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STIMULATE-ICP [COV-LT2-0043]

Title: Symptoms, Trajectory, Inequalities and Management: Understanding Long-COVID to Address and Transform Existing Integrated Care Pathways

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Plain English Summary

In a broad programme of work in the science and care of Long COVID, we have shown that Long COVID has a major disease burden and healthcare utilisation associated with it at system level. We have highlighted that the specialised Long COVID clinics are likely to have been effective for Long COVID care, compared with standard primary care, particularly in terms of healthcare utilisation and cost.

In our trial, we showed that the combination of antihistamines (loratadine/famotidine) and colchicine led to a small, but significant, improvement in fatigue and quality of life. There was an improvement in fatigue in all arms during the duration of the trial, which is likely to be associated with specialist Long COVID care in the dedicated clinics in England, where our trial was based, but may also represent an improvement during the natural trajectory of Long COVID. We found no improvement in fatigue with the implementation of an early, multi-organ Magnetic resonance imaging (MRI) strategy in Long COVID management, probably due to incomplete understanding of the mechanism of Long COVID and current lack of evidence-based, targeted therapies. We showed a small improvement in quality of life at 6 months with a digital rehabilitation platform.

Current care for Long COVID, even with the specialised Long COVID clinics in England was variable in delivery and access across the country, and some individuals with Long COVID continue to face substantial barriers to timely, effective care. Integrated care of Long COVID is needed, alongside other long term conditions, and this is recommended by both patients and health professionals. Taken together, long term effects of pandemics, such as Long

COVID, should form part of pandemic preparedness and planning in future. We have shown that pragmatic, data-driven research co-led by patients and public can be conducted in Long COVID in the pandemic context.

Executive Summary

Aim: To develop integrated care pathways (ICPs) for Long COVID, and to evaluate effectiveness and cost-effectiveness, compared with usual care.
Objectives:
WP1.SCIENCE: Define clinical problem and evaluate usual care
(a)Define clinical trajectories and healthcare utilisation
(b)Investigate effectiveness of current services
WP2.EVIDENCE: Design, implement and evaluate integrated care pathways
(a)To evaluate integrated care versus usual care
(b)Evaluate potential treatments
WP3.CARE: Evaluate and address inequalities in and transferability of care
(a)Design and evaluate interventions to minimise inequalities
(b)Assess transferability of care to other long-term conditions

Background: Long COVID spans multiple healthcare challenges, in particular delivering sustainable, high-quality care for multimorbidity and long-term conditions (LTC). There are inequalities in health, access to healthcare; incomplete pathways across community and hospital care; inadequate research translation to practice; and insufficient resources. Integrated care pathways (ICP) are structured multidisciplinary care plans of essential steps in care of specific conditions. An effective and deliverable ICP for Long COVID could reduce direct and indirect pandemic effects and improve LTC care beyond COVID-19. Long COVID services were initiated while ongoing research is defining epidemiology and pathophysiology, and guidelines are developing in absence of evidence. An ICP approach offers coordination across specialties, across investigation, treatment and rehabilitation, as well as opportunities for real-time iterative improvements in service design and delivery.
Why is this research important? Long COVID is estimated to have a substantial population burden, with up to 2 million people affected in the UK, at peak. Even in nonhospitalised individuals, up to 14% of people with COVID-19 may have persistent symptoms, suggesting major healthcare and economic burden. We are challenged "to design research that integrates reported lived experience needs with clinical models of care". Guidelines recommend referral to Long COVID clinics if symptoms persist for 4-12 weeks. However, neither the syndrome nor effective care are defined. Despite the roll-out of 100 centrally-funded Long COVID clinics at the peak of the pandemic, the most effective ICP remains unknown because elements of the pathway and their delivery are lacking in evidence. Patients and the public want "recognition, research and rehabilitation" simultaneously, as well as timely tests and treatment, which

may be more deliverable via ICP. We proposed urgent, practice-based evidence generation through "learning health system" approaches, connecting "science" (what is Long COVID and how is it being managed?), "evidence" (does evidence support an ICP approach to Long COVID management?), and "care" (how can we implement effective and equitable Long COVID care?) across silos: patients, data and specialists, and "implementation science" for rapid system learning and effective interventions.

Methods: We attempted to define optimal Long COVID care pathways (investigation, treatment, rehabilitation) in an adaptive, 4-year programme (originally planned to be over 2 years) with three work packages involving: Long COVID clinics in twelve regions; patient support groups; policymakers; specialist health professionals and academics in Long COVID and integrated care. We studied patient trajectories, healthcare utilisation, effectiveness and cost of usual Long COVID care using: (i) UK linked national records (n=56million); (ii) prospective cohort study of non-hospitalised long COVID (n=500); (iii) Long COVID clinics (n=6); (iv) qualitative interviews (n>40), and (v)"deep phenotyping"(e.g. omics, imaging, physiology) of common symptom groupings(n=300).In a pragmatic cluster (primary care network-level)-randomised trial, we evaluated ICPs with early, supported investigation (multi-organ MRI with Coverscan and clinical decision support) and enhanced rehabilitation (Living with COVID Recovery), compared with usual care(basic investigations and YourCOVIDRecovery self-management), recruiting adults with suspected Long COVID at referral. We originally planned to recruit 4520 individuals. In a nested, multi-arm, randomised (patient-level) drug trial, we assessed rivoraxaban, colchicine and loratidine/famotidine versus standard of care. Primary outcome was fatigue assessment scale at three months. We contributed to development of a Long COVID core outcome dataset for research and will assess cost-effectiveness of interventions. With patients, we co-developed interventions (enhanced case-finding) to improve access to care and support. In Long COVID clinics, our trials and national data, we investigated inequalities by geographic location, socioeconomic status, ethnicity and pandemic stage. Outputs for Long COVID policy and research include: (i) evaluation of current care and clinical trajectory; (ii) effective and equitable care pathways, transferable to other long-term conditions; (iii) platform design for future trials; and (iv) biobank for investigating outcome and treatment response.

Results

WP1(a) Define clinical trajectories and healthcare utilisation - We showed significant risk of Long COVID in those infected with SARS-CoV2, particularly in the pre-vaccination era and in the early waves of the pandemic. Based on MRI scanning, we showed single- and multi-organ impairment in 69% and 23% at

baseline, persisting in 59% and 27% at follow-up of 12 months, respectively in individuals with Long COVID.
Post-COVID-19 symptoms were significant in post-hospitalised and non-hospitalised patients, with significant ongoing healthcare needs and utilisation. In the largest Long COVID cohort from a single specialist post-COVID service to-date, only one-third of individuals under follow-up achieved satisfactory recovery. Fatigue severity and COVID-19 vaccination at presentation, even after initial COVID-19 infection, was associated with Long COVID recovery.
Healthcare utilisation per person (per month/year) was higher in LC than controls across GP (General Practitioner), OP (Outpatient) and ED (Emergency Department). For IP (Inpatient), LC had higher healthcare utilization than pre-LC and contemporary non-COVID (all $p < 0.0001$). Healthcare utilisation of the LC group increased progressively between 2020 and 2023, compared with controls. Median cost per patient/year was also higher in individuals with LC than all control groups.
WP1(b) Investigate effectiveness of current services - Long COVID care in England is not uniform across all locations. Post-COVID services in England may be effective in reducing the significant healthcare utilisation burden associated with Long COVID; despite this, there is evidence that socio-demographic factors are associated with poorer access to such services and subsequent outcomes.
WP2(a) To evaluate integrated care versus usual care Specialist clinical care is associated with fatigue reduction in LC, irrespective of an additional multi-organ MRI-based intervention. Digital rehabilitation could be useful in longer-term fatigue management in LC.
WP2(b) Evaluate potential treatments - In individuals with LC, severe fatigue improved with specialist care, and further reduced with colchicine and famotidine/loratadine, but not rivaroxaban. Prior CardioVascular disease (CVD) and high CardioVascular (CV) risk are associated with increased hospitalization and mortality in COVID-19 and LC. Targeted COVID-19 vaccination and CVD prevention are priority interventions.
WP3(a) Design and evaluate interventions to minimise inequalities - We found significant stigma and barriers faced by people living with Long COVID in England, by gender, region, ethnicity and comorbidities. We co-developed a case-finding intervention to help signpost care and rehabilitation for patients and their health professionals.
WP3(b) Assess transferability of care to other long-term conditions. Our mixed-methods research strongly recommended integrated care for Long COVID and other long term conditions.

Key findings: Long COVID has been associated with substantial, persistent healthcare utilisation and cost over the last five years. Dedicated, specialist Long COVID clinics are likely to have been effective in reducing utilisation and

cost of healthcare for people with Long COVID. Antihistamines and anti-inflammatory drugs can lead to small improvements in fatigue and quality of life for people with Long COVID, but further research in the form of clinical trials with other drugs are urgently required. Digital rehabilitation may be effective in reducing fatigue and a scalable way to provide rehabilitation at population level. Long COVID and other post-viral conditions require integrated care provision, alongside other long term conditions.
Long COVID and long term consequences of viral infections should form part of pandemic preparedness and planning in future.

Conclusions and recommendations for further research: Pragmatic research, including large-scale clinical trials are possible and necessary for Long COVID and post-viral conditions, even in the pandemic context. Long COVID has been and remains a health and healthcare priority over the last 5 years and integrated care models from diagnosis through to rehabilitation are likely to represent the most effective way to deliver this care. We recommend (1) integrated care across Long COVID and other long term conditions; (2) clinical trials at scale of repurposeable drugs in combination with scaled up mechanistic research to better understand pathophysiology; and (3) ongoing mixed methods research to tackle inequalities in care which exist in Long COVID care.

Dissemination plans: As well as publications, presentations and media engagement, we have had focused engagement with policymakers. We have also planned dissemination activities with our PPI panel.

Expected influence/impact: In policy spheres, our work signals the important of post-viral infections in health service and pandemic planning, the feasibility of conducting pragmatic clinical trials in diseases such as Long COVID and the need for more "learning health system" research in new diseases alongside their routine care. For service providers, specialised, integrated care of Long COVID and long-term conditions is possible and recommended by the evidence. For patients and public, we provide evidence and recommendations to ensure that Long COVID is diagnosed in a timely manner and care, which is still very much evolving with many channels of ongoing research, can be delivered in as effective and equitable a way as possible.

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Glossary

CV(D)	CardioVascular (Disease)
ED	Emergency Department

GP	General Practitioner
ICPs	Integrated care pathways
IP	Inpatient
LTC	Long-term conditions
MRI	Magnetic resonance imaging
OP	Outpatient
PPI	Patient and Public Involvement

Key Publications

1. STIMULATE-ICP Consortium (2026) Integrated care pathway in individuals with Long COVID: STIMULATE-ICP, a cluster-randomized, phase 3 trial. *Nature Med*
2. STIMULATE-ICP Consortium (2026) Efficacy and safety of rivaroxaban, colchicine, and famotidine–loratadine with specialist supportive clinical care for fatigue in patients with post-COVID-19 condition in the UK: a multisite, open-label, randomised controlled trial. *The Lancet ID*
3. D. Clutterbuck et al (2024) Exploring the help-seeking journeys for Long Covid from a health inequalities perspective: a qualitative study in England. *Qualitative Health Research.*
4. Y. Mu et al (2024) Healthcare Utilisation of 282,080 Individuals with Long COVID Over Two Years: A Multiple Matched Control Cohort Analysis. *Journal of the Royal Society of Medicine.*
5. H.I. Wang et al (2024) Prevalence, Risk Factors, and Characterization of Individuals with Long COVID Using Electronic Health Records in Over 1.5 Million COVID Cases in England. *Value in Health.*
6. H.I. Wang et al (2024) Prevalence, risk factors and characterisation of individuals with long COVID using Electronic Health Records in over 1.5 million COVID cases in England. *Journal of Infection.*
7. D. Clutterbuck et al (2024) Supporting Long Covid Care: a webtool to facilitate help-seeking among people with Long Covid. *European Journal of Public Health.*
8. A. Dashtban et al (2024) Vaccinations, cardiovascular drugs, hospitalisation and mortality in COVID-19 and Long COVID. *International Journal of Infectious Diseases.*
9. D. Sunkersing et al (2024) Long COVID symptoms and demographic associations: A retrospective case series study using healthcare application data. *JSRM Open.*
10. C.M. van der Feltz-Cornelis et al (2024) Integrated care policy recommendations for complex multisystem long term conditions and long COVID. *Scientific reports.*
11. D. Clutterbuck et al (2024) Barriers to healthcare access and experiences of stigma: Findings from a coproduced Long Covid case-finding study. *Health Expectations.*

12. F. Turk et al (2024) Accessing care for Long Covid from the perspectives of patients and healthcare practitioners: A qualitative study. *Health Expectations*.
13. C.M. van der Feltz-Cornelis et al (2024) Prevalence of Mental Health Conditions and Brain Fog in people with long COVID: A Systematic Review and Meta-analysis. *General Hospital Psychiatry*.
14. D. Sunkersing et al (2024) What is current care for people with Long COVID in England? A qualitative interview study. *BMJ Open*.
15. F. Turk et al (2023) Pathways to care for Long COVID and for long-term conditions from patients' and clinicians' perspective. *Journal of Evidence-based Medicine*.
16. C.M. van der Feltz-Cornelis et al (2023) Integrated care pathways: a new approach for integrated care systems. *British Journal of General Practice*.
17. N.A. Alwan et al (2023) Long Covid active case finding study protocol: A co-produced community-based pilot within the STIMULATE-ICP study [Symptoms, Trajectory, Inequalities and Management: Understanding Long-COVID to Address and Transform Existing Integrated Care Pathways]. *PLoS One*.
18. A. Routen et al (2023) Patient and public involvement within epidemiological studies of long COVID in the UK. *Nature Medicine*.
19. C.M. Van der Feltz-Cornelis et al (2023) Neurological Dysfunction in Long COVID Should Not Be Labelled as Functional Neurological Disorder. *MDPI Viruses*.
20. A. Roca-Fernandez et al (2023) Cardiac abnormalities in Long COVID 1-year post-SARS-CoV-2 infection. *BMJ Journals Open Heart*.
21. A. Dennis et al (2023) Multi-organ impairment and long COVID: a 1-year prospective, longitudinal cohort study. *Journal of the Royal Society of Medicine*.
22. D. Forshaw et al (2023) STIMULATE-ICP: A pragmatic, multi-centre, cluster randomised trial of an integrated care pathway with a nested, Phase III, open label, adaptive platform randomised drug trial in individuals with Long COVID: a structured protocol. *PLOS ONE*.
23. PPIE team of the study (2023) Stolen Lives: The Reality of Living with Long Covid. *ebook (open access)*.
24. L.L. O'Mahoney et al (2022) The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. *EClinicalMedicine*.
25. M. Heightman et al (2021) Post-COVID-19 assessment in a specialist clinical service: a 12-month, single-centre, prospective study in 1325 individuals. *BMJ Open Respiratory Research*.