Issue in Remote Assessment of Lung Disease and Impact on Physical and Mental Health (RALPMH): Protocol for Prospective Observational Study

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Abstract

Background: Chronic Lung disorders like COPD and IPF are characterised by exacerbations which are a significant problem: unpleasant for patients, and sometimes severe enough to cause hospital admission (and therefore NHS pressures) and death. Reducing the impact of exacerbations is very important. Moreover, due to the COVID-19 pandemic, the vulnerable populations with these disorders are at high risk and hence their routine care cannot be done properly. Remote monitoring offers a low cost and safe solution of gaining visibility into the health of people in their daily life. Thus, remote monitoring of patients in their daily lives using mobile and wearable devices could be useful especially in high vulnerability groups. A scenario we consider here is to monitor patients and detect disease exacerbation and progression and investigate the opportunity of detecting exacerbations in real-time with a future goal of real-time intervention.

Objective: The primary objective is to assess the feasibility and acceptability of remote monitoring using wearable and mobile phones in patients with pulmonary diseases. The aims will be evaluated over these areas: Participant acceptability, drop-out rates and interpretation of data, Detection of clinically important events such as exacerbations and disease progression, Quantification of symptoms (physical and mental health), Impact of disease on mood and wellbeing/QoL and The trajectory-tracking of main outcome variables, symptom fluctuations and order.
The secondary objective of this study is to provide power calculations for a larger longitudinal follow-up study.

Methods: Participants will be recruited from 2 NHS sites in 3 different cohorts - COPD, IPF and Post hospitalised Covid. A total of 60 participants will be recruited, 20 in each cohort. Data collection will be done remotely using the RADAR-Base mHealth platform for different devices - Garmin wearable devices, smart spirometers, mobile app questionnaires, surveys and finger pulse oximeters. Passive data collected includes wearable derived continuous heart rate, SpO2, respiration rate, activity, and sleep. Active data collected includes disease-specific PROMs, mental health questionnaires and symptoms tracking to track disease trajectory in addition to speech sampling, spirometry and finger Pulse Oximetry.
Analyses are intended to assess the feasibility of RADAR-Base for lung disorder remote monitoring (include quality of data, a cross-section of passive and active data, data completeness, the usability of the system, acceptability of the system). Where adequate data is collected, we will attempt to explore disease trajectory, patient stratification and identification of acute clinically interesting events such as exacerbations. A key part of this study is understanding the potential of real-time data collection, here we will simulate an intervention using the Exacerbation Rating Scale (ERS) to acquire responses at-time-of-event to assess the performance of a model for exacerbation identification from passive data collected.

Results: RALPMH study provides a unique opportunity to assess the use of remote monitoring in the study of lung disorders.

The study is set to be started in mid-May 2021. The data collection apparatus, questionnaires and wearable integrations have been set up and tested by clinical teams. While waiting for ethics approval, real-time detection models are currently being constructed.

Conclusions: RALPMH will provide a reference infrastructure for the use of wearable data for monitoring lung diseases. Specifically information regarding the feasibility and acceptability of remote monitoring and the potential of real-time remote data collection and analysis in the context of chronic lung disorders. Moreover, it provides a unique standpoint to look into the specifics of novel coronavirus without burdensome interventions. It will help plan and inform decisions in any future studies that make use of remote monitoring in the area of Respiratory health. Clinical Trial: https://www.isrctn.com/ISRCTN16275601

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Issue in Remote Assessment of Lung Disease and Impact on Physical and Mental Health (RALPMH): Protocol for Prospective Observational Study

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Abstract

Background

Chronic Lung disorders like Chronic obstructive pulmonary disease (COPD) and Idiopathic pulmonary fibrosis (IPF) are characterised by exacerbations which are a significant problem: unpleasant for patients, and sometimes severe enough to cause hospital admission (and

therefore National Health Service (NHS) pressures) and death. Reducing the impact of exacerbations is very important. Moreover, due to the coronavirus disease (COVID-19) pandemic, the vulnerable populations with these disorders are at high risk and hence their routine care cannot be done properly. Remote monitoring offers a low cost and safe solution of gaining visibility into the health of people in their daily life. Thus, remote monitoring of patients in their daily lives using mobile and wearable devices could be useful especially in high vulnerability groups. A scenario we consider here is to monitor patients and detect disease exacerbation and progression and investigate the opportunity of detecting exacerbations in real time with a future goal of real time intervention.

Objectives

The primary objective is to assess the feasibility and acceptability of remote monitoring using wearable and mobile phones in patients with pulmonary diseases. The aims will be evaluated over these areas: Participant acceptability, drop-out rates and interpretation of data, Detection of clinically important events such as exacerbations and disease progression, Quantification of symptoms (physical and mental health), Impact of disease on mood and wellbeing/Quality-of-Life(QoL) and The trajectory-tracking of main outcome variables, symptom fluctuations and order.

The secondary objective of this study is to provide power calculations for a larger longitudinal follow-up study. Power calculations will be centered around understanding the number of exacerbations according to sample size and duration.

Methods

Participants will be recruited from 2 NHS sites in 3 different cohorts - COPD, IPF and Post hospitalised Covid. A total of 60 participants will be recruited, 20 in each cohort. Data collection will be done remotely using the RADAR-Base (Remote Assessment of Disease And Relapse) mHealth (mobile health) platform for different devices - Garmin wearable devices, smart spirometers, mobile app questionnaires, surveys and finger pulse oximeters. Passive data collected includes wearable derived continuous heart rate, oxygen saturation (SpO2), respiration rate, activity, and sleep. Active data collected includes disease-specific Patient Reported Outcome Measures (PROMs), mental health questionnaires and symptoms tracking to track disease trajectory in addition to speech sampling, spirometry and finger Pulse Oximetry.

Analyses are intended to assess the feasibility of RADAR-Base for lung disorder remote monitoring (include quality of data, cross-section of passive and active data, data completeness, the usability of the system, acceptability of the system). Where adequate data is collected, we will attempt to explore disease trajectory, patient stratification and identification of acute clinically interesting events such as exacerbations. A key part of this study is understanding the potential of real-time data collection, here we will simulate an intervention using the Exacerbation Rating Scale (ERS) to acquire responses at-time-of-event to assess the performance of a model for exacerbation identification from passive data collected.

Results

RALPMH study provides a unique opportunity to assess the use of remote monitoring in the

study of lung disorders. The study is set to be started in mid-June 2021. The data collection apparatus, questionnaires and wearable integrations have been set up and tested by clinical teams as of 24th April 2021. While waiting for ethics approval, real-time exacerbation identification models are currently being constructed. The models will be pre-trained daily on previous days data but the inference will be run in real-time (with inputs from the wearable sensor data collected which is real-time) to acquire responses at-time-of-event to assess the performance of a model.

Conclusions

Remote Assessment of Lung Disease and Impact on Physical and Mental Health (RALPMH) will provide a reference infrastructure for the use of wearable data for monitoring lung diseases. Specifically information regarding the feasibility and acceptability of remote monitoring and the potential of real-time remote data collection and analysis in the context of chronic lung disorders. Moreover, it provides a unique standpoint to look into the specifics of novel coronavirus without burdensome interventions. It will help plan and inform decisions in any future studies that make use of remote monitoring in the area of Respiratory health.

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KEYWORDS:
mHealth, Remote Monitoring, Wearables, IoT, Lung Diseases, Respiratory Health, Mental Health, Cardio-Pulmonary diseases

Introduction

Patients with chronic conditions like COPD and Interstitial lung disease (ILD) must often manage their disease from a community setting, this presents natural challenges in monitoring patient health status. Currently, COVID-19 presents additional challenges, but especially for vulnerable patients with pre-existing conditions and diseases where, due to shielding, their routine care cannot be done properly[1]. Remote monitoring of the physiology and symptoms of patients via wearable devices could provide convenient and useful advantages over conventional care for patients managing their healthcare in real world settings. These can include detailed information on their historical health, current health status and potential to intervene during acute events, but also prognosis of future health and disease trajectory. Remote monitoring may also provide opportunity during events like the COVID-19 pandemic to safely monitor disease exacerbation or progression without putting patients in situations where risk of exposure to COVID-19 is increased.

Remote Monitoring

This study aims to use the open-source RADAR-base mHealth platform to collect and analyse multiple datasets associated with respiratory disorders. Several cardiopulmonary parameters are now available in modern consumer wearable devices, and due to close coupling of heart and lung, measurements of the function of these organs are expected to provide good characterisation of

these diseases. This study will include continuous data collected from wearable devices (e.g. heart rate, respiratory rate, SpO2), including pulse oximeters, spirometer, mobile phones (audio), digital tests and smartphone symptoms questionnaires.

The RADAR-base community emerged from the Innovative Medicines Initiative (IMI) project RADAR-CNS (Remote Assessment of Disease and Relapse – Central Nervous System), where a consortium of clinicians, developers, researchers, patient organizations and The European Federation of Pharmaceutical Industries and Associations (EFPIA) partners joined forces to explore the potential use of sensor data from wearable devices like fitness trackers and smartphones in research and healthcare. The RADAR-base platform is a scalable and inter-operable mHealth platform that provides capabilities for remote monitoring using passively (e.g. sensor data, wearables, Internet of things(IoT)) and actively (e.g. questionnaires, digital tests). The platform developed at King's College London and the Hyve in the Netherlands is already being used in a number of large-scale longitudinal mental and physical health-related disorder projects [2,3]. The complete RADAR-base technology stack is available under an Apache 2 open source license and is supported by an active community of developers, researchers and clinicians who focus on continuously improving data quality, user experience, validation and extending the platform with new features and data sources.
All the data collected and aggregated using the RADAR-Base platform is standardised using Avro schemas [4] and harmonised across various data streams.
RADAR-base also provides the potential to respond or alert in near-real-time based on some state of the data being collected; this could include identifying e.g. an exacerbation and triggering a response, such as an intervention or follow-up questionnaires/tests or confirmation.

This pilot will help answer how remote monitoring may be used for lung disease patients who in many cases due to the pandemic may be shielding and offers additional benefits including participation without additional risk of travel or interaction with hospital staff.

Interstitial Lung Disease (ILD)

ILD, or lung fibrosis, is one of a spectrum of fibrotic diseases, associated with ageing, obesity, diabetes and pollution, that are responsible for ~45% (9 in 20) of premature deaths in Western Europe. Of >90,000 patients in the UK (United Kingdom) with ILD, ~30,000 have idiopathic pulmonary fibrosis, IPF, the most severe form. IPF is a disease of unknown aetiology that is more frequent in males presenting mainly in the sixth and seventh decades of life[5]. There is no cure and median survival, just 3-5 years following diagnosis is worse than for many cancers. As the fibrosis progresses this leads to impaired pulmonary function, respiratory failure and ultimately death. Throughout its course, IPF has significant effects on physical (dyspnoea, dry cough, weight loss and fatigue) and social (recreational activities, relationships) function, with severe consequences for the patient’s health-related quality of life (HRQoL). Clinical courses are punctuated by episodes of worsening disease that may result in death. These acute exacerbations (AE-IPF) are estimated to occur in 4-20% (1-4 in 20) of patients each year but the true incidence and impact are not known[6].

Management of AE-IPF involves establishing the diagnosis and excluding other causes of increasing dyspnea, excluding infection and considering the use of steroids, antibiotics and/ or anticoagulation- none of which has been shown to be of benefit. The trajectory of patients with IPF is heterogeneous with great variability in the disease course, some progress slowly whereas others progress more rapidly, and this can cause emotional distress and anxiety. Patient-Reported Outcome Measures (PROMs) are used to measure HRQoL, assess symptoms and evaluate disease progression. The management of patients with IPF is multifaceted and consists of patient education and support, regular outpatient surveillance, symptom relief, pulmonary rehabilitation, annual vaccinations to prevent respiratory infection, identification and management of AE-IPF, supplemental oxygen, managing of comorbidities and ultimately palliative care or, in a minority of patients, referral for lung transplantation[7].

Two anti-fibrotic treatments became available for patients who meet the stringent National Institute for Health and Care Excellence (NICE) criteria. Pirfenidone and Nintedanib neither cure, nor reverse the fibrosis, and have little impact on symptoms, but have been shown to reduce rates of lung function decline and, in the case of Pirfenidone, reduce AE-IPF and improve progression-free survival[8].

Impact on health care systems: IPF is a cost- and resource-intensive disease encompassing hospitalisations, home-care and long-term-care, and anti-fibrotic therapy. The full health-burden on the NHS and UK economy is unknown but data from the British Lung Foundation, and projected estimates from our patient cohort, suggest that there are approximately 30,000 IPF diagnoses each year. Health-care costs alone for IPF are estimated at £11-57K per patient-year. [6]

Need for biomarkers for precision management: Disease progression in IPF is highly variable with individuals experiencing very different trajectories. Response to anti-fibrotic therapy is also inconsistent with some patients tolerating the medication well and others experiencing significant side-effects. Currently, there is a lack of valid endpoints, apart from the change in Forced vital capacity (FVC), which has poor sensitivity and specificity, to accurately assess disease activity or response to treatment[9]. This makes it difficult to predict individual prognosis, or reliably detect early treatment response or failure which is important for developing treatment plans and providing patients with accurate prognostic information which allows them to plan for their future. Remote monitoring may allow clinicians and patients access to more granular longitudinal data on disease progression, rate of AE-IPF, and effects on QoL and begin to offer personalised treatment approaches in this cohort. Remote monitoring may also reduce patients' attendance at the hospital for clinical follow-up, or when taking part in clinical trials of novel agents. Remote monitoring may allow early identification of AE, and a better understanding of the frequency and impact of these events, and the potential to develop clinical trials of treatments in these patient groups.

Chronic Obstructive Pulmonary Disease (COPD)

COPD is a common, long term condition of the lungs that is usually caused by cigarette smoking. In addition to daily symptoms and limitations in activities, patients are prone to developing chest infections called ‘exacerbations'[10-11]. Exacerbations are a significant problem: unpleasant for patients, and sometimes severe enough to cause hospital admission (and therefore NHS pressures)

and death. Reducing the impact of exacerbations is very important[12]. We have previously shown that earlier treatment of COPD exacerbations results in faster recovery, and reduced chance of hospital admission. Helping patients to detect exacerbations early is therefore important. We have also recently shown that monitoring heart rate and oxygen saturation via a finger probe may assist in this, especially overnight when the physiological signal is cleaner[13]. Integration of these signals with additional symptom data, and use of innovative data analysis methodology, is likely to result in the greatest chance of supporting early detection of exacerbations, and assessment of disease progression. This is even more important in the era of COVID where many patients with COPD are classified as 'clinically extremely vulnerable' and thus remote monitoring provides the safest way to support management in partnership with their clinicians.

Post-Hospitalisation COVID19 Lung Disorders (PH-COVID)

Recovery from COVID19 has many unknowns, especially in the long term[14]. Symptoms of COVID-19 have varied among those who have tested positive: some have displayed no symptoms, while others have developed severe pneumonia, progressing to lung injury and acute respiratory distress syndrome (ARDS) and, in the longer term, pulmonary fibrosis. Notably, the consequences of COVID-19 include effects on other organs including heart, kidneys, and brain. Correspondingly, a diverse set of associations have been observed that together have been called 'Long COVID', prolonged and delayed recovery from the acute illness including fatigue, shortness of breath and cough that is associated with mental health and neurological disorders such as fatigue, trauma and anxiety/depression[15-16]. For those who were hospitalised, and have since been discharged, it is not yet clear what their medical, psychological and rehabilitation needs will be to enable them to make as full a recovery as possible.

Given this need to follow-up post-hospitalised COVID-19 patients, we consider remote monitoring to provide some key opportunities. Firstly, observation of chronic symptoms will necessitate home-based monitoring as the scope of regularly interfacing with participants in-clinic may be limited due to the likelihood of further periods of lockdown and self-isolation of this population. Secondly, there needs to be a greater focus on understanding how daily life is affected by this disease. Remote monitoring, therefore, provides an ideal opportunity to collect multiple, continuous data streams from participants to report on physiology, QoL, environment and functional level. Building on our existing experience in using wearables to monitor participants who develop COVID-19[17], we aim to extend this to enable detailed observation of patients as they experience symptoms of Long-COVID. By taking a longitudinal high frequency and largely passive monitoring approach we aim to develop an understanding of disease trajectory and fluctuation of symptoms.

THEORETICAL FRAMEWORK

RALPMH will use a prospective cohort study framework. This will leverage our RADAR-base software platform, existing experience working on remote monitoring projects such as RADAR-CNS[18] and take a similar approach to the Major depressive disorder (MDD) protocol[19]. In addition to this, we have recently developed RADAR-base capabilities to deliver notifications dependent on real-time processing of participant data streams. This module of RADAR-base will be evaluated here by deploying an exacerbation detection algorithm (using Heart Rate, SpO2 and other measures), participants will be asked in near real-time to confirm/reject and score the

algorithm's assertion via a short questionnaire, the Exacerbation Rating Scale (ERS) close to or during the period of exacerbation, to provide accurate feedback independent of recall. The ERS scoring will be used to both evaluate the algorithm sensitivity/specificity and also be used to evaluate options for personalised exacerbation detection.
Previous studies [12][13] on exacerbations in COPD found that changes in Resting Heart Rate(RHR), Pulse Oxygen Saturation (SpO2) and Peak Airflow (PEF) are highly correlated with Pre, During and Post exacerbation onset as shown in Figure 1.

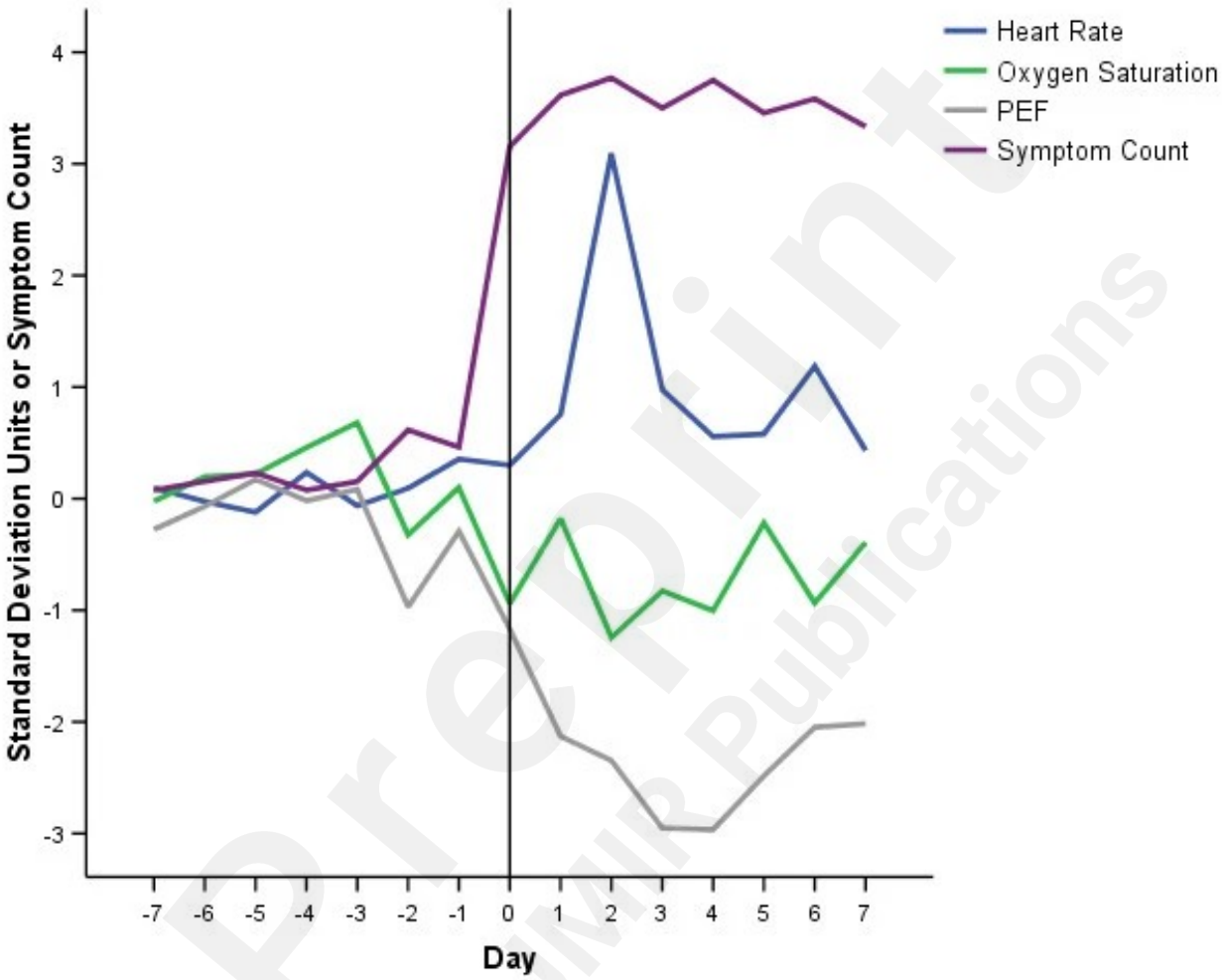

Figure 1 - Time Course of Symptoms and Oximetry Variables at Exacerbation [11].

Another study[20] looks at the identification and subsequent prediction of exacerbations in Chronic Obstructive Pulmonary Disease (COPD). They used features derived from pulse oximeters to predict exacerbations using logistic regression. They found that all 3 vital signs (Oxygen saturation, pulse rate and respiratory rate) are predictors of exacerbations, with oxygen saturation being the most predictive. Another study[21] which looked at the correlation between Resting Heart Rate (RHR) and acute exacerbations in COPD found that patients with higher resting heart rate following exacerbation demonstrated an increased risk of exacerbation.

There is evidence in the literature that pulmonary diseases (like COPD, Lung Fibrosis, etc) are closely related to the heart[22]. Pulmonary vascular abnormalities are frequently present in patients with respiratory disorders. Similar correlations were found with heart rate in the Severe Acute Respiratory Syndrome (SARS) where the patients were found to have a high heart rate and low blood pressure[23].

One interesting and relatively novel approach to understanding the changes in respiratory disorders is through capturing breathing sounds to measure breathing rate and detect features such as wheeze, cough, sneeze, and snoring using audio data. Two exciting works in this field are the mLung++ [24] and SonarBeat[25].

A number of mappings between Data Types and Analytical approaches under consideration are shown in Table 1:

Data Type	Methods	Labels
Active Raw Audio	MFCC, SVM, Adaboost	Questionnaires, Tasks, Spirometry
Passive Wearable Sensor	KNN, Least Squares regression, Adaboost, HMM	Questionnaires, Tasks, Event diary, Spirometry
Multimodal Sensor	DeepSense (CNN+RNN), GIR, hierarchical HMM	Questionnaires, Tasks, Spirometry

Table 1 - Data Analysis Methods

AIM(S)

Our goal is to investigate acceptability and feasibility of remote monitoring of patients with pulmonary disorders for quantification of symptoms, understanding the disease trajectory and detection and prediction of clinically important events (such as exacerbation) in 3 disorder areas - COPD, ILD, Post-Hospitalisation COVID.

Objectives

Primary objectives

The primary aim of the study is to evaluate cardiopulmonary disorders as potential targets for real-time, continuous, real-world remote monitoring. This study will investigate the potential benefit, acceptability, and feasibility of multiparametric remote monitoring of patient symptoms and physiology using commercially available wearables sensors for heart rate, activity, SpO2; spirometry, phone sensors, questionnaires and digital tests in patients with a range of pulmonary disorders.
The evaluation will be based on Patient acceptability, drop-out rates and interpretation of data, Detection of clinically important events such as exacerbations and disease progression, Quantification of symptoms (physical and mental health), Impact of disease on mood and wellbeing/QoL, and The trajectory-tracking of main outcome variables, symptom fluctuations and order.

Secondary Objectives

The secondary objective of this study is to provide data for power calculations [26] for a follow on study. Power calculations will be centered around understanding the number of exacerbations according to sample size and duration. The power is effectively how good the signal is.
This will help plan future studies where we need to decide the sample size and duration to get accurate and acceptable exacerbations and the data associated with them.

Outcomes

Acceptability of the remote monitoring system in the 3 disease areas

The acceptability of the platform will be determined in terms of recruitment, retention, data completeness and qualitative experience of participants. The Exit survey Technology Assessment Model Fast Form (TAM-FF) will also be used to evaluate data collection infrastructure with participant feedback. The study will test both the feasibility and acceptability of tasks for participants. On completion of data collection periods a measurement of total available data as a function of a theoretical maximum and data quality measured by a range of criteria including missingness and contiguity.

Assess the potential of remote monitoring in COPD, IPF and COVID-19

The potential of remote monitoring will be evaluated in the context of cardio-pulmonary disorders. This will involve developing methods to quantify disease trajectory as compared with standard clinical measures (in IPF these would be changes in FVC and death), detecting exacerbation/symptom e.g. changes in wearable data (e.g. HR, SpO2, Activity) during the reported period of exacerbation(A real-time algorithm will be included to predict exacerbations with patients notified with the Exacerbation Rating Scale (ERS) to confirm the prediction at or close to the time of the event), detecting exacerbation prior to or after the reported period of exacerbation (e.g. signal that may precede participant awareness of the exacerbation/symptom), detecting subclinical exacerbations in patients with lung fibrosis, tracking self-reported symptoms and outcomes (including precursors presymptomatic signal) and their frequency and order, and reporting longitudinal mental health symptoms measures as reported by GAD7 and PHQ8 associated with the three diseases. This will provide the potential to assist with future applications around self-management of disease. In the case of the Post-hospitalisation Covid cohort, assess the remote monitoring as patient symptom collection and long term low-burden monitoring solution. Fatigue will be assessed by Garmin Body Battery value and Fatigue Severity Scale (FSS) while Long-Covid Impairments are measured weekly on the WHO COVID-19 Long Term Effects (CCLTE) symptoms list and Post Covid Function Status (PCFS), a COVID-19 specific widely used questionnaire on health-related impairments physical functioning scale.

Data for Future calculations

This study will provide data and information for future power calculations for larger cohort studies including informative data types established by analysis of correlates with symptoms or outcomes of interest. An informative minimal dataset can then be derived from this superset. This will also

provide the unit cost of data collection for the full and minimal datasets for the planning of any future studies.

Remote monitoring provides the opportunity to continuously monitor patients in their daily lives outside of the hospital, with the potential to automate the detection of disease exacerbations and monitor long term evolution of disease trajectory. Acceptability and feasibility of remote monitoring using measures of heart and lung function in patients with lung diseases is a necessary first step in this process which this study aims to evaluate.

Methods

Study Design: Methods Of Data Collection

RADAR-Base mHealth platform

Active Data Collection:

The Active Remote Monitoring Technology App (aRMT) (Android, iOS) will be used to collect data from patients issuing questionnaires and tests that require some conscious action to perform. These will include questionnaires for all participants quality of life and mental health (GAD7, PHQ8) and disorder-specific questionnaires for symptom tracking COPD (CAT), ILD (L-IPF), Post-Hospital COVID (PCFS, CCLTE, WCS) these are summarised in Table 2. Participants will be issued a notification at the appropriate time that will open the corresponding questionnaire to be filled on the phone app. Further to the scheduled questionnaires, the app will also be used to generate dynamic notifications for questionnaires to validate the performance of symptom classification and prediction in near real-time.

This study will also include a battery of experimental digital tests to explore the potential to assess lung breathing function through the use of audio capture or other interactive means. Audio data is readily available through the phone built-in microphone (or the addition of an auxiliary Bluetooth microphone for improved or standardised sound capture). Participants will be issued a notification to complete the relevant task, selecting this will open the corresponding test on the mobile phone with instructions on how the test is to be performed. Active audio tasks such as pronouncing sustained vowels or counting from 1 to 20 will provide additional information on voice production dynamics that might be affected by lung disorder symptoms. A lung sounds test which will record audio during breathing by placing the microphone against the chest during a sequence of breaths[27-28] might be evaluated in a further study based on this protocol.

Furthermore, the audio tasks will be validated in conjunction with patient tests and protocol development to ensure that they capture the relevant information. Quality assurance mechanisms will be implemented to ensure that incoming audio signals are valid (e.g. checking if the signal-to-noise ratio is within an acceptable scope or if the voice is contained within a sample).

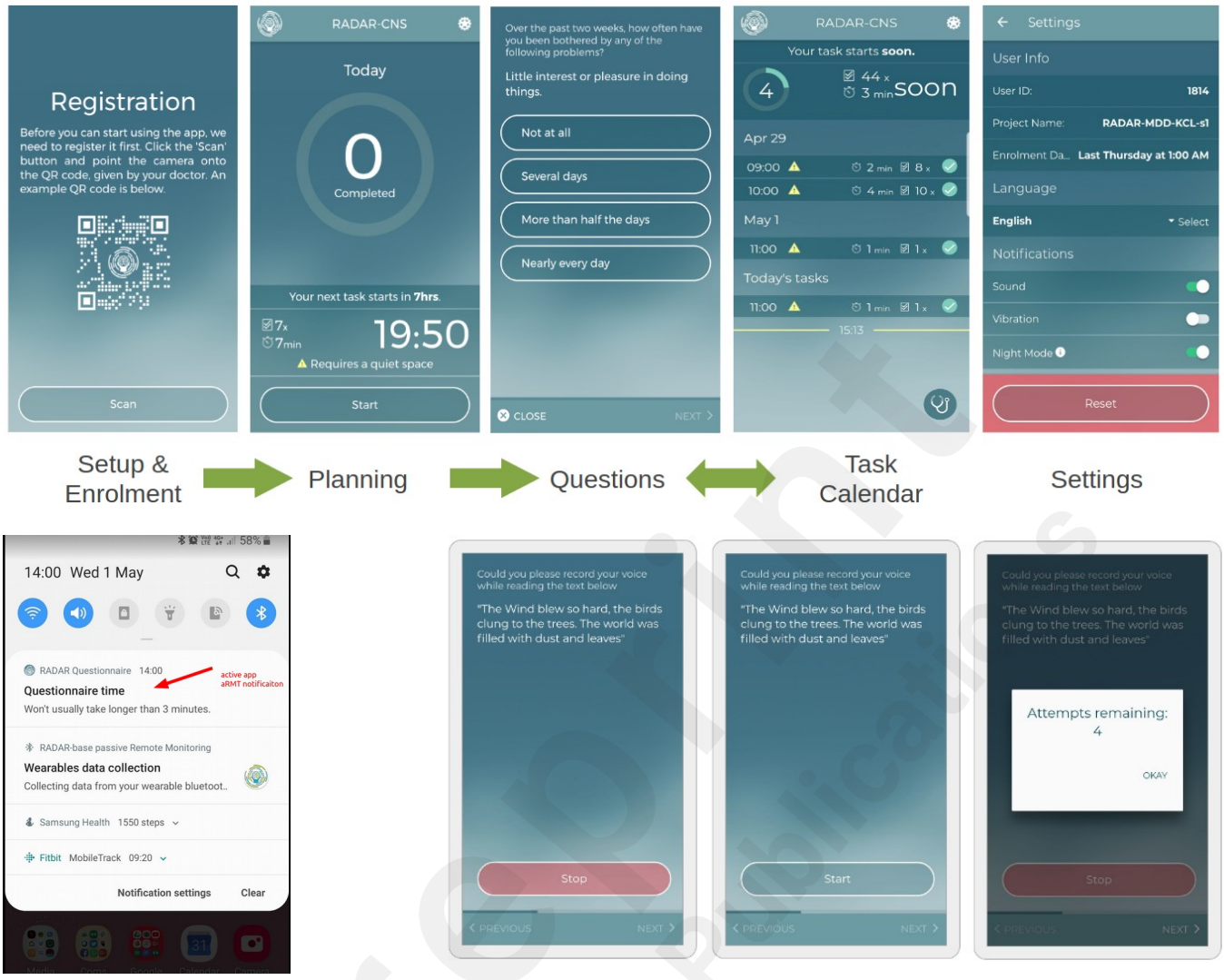

Figure 2 - Active App (aRMT). Used to collect phone delivered questionnaires in Table 2. app screens and e.g. questionnaire (top); e.g. notification to complete the questionnaire (bottom left); speech task (bottom right)

Passive/background data collection:

Garmin Vivoactive 4 is the selected wrist-worn wearable device. Several parameters of interest are reported continuously by the wearable device these include: Activity (steps, exercise as calories consumed), Sleep, Fatigue, Heart Rate (HR), Fatigue levels as Body Battery, Heart Rate Variability (HRV), Respiratory Rate (RR) and Pulse Oximetry (SpO2), see Table 2.

Additional periodic data collection will be done with finger pulse oximetry and spirometry, see Table 2. Participants will receive a notification to carry out a pulse oximeter and spirometry test at a convenient time on a daily basis, values will be recorded on the Active Remote Monitoring Technology App (aRMT).

Data Sources

Data from wearable devices, mobile phone apps and questionnaires

Remote Monitoring Parameter	Data Source	Collection Frequency	Cohort	Purpose
Speech and audio				
Speech – active RMT (aRMT)	Digital test / aRMT phone app	Weekly	All	Voice production tasks via the phone. These tasks will assess change in the phonatory-respiratory system[3]
Activity, functioning and fatigue				
Activity	Wrist wearable device	Continuous	All	Measure of exercise levels, combine and compare HR for measure of proportional non-resting HR. Impacts on lifestyle including physical activity and mobility[29]
Sleep Parameters	Wrist wearable device	Continuous	All	Evaluation of duration and quality of sleep[30]
Fatigue Severity Scale (FSS)	Questionnaire / aRMT phone app	Weekly	All	Subjective experience of fatigue[31]
Passive Fatigue Measure	Wrist wearable device	Continuous	All	Heart rate variability (HRV), time into bed, Garmin BodyBattery level[32-33]
Cardiopulmonary				
Heart Rate (HR)	Wrist wearable device	Continuous	All	Continuous measure of baseline heart rate for i) resting heart rate (sedentary, sleeping) ii) non-resting heart rate (under light, medium, and high activity or stair climbs) iii) cardio-pulmonary performance[34]
Heart Rate Variability (HRV)	Wrist wearable device	Continuous	All	Continuous measure of the variation in time intervals between consecutive heartbeats. Low resting HRV is an indication of high levels of physical or mental stress[35]
Respiratory Rate	Wrist wearable device	Continuous	All	Respiration Rate [36]
Pulse Oximeter, SpO2	Wrist wearable device (continuous)	Continuous [nighttime]	All	Blood oxygenation as measured by PPG sensors on the wrist wearable device, this measure should be continuous at least during the nighttime[37]

Pulse Oximeter, SpO2	Finger Pulse Oximeter (periodic)	Daily	All	Periodic assessment with a clinically approved finger worn device will be provided to validate the daily measure and may be included for dynamic spot checks
Breathing	Digital test / aRMT phone app	Weekly	All	Measure lung function and volume by Inspiration, Expiration using tests delivered through the aRMT app and audio capture
Spirometry	Spirometer	Daily	All	Lung function measurement
Questionnaires - Symptoms, Mental Health, QoL (aRMT)				
Post-COVID-19 Functional Status scale, PCFS	Questionnaire / aRMT phone app	Weekly	COVID-19	Establish post COVID-19 functional status[38]
CDC COVID-19 Long Term Effects (CCLTE) (aRMT)	Questionnaire / aRMT phone app	Daily	COVID-19	Establish degree of long-term COVID-19 effects[15]
WHO COVID-19 Symptoms (WCS) list, (aRMT)	Questionnaire / aRMT phone app	Daily	COVID-19	Establish degree of symptoms persistent COVID-19 symptoms[39]
COPD Assessment Test (CAT)	Questionnaire / aRMT phone app	cohort: Daily	All	COPD Assessment Test (CAT) to measure the impact of COPD on a person's life. Unidimensional, assesses cough, sputum, dyspnoea and chest tightness. 8 questions[40-41]
IPF-PROM	Questionnaire / aRMT phone app	Weekly	ILD	ILD Quality of Life self report
L-IPF	Questionnaire / aRMT phone app	Daily	ILD	ILD Quality of Life self report

Visual Analogue Scale (VAS) Cough	Questionnaire / aRMT phone app	Monthly	ILD	Score symptoms (Cough)
St. George's Respiratory Questionnaire (SGRQ)	Questionnaire / aRMT phone app	Quarterly	All	Assess the impact of overall health, daily life, and well-being in patients.
Pittsburgh Sleep Quality Index (PSQI)	Questionnaire / aRMT phone app	Monthly	ILD	Sleep scoring questionnaire
Exacerbation Rating Scale (ERS)	Questionnaire / aRMT phone app	Dynamic / On Demand	All	A confirmatory rating scale for detected exacerbations, in real time participants will be sent notifications to complete these
PHQ-8 and GAD-7 (aRMT)	Questionnaire / aRMT phone app	Fortnightly	All	Establish depressive and anxiety symptoms[42-43]
eCRF (and Surveys)				
Epworth Sleepiness Scale	eCRF REDCap	Baseline	All	Used to diagnose obstructive sleep apnea (OSA).
STOPBang Questionnaire	eCRF REDCap	Baseline	All	Used to diagnose obstructive sleep apnea (OSA).
MRC Breathlessness	eCRF REDCap	Baseline	All	** Dyspnoea scale that is evaluate the impact of breathlessness on daily activity
Demographics	eCRF REDCap	Baseline	All	Patient demographics form
Study	eCRF	Baseline	All	Study related information collected at

Information	REDCap			baseline e.g. phone and device registration and administrative information.
Contact Information	Local Site File	Baseline	All	Contact information
Technology Assessment Measurement Fast Form (TAMFF)	eCRF REDCap	End of Study	All	Measure the impact of the technology being used and evaluate its acceptability, usability and performance.
Experience of participation (EoP)	eCRF REDCap	End of Study	All	Exit interview (semi-structured)

Table 2 - Remote Monitoring Measures

Clinical Data

Participants will be requested to consent to their medical records (routine clinical and GP records) via the clinical team and anonymised data being made available to the study team throughout the study. Where possible, specific datasets from routinely acquired clinical records may be included.

Data Analysis

Multimedia Appendix 1 summarises the data analysis algorithms and models under consideration in this study.

Analyses are intended to assess the feasibility of RADAR-Base for lung disorder remote monitoring (include quality of data, the cross-section of passive and active data, data completeness, the usability of the system, acceptability of the system).
Generate descriptive statistics for demographics, attrition rate, and the number of participants using the remote assessment measurements without loss or damage and providing adequate quantity and quality data and for the duration of the study period.
Using classification/regression/machine learning approaches, we will investigate whether any demographics and/or other numerical information obtained during the baseline and longitudinal data collection period of the study might serve as a predictor for subjects drop out and percentage of adequate data.
Establish the appropriate setup of the data collection and parameters of the study which would be required to conduct a future larger longitudinal study.

Feasibility and acceptability of the wearable device will be assessed by answering the following questions- Are the sensors on the device (not a gold standard) feasible and acceptable to conduct remote monitoring of the pulmonary diseases? Is Garmin a feasible device for measuring changes in key physiological parameters such as HR and SPO2? These will be evaluated against the gold standard device - pulse oximeter and spirometry.
The feasibility of the symptoms questionnaire will be evaluated against the gold standard from spirometry. Technology Assessment Measurement Fast Form (TAMFF) plus the Experience of participation (EoP) exit interview will be used to determine the overall feasibility and acceptability of the technology and the protocol used in the study.

If adequate data is collected in the pilot, explore methods to establish the feasibility of the data collection apparatus as a means to study disease trajectory and patient stratification.
This will involve using data from heart rate, SpO2, Sleep, Activity, Respiratory Rate, Questionnaires and other collected measures to model participant stratification and differential disease trajectory.

Explore identification of acute clinically interesting events such as exacerbations or rapid change in clinical conditions or physiological data streams.
Use of Pulse-Respiration Quotient[44] and Pulse-Activity Quotient as a measure of the change in respiration efficacy and exacerbation.
Use machine learning approaches to perform both cross-sectional and individualised classification for the identification of events such as exacerbation using a questionnaire or other active data as labels providing context to passive data streams such as HR, SpO2, Respiratory Rate and others.
Using the multi-modal datasets, characterise the periods of time around acute events such as exacerbations, to include pre-exacerbation period, during exacerbation and post-exacerbation exacerbation.
Investigate the potential of the data collected to identify putative sub-clinical exacerbations or other lower-level fluctuation in participant symptoms.
If adequate numbers of events are generated in the study, then an opportunity to apply anomaly/novelty detection methods will be possible. In this way, we will use these approaches to learn the baseline state for the participant and establish significant deviations from this.

Using the real-time aspect of the data collection, we will use the real-time Exacerbation Rating Scale (ERS) to acquire real-time responses to evaluate and assess the performance of a model for Exacerbation detection and refine an individual-level model for exacerbation detection.
Since we do not have enough prior data, we plan to consider real time anomaly detection methods and pre-process the data based on prior knowledge. The models will be pre-trained on a daily schedule (using previous N days of data, N yet to be decided but initially considering 21 days) and ready for running inference in real-time (using wearable sensor data as inputs which is collected in real-time) and taking action based on the results of the inference (sending an Exacerbation Rating Scale (ERS) assessment through the aRMT mobile application) to acquire responses at-time-of-event to assess the performance of the model.

STUDY SETTING

The principle study setting will be remote, near-real-time, home-based monitoring, data will principally be collected under these settings. Participants will also attend baseline and exit study face-to-face visits with the clinical team, during which the initial baseline and exit data and assessments will be conducted.

SAMPLE AND RECRUITMENT

Inclusion criteria

Inclusion Criteria	COPD	ILD	PH-COVID
Clinical Conditions	20 patients with a diagnosis of COPD	20 patients with a diagnosis of interstitial lung disease	a clinical diagnosis of COVID-19 (within 4-13 weeks of enrolment) who either and report symptoms interfering with day to day activity present for more than 28 days following the onset of COVID-19
Gender	M/F	M/F	M/F
Age range	18+	18-90	18+
Prior mobile phone use	required	required	required
Willingness to use monitoring devices and complete study questionnaires.	required	required	required
History of exacerbation	2 or more exacerbations in last 1 yr	N/A	N/A

Table 3 - Inclusion criteria

Exclusion criteria

Exclusion Criteria	COPD	ILD	PH-COVID
Non-English language Speaker	x	x	x
Lack of physical capability to take part e.g. Heart Failure	x	x	x
Pregnancy	x	x	x
Lack of capability to consent	x	x	x

Table 4 - Exclusion criteria

Sampling

Convenient sampling will be employed for this pilot study.

Size of sample

20 participants for each of the 3 disease areas. This is a small sample feasibility study to assess the practical use of remote monitoring in three lung disease areas, the sample size will adequately allow objective assessment of the system deployed for this type of data collection in the typical patient population.

Sampling technique

Sequential participants that fit the in/exclusion criteria will be identified from the respiratory outpatients' clinics at the University College London Hospital(UCLH) and Royal Free Hospital(RFH).

Recruitment

Participants that fit the in/exclusion criteria will be identified from the respiratory outpatients' clinics at the UCLH and RFH.

Sample identification

Participant Search and Consent
A participant search meeting the inclusion/exclusion criteria for each cohort will be identified from clinics at RFH or UCLH. Recruitment will be done either in-person (via a cleanroom) or remotely (by phone or video call) by clinicians providing information about the study in an easily accessible form reviewed by the patient advisory board. As part of the consent process, participants will be informed that the data they provide will not be actionable (in other words will not trigger a clinical investigation or intervention). Written informed consent will be obtained prior to performing any study assessments or procedures. Participants will be requested to consent to their medical records being made available to the study team throughout the study.

Participant Cohorts

ILD / IPF
20 participants recruited from UCLH ILD Service followed for 6 months. We will recruit patients across the spectrum of progressive to stable disease. We will analyse whether monitoring is able to detect progression earlier than the current standard (3 monthly lung function or patient report to the clinician) and could help us identify progression earlier.

COPD
We will recruit 20 patients with COPD from our services in London and follow them for up to six months or until the first exacerbation, whichever is sooner. We will recruit patients with a past history of exacerbations to increase the likelihood of identifying patients that would experience

events during the study. We will analyse whether monitoring was able to detect exacerbations earlier than the current gold standard (patient report to a clinician), and therefore could be used to help patients get treatment earlier.

PH-COVID
UCLH Participants: We will define the population under study as (a) people with a clinical diagnosis of COVID-19 (within 4-13 weeks of enrolment) who either (b) report troublesome symptoms interfering with day to day activity present for more than 28 days following the onset of COVID-19 (n=20). Baseline assessment will be conducted remotely via a web-based questionnaire, which will gain information on demographics, past medical and psychiatric history, health behaviours and medications. Participants will be asked about the symptoms, severity, and consequences (e.g. hospitalisation, ventilatory support) of their acute illness.

Consent

Informed consent will be sought at the end of the screening process and prior to the baseline clinical team meeting. Patients will have the study explained to them and will be given a copy of the Participant Information Sheet(PIS). They will be given adequate time to consider taking part in the study and to ask any questions. Patients that are unable to give informed consent will not be recruited. Due to the nature of the remote monitoring study, we will optionally include a remote consent process for participants that are not able to attend the clinic in person. The remote consent process will be implemented using the REDCap eCRF e-Consent module to deliver the consent form, however, it is our preference to seek to keep wet-signature/paper based consent forms. These will be held both as electronic copies and on hardcopy.

Upon receipt of consent forms, participants will be booked for the enrollment training session. Prior to the session participants will be provided a RALPMH study pack including study devices (Garmin, spirometer, finger pulse oximeter) and equipment either by post or during a face-to-face session (via a cleanroom) if this is possible. Participants will receive a 45-60 minute training session on the use of wearable devices, mobile sensors, and aRMT smartphone app. This will include a Participant Information Sheet leaflet summarising key information and researcher contact details for future reference. The purposes of the study will be clearly explained, as well as practical information such as how to switch devices on and off, how to charge devices, and how to respond to questionnaires and digital tests on a notification via the app. Participants will receive a follow-up call one week after the start of data recording to provide any additional support as required. Where participants do not have a suitable phone we may provide one from a limited number of reserve devices. Pre created accounts for e.g. Garmin devices will be registered using a study email address (e.g. RALPMH022@domain.com) and dummy contact details. Baseline data will be collected in this first session via the study REDCap eCRF project instruments.

RESULTS

Study Flow Chart

The study flowchart is shown in Figure 3.
On the start of the study, a participant is remotely consented and provided the Participant information

sheet. They are then provided a set of Enrolment or baseline assessments to complete online.
All the scheduled active assessments(self-reports) that need manual input periodically are shown on the left which are piped through the Active data collection app to the RADAR-Base platform.
The wearable device provided to participants connects to the wearable vendor's application and the data is uploaded to the vendor's server which is then synchronised to the RADAR-Base platform. On getting all the data the RADAR-Base platform runs real-time data processing and based on a threshold for exacerbation sends a notification+assessment for confirmation of the exacerbation in the form of Exacerbation Rating Scale (ERS).On exit or completion of the study, the participants will be asked about their experience of the technology and the study.

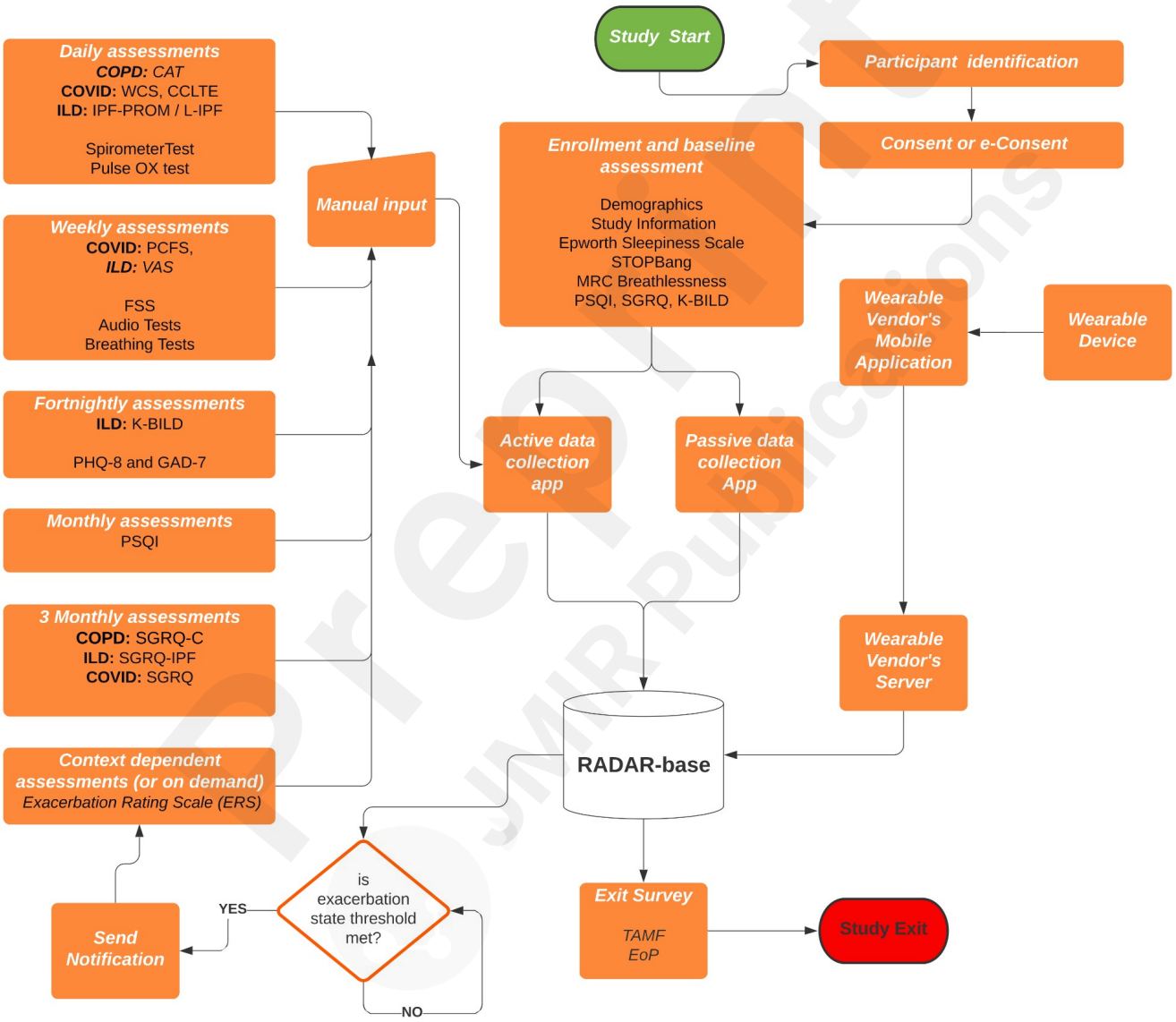

Figure 3 - Study Flow diagram

4.2 Timeline

The timeline for the study is shown in Figure 4.
The planning and technical support for the study is being set up from March 2021. The recruitment and data collection phase is planned to start in June 2021 till June 2022 (1 year). At various points

during this period a review of the data quality and quantity will be performed. Data processing and analysis is planned to start from July 2021 to October 2022. The publications write-up and publishing is from September 2021 to December 2022.

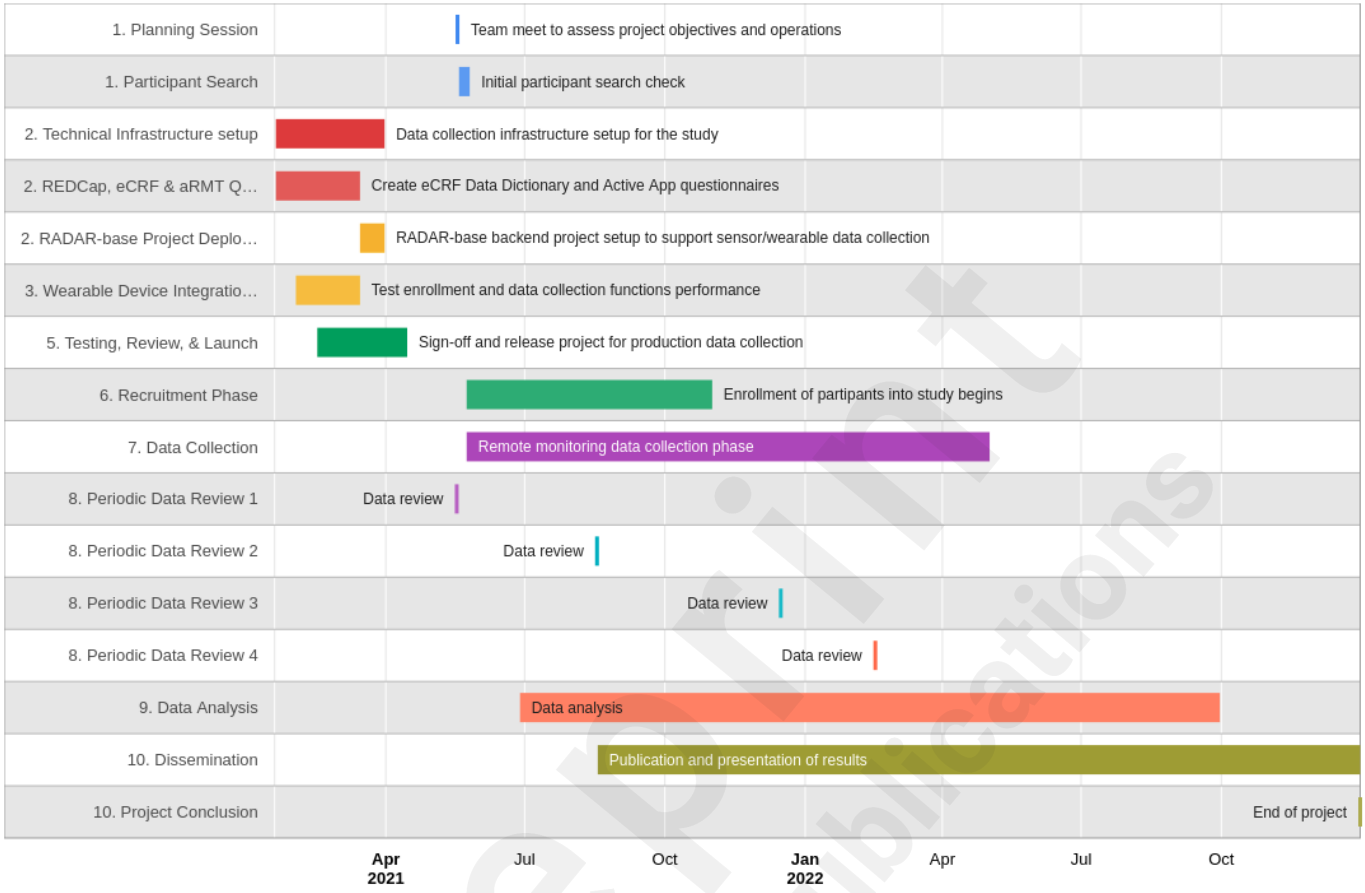

Figure 4 - Study Timeline

Progress to Date

The study is set to be started in mid-June 2021. As of 24th April 2021, the data collection apparatus has been set up and tested by clinical teams. All the questionnaires and their schedules are ready to be served either via the RADAR active application or Redcap. Device selection (Oximeter, Spirometer, Wearable) is complete and the process of ordering devices is on the way. Garmin device (the choice for wearable in the study) integration is complete and is tested with 3 dummy Garmin accounts for data sanity checks. All documentation required for the study is complete and has approval for funding and sponsorship. Patient and Public Involvement (PPI) feedback on the app and schedule was arranged with a demonstration of application and protocol to participants. The relevant changes have been incorporated based on PPI feedback. The ethics application has been submitted and we are waiting on the approval to start recruitment. The real-time exacerbation detection system is developed and most of the parts of the infrastructure have been deployed and tested. The test data is also processed and ready to feed into the algorithm. Currently, the algorithm development is in progress and we are using analysis from a priori datasets [13] and results from similar studies to inform the design of our algorithm.

DISCUSSION

The RALPMH study was meticulously planned with collaboration from clinical teams, technical teams and data analysis teams to provide a reference infrastructure for the use of wearable data for monitoring lung diseases. Specifically information regarding the feasibility and acceptability of remote monitoring and the potential of real-time remote data collection and analysis in the context of chronic lung disorders. Moreover, it provides a unique standpoint to look into the specifics of novel coronavirus without burdensome interventions. It will help plan and inform decisions in any future studies that make use of remote monitoring in the area of Respiratory health.

Ethical And Regulatory Considerations

Assessment and management of risk

Description of risk (indicate the level of likelihood: Low/Medium/High)	**Risk Priority Low, Med, High**	**Risk Owner**	**Proposed risk-mitigation measures**
Data protection e.g. from intrusions	Low	KCL/ SLAM	Restrict access control to the data and use data sensitivity tiering. Encryption of data in transmission and at rest. De-identification/pseudonymisation once data is collected, linked strong-identifiers will be removed. Maintenance of software updates.
Threats to patient privacy	Low	KCL/ SLAM	Data is handled with attention to de-identification and encryption. Higher risk data will typically be processed on edge devices with only aggregated data sent forward.
Patient fatigue with active or passive components of the data collection	Med	KCL /UCL	Early engagement of acceptable burden levels to define expected tolerance levels. Opportunity to adapt the active data collection components in the course of the study.

Table 5 Risk Assessment

Patient & Public Involvement

This project was developed following discussions with patients and their families who wanted to ensure that their lung disease could be safely monitored at home. Patients from IPF and COPD groups have read a draft protocol in full and their feedback was used to improve the final submitted protocol. Information for patients and the public will be posted on the Breathing Matters website [45] and the final results will be shared with the patients.

Protocol compliance

A repeating form on REDCap will be used to log any contact with participants, document any deviations from the protocol. Notification to CI or sponsor will be reported appropriately.

Significant deviation from the protocol or non-compliance may result in the removal of the participant from the study upon review.

Logged telephone contact will be made with participants throughout the course of follow-up if there is a loss of data stream from a device. The participant will be contacted by telephone to ensure compliance and correct use. These contacts will be recorded as evidence of feasibility and acceptability outcomes. In addition to the telephone call provided after the introductory training session, participants will receive a further call after one month to address any further concerns or questions.

Access to the final study dataset

The full dataset for analysis will be limited to the immediate research groups, to members who must additionally hold current contracts with KCL or UCL. The data analysis will be conducted in the appropriate data safe havens and university compute infrastructure.

A secondary pseudonymised (removing any potential identifiers such as raw location and audio data will be restricted to the locked primary dataset), post-processed and de-identified set of derived features (e.g. activity, HR, sleep features) may be published for reference, benchmarking and review as part of academic literature generated from this project.

Limitations

The size of the cohorts and the duration of the study might not be enough to get accurate and expected results, but this is typical for most pilot studies as we intend to figure out the correct size and duration of the study required for expected results which can be further used to plan future longitudinal studies. This can also be partly mitigated by attempting to recruit people who are at high risk of exacerbation.

Dissemination Policy

Analysis and access to the primary dataset will remain on secure KCL/UCL infrastructure and jointly owned by the co-investigator groups & institutions. The secondary de-identified and pseudonymised dataset may be published by the project partners as part of analysis and publication dissemination activity, this may include the use of repositories such as Synapse [46] with the intended aim of 12-18 months after the conclusion of data collection. Partners may be notified of the published results on the project website [47].

Multimedia Appendix 1: Data analysis algorithms and models

Multimedia Appendix 2: CONSORT-EHEALTH Checklist.

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Abbreviations

COPD: Chronic obstructive pulmonary disease
IPF: Idiopathic pulmonary fibrosis
NHS: National Health Service
COVID-19: coronavirus disease

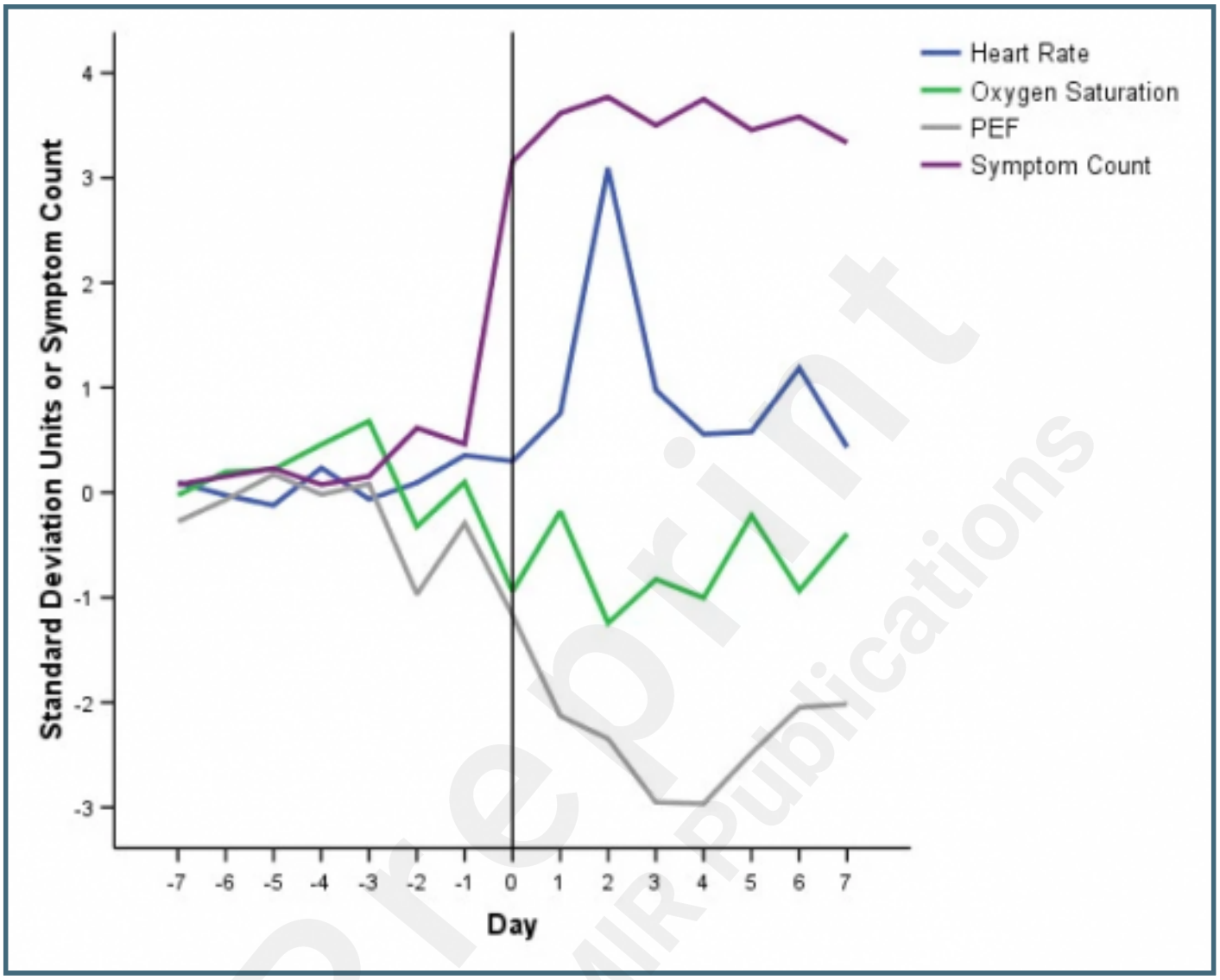
QoL: Quality of Life
RADAR: Remote Assessment of Disease and Relapse
mHealth: mobile health
SpO2: Pulse Oxygen saturation
PROMs: Patient Reported Outcome Measures
ERS: Exacerbation Rating Scale
RALPMH: Remote Assessment of Lung Disease and Impact on Physical and Mental Health
ILD: Interstitial lung disease
IMI: Innovative Medicines Initiative
RADAR-CNS: Remote Assessment of Disease and Relapse – Central Nervous System
EFPIA: The European Federation of Pharmaceutical Industries and Associations
IoT: Internet of things
UK: United Kingdom
HRQoL: Health-Related Quality of Life
AE-IPF: Acute Exacerbations of Idiopathic Pulmonary Fibrosis
NICE: National Institute for Health and Care Excellence
FVC: Forced Vital Capacity
ARDS: Acute Respiratory Distress Syndrome
MDD: Major depressive disorder
RHR: Resting Heart Rate
PEF: Peak Airflow
COPD: Chronic Obstructive Pulmonary Disease
SARS: Severe Acute Respiratory Syndrome
MFCC: Mel-Frequency Cepstral Coefficients
SVM: Support Vector Machine
KNN: K Nearest Neighbour
HMM: Hidden Markov Model
TAM-FF: Technology Assessment Model Fast Form
HR: Heart Rate
GAD7: The Generalized Anxiety Disorder scale
PHQ8: Patient Health Questionnaire depression scale
FSS: Fatigue Severity Scale
WHO: World Health Organization
CCLTE: WHO COVID-19 Long Term Effects
PCFS: Post Covid Function Status
aRMT: Active Remote Monitoring Technology App
CAT: COPD Assessment Test
L-IPF: Living with Idiopathic Pulmonary Fibrosis
WCS: WHO COVID-19 Symptoms
HRV: Heart Rate Variability
PPG: PhotoPlethysmoGram
IPF-PROM: IPF Patient Reported Outcome Measure
VAS: Visual Analogue Scale
SGRQ: St. George's Respiratory Questionnaire
PSQI: Pittsburgh Sleep Quality Index
OSA: Obstructive Sleep Apnea
EoP: Experience of participation

GP: General Practitioner
LSTM: Long Short-Term Memory
EARS: Early Aberration Reporting System
GIR: Global iterative replacement
CNNs: Convolutional Neural Networks
RNNs: Recurrent Neural Networks
DBMs: Deep Boltzmann Machines
UCLH: University College London Hospital
RFH: Royal Free Hospital
PIS: Participant Information Sheet
eCRF: electronic Case Report Form
PPI: Patient and Public Involvement
SLAM: South London and Maudsley NHS Foundation Trust

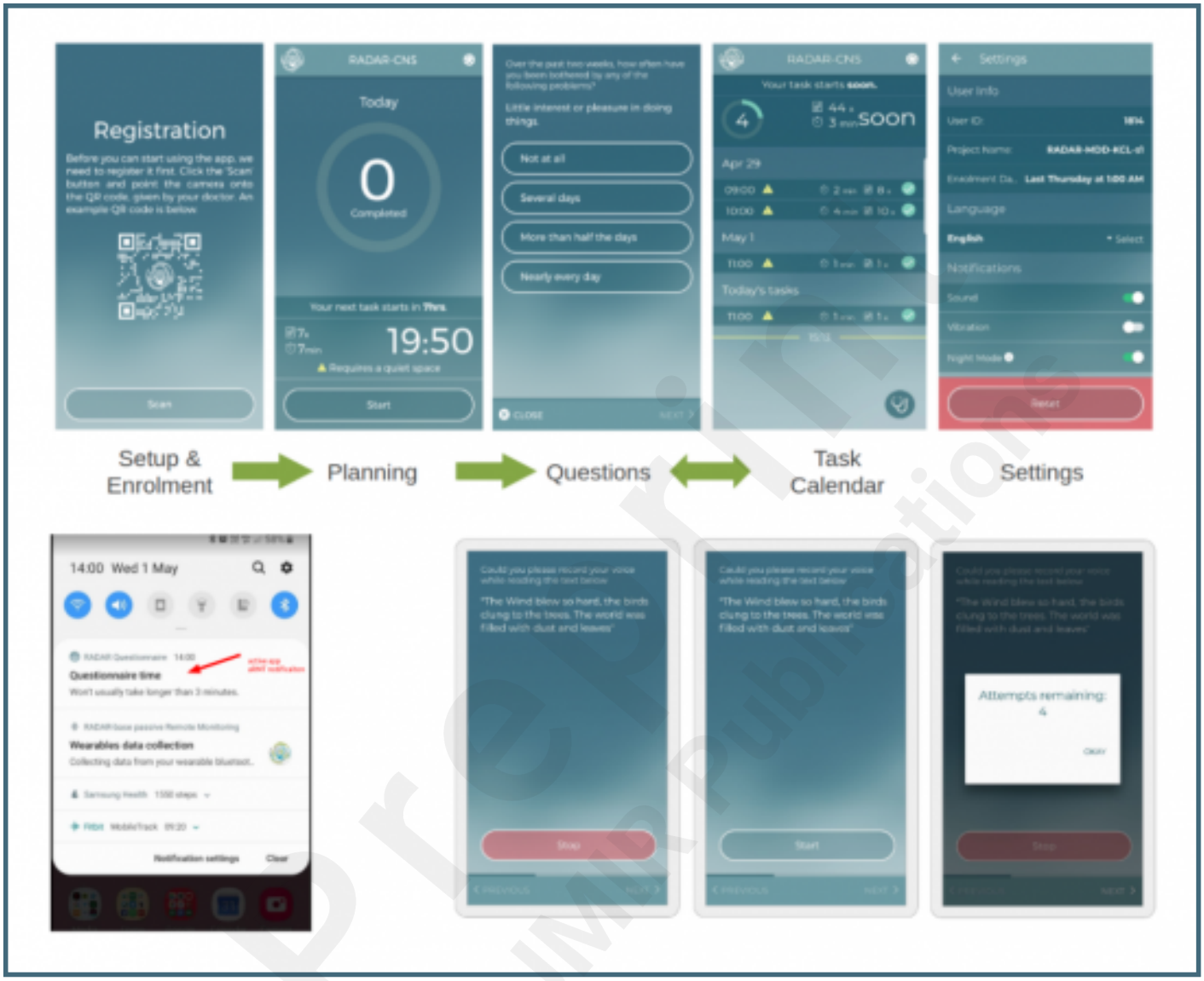
Supplementary Files

Figures

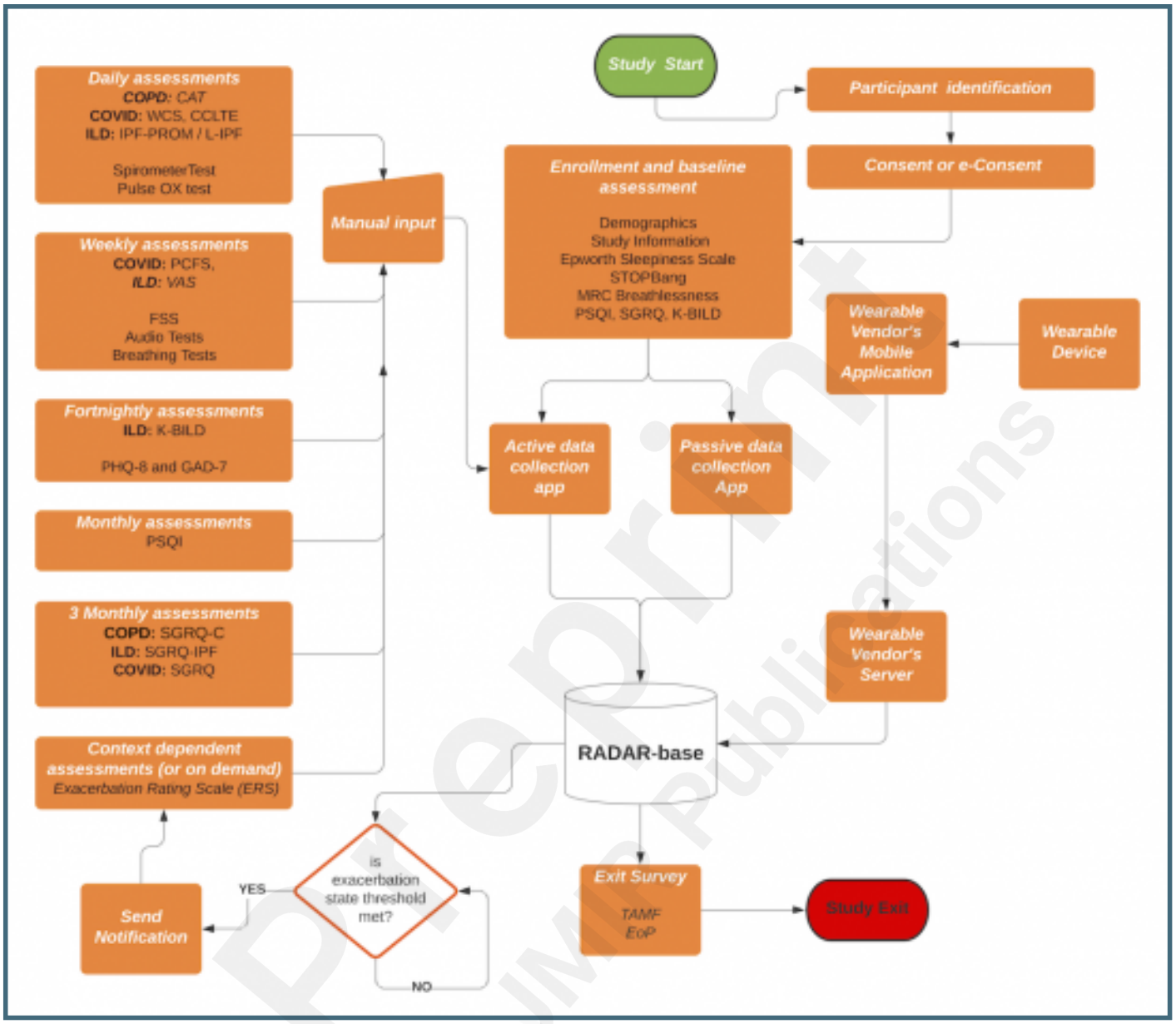
Time Course of Symptoms and Oximetry Variables at Exacerbation [11].



Active App (aRMT). Used to collect phone delivered questionnaires in Table 2. app screens and e.g. questionnaire (top); e.g. notification to complete the questionnaire (bottom left); speech task (bottom right).



Study flow diagram.



Study Timeline.

Multimedia Appendixes

Data analysis algorithms and models.
URL: http://asset.jmir.pub/assets/8e7cc908af57a7f2190c77b44b3d35fd.docx

CONSORT-EHEALTH Checklist.
URL: http://asset.jmir.pub/assets/4dda9f18456291d5d5d6facee1b77a71.pdf