Full Study Title:

Supported remote rehabilitation post Covid-19: development, deployment, and evaluation of a digitally enabled rehabilitation programme.

Short Title:

Covid Recovery

Chief Investigators:

Professor Elizabeth Murray / Dr Henry Goodfellow

Funder

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Protocol version number and date:

Version 1.4, 31.08.2022

Study Registration Number:

Researchregistry6173

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PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Protocol updated (& finalised by);
Original	v1.4	31.08.2022	CC (HG)

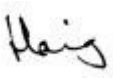
DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

I (investigator) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I (investigator) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:

Signature:  Date: 31/08/22

Print Name (in full): Henry Goodfellow

Position: Academic Clinical Lecturer in General Practice

On behalf of the Study Sponsor:

Signature:..... Date...../...../.....

Print Name(in full):.....

Position:.....

STUDY SUMMARY

Identifiers	Covid, rehabilitation, digital health
IRAS Number	288199
REC Reference No	
Sponsor Reference No	138295
Other research reference number(s) (if applicable)	Project code: Z6364106/2021/01/72
Full (Scientific) title	Supported remote rehabilitation post Covid-19: development, deployment and evaluation of a digitally enabled rehabilitation programme
Health condition(s) or problem(s) studied	Covid-19 and rehabilitation and recovery
Study Type i.e. Cohort etc	A mixed methods multi-centre, multi-disciplinary study to develop and implement a digital health intervention in routine care for Covid-19 patients.
Target sample size	1000 registered service users for the service evaluation Up to 210 interview participants for the research
STUDY TIMELINES	2 years
Study Duration/length	3 years
Expected Start Date	1st of October 2020 for the service evaluation 1st January 2020 for the research interviews
End of Study definition and anticipated date	Optimised digitally-enabled Covid Recovery Programme, in use in multiple NHS sites, with data on impact. 30 September 2023.
Key Study milestones	Final Protocol Approvals REC Approval First Site Initiated First Participant Recruited Last Participant Recruited Start Work Package 1 Start Work Package 2

	Start Work Package 3 Start Work Package 4 Last Data Collected Data Freeze Statistical Analysis End of Study Report Submitted Publication and Dissemination of Findings Archiving Complete
FUNDING & Other	
Funding	NIHR
Other support	UCL PartnersPartners Academic Health Science Network
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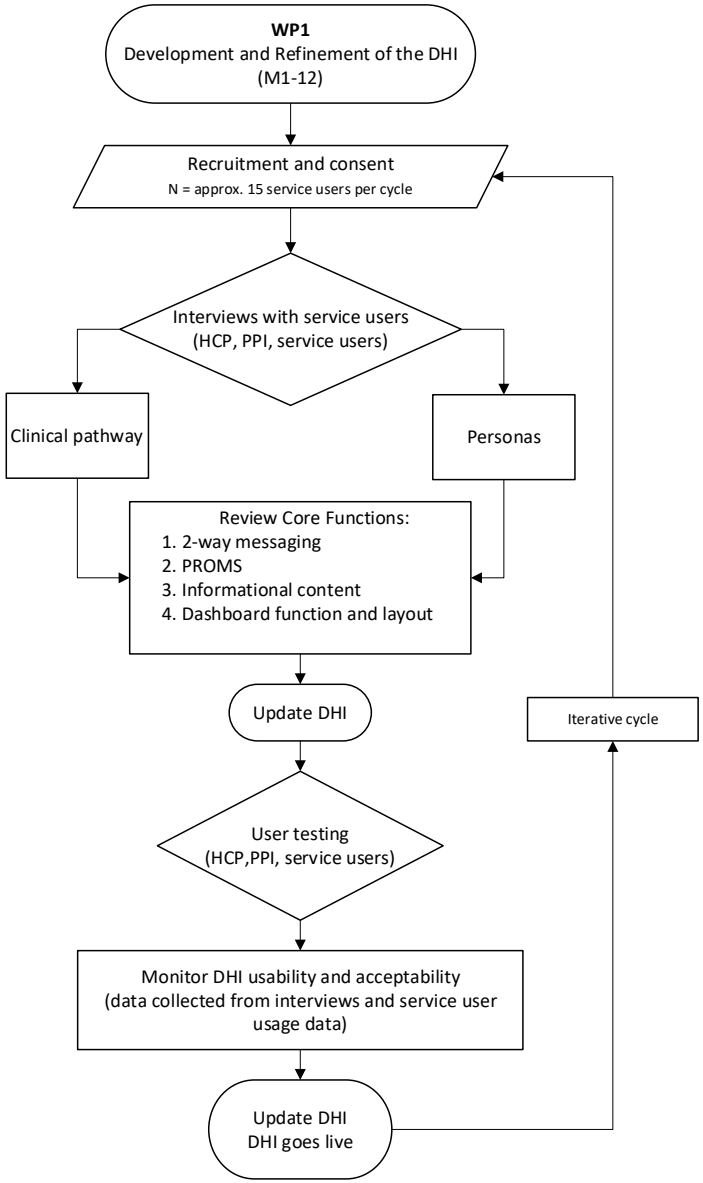
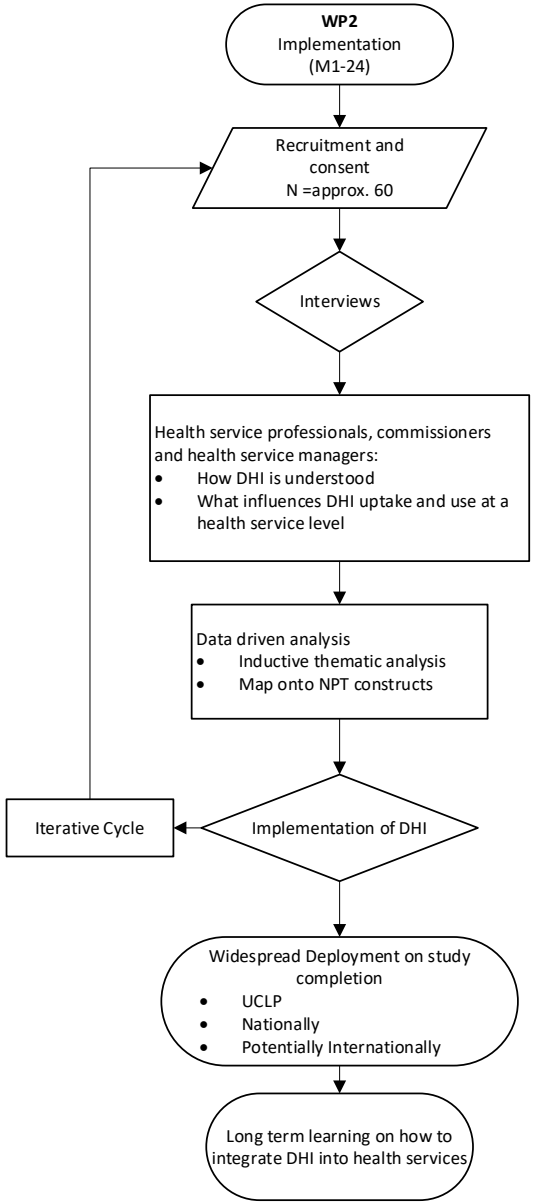
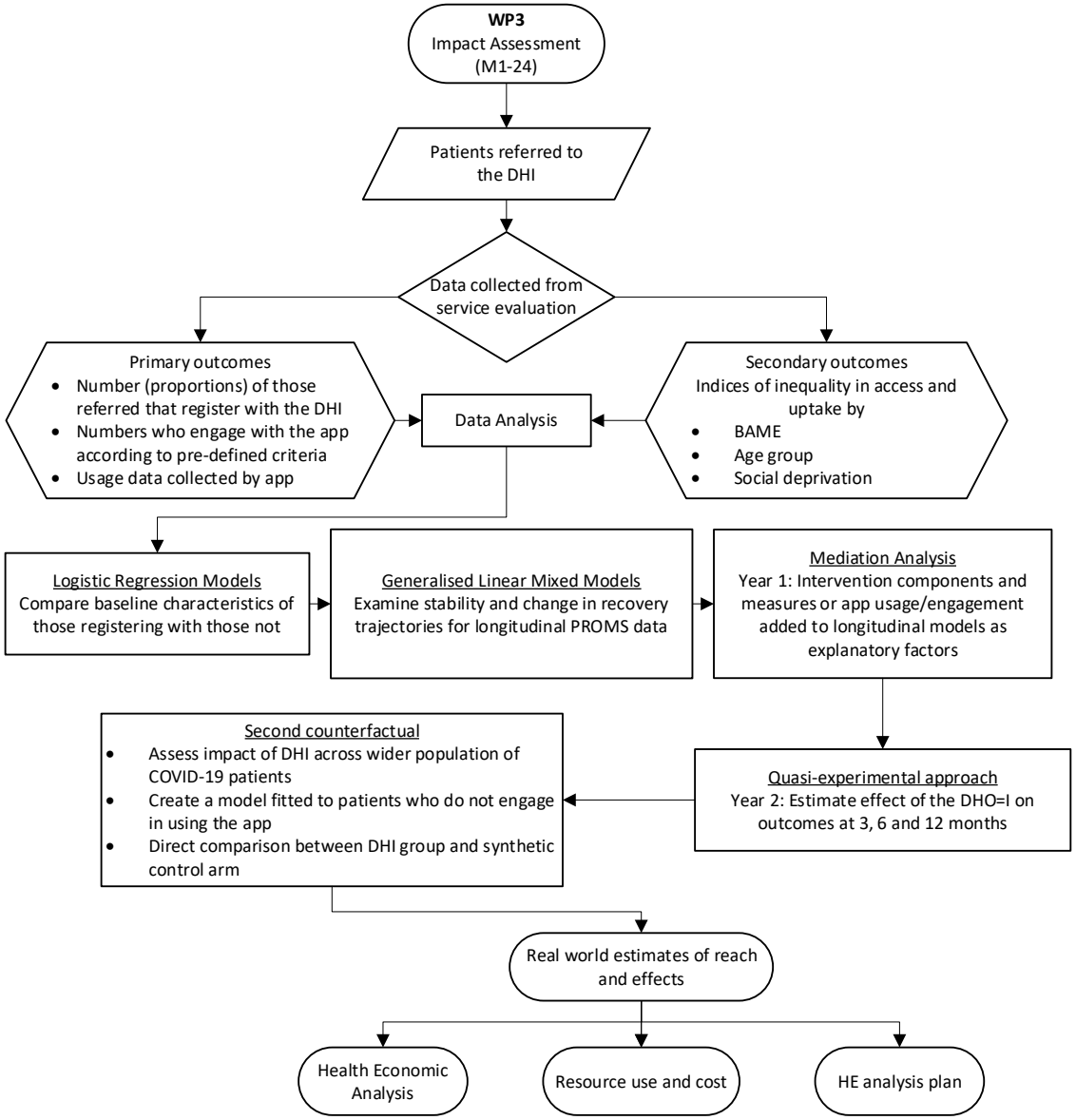
TRIAL SCHEMA






WP3
Impact Assessment
(M1-24)
Patients referred to the DHI
Data collected from service evaluation
Primary outcomes
Number (proportions) of those referred that register with the DHI
Numbers who engage with the app according to pre-defined criteria
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Age group
Social deprivation
Logistic Regression Models
Compare baseline characteristics of those registering with those not
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Examine stability and change in recovery trajectories for longitudinal PROMS data
Mediation Analysis
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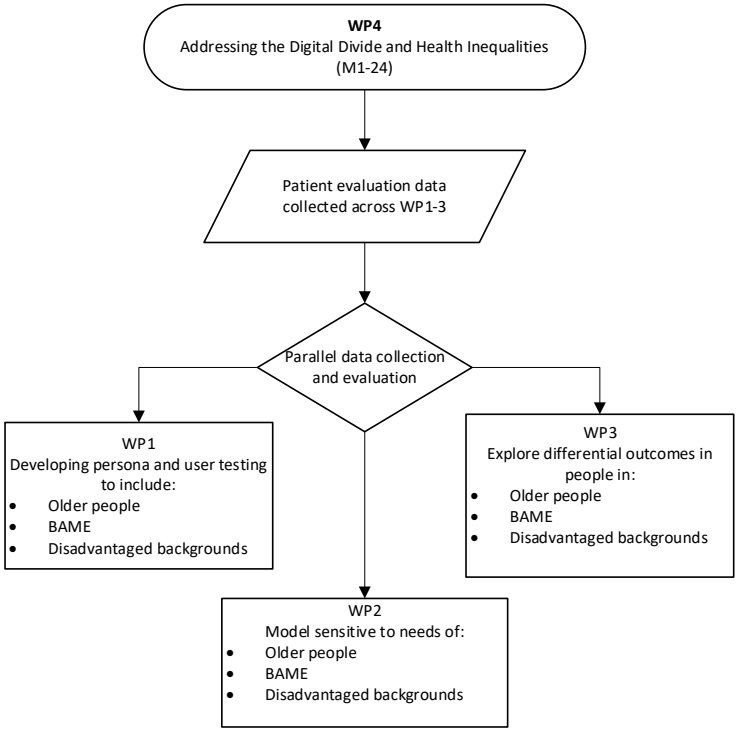
Create a model fitted to patients who do not engage in using the app
Direct comparison between DHI group and synthetic control arm
Quasi-experimental approach
Year 2: Estimate effect of the DHO=I on outcomes at 3, 6 and 12 months
Real world estimates of reach and effects
Health Economic Analysis
Resource use and cost
HE analysis plan


WP4
Addressing the Digital Divide and Health Inequalities
(M1-24)
Patient evaluation data collected across WP1-3
Parallel data collection and evaluation
WP1
Developing persona and user testing to include:
Older people
BAME
Disadvantaged backgrounds
WP3
Explore differential outcomes in people in:
Older people
BAME
Disadvantaged backgrounds
WP2
Model sensitive to needs of:
Older people
BAME
Disadvantaged backgrounds

KEY ROLES AND RESPONSIBILITIES

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the RE of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

PRINCIPAL INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

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Work Package 1

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Chris Robson, Living With

Work Package 2

Prof Fiona Stevenson, University College London

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KEYWORDS

Digital; Health; Covid; Recovery; Rehabilitation; Remote; Develop; Implement; Mixed methods

LIST OF ABBREVIATIONS

AE	Adverse Event
AHSN	Academic Health Science Networks
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CSP	Chartered Society of Physiotherapists
DHI	Digital Health Intervention
DMC	Data Monitoring Committee
F2F	Face-to-face
HCI	Human Computer Interaction
HCP	Heath Care Professional
ICF	Informed Consent Form
ICU	Intensive Care Unit
NPT	Normalisation Process Theory
PI	Principal Investigator
PIS	Participant Information Sheet
PROMS	Patient Reported Outcome Measures
REC	Research Ethics committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File
WP	Work Package
UCD	User-Centred Design
UCLP	University College London Partners

CONTENTS

1 INTRODUCTION

In 2019, Covid-19 was identified in Wuhan, China, and by July 2020, Government data reported 284,276 confirmed cases in the UK, of which 128,737 were admitted to hospital and 44,198 had died (1). Some people experience an asymptomatic infection, and others have experienced severe pneumonia and require admission to Intensive Care.

Many of those affected experience prolonged moderate-to-severe symptoms following infection, particularly fatigue, breathlessness and anxiety (2, 3). While an unknown proportion of patients are breathless due to serious pulmonary complications, such as interstitial lung disease, many more experience distressing breathlessness from deconditioning and breathing pattern disorders. In a case series of 384 patients (from 1139 eligible) followed up 4–6 weeks after discharge from 3 hospitals in North Central London, 69% reported persistent fatigue and 53% persistent breathlessness (4). Unpublished data from Barts indicate that at 12-week follow-up, 60% of patients report their activity being limited by fatigue, and 40% are limited by breathlessness (Pfeffer, personal communication). Persistent symptoms aren't limited to those who have been in hospital (5): data tracking daily symptoms from nearly 4 million people suggests that around 10% of those affected have persistent symptoms preventing a return to normal activity and that the symptom duration may not be related to initial severity (6).

There is strong evidence from randomised controlled trials (RCTs) that physiotherapy and cognitive behavioural therapy (CBT) are effective in treating fatigue and deconditioning (7), breathing pattern disorders (8) and anxiety (9); the challenge is to provide these treatments to large numbers of people, within existing NHS resources, while also identifying those who need further investigation and treatment.

Traditional face-to-face (F2F) services will struggle to meet this challenge, partly due to being overwhelmed by the numbers affected, and partly due to difficulties in delivering F2F care during the pandemic, with calls to meet this challenge with digital technology (10). There are, however, some real concerns about digital health. These include anxieties around the digital divide and the potential widening of health inequalities (11-14); low uptake and use of digital treatments (15); and some high-profile failures in implementation (16). Hence, a digitally-mediated service should only be implemented as part of a research programme.

There is an extensive literature supporting the use of DHI to deliver healthcare, with high quality evidence from RCTs and systematic reviews demonstrating that DHI can successfully support behaviour change, self-management (30), rehabilitation (31-35) and be as effective as F2F treatment for anxiety and depression (9). However, to date, digital health has failed to

deliver the expected benefits, with remarkably few examples of successful integration of DHI into routine care.

Challenges to the successful delivery of digital health include:

- Problems with low engagement (uptake and use), impairing effectiveness (36).
- Concerns around the digital divide, and whether the use of DHI will widen health inequalities (37, 38).
- Recurrent problems with effective implementation (39, 40).
- Uncertainties around funding models and how best to realise the cost-effectiveness of DHI associated with use at scale (41).
- Uncertainties around how to best to evaluate DHI (42, 43), including health economics (44).

The team leading on the four work packages (referred to as the core research team) in this study have been at the forefront of work to understand and address these challenges. There has been evidence to show DHI can be successfully mainstreamed (e.g. HeLP-Diabetes has been licensed by NHSE for national rollout (45); POWeR forms part of the national Digital Diabetes Prevention Programme). Successful implementation requires attention to implementation science theory and an iterative approach (26, 46). The digital divide can be mitigated by ensuring interventions are developed to meet user requirements (47), can be used by people of low literacy (48), are integrated into clinical pathways and have adequate human support (25).

The aim of this study is to develop, deploy and evaluate a digitally-mediated, remote, supported rehabilitation programme for patients affected by Covid-19 to reduce face-to-face contact.

Methods common to engineering and computer science (focused on developing a product that is safe, stable and meets user requirements) will be combined with those familiar to biomedical and health service researchers (focused on effectiveness and population impact). The Medical Research Council (MRC) Framework for the development and evaluation of complex interventions (Phases 1, 2 and 4), User-Centred Design (UCD) and the ISO 9241 Human-Computer Interaction (HCI) Lifecycle for intervention development will be applied.
Behavioural theory and behaviour change techniques will inform content and delivery; Normalisation Process Theory will inform implementation.

The data evaluation will use mixed methods, combining qualitative (interviews) and quantitative data. Quantitative data will include referral, registration, and usage rates, demographic and clinical characteristics of patients, and patient-reported outcomes including breathlessness (MRC dyspnoea and Dyspnoea 12 scales); fatigue (FACIT-F); anxiety (GAD-7) and nutrition (MUST). All qualitative data is being collected as part of ethics approved research, and all quantitative data is collected as part of a service evaluation by the app.

Key outcomes will be:

- A digital health intervention (DHI) to support Long Covid rehabilitation;
- A modifiable DHI to support rehab and self-management in other conditions;
- Generalizable learning on digital health, including overcoming the digital divide; using AI to improve engagement; implementing DHI into routine clinical practice; enabling efficient review of large numbers of patients; costs and resources needed for sustainable digitally-mediated care; and appropriate funding models.

The DHI will be available for use across the NHS. Transfer of knowledge will be facilitated through the AHSN and ARC networks as we are supported by UCLP, ARC North Thames and NHS Innovation Accelerator, and underpinned by academic peer-reviewed publications, supported by targeted media and social-media activity.

2 BACKGROUND AND RATIONALE

The need for digital rehabilitation has been recognised by NHS England (NHSE) (17), who announced a product on 5 July 2020, however, the product is, as yet, under-specified and primarily acts as an information resource. In an area of strategic importance, particularly when digital technology is involved, it is important to maximise the chances of success, by not relying on one potential solution. This problem was recently highlighted with the government's Track and Trace app (1)

This DHI, named Living With Covid Recovery, is required because patients are in urgent need of treatment and this is a product that has the potential to meet their needs. The DHI includes integration into a clinical pathway, and 2-way messaging, clinician-facing dashboard, and patient-facing app with evidence-based treatments for deconditioning, breathing pattern disorders, anxiety and fatigue.

Furthermore, the core research team's combined experience will facilitate DHI success in real-world practice. The team has broad experience across multiple disease areas and behaviours to address a multi-system disorder like Covid-19. The team has developed programmes to support physical activity in older people (18), fatigue in cancer (19, 20), healthy eating (21, 22), breathing retraining in asthma (8) and emotional distress (23). The team will follow an established method for developing effective digital programmes (24); and have a track record of demonstrating effectiveness in RCTs (21, 22); and of achieving national rollout of effective DHI (23, 24). This experience includes exploring and addressing the digital divide (25, 26).

Also, this study will generate new generalisable knowledge in AI, Human-Computer Interaction (HCI), implementation science and health economics, relevant to rehabilitation and self-management across multiple conditions.

Since May 2020 the Covid Recovery DHI has been developed and in August 2020 the DHI v1.0 was launched at Barts Health NHS Trust (4 hospitals covering a population of 1 million). The relationship of the DHI v1.0 to the final version can be illustrated by thinking of a scale from 1–10, where a leaflet, or information only website like NHS Choices scores 1, and unlimited face-to-face access to as many highly skilled rehabilitation professionals for as long and as frequently as wanted by a patient scores 10. On this scale, Version 1.0 is a 3-4 whereas our target for the final, optimised intervention is an 8-9 which we aim to reach through iterative cycles of user feedback and DHI updates.

The data collected in this study will contribute to understanding the sequelae of Covid-19 and it's management, specifically rehabilitation, to aid the longer-term recovery of Covid patients. It is anticipated that Living With Covid Recovery programme will provide real-world benefits to NHS staff and patients within 24 months. The DHI will be designed, developed and tested in real-time by patients and clinicians for the benefit of diagnosis, monitoring and management of the virus and its sequelae.

Additionally, this study aligns with the WHO Global Roadmap (29) research priorities of defining the natural history of Covid-19 infection and recovery; determining interventions that improve clinical outcomes, and determining optimal clinical practice strategies to improve the processes of care.

3 OBJECTIVES

3.1 Primary Objective

To refine, deploy and evaluate a digitally mediated, remote, supported rehabilitation programme for patients affected by Covid-19

3.2 Secondary Objectives

1. To develop and refine a DHI that supports patient monitoring, remote rehabilitation and identifying patients needing further specialist investigation. To include:

- Clinical pathways aligned with NICE (27) / British Thoracic Society (BTS) (28) guidelines.

- A clinician-facing digital dashboard which synthesises data about individuals and selected cohorts.

- A patient-facing mobile app to provide targeted, tailored rehabilitation according to patient symptoms. The app will collect patient-reported outcomes (PROMS) data, and use intelligent algorithms and machine learning to promote engagement and tailor treatment advice under clinician guidance.

2. Determine implementation strategies to promote adoption, scale-up, spread and sustainability with a view to maximising population impact. To assess:

- How best to integrate the DHI into clinical workflows, so it becomes fully normalised for healthcare professionals (HCP), and patients experience seamless care.

- The optimal amount of HCP input (time, skillset) required to support patients to engage effectively with the DHI, including those with low digital literacy, while managing large patient workloads safely.

- Funding and commissioning models to promote long-term sustainability.

3. Assess the population impact of this model of care. To include:

- Determining the reach (uptake and engagement) of the DHI, as a proportion of eligible patients and how this varies by demographic characteristics.

- Assessing the cost implications to the NHS of scaling-up and sustaining it.

- Exploring its impact on patient-reported outcomes and recovery trajectories.

4. Determine and mitigate the effect of the digital divide on health inequalities.

- Identify patterns of differential uptake, use and apparent benefits of the DHI in different age groups, for people from Black and Minority Ethnic (BAME) or socially disadvantaged backgrounds.

- Identify and test actions to mitigate any observed differential, e.g. ensuring the app is accessible to people with low literacy / English as a second language; integrating the DHI into routine clinical care; providing additional HCP support to enable registration and encourage ongoing use.

4 STUDY DESIGN

This will be a mixed-methods multi-centre, multi-disciplinary study to develop, deploy and evaluate a digitally-enabled, remote, supported rehabilitation for patients with Long Covid. Appendix 1 demonstrates the timeline and milestones of the study.

The Living With Covid Recovery programme is a patient-facing app and clinician dashboard that is being used at Barts Health NHS Trust and has been developed as part of a service-evaluation in partnership with the health tech company Living With. Living With collect patient-facing Covid Recovery app data including usage data (section 5.5.2) and Patient Reported Outcome Measures (PROMS) and demographic and health service use information in a pseudonymised manner as determined in the Living With Terms and Conditions accepted by the Trust using the programme.

Informed consent for research will be obtained to receive participant contact details to discuss the study and invite them to interview. Any qualitative data collected is not part of the service evaluation and is subject to consent received by the core research team (work package leads). All Interviews will include a guide for topics to be discussed with patients (Appendix 2), clinicians (Appendix 3) and for commissioners and service management (Appendix 4).

4.1 Design

The study will be divided into four work packages as outlined in Sections 5, 6, 7 and 8.
In summary, the research team will work with sites to develop a digital product that can integrate into a clinical pathway and is optimised for the treatment of Long Covid patients.

The digital product uses a clinician-facing dashboard which is accessed on a web browser and the patient-facing app is software used on a smartphone. The dashboard, app and clinical pathway are referred to as the digital health intervention (DHI) called Living With Covid Recovery programme.

4.1.1 Setting

Up to 30 sites across primary, secondary and community care sites in England will be included, targetting the study population

There are two populations for this research:

a) Patients with Long Covid

b) Healthcare professionals (HCP) caring for patients with Long Covid, delivering the Covid Recovery programme, or making decisions about deployment of the Covid Recovery programme.

a) Patients with Long Covid: Adults, aged 18 or over, who remain symptomatic and in need of rehabilitation 6 – 12 weeks after an acute Covid-19 infection. Patients are referred to the digitally-enabled, remote supported rehabilitation programme, Living With Covid Recovery after being assessed as ***safe for rehab*** (e.g. not having serious complications requiring bespoke medical care, for example, pulmonary emboli) and ***suitable for rehab*** (i.e. having symptoms which are likely to respond to rehabilitation treatments). This assessment is usually undertaken by a secondary care physician, often a respiratory physician, although the exact details of who undertakes this assessment is a decision taken by the participating NHS Trusts.

b) Healthcare professionals: Clinicians (physicians, allied health professionals) involved in caring for patients with Long Covid and health service managers involved in setting up, monitoring and delivering local Long Covid care pathways.

Up to 210 participants will be interviewed as part of the ethically approved research, and the service evaluation will be based upon registered users of the DHI (approximately 1000 users in year 1).

4.1.2 Health economic evaluation

The economic evaluation will take the perspective of the NHS and personal and social services. To generate costs from the resource use data, appropriate unit costs; e.g. price lists from the DHI developer to cost items related to DHI development, and Unit Costs for Health and Social Care (64) to cost staff time will be applied.

The health economic evaluation will include three interrelated components:

- The costs of delivering digitally-supported rehabilitation for the target population.
- A cost-consequence analysis that provides a comprehensive assessment of the costs and benefits of the proposed model of care compared to alternative options.
- A budget impact analysis that assesses the cost implications for health commissioning and funding from scaling up the proposed DHI

5 WP 1 DEVELOPMENT AND REFINEMENT OF THE DHI (M1 – 12)

5.1 Summary

WP 1 will determine user requirements, develop the DHI, and test it against user requirements. Effectiveness will be optimised by:

- Integrating behaviour change techniques known to be effective in improving diet, physical activity and engagement with the App component of the DHI (50, 51).

- Applying AI learning to increase the personalisation of the app and tailoring of treatments offered, to enhance engagement with the DHI and treatments.

- Addressing additional symptoms, prioritised by prevalence, level of distress caused, and the existence of effective non-pharmacological treatments that can plausibly be delivered digitally.

- Integrating the DHI with the clinical electronic health record as seamlessly as possible.

- Improving the onboarding experience.

- Improving the clinician-facing dashboard component of the app to make it more user friendly for health care professionals

5.2 Aim

Improve usability, acceptability, engagement and reach for service users through bi-monthly DHI updates and review of the broader service provision (e.g., how patients are introduced to the app (“onboarding”) and how they engaged with their clinical team through it).

5.3 Design

A combination of patient Covid Recovery app usage data, one-to-one and /or group-based interviews with HCPs and patients and observations of clinician-patient interactions will be used to gain insights on how to improve the DHI. The observation will be focused on the onboarding experience, described as the process used for the patient to register to the app. Referred patients will be sent a unique link via email to allow the patient to set up an account on the app, once complete the patient can download the app to their chosen device and log in with a generated username and password.

Additionally, the core research team will review the scientific literature and discuss relevant guidelines when they are released.

5.4 Participants

Up to 50 HCPs and 100 patients will be recruited for WP1, at a pace of approximately 15 service users per iteration (2 months) across participating sites. Participants will be determined for interviews and focus group discussions dependent on the eligibility criteria (section 11, p.41); all eligible participants will then be invited to interviews or allocated to groups dependent aims and objectives of each work package.

5.4.1 Health Care Professionals

HCPs will be invited initially through the existing research team in Barts Health NHS Trust, and snowball to teams in sites that engage with the DHI. Interview topics will include; experiences of using the dashboard, how it supports clinician decision making, how it fits in with their workflow and views on patients experiences of using the service including the app.

5.4.2 Patients

The recruitment of patients in WP1 will begin with the PPI group and will expand to include eligible patients. Participants will be selected purposively to be interviewed. The patient Interview guide (Appendix 2) consists of topics for discussion including: what they expect from the Covid Recovery app, prior experience with health apps, whether and how they engage with the app, how they perceive it as part of the service, what could be changed and current levels of social support.

5.5 Data collection

5.5.1 Qualitative data collection

Service users will be approached by a member of the clinical team for semi-structured interviews by a trained member of the research team in line with the iterative cycle. Interviews will take place at the convenience of the interviewee and participants will be able to withdraw at any time, for which they do not have to give a reason for, and this decision will not affect the care they receive (or are receiving). Group or one-to-one interviews will take place either by phone or video call (whichever is more convenient to the participant) with the aim of collecting data that will facilitate DHI content development. Both audio and video data will be recorded with permission. Data collection will continue until site saturation is reached. All interviews are expected to last for 60 minutes.

5.5.2 Quantitative data collection

Pseudonymised collated data on patient referrals, registrations, patient engagement with the app (e.g. log-ons, page views), completion of rehabiltation activites, and change in PROMS will be collected as part of the service evaluation covered by the terms and conditions of using the Living With Covid Recovery programme.

5.6 Data analysis

Qualitative and quantitative data analysis will take place in parallel with data collection, with an emphasis on identifying and operationalising user needs, maximising behaviour change, and DHI integration into a clinical pathway.

5.6.1 Qualitative Analysis

The video call and telephone interviews will be both be recorded, transcribed verbatim and identifying information will be anonymised.

To familiarise and verify the data, transcripts will be first listened to and then read in full by at least two members of the core research team. Interview transcripts will be analysed using a thematic methodology with a directed approach to ensure that the data informs development. Tentative *a priori* themes will be used initially based on the data collected from the WP1 service evaluation work, which will be adapted as new emerging themes develop from the data.

A data agreement will be considered to achieve GDPR compliance, in which a research contract will be agreed upon by members of the research to use a suitable transcribing organisation (Transcript Diva). It will be ensured that all personal identifiers are removed before recordings are sent to the transcription company. Only then suitable transcribing software (for example, NVivo 10) will be considered to categorise, code and facilitate data storage. Disconfirming evidence and outlying data will be searched for to further enhance the reliability and rigour of the analysis process and findings. The overall interpretation of meaning and explanations and their implications will be considered, with input from the entire research team including PPI member.

5.6.2 Quantitative Analysis

Quantitative data will be analysed to measure the effects of changes in the interface design and to identify questions that need further exploration through qualitative data gathering in subsequent iterations. For example, data over sequential releases of the app will provide evidence on overall user engagement and specifics of how users navigate through the various app resources, while the details of common user interaction paths will inform subsequent design decisions and qualitative data gathering about what matters to users and why they navigate in particular ways.

As part of the service evaluation, pseudonymised quantitative data will be analysed descriptively to explore models of engagement by users, and describe recovery trajectories. Graphical methods and summary statistics will be used to profile temporal changes in usage patterns across the one-year development/refinement phase and for different iterations of the Living with Covid Recovery app. This will include identifying frequencies of engagement with different intervention components and will integrate with the larger-scale mediation analysis planned in year 1 of WP3 (see Section 7.6.3). Results will be interpreted through triangulation with the findings of the qualitative analysis.

5.6.3 Personalised Models

Design of personalisation models will be driven by UCD and HCI analyses and data-analytics, aggregating qualitative and quantitative data on usage and outcomes using well-established machine learning and AI supervised, unsupervised, and probabilistic models. Such models will be used to identify clusters of users for whom similar advice and pathways through the app are appropriate. Clusters may be based on patients specific clinical needs, health beliefs, technology literacy, self-efficacy, coping style, and other individual attributes identified through the study to shape individuals' engagements with the app, the service and their recovery.

6 WP 2 IMPLEMENTATION (M1-24)

6.1 Summary

WP 2 will focus on maximising the likelihood of successful DHI implementation across different healthcare settings and to generate knowledge for future DHI.

This will be achieved by:

- Using a theoretical framework (Normalisation Process Theory) and implementation science methods.
- Exploring how best to integrate and normalise Living With Covid Recovery into clinical workflows.
- Establishing the optimal amount of HCP input required to safely support patients through the DHI.
- Developing funding and commissioning models to promote long-term sustainability.

6.2 Aims

The overarching aim of this WP is to determine implementation strategies to promote adoption, scale-up, spread and sustainability of the Covid Recovery DHI, with a view to maximising

population impact of this specific DHI and generating transferable learning about effective implementation of digital health into routine health care.

6.3 Design

Real world implementation, with associated evaluation using mixed methods. Quantitative data will be collected on numbers of sites, users (healthcare professionals and patients) and usage as part of the service evaluations. Qualitative data will be collected across multiple implementation sites using the following methods:

a) Participant and non-participant observation of meetings where implementation of Living With Covid Recovery is discussed;
b) Individual semi-structured interviews with key stakeholders;
c) Document analysis, both of documents associated with implementation of Living With Covid Recovery in participating sites and national documents providing insights into contextual factors.
d) Video- or audio-recordings of HCP-patient interactions around use of the Living With Covid Recovery programme, including onboarding and subsequent ongoing use.

6.4 Participants

Our sampling framework will reflect our categorisation of macro, meso and micro levels. To understand factors acting at the macro level we will collect data from decision-makers and senior managers involved in the decisions about whether to implement Living With Covid Recovery, and how to make it happen. This will include:

- Senior Clinical Leads for Covid services (e.g. respiratory consultants, Allied Health Professional leads);
- Senior Managers (e.g. Chairs of CCGs, CEOs of AHSNs, senior managers in NHS England)
- IG leads
- IT leads

At meso level, we will collect data from clinicians and managers tasked with setting up and delivering the Living With Covid Recovery Programme “on the ground”. This will include clinic managers, senior AHP, local IT, and healthcare professionals assessing patients and delivering care.

At micro level, we will collect data from individual patients and healthcare professionals using the Living With Covid Recovery Programme.

6.4.1 Health Service Professionals, Commissioners and Health Service Managers.

Recruitment will begin with Co-Investigators and snowball out to potential HCP interviewees that are responsible for the care and rehabilitation of patients with Long Covid (including but not limited to; respiratory physicians, physiotherapists, occupational therapists and psychologists). Stakeholders responsible for decisions surrounding service innovation and delivery for Covid patients will also be interviewed.

Interview topics (Appendix 3 and 4) will include: challenges of providing a service to this patient population within existing resources; options explored for meeting NHS England requirements; the rationale for adopting the Living With Covid Recovery programme; challenges of implementation and how these are being/were met; reflections on the success or otherwise of the Living With Covid Recovery Programme; suggestions and learning for future similar implementations. Overall we will seek to understand the possibilities for normalisation of DHIs into the NHS.

6.4.2 Patients

Patients will be recruited using a sampling frame that takes account of characteristics such as gender, age, ethnicity and socioeconomic status to ensure a range of opinions are presented. Suitable candidates for the study will be selected purposively dependent on these characteristics and the eligibitly criteria (Section 11.1).

Respondents will be asked about why they decided to use the app, how the app integrates with their use of healthcare, how they have used it and how they think apps like this could be used in the future. Overall we will seek to understand the extent to which the app can be seen to have delivered seamless care and the acceptability of DHIs such as this app as a means of supporting patient care for the future.

With permission from the interviewee, interviews will be repeated at a sampling frame basis to explore how views and the decisions evolve and implementation occurs over time.

6.5 Data collection

There will be four main methods of data collection:

a) Participant and non-participant observation of meetings where implementation of Living With Covid Recovery is discussed;
b) Individual semi-structured interviews with key stakeholders;

c) Document analysis, both of documents associated with implementation of Living With Covid Recovery in participating sites and national documents providing insights into contextual factors.
d) Video- or audio-recordings of HCP-patient interactions around use of the Living With Covid Recovery programme, including onboarding and subsequent ongoing use.

At the preference of the interviewee, semi-structured interviews will take place for 60minutes, in a one-to-one or group setting via video call or telephone by a trained member of the team.

Topic guides informed by NPT will be used to explore how the DHI is understood, how it fits with local and national policies and priorities, what the existing workflows and skillsets for Covid-19 patients are, and what influences uptake and DHI use at a health service system and patient level.

6.6 Data analysis

Data will be transcribed verbatim and checked for accuracy against recordings by licensed transcription services (Transcript Divas). Identifying information will be anonymised. Inductive thematic analysis will be used to generate data-driven themes that will subsequently be mapped on to NPT constructs by experienced qualitative researchers. All transcripts will be thoroughly read by two researchers, views and thoughts of participants will be identified along with words and phrases that hold significance.

Data analysis will be conducted concurrently with data collection which will allow for topic guides to be amended and applied to subsequent interviews. Recordings from onboarding interviews will be transcribed verbatim and a conversation analytic informed thematic analysis (6).

The topic guides will then be applied to subsequent interviews and analysed in line with WP1 methods (section 5.6.1).

7 WP 3 IMPACT ASSESSMENT (M1 – 24)

7.1 Summary

WP 3 will be an impact assessment to determine the real-world costs and population impact of the DHI. Population impact will be defined as reach multiplied by the effect.

7.2 Aims

To determine DHI reach via uptake and engagement as a proportion of eligible patients and how this varies by demographics characteristics.

To assess the cost implications to the NHS of scaling up and sustaining the service.

To explore the DHI impact on patient-reported outcomes and recovery trajectories.

7.3 Design

The impact assessment will be achieved by reflecting the two phases of the study, with year 1 focusing on the iterative development and year 2 focusing on the roll-out and summative assessment.

7.4 Participants

Pseudoanonymised patient data from registered users of the app will be used and collated after obtaining consent. The target for year 1 will be to recruit 1,000 patients registering with the DHI. This was chosen as a feasible target during the roll-out of the intervention to selected NHS trusts and will enable us to estimate the overall proportion of patients engaging with the app (primary outcome) with a high-level of precision (maximum width of 95% confidence interval is +/- 3.2%). Similar or increased levels of precision will be achieved when estimating the proportion of those referred who register with the intervention (the other primary outcome).

The sample size in year 2 has not been pre-specified and will depend upon practical constraints imposed by the scale of the pandemic as the digital intervention is rolled out nationally. Power calculations will be carried out for the year 2 analyses based on the ‘pilot’ data from year 1. This will include power for the proposed quasi-experimental analysis of the effect of the DHI on outcomes at 3- and 6-months follow-up.

7.5 Data collection

Data for study participants will be collected through the DHI. Further data required for the creation of a synthetic control arm in year 2 will be received through data access agreements with providers holding data on suitable comparator cohorts of long Covid patients, such as BREATHE, the Health Data Research UK Digital Innovation Hub for Respiratory Health Patient characteristics

Demographic and clinical characteristics of patients used, will be collated through the app, including year of birth, gender, ethnicity, Index of Multiple Deprivation, the highest level of educational attainment calculated from postcode.

7.5.1 Engagement

Data will be collected on the number of patients referred that go on to register with the DHI patient-facing app, proportions of engagement within the app and usage data.

7.5.2 Health Service Use

Service use questions will be requested through the Covid Recovery app every 4 weeks. This will include information about hospital outpatient visits, as well as primary care visits related to GP, psychotherapist, physiotherapist and other specialists. The number of days off work due to Covid-19 symptoms or rehabilitation care will also be collected

7.5.3 Equality data

Data will be collected on access and uptake by ethnic group, age group and social deprivation.

7.5.4 PROMS data

Patient-reported outcomes will be collected at 3, 6 and 12-month from app registration through the patient-facing app including; breathlessness, dyspnoea, fatigue, anxiety, brain fog and nutrition.

7.6 Data analysis

7.6.1 Usage and engagement

In both phases of the impact assessment, factors influencing recruitment rates will be identified through logistic regression analysis to compare baseline characteristics of patients registering with the DHI with those not registering. A similar approach will be used to identify predictors of DHI engagement and retention. Multivariate methods including hierarchical clustering and random forests will be used to model patterns of app engagement over time since registration.

7.6.2 Recovery trajectories

Generalised linear mixed models (GLMM) will be used to examine stability and change in recovery trajectories for the longitudinal PROMS data. Time since app registration will initially be included as a linear covariate but we will explore the functional form of the effect of time (to allow for phenomena such as a plateau in symptom recovery or a sudden period of rapid improvement). Models will include random slopes and intercepts, allowing individualised differences in severity of baseline symptoms and subsequent trajectories. Fixed effects will include age at baseline, sex, ethnicity, IMD and education level.

7.6.3 Mediation analysis of intervention components

In year 1, a mediation analysis will be undertaken in which intervention components and measures of patient app usage and engagement will be added to longitudinal models as

explanatory factors. This will help inform an exploratory assessment of the impact of different modifications to the DHI and the results will be fed back to the implementation team as part of an iterative design cycle.

7.6.4 Effectiveness of the DHI

In year 2, a quasi-experimental approach will be used to estimate the effect of the DHI on 3, 6- and 12-month patient follow-up outcomes. The patient-reported outcomes will be compared to outcome data for a synthetic control arm created from patients with long Covid enrolled in suitable comparator cohorts (such as the PHOSP – Covid study (60) or other cohorts hosted in BREATHE with follow-up of Long Covid patients). Sources of baseline imbalance between cohorts will be addressed using inverse probability of treatment weighting on the propensity score and other methods of dealing with confounding by indication in comparative effectiveness research.

A second counterfactual will be created using a statistical model fitted to patients in years 1 and 2 who do not engage with the app. Direct comparisons will be made between patients receiving the evidence-based interventions and this comparator group in multivariable GLMMs. Propensity score methods will be used to provide additional control for measured confounders and obtain “doubly robust” estimates of the average treatment effect in the target population (61). We will investigate whether there is a dose-response relationship between usage of the app and change in outcomes.

7.6.5 Equality

The acceptability of the intervention for population groups with increased Covid-19 susceptibility, including elderly and BAME populations, will be explored through logistic regression analysis of these factors as predictors of recruitment, usage and retention in Section 7.6.1. Differential effects of the DHI on outcomes for susceptible and disadvantaged groups will be investigated through inclusion of interactions between intervention uptake and ethnicity, age and other demographic characteristics in the GLMMs in Section 7.6.4.

7.6.6 Missing data

Sensitivity analyses will be conducted to examine the influence of missing data on the key study findings. This will include the use of multiple imputation methods where assumptions are met.

7.6.7 Analysis planning and reporting

Analyses and reporting will follow STROBE guidance. A full statistical analysis plan will be developed during the initial phases of the project and signed off prior to database lock for the evaluation in year 2.

7.7 Health economic evaluation

The health economic evaluation will estimate the cost of delivery the DHI for the target population, the cost consequences of the DHI for the NHS services compared to alternative options, and a budget impact analysis that assesses the cost implications for commissioning and funding the proposed DHI.

7.7.1 Cost of delivery

To generate costs from the resource use data, appropriate unit costs; e.g. price lists from the app developer to cost items related to app development, and Unit Costs for Health and Social Care (62) to cost staff time, will be applied.

7.7.2 Cost consequence analysis

The cost consequence analysis will provide a comprehensive assessment of the costs and benefits of the proposed DHI compared to existing care pathways. Unlike a NICE-type economic evaluation, cost consequence analysis provides a simple, disaggregated summary of all costs and benefits, without attempting to combine them into a single measure such as a cost per QALY (63). This type of analysis allows the decision-maker (e.g. local health commissioner) to decide which costs and benefits are most relevant to their decision context, and to determine whether the relevant benefits are worth the additional costs that might be incurred.

Relevant costs will be identified by examining how the DHI impacts the patient, hospital, and the health care system. These will include:

- Resources associated with the development and hosting of the patient-facing app.
- Resources incurred with the scaling up the DHI, such as maintenance, updating, data storage, implementation, and training.
- Resource use associated with HCP support of patients using the service.
- Impact on health service use.

7.7.3 Budget Impact Analysis

The Budget Impact Analysis (64) will estimate the total yearly budget impact over the next 3-5 years in terms of costs and potential savings to the healthcare system of implementing the proposed DHI. The viewpoint in this analysis is that of the budget holder, which may be narrower than that of the cost-consequence analysis. Given the limited evidence about existing rehabilitation pathways, the budget impact analysis will undertake sensitivity analyses that consider alternative, plausible scenarios about current care pathways.

7.8 Outcome

Real-world estimates of reach and effects of this model of remote supported rehabilitation.

8 WP 4 ADDRESSING THE DIGITAL DIVIDE AND HEALTH INEQUALITIES (M 1 – 24)

8.1 Summary

The Covid-19 infection disproportionately affects people from BAME (65) or socially deprived backgrounds (66) and older people (67, 68). There is concern that delivering care digitally will exacerbate health inequalities.

8.2 Aim

To address health inequalities as a cross-cutting theme, running through WP 1 – 3.

8.3 Design

The leads will act as “health equality champions”, ensuring that the work undertaken in WP 1-3 is fully sensitive of the needs of BAME, socially disadvantaged or older people, identifies evidence of the digital divide and health inequalities, and crucially, acts to mitigate these.

8.4 Participants

All patients that have consented via the Covid Recovery-app will be included. In addition, Digital Health Champions (DHCs) from different sites that are onboarded to the study, will also be included and interviewed (maximum of 30 DHCs will be interviewed).

8.5 Outcome

8.5.1 WP1

Ensure development personas and user testing participants include older people and people of BAME and disadvantaged backgrounds.

Additionally, confirm that patient material is presented in a manner accessible to people of low literacy; cultural sensitivity in the provision of advice around nutrition and exercise. Also, to evaluate the usability of the Covid Recovery app by people unfamiliar with digital technology.

8.5.2 WP2

Ensure implementation models are sensitive to the needs of BAME, older and socially disadvantaged patients.

Also, advocate for adequate human support to enable patients with low digital literacy to use the digital tool effectively.

Lastly, monitor uptake and use by BAME, older and socially disadvantaged patients and explore causes, and advocate for action to address, any observed disparities.

8.5.3 WP3

Ensure appropriate demographic data are collected, including ethnicity, post-code (to allow calculation of IMD) and educational attainment (predictive of both health and digital literacy), as well as year of birth, gender, and relevant clinical characteristics.

Furthermore, review WP3 analysis for differential outcomes in people from BAME, socially disadvantaged backgrounds and/or people with low educational attainment.

9 STUDY SCHEDULE

Please refer to appendix 2 for specific timepoints.

Figure 1. Study Schedule

COVID Gantt Chart and milestones updated August 2022

Colour Code Service Delivery and Evaluation Milestones		Year/ Month	Unpacted exension period 2020/21 Year 1 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	2022 Year 2 16	17	18	19	20	21	22	23	24	25	26	27	2023 Year 3 28	29	30	31	32	33	34	35	36
Grant award duration	**Start**	**Finish**	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S
PHASE 1: Pre-project Work																																						
Develop essential documents (Protocol, Patient Materials etc)																																						
Submit to HRA																																						
Approvals granted (milestone)																																						
PHASE 2: Study Management, Governance and Reporting																																						
Contract NIHR and UCL																																						
Subcontract Living With																																						
Subcontract with partner Universities																																						
Nominations for external Trial Steering Committee																																						
External Trial Steering Committee Meetings																																						
Trial Management Group Meetings																																						
Work Package Meetings																																						
PPI Meetings																																						
Annual REC reports																																						
NIHR progress reports																																						
NIHR draft final report																																						
PHASE 3: WP1_Development and refinement of DHI	1	12																																				
Invitations, PIS and consent of participants																																						
Interviews with HCP																																						
Interviews with users (patients and PPI)																																						
Useage, PROMS and HE data collection from DHI																																						
Update DHI from outcomes																																						
User testing HCP																																						
User testing PPI																																						
Service Evaluation of DHI																																						
Data Collection and Analysis																																						
Update DHI from feedback																																						
PHASE 4: WP2_Implementation	1	24																																				
Site 1 Set-up																																						
Site 2 Set-up																																						
Site 3 Set-up																																						
Site 4 Set-up																																						
Training staff																																						
Patients referred to DHI																																						
Interviews																																						
Interviews with HCP/management																																						
Invitation, PIS and consent of patients																																						
Interviews with Patients																																						
Data Collection from app and Analysis																																						
Update DHI from outcomes																																						
PHASE 5: WP3_Impact assessment	1	24																																				
Useage, PROMS and HE data collection from DHI																																						
Update DHI from outcomes																																						
Analysis and writing up baseline patient data																																						
Analysis and writing up recovery trajectories																																						
Impact assessment / Health Economics Analysis																																						
PHASE 6: WP4_Addressing digital divide and health inequalities	1	36																																				
Parallel evaluation and data collection																																						
PHASE 7: Analysis and close down																																						
Recruit and contract RA to assist with analysis and writing publications																																						
Final Analysis																																						
Write Publications and disseminate																																						
Write Study Draft Final Report																																						
Report submitted milestone																																						
Study closeout																																						
Archiving																																						

9.1 Site identification

Sites will be recruited through Clinician Research Networks (CRN) across a number of different regions. Sites who respond with an expression of interest will be contacted by a member of the research team to answer any questions and confirm that they would like to become a participating site. Sites will sign a site agreement, complete a delegation log and be trained in all aspects of the service (i.e. patient-facing app and clinician facing dashboard). To facilitate implementation, site set-up will include discussions around the development and integration of the DHI into a clinical pathway for Covid-19 patients.

9.2 Recruitment

Active recruitment will take place for work package 1, 2 and 3.

9.2.1 Patients

The existing PPI group will be the first group of patient users for WP 1. Beyond the PPI group, eligible patients for WP 1 and 2 will be referred to the service through the treating clinician. Patients will be provided access to the Covid Recovery patient-facing mobile phone application where once registered, they will be given the opportunity to take part in the study.

For interviews, the core research team will use sampling frame that takes account of characteristics such as gender, age, ethnicity and socioeconomic status to ensure a range of opinions are presented.

If recruitment to the study is low, HCPs will be asked to approach registered users of the app (that have not consented to the study) to briefly explain the trial and ask if they would allow a member of the research team to contact them.

9.2.2 Health Care Professionals, Commissioners and health service managers

The Co and Principal Investigators, Nurses and Allied Health Professionals (e.g. physiotherapists, occupational therapists, psychologists) that are registered to the clinician dashboard and work with Covid-19 patients at participating sites will be approached to participate in WP 1 and/or 2. Healthcare commissioners and managers will also be identified and approached through the set-up of the service, with snowballing used to identify key stakeholders and informants. They will be given the option to be interviewed in a one-to-one or group environment (interviewee preference).

9.3 Participant withdrawal criteria and procedures

Participation in the study is voluntary. Participants have the right to withdraw at any time with no consequence.

If a patient consents, and later wishes to withdraw from the study, a clear distinction will be made with regards to what they are withdrawing from. For example:

1. Withdrawal from current or future interviews
2. Withdrawal from the entire study and retraction of any/all data provided.

It will not be possible for the participant to withdraw their data once the analysis has started because the data collected will already be pseudonymised and have been used.
Participants can withdraw from the study without giving a reason by contacting the research team.

10 CONSENT

10.1 Patient

10.1.1 WP 1 and 2 Interviews and observations

Online consent for the research team to contact the patient will be received via a tick box on the Living With Covid Recovery mobile patient-facing app.

Patients that consent will receive a phone call to explain the study and provide an opportunity to ask any initial questions. With permission, a participant information sheet (PIS) and informed consent form (ICF) will be sent via email. If the patient is unable to answer the phone a voicemail or text message will be left asking for a convenient time to contact them.

At least 24 hours will be allowed between the patient receiving the PIS and ICF documentation and a consented interview. Consent will be verbally recorded via video call or audio recording prior to any study activity. To achieve this, each consent point will be read out and responded to by the participant, any questions answered, and a final sentence provided by the participant to consent to the study will be received before any study activity begins.

Written consent will not be obtained for this activity to minimise additional burden to the patient (e.g. printing, scanning), mitigate the risk of missing return post due to office closures and minimise the risk of spreading Covid.

10.1.2 WP 1, 2 and 3 Mobile application data

Pseudonymised data is collected as part of the terms and conditions of the mobile application. The patient must agree to the terms and conditions in order to use the app.
Patients that consent to being interviewed with have the option of providing consent for the core research team to de-anonymise mobile application data to synthesise the qualitative and quantitative data to generate a better-informed analysis.

To understand how the app is affected by social and BAME inequalities, all patients using the app will be able to provide demographic data to be collected and analysed pseudonymously as part of the service evaluation.

To understand the impact of the DHI on health service use, all patients using the app will receive an option to complete a health service use questionnaire every 4 weeks, which will be collected and analysed pseudo anonymously as part of the service evaluation.

Example of a message seen by all patients using the mobile app to ask if they wish to enrol in the study:

Hello from the Living With Covid Recovery research team

Are you interested in being contacted by the team in regards to being part of a research study to improve this Living With Covid Recovery App?

Yes ☐ *No* ☐

By ticking 'Yes' you agree that the research team can securely receive your contact information (email and/or phone number) to contact your about taking part.

If you have selected 'No', you will not be contacted, and can disregard this message.

Those who agree to take part will give the research team permission to send Consent forms and Patient Information sheets via their contact details (email). Those who refuse to take part, will still be able to register to and use the app without giving consent to participate in the study with no consequence.

10.2 Health Care Professionals

10.2.1 WP 1 and 2 – Qualitative data

Consent from HCPs will be sought only after a full explanation of the study has been given, a PIS offered and time allowed for consideration. Consent will be received via recorded audio or video call prior to any study activity. To achieve this, each consent point will be read out and responded to by the participant, any questions answered, and a final sentence provided by the participant to consent to the study will be received before any study activity begins.

10.2.2 WP 1 and 2 – Quantitative data

Pseudonymised data is collected as part of the terms and conditions of the clinician dashboard. The site must agree to the terms and conditions in order to use the Living with Covid Recovery programme.

10.3 Commissioners and Management

10.3.1 WP 2

Informed consent from commissioners and management involved in the innovation and delivery of new services will be sought only after a full explanation of the study has been given and a PIS offered and time allowed for consideration. Consent will be received via recorded audio or video call, prior to any study activity as per the HCP consent process in section 10.2.1.

10.4 Who will approach for consent?

A member of the core research team will contact potential participants through email, phone or video call to explain the study. If the participant would like to enrol onto the study a member of the core research team will receive recorded consent.

10.5 Documentation of ineligibility and non-participation

Ineligible and screen failure patients are not applicable in this study because there is no screening process and all patients referred to the app are eligible to participate in the research interviews. Documentation of non-participation is not required for all other participants (e.g. HCP, Commissioners).

11 ELIGIBILITY CRITERIA

11.1 Patients

Inclusion criteria

1. Aged 18 years or older
2. Have access to a Smartphone or tablet with internet. This could be via a family member or friend.
3. Deemed safe and suitable for rehabilitation by a responsible clinician
4. Referred for rehabilitation by a responsible clinician.
5. Registered to use the Living With Covid Recovery Programme
6. Experiencing Covid symptoms
7. Provided informed consent

Exclusion criteria

1. Unable to provide informed consent
2. Unable to understand and communicate verbally in English.

11.2 HCP, Commissioners and health service managers

Inclusion Criteria

1. Involved in delivering care to patients with Long Covid, (registered to use the Covid Recovery dashboard) or:
2. Involved in the decision-making processes around implementation of care for patients with Long Covid, including expertise in information governance, information technology, procurement and contracts; or
3. Involved with ongoing monitoring and review of care processes and contracts.

12 STATISTICAL METHODS

12.1 Justification for sample size in year 1

A sample size of up to 1,000 patients will be recruited for the impact assessment in year 1. As outlined in Section 7.4, this represents a feasible target for recruitment as the DHI is rolled out to selected NHS trusts and provides a high degree of precision when assessing overall engagement with the app.

A core focus of the impact assessment in year 1 is on estimating baseline factors influencing recruitment and engagement rates, and the acceptability of the intervention to population groups with increased Covid-19 susceptibility. These analyses will be conducted using

multivariable logistic regression (LR) models. A common rule of thumb when choosing a sample size for LR analysis is to ensure at least 10 events per candidate variable (where candidate variables are those considered for inclusion in the model before any variable selection). However, recent simulation studies suggest that 20-50 events per variable (EPV) may be needed to ensure adequate model performance (73). Based on a conservative EPV of 50, our chosen sample size will allow for multivariable modelling of up to 10 predictors of engagement (primary outcome), assuming 50% of patients engage with the app. Similar considerations indicate that the sample size in year 1 will be sufficient for multivariable logistic regression analysis of factors associated with other key outcomes including rates of registering for the digital intervention, usage and retention. Even with usage rates as low as 20%, the chosen sample size will allow for multivariable modelling of up to 4 predictors under conservative assumptions.

Another element of the impact assessment in year 1 is modelling stability and change in recovery trajectories for the longitudinal PROMS data using generalised linear mixed models (GLMM) (secondary outcomes). Such analyses involve estimating a range of parameters (including those relating to the functional form of the recovery trajectories, between-person variability in slopes and the impact of covariates), and the lack of relevant prior data on these parameters in the context of Covid-19 recovery makes power calculations challenging. However, previous simulation studies provide a guide for assessing power when modelling trajectories in longitudinal data. For example, Thierno et al. (2014) show that moderate sample sizes (N=200) are sufficient to detect piecewise linear trajectories with 80% power when fitting latent growth curve models under a range of conditions. Even after allowing for potential drop-out of 20%, the target sample size of 1,000 in year 1 should provide adequate power for analysis of the PROMS data. With regards to the proposed mediation analysis in which intervention components are added to the longitudinal model as explanatory factors, further simulation studies (75) show that the sample size required to achieve 80% power is comfortably below 1,000 for a broad range of assumptions.

13 PATIENT AND PUBLIC INVOLVEMENT (PPI)

This proposal was discussed with and reviewed by 4 PPI who have had Covid-19 in the community (2 BAME women, 1 White woman, 1 White man), and 1 PPI (BAME woman) who has been in ICU, though not for Covid-19.

It was prioritised by the PPI group in the UCL eHealth Unit, which included people post-Covid. PPI feedback has emphasised their levels of anxiety about ongoing symptoms, desire for

tailored advice on breathing exercises, general return to activity, nutrition, managing fatigue and help with mental health sequelae. They have spoken about their uncertainty about how best to help themselves, feelings of isolation, feeling abandoned by the NHS, and their need for a structured, supportive recovery programme which takes an integrated approach to mental and physical health. All have warmly welcomed this proposal, and offered ongoing input and support. One of our PPI (co-I Julia Bindman) has been intimately involved with the work undertaken since the application to the Rapid Response Rolling Call was submitted. She has put a PPI perspective into all decisions on content, look and feel, functionality, and navigation that have been made so far, as well as contributing very substantially to re-writing and reviewing content provided by our Allied Health Professionals (physiotherapists, dieticians, psychologists) on rehabilitation, including exercises, nutrition and mental health. She has helped us ensure the material is accessible to people of low literacy (aiming for a reading age of 12, equivalent to Key Stage 3, attained by 80% of the UK population) and people for whom English is a second language. She has emphasised the importance of maintaining a positive outlook and staying motivated, as well as emphasising that patients experience their symptoms as a whole, and therefore expect their treatments to address all their symptoms in an integrated, rather than siloed, fashion.

Since being funded, we have expanded our pool of PPI, and currently have around 25 PPI supporting the work. This includes 2 PPI members of our steering group, a PPI Advisory group which meets monthly, and 2 PPI members of each work package management group. All these groups meet at least monthly for 1 – 2 hours. In addition, we have a virtual network of PPI who comment on specific issues in an ad hoc manner.

14 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the UCL/UCLH Research Office, and deemed sufficient to cover the requirements of the study. NHS costs will be supported via UCLH and/or the Local Clinical Research Network.

The duties assigned to the study sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

The research costs for the study have been supported by:
Funding body: NIHR
Grants secured: UKRI/NIHR Covid recovery and learning fund (reference no: NIHR132243)
Cost: £781,964.53

Date of award: 15 October 2020

15 DATA MANAGEMENT

The study is compliant with the requirements of General Data Protection Regulation (2016/679) and the Data Protection Act (2018). All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679) with regards to the collection, storage, processing and disclosure of personal information, and will uphold the Act's core principles

Participant data is pseudo anonymised by assigning each participant a participant identifier code which is used to identify the participant during the trial and for any participant-specific clarification between the relevant parties (e.g. site and the research team).

The Participant Information Sheet and Informed Consent Form will outline the participant data to be collected and how it will be managed or might be shared; including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Personal information and contact details will be securely stored within the UCL Data Safe Haven (IDHS), which conforms to the NHS Information Governance Toolkit. Access to this information will be on a need-to-know basis, and restricted to the relevant members of the core research team.

Verbally recorded consent will be edited from recorded interviews and copied to and stored on the data safe haven at UCL within 24 hours of being taken. Any original or copy of the verbal consent will be deleted from the hard drive of the computer.

15.1 Interviews

Interview and consultation recordings by either video or audio will be taken using GDPR compliant recording feature on the web call platform (i.e., Microsoft Teams). The video and audio recordings will be copied to and stored on the data safe haven at UCL within 24 hours of being taken. The video / audio recording will be deleted from the computer hard drive and/or web call server as soon as it is copied to the data safe haven. The audio recording of the interview or consultation will be sent to a licensed transcription services (Transcript Divas) who will transcribe the audio and video recordings and send the word document of the transcript to us through secure message via the Data Safe Haven The allocated transcriber will ensure all identifiable data is removed and anonymised using a unique identifier. The de-identified transcripts will then be sent back for thorough rechecking by the research team. The

original recording will be copied to the data safe haven and an anonymised copy made and stored on UCL cloud storage to be used for analysis.

15.2 Clinician dashboard

Pseudonymised interaction log data including clinician time spent on dashboard will be collected by Living With and shared with the core research team via GDPR compliant secure web servers.

15.3 Patient facing mobile application

The terms and conditions of using the app provided by Living With will be shown to the user upon registering for the service. Agreement to the terms and conditions provides permission for anonymised app data to be collected and used by Living with and the research team. Living with will transfer the data to the UCL data safe haven through a safe and secure link.

Patient facing app data collection includes:

- Date onboarded (date and time)
- Patient log on (date and time)
- Patient page views (date, order and time of page view)
- Patient reported outcomes measures (breathlessness, fatigue etc)
- Demographic data (year of birth, ethnicity, gender etc)
- Rehabilitation activity engagement

Access to study data will be granted to authorised personnel from the Sponsor for monitoring and/or audit purposes.

All laptops will be password protected, and no identifiable data will be kept on laptops. Analysis will only be by pre-defined members of the research team. The data will not be exported outside the UK.

Pseudonymised data will be retained for 10 years before being destroyed. Any personal information collected will be deleted once the study is closed and all reporting/ publications are complete (maximum term of 3 years).

16 PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by UCL.

Having discussed with the UCL Research Office the Sponsor considers the procedure for obtaining funding from (NIHR) to be of sufficient rigour and independence to be considered an adequate peer review. A confirmation of the award letter is presented in Appendix 8
The study protocol has been submitted to the Health Research Authority and received the favourable opinion of a Research Ethics Committee.
This study is not considered a clinical trial of a medicinal product, therefore clinical trial authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) is not applicable.

17 STUDY OVERSIGHT GROUPS

17.1 STUDY MANAGEMENT GROUP (SMG)

The SMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The Chair of the SMG will be the Chief Investigator of the study.

The Covid Recovery SMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the SMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

17.2 STUDY STEERING COMMITTEE (SSC)

The SSC act as the oversight body on behalf of the Sponsor and Funder. The SSC will meet yearly. Membership of the SSC will be in accordance with NIHR guidance, and members will be appointed by NIHR.

The Covid Recovery SSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the SSC, including the timing of meetings, frequency and format of meetings and relationships with other study committees.

17.3 DMEC

The role of the DMEC will be assumed by the SSC.

18 ASSESSMENT AND MANAGEMENT OF RISK

18.1 Intrusion/Inconvenience

Initial interviews will last a maximum of 60 minutes, with subsequent interviews expected to last approximately 15 minutes. The interviews will be scheduled at convenient times for all consenting participants.

18.2 Psychological Distress

There is a risk of distress to participants from discussing sensitive issues involving mortality and morbidity. Participants can stop the interview at any point or refuse to answer a question. There will be clear ground rules established for interviews which interviewer will ensure are respected. Participants that are unable to obey these rules will be asked to

leave the study and the interview terminated. If there is any indication or signs that a participant has become distressed, then the interview will be paused. The affected participant will be asked if they want to take a break and be offered support. If the participant remains distressed then they will be offered a support outlet depending on their personal issue selected from a variety of different outlets including, bereavement counselling, Age UK, Samaritans and ICOPE. They will also be advised to speak to their GP or clinical team to discuss other options if they so wish. If a member of the research team becomes upset after or during an interview they will be advised to discuss it with another member of the research team/line manager in the first instance. If they remain upset they will also be directed towards appropriate support from their GP or through university channels.

18.3 Physical health

There is minimal chance of any physical harm to participants during interviews. All contact with participants will be done remotely over video or audio chat. Research member meetings and interactions will also be completed remotely until it is considered safe to meet in person. Any meeting between members of the research team will be using the current guidelines determined by the government and UCL Covid-19 rules and regulations.

18.4 Breach of confidentiality

Any breaches or suspected breaches will be reported using the existing UCL GDPR channels.

19 RECORDING AND REPORTING OF EVENTS AND INCIDENTS

19.1 Definitions of Adverse Events

Term	Definition

Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the procedure involved.
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

19.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

19.2.1 Severity

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort

Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

19.2.2 Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g., the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g., the participant's clinical condition).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

19.2.3 Expectedness

Category	Definition
Expected	An adverse event which is consistent with the information about the study listed in the patient information sheet.
Unexpected	An adverse event which is not consistent with the information about the study listed in the patient information sheet.

19.3 Recording adverse events

All adverse events relating to the study will be recorded in the patients medical records and AE CRF form until the participant completes the study.

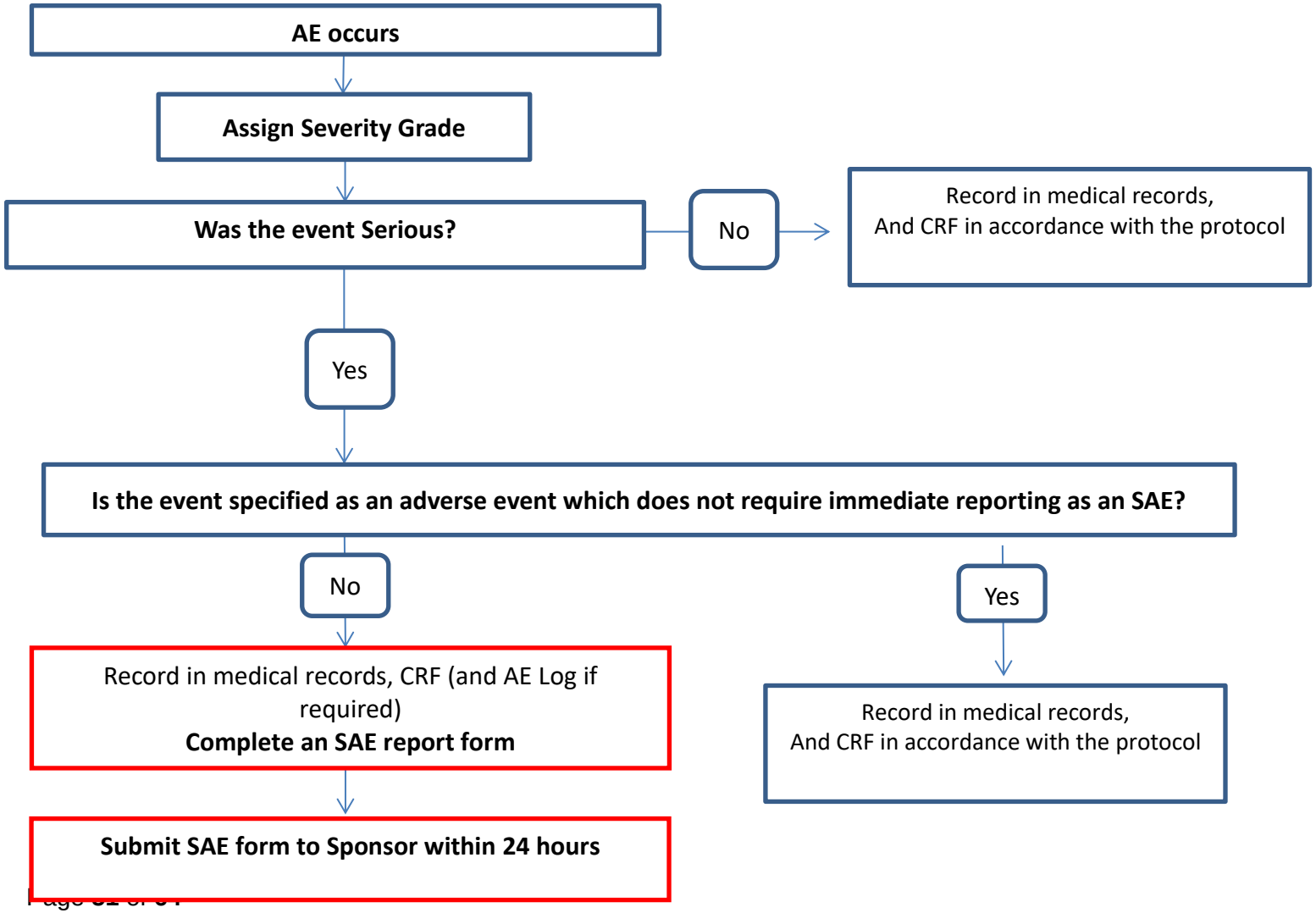
If sites do not have their own SOP, and SOP will be provided. Participating sites will inform the Sponsor of any SAE's within 24 hours of becoming aware of the event. SAE reports will be provided to the main Research Ethics Committee and the SSC Committee within 15 days of the CI becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the relevant parties as soon as possible.

All serious adverse events will be recorded in the patients medical records, the CRF, and the sponsor's AE log. The sponsors AE log is used to collate SAEs and AEs so that the CI can review all in one place for trend analysis.

All SAEs (except those specified in section 17.4 as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form.

SAE's must be reported within 24 hours of becoming aware of the event to the Sponsor
Email forms to randd@uclh.nhs.uk

Flow Chart for SAE reporting



19.4 Serious Adverse Events that do not require reporting

All serious adverse events will be reported to the sponsor.

19.5 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

19.6 Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations that have been logged by the site and core research team.

A protocol violation is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the study.

The CI and sponsor will be notified immediately of any case where the above definition applies during the study conduct phase.

19.7 Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.

b. It is contrary to specified or expected standard of patient care or service.

c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.

d. It puts the Trust in an adverse position with potential loss of reputation.

e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.

A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.

b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

20 MONITORING AND AUDITING

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the sponsor if there are concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

21 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files

21.1 Research team members training

Research members will be chosen with or given the necessary training to carry out all their individual responsibilities required of the study including interviewing patients, and data analysis. If a member of the research team feels unable to carry out their intended responsibilities they should inform the Chief Investigator.

21.2 PPI training

In the past, PPI have asked for training in both generic skills, such as working in groups or reviewing and commenting on documents, and research -specific skills, such as an introduction to different research methods. Both forms of training will be provided.

21.3 Clinician Training

Living With will provide 60 minutes of training to clinicians using the Livign With Covid Recovery programme and be available for ongoing support as per agreement with the participating site(s).

22 INTELLECTUAL PROPERTY

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCL. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to UCL and to disclose all such know-how to UCL with the understanding that they may use know-know gained during the study in clinical services and teaching to the extent that such use does not result in disclosure of UCL confidential information or infringement of UCL IPRIPR.

IP pertaining to the software underpinning the Living With Covid Recovery programme remains with Living With.

23 INDEMNITY ARRANGEMENTS

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

24 ARCHIVING

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the study master file at University College London for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his/her respective site's study documents as per their local policy and in line with all relevant legal and statutory requirements.

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26 APPENDICES

26.1. Appendix 1. Timelines and Milestones

Date	Activity	Milestone
May – July 2020	Start development of DHI v1.0	
14 July 2020	Grant application submitted	Application submitted
31 July 2020	DHI v1.0 launched in Barts Health NHS Trust WP 1 and 2 service evaluation start	Start WP 1 and 2
20 August 2020	Outcome of funding decision	
August 2020	DHI v1.1 launched	
October 2020	WP 3 service evaluation start First Trial Management Group meeting (monthly thereafter)	Start WP 3
December 2020	REC/HRA application submitted DHI v1.2 launched First PPI Advisory Group meeting (Every third month until study completion)	Final Protcol Approvals
	Establish site set up process. To include determining clinical pathways, responsible clinician input, integration with electronic health records.	
January 2021	Provide details of Project Oversight Group(s) to NIHR Outcome of ethics committee decision and response to any modifications requested DHI v2.0 launched Start recruiting participants and collecting WP 1-4 study data. Open first site outside of Barts Health NHS Trust	 REC/HRA approval Start of WP 4 First site initiated First study participant recruited

January 2021 – June 2022	Continue iterative cycles of review and improvement; application of machine learning algorithms to enhance engagement; addition of new content; expansion to additional trusts	
February 2021	Provide evidence of ethics approval to NIHR	
01 April 2021	Progress Report to NIHR	
01 October 2021	Progress Report to NIHR	
Dec 2021 – Feb 2022	Pilot collection of health economics data and develop the health economic analysis plan.	
March 2022	DHI v3.0 launched	
March – June 2022	Undertake exploratory impact analyses; develop and finalise statistical analysis plan; negotiate access to PHOSP-Covid data to act as counterfactual;	
April 2022	Final Progress Report to NIHR	
September 2022	Statistical Analysis and Health Economic Analysis Plans signed off	Last Patient Recruited Last Data Collected Data freeze
	Agree final iteration of Covid Recovery DHI, fully optimised for accessibility, engagement, clinical effectiveness, and efficient use of clinician time.	
July 2022 - September 2023	Write papers for publication	End of Study
September 2023	Dissemination event Write final reports for NIHR, ethics	Publication and Dissemination of Findings Final reports submitted.
13 October 2023	Submit Draft Final Report to NIHR	Study Archived

30 December 2022 Upload Financial Reconcilitation to NIHR

26.2. Appendix 2. Summary of Significant Changes to the Protocol

Protocol date and version	Summary of significant changes
v1, 29 November 2020	Original development of the protocol
V1.1 8.01.2020	Protocol edited and amended
V1.2 22.02.2021	Protocol edited and amended
V1.3	Protocol edited and amended
V1.4	Protocol edited and amended