID-19.	10.3%	11.7%	71.1%	8.1%
People living with long COVID should be encouraged to participate in regular physical activities if symptoms allow.	48.2%	14.3%	30.5%	8.8%
People living with long COVID can expect to make a full recovery.	11%	26.8%	22.8%	41.2%
Individuals living with long COVID should receive a different form of rehabilitation than those who were hospitalised with COVID-19.	60.3%	16.2%	11%	12.5%
People who have been hospitalised with COVID-19 should receive rehabilitation in hospital until they are discharged.	46.8%	14.8%	19.5%	18.8%
People living with long COVID should complete a formal assessment before being encouraged to complete physical activity independently.	77.6%	8.8%	9.5%	4%
Laboratory tests should play an important role in diagnosing and treating long COVID.	64.3%	14%	9.9%	11.8%
People with long COVID should receive a psychological assessment as part of long COVID care.	73.3%	12.1%	9.5%	5.1%
There is currently adequate support available from healthcare services for people living with long COVID.	6.2%	4%	87.2%	2.6%
There are clear referral pathways to support for people living with long COVID.	14.3%	7.3%	74.7%	3.7%
Healthcare professionals are aware of how to treat long COVID.	9.9%	9.2%	74.7%	6.2%
Long COVID diagnosis and support should be based on clinical assessment.	76.9%	11%	5.5%	6.6%
Respiratory rehabilitation for people with long COVID should be similar to that of pneumonia patients.	14.7%	18.7%	23.1%	43.6%
Respiratory rehabilitation for people with long COVID should be similar to that of chronic obstructive pulmonary disease.	13.5%	19.4%	24.2%	42.9%
Long COVID rehabilitation should be based on research of pre-existing conditions with similar symptoms (e.g., chronic fatigue syndrome and pneumonia).	55.3%	12.5%	14.6%	17.6%
Long COVID rehabilitation plans should be similar for each patient.	4.8%	10.7%	78%	6.6%

Those undergoing long COVID rehabilitation should be closely monitored for safety.	79.5%	12.1%	4.1%	4.4%	
How important is it for long COVID rehabilitation to focus on the following…	**Very Important**	**Moderately/ Slightly Important**	**Neither**	**Not Important**	**Unsure**
Anxiety	66.8%	24.7%	3.3%	2.6%	2.6%
Depression	66.9%	25.6%	3%	2.2%	2.2%
Exercise capacity	75.3%	18.1%	1.8%	3%	1.8%
Psychological distress	77.7%	17.1%	1.9%	1.5%	1.9%
Emotional support	79.4%	16.9%	1.5%	1.1%	1.1%
Other	54.9%	15.9%	4.4%	0%	24.7%
How important is it for long COVID rehabilitation to include the following…					
Light to moderate physical activity (e.g., anything that raises the heart rate but still allows you to have a conversation at the same time)	48.5%	19.3%	5.6%	14.4%	12.2%
Activity focusing on muscle use (e.g., Yoga Pilates, Gardening)	58.6%	23.1%	5.2%	6.7%	6.3%
Increased cardiorespiratory demand as a result of daily activities (e.g., walking up and downstairs getting dressed and self-hygiene).	69.2%	13.4%	4.5%	4.5%	8.6%
Flexibility and stretching exercises	58%	29.2%	2.2%	4.9%	5.6%
Graded Exercise Therapy (GET)	27.8%	14.9%	8.6%	34.9%	13.8%
Relaxation techniques (e.g., deep breathing, meditation, yoga, mindfulness)	73.9%	17.3%	2.2%	2.2%	4.4%
Nutritional support	75.3%	18.9%	0.7%	1.5%	3.7%
In person / face to face interventions	68.80%	16.50%	4%	4%	6.60%
Interventions that can be completed virtually / at home.	74.70%	13.20%	3.3%	2.2%	6.60%
Categories collapsed: Strongly agree+agree, strongly disagree+disagree; very important+important.					

Percentage agreement for statements that achieved consensus (>80%) following Round 2 (N=17).

	Agree	Neither	Disagree
It is unknown whether individuals living with long COVID will make a full recovery.	92.5%	3.2%	4.3%
Long COVID support and rehabilitation should be individualised to the patient's needs.	99.5%	0.5%	0
Patients in hospital with COVID-19 should receive tailored rehabilitation and support before being discharged.	90.3%	8.1%	1.6%
Individuals experiencing symptoms consistent with ME/CFS and PEM should be carefully supported before participating in physical activity.	95.7%	3.8%	1%
Laboratory tests and functional screening assessments should be considered when diagnosing and treating long COVID.	94.1%	4.8%	1.1%
There is inadequate and inconsistent support amongst all healthcare services for individuals living with long COVID.	93%	3.8%	3.3%
There is a lack of clear referral pathways to support people living with long COVID throughout all healthcare settings.	86.6%	8.6%	4.8%
Screening and detailed clinical assessment should be an important part of the diagnosis and support long COVID receive.	97.3%	2.7%	0
Long COVID rehabilitation and support should consider research of pre-existing conditions with similar symptoms e.g., myalgic encephalomyelitis / chronic fatigue syndrome.	91.4%	5.4%	3.2%
Long COVID rehabilitation and support mechanisms should be dependent on each individuals' symptoms.	97.4%	2.2%	0.5%
Those completing long COVID rehabilitation and support interventions should have regular communication and monitoring with care providers.	100%	0	0

How important is it for long COVID rehabilitation and support to consider the following:	**Very Important / Important**	**Moderately Important / Slightly Important**	**Not at all Important**	**Unsure**
The mental impact of living with long COVID	92%	7%	1.1%	0
Tolerance to physical activity and physical activity	98.4%	1.6%	0	0
Emotional distress	87.1%	10.8%	1.6%	0.5%
Emotional wellbeing	87.6%	10.2%	1.6%	0.5%

How important is it for long COVID support mechanisms to include:				
Relaxation techniques and breathing techniques (e.g., meditation, mindfulness)	81.2%	12.4%	1.6%	4.8%
Patient preference on how they attend their interventions and support, and what is most suitable for them at the time	95.7%	2.2%	0	2.2%

Categories collapsed: Strongly agree+agree, strongly disagree+disagree; very important+important.

Percentage agreement for statements that did not achieve consensus (<80%) following Round 2 (N=15).

	Agree	Neither	Disagree
The severity of COVID-19 symptoms at the acute phase (first 2 weeks of infection) is not an indicator of whether someone is at risk of developing long COVID.	78.5%	7%	14.5%
If their symptoms allow and it is deemed safe to do so, people living with long COVID should participate in their regular physical activities.	60.7%	17.2%	22%
People with long COVID should receive a psychological assessment as part of integrated long COVID support.	69.9%	20.4%	9.6%
Appropriate treatment and support pathways are unknown to health care professionals.	79.5%	14%	7.5%
Respiratory rehabilitation and support mechanisms for people with long COVID should consider findings from pneumonia research.	60.8%	32.3%	7%
Respiratory rehabilitation and support mechanisms for people with long COVID should consider findings from chronic obstructive pulmonary disease.	55.3%	36%	8.6%

How important is it for long COVID support mechanisms to include:	Very Important / Important (%)	Moderately Important / Slightly Important (%)	Not at all Important (%)	Unsure (%)
Low level physical activities (e.g., anything that raises the heart rate but still allows you to have a conversation at the same time)	59.1%	14.5%	13.4%	12.9%
Muscle strengthening activities (e.g., yoga, Pilates, gardening)	66.1%	21.5%	4.8%	7%

Daily activities that increase heart rate and breathing rate (e.g., walking up and down stairs, getting dressed, self-hygiene)	65%	12.9%	12.9%	9.1%
Flexibility and stretching exercises	66.7%	24.2%	3.8%	5.4%
Nutritional / Dietary knowledge and guidance	79.5%	15%	1.6%	3.8%
In person / face to face interventions	59.7%	30.6%	4.3%	5.4%
Interventions that can be completed virtually at home	73.6%	20.4%	2.2%	3.8%
Hybrid model of both face to face and virtual interventions	78%	14%	2.2%	5.9%
How important is it for Graded Exercise Therapy (GET) to be avoided by people with long COVID experiencing post exertional malaise, chronic fatigue, and post-exertional symptom exacerbation?	67.7%	14.5%	8.6%	9.1%

Categories collapsed: Strongly agree+agree, strongly disagree+disagree; very important+important.

Table S5: Percentage agreement for statements that achieved consensus (>80%) following Round 3 (N=5).

	Agree	**Neither**	**Disagree (%)**	
Long COVID cannot be predicted by the severity of symptoms during the acute phase (first 2 weeks) of COVID-19 infection.	88.4%	7.2%	4.3%	
Long COVID services should offer psychological well-being support for those who require it.	93.5%	5.8%	0.7%	
There is a lack of understanding from healthcare professionals on how to support people with long COVID.	91.3%	3.6%	5.1%	
How important is it for long COVID rehabilitation and support mechanisms to include the following:	**Very Important / Important**	**Moderately Important / Slightly Important**	**Not at all important**	**Unsure**
Advice on modifying/adapting daily activities such as using aids to all greater functional ability.	91.2%	5.9%	0.7%	2.2%
A model that contains face to face and virtual sessions.	80.3%	13.2%	3.6%	2.9%

Percentage agreement for statements that did not achieve consensus (<80%) following Round 3 (N=10).

	Agree	Neither	Disagree	
If regular physical activities do not provoke symptoms or post exertional symptom exacerbation, then people with long COVID can participant in their regular physical activities.	68.9%	18.8%	12.3%	
Those designing support mechanisms for Long COVID can learn lessons from other acute respiratory infections (e.g., pneumonia).	57.3%	28.3%	14.5%	
Those designing support mechanisms for Long COVID can learn lessons from other chronic respiratory diseases (e.g., asthma and COPD).	60.2%	26.8%	13%	
Graded Exercise Therapy should not be part of Long COVID rehabilitation and support services.	70.3%	13%	16.7%	
How important is it for long COVID rehabilitation and support mechanisms to include the following:	**Very Important / Important**	**Moderately Important / Slightly**	**Not at all Important**	**Unsure**
Low level physical activities (e.g., walking) that results in moderate increased in heart rate.	52.9%	18.1%	18.8%	10.1%
Activities incorporating muscle use.	58.9%	25%	8.1%	8.1%
Support to increase flexibility and functional movement proficiency.	67.7%	22,1%	5.9%	4.4%
Advice on nutrition and diet to support recovery.	74.3%	19.1%	4.4%	2.2%
Interventions should be delivered face to face and make use of specialist facilities and personnel.	53.7%	34.6%	6.6%	5.1%
Interventions that can be completed remotely and away from clinical settings.	64.9%	26.9%	3.7%	4.5%

Categories collapsed: Strongly agree+agree, strongly disagree+disagree; very important+important.