**FULL/LONG TITLE OF THE STUDY**

**Rehabilitation for Cardiac Arrhythmia in COVID-19 and NON COVID-19 Patients.**

**SHORT STUDY TITLE / ACRONYM**

**Rehabilitation for Cardiac Arrhythmia.**

**PROTOCOL VERSION NUMBER AND DATE**

**Version 2.0**

**Date 24/5/2021**

**RESEARCH REFERENCE NUMBERS**

**IRAS Number: 289997**

**SPONSOR Number: 138909**

**This protocol has regard for the HRA guidance**

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## 1. AMENDMENT HISTORY

| Amendment No. | Protocol version no. | Date issued | Author(s) of changes | Details of changes made |
|---|---|---|---|---|
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## 2. ABBREVIATIONS

| | |
|---|---|
| AF | Atrial Fibrillation |
| AE | Adverse Events |
| BRC | Biomedical Research Centre |
| CAT | COPD Assessment Test |
| CI | Chief investigator |
| COVID-19 | Corona Virus Disease 2019 |
| CRF | Case Report form |
| CR | Cardiac Rehabilitation |
| EPR | Electronic Patient Record |
| ESC | European Society for Cardiology |
| FACIT-FS | Functional Assessment Chronic Illness Therapy Fatigue Scale |
| GCP | Good Clinical Practice |
| GDPR | General Data Protection Regulation |
| HADS | Hospital Anxiety and Depression Scale |
| HRA | Health Research Authority |

| | |
|---|---|
| HRQoL | Health Related Quality of Life |
| ISF | Investigator Site File |
| ISWT | Incremental Shuttle Walking Test |
| $Vo_2$ Peak | Maximum rate of oxygen consumption |
| 6MWT | Six Minutes Walking Test |
| 6MWD | Six Minutes Walking Distance |
| NIHR | National Institution for Health Research |
| PA | Physical Activity |
| PPI | Patient and Public Involvement |
| QoL | Quality of Life |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Events |
| SF-36 | Short Form Health Related Quality of Life Questionnaire |
| SOP | Standard Operation Procedure |
| SPSS | Statistical Package for the Social Sciences |
| SACB | Saudi Arabian Cultural Bureau |
| TSC | Trial Steering Committee |
| UHL | University Hospitals of Leicester |
| UoL | University of Leicester |

## 3. SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

**For and on behalf of the Study Sponsor:**

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

Name (please print):
.....

Position:
.....

**Chief Investigator:**

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

Name: (please print):
.....

## 4. KEY STUDY CONTACTS

| | |
|---|---|
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| **Sponsor** | University Hospitals of Leicester (UHL) |
| **Funder(s)** | This is a PhD research study funded by the Saudi Arabian Cultural Bureau (SACB). |

## 5. STUDY SUMMARY

<table>
<tr><td colspan="2">Study Title</td><td colspan="2">Rehabilitation for Cardiac Arrhythmia in COVID-19 and non COVID-19 Patients.</td></tr>
<tr><td colspan="2">Internal ref. no. (or short title)</td><td colspan="2">Rehabilitation for Cardiac Arrhythmia.</td></tr>
<tr><td colspan="2">Study Design</td><td>Planned Size of Sample</td></tr>
<tr><td>Stage 1</td><td>a) Survey to understand patients attitude an expectation toward rehabilitation programme.<br><br>b) Qualitative interview to understand patients experience with AF and their facilitators and barriers to rehabilitation programme.</td><td>a) a sample of 40 participants is anticipated.<br><br>b) Participants will be recruited until both theoretical saturation and the diversity of the sample required has been met; a sample of approximately 20 patients is anticipated.</td></tr>
<tr><td>Stage 2</td><td>- Qualitative interview to understand staff attitudes toward AF management , exercise for AF patients and facilitators and barriers to rehabilitation programme.</td><td>- Participants will be recruited until both theoretical saturation and the diversity of the sample required has been met. a sample of approximately 20 participants is anticipated.</td></tr>
<tr><td>Stage 3</td><td>- Observational study to assess the impact of rehabilitation on autonomic function in COVID-19 patients.</td><td>- We aim to recruit 30 participant.</td></tr>
<tr><td colspan="2">Study Participants</td><td colspan="2">• Patients with atrial fibrillation who are awaiting for an ablation procedure.<br>• COVID-19 patients.<br>• Health care professionals.</td></tr>
<tr><td colspan="2">Follow up duration (if applicable)</td><td colspan="2">N/A</td></tr>
<tr><td colspan="2">Planned Study Period</td><td colspan="2">24 Months</td></tr>
<tr><td colspan="2">Research Questions</td><td colspan="2">1. What are the patients attitude and expectation toward rehabilitation programme?<br><br>2. What are the staff attitude and expectation toward rehabilitation programme ?</td></tr>
</table>

| | |
|---|---|
| | 3. What is the impact of rehabilitation on autonomic function in COVID-19 patients? |

## 5.1 KEY WORDS

Arrhythmia
Atrial Fibrillation
Autonomic Functions
COVID-19
Rehabilitation
Breathlessness
Health Related Quality of Life
Incremental Shuttle Walk Test
Exercise Capacity

# 6. FUNDING AND SUPPORT IN KIND

## 6.1 Role of study sponsor and funder

The funder (SACB) is providing the finance for the study but has no other role in the conduct of the study. The funder will not be part of the study conduct, data analysis and interpretation, manuscript writing, and dissemination of results. The study sponsor (UHL) will assume overall responsibility for the initiation and management of the study and will maintain oversight, so it can ensure compliance with its responsibilities and regulations. However, like the funder, the sponsor will not be part of the data analysis and interpretation, manuscript writing, and dissemination of results.

## 6.2 Roles and responsibilities of study management committees/groups & individuals

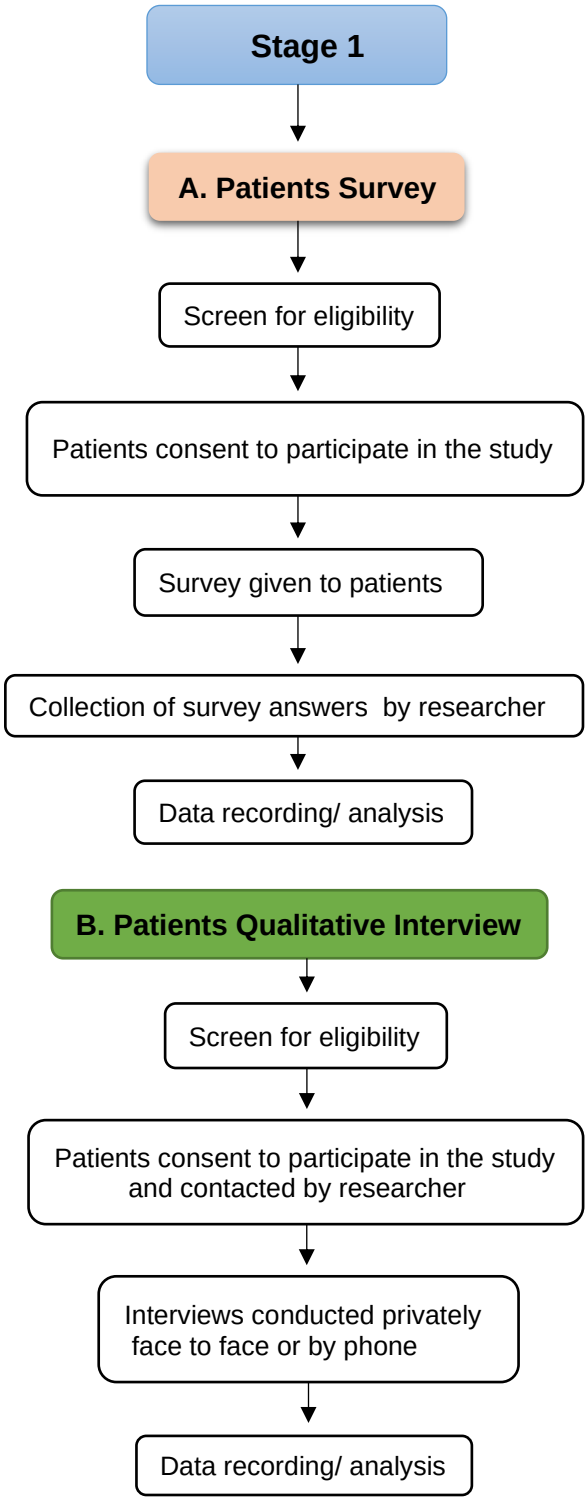
### 6.2.1 Study Steering Groups

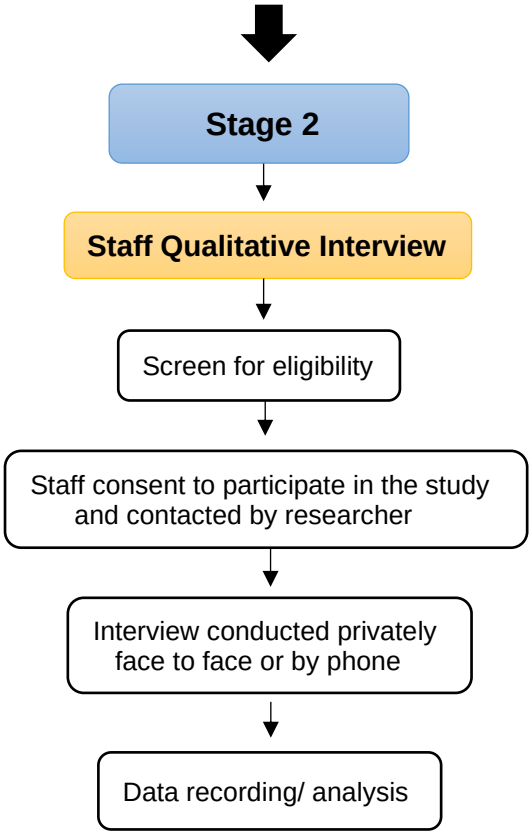
A project steering committee, comprising of Chief investigator, co-investigators and patient representative members will meet during the lifespan of the project (approximately every 6 months), with a view to reviewing project targets and progress made. The group will seek solutions to problems as necessary. The group will also discuss interpretation of the findings, the adherence to the protocol, consideration of new information of relevance to the research question and dissemination plans for the study. Additional meetings will be arranged with co-investigators when required depending on expertise and the nature of enquiry.

# 7. PROTOCOL CONTRIBUTORS

The protocol has been written by the study CI with advice taken from the study steering group as required. The funders and sponsor have had no role in drafting the protocol. Final decisions on the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results will rest with the study steering committee.

## 8. STUDY FLOW CHART/ TIME TABLE




Stage 2
Staff Qualitative Interview
Screen for eligibility
Staff consent to participate in the study and contacted by researcher
Interview conducted privately face to face or by phone
Data recording/ analysis

**Stage 3**

**Study Time Table for Stage 3**

| Week No. | Visit No. | Data to be collected |
|---|---|---|
| **1** | **1** | - Written consent.<br>- Demographics.<br>- Medical history.<br>- Current medications.<br>- **Questionnaires**<br>1. EQ5D QoL questionnaire.<br>2. CAT assessment tool.<br>3. FACIT-FS questionnaire.<br>4. Anxiety and depression (HADS).<br>- Familiarisation ISWT.<br>- ISWT (Test 1).<br>- Provide physical activity monitor.<br>- connect a 12-lead ECG for 10 mins.<br>- connect a 12-leads Holter ECG monitor for 24 hrs. |
| **Starting of Rehabilitation Programme**<br>( Activity monitor will be collected at session 1 of the programme and it will be provided to patient at week 5, then it will be collected again at week 6 of the programme ) | | |
| **After 6 weeks**<br>(Finishing rehabilitation programme) . | **2** | - ISWT (Test 2).<br>**- Questionnaires**<br>1. EQ5D QoL questionnaire.<br>2. CAT assessment tool.<br>3. FACIT-FS questionnaire.<br>4. Anxiety and depression (HADS).<br>- connect a 12-lead ECG for 10 mins.<br>- connect a 12-leads Holter ECG monitor for 24 hrs. |
| | | |

# 9. STUDY PROTOCOL

## 9.1 Background and rationale

Cardiac arrhythmia is defined as an irregular heart rhythm caused by altered electrical impulses in the heart.[1] Atrial Fibrillation (AF) is considered the most common type of cardiac arrhythmias that occurs in aging population.[2] In addition to age, definite factors such as obesity, smoking, hypertension, diabetes mellitus, chronic lung diseases, chronic kidney disease, congestive heart failure and valvular heart diseases are associated with development of AF.[3,4] Furthermore, studies showed that young athletes doing intensive endurance exercises also considered at risk of developing AF.[5-7]

The prevalence of AF is estimated to increase in the United States to 12 million by the coming decades.[8] Additionally, the reports showed a similar prevalence across Europe.[9]

AF is correlated with incidents of heart failure, stroke and other cardiovascular events which leads to increase hospitalization and mortality.[10]

The common symptoms associated with AF are palpitations, chest pain, breathlessness , fatigue, dizziness, diaphoresis, sleep disturbance, exercise intolerance, anxiety and depression which leads to reduced functional capacity and impaired quality of life (QoL).[11-14]

In clinical practice, AF is mainly classified into five categories: first- diagnosed (patient present for the first time with AF), paroxysmal AF (which is self-limiting and arrhythmic episodes usually converts to normal rhythm within 48 hours without treatment needed), persistent AF, which episode lasts for 7 days or longer), long-standing persistent AF (which arrhythmia exceeds one year), permanent AF (where arrhythmia is present all the time and is accepted by physician and patient and no interventions or treatments are used).[11,15]

European Society for Cardiology(ESC) has published a clinical guidelines to treat and manage patients with AF. This management concentrated mainly on controlling rate and normal sinus rhythm, reducing symptoms, cardiovascular and thromboembolic complications related to the disease.[11]

This guidelines recommended using antiarrhythmic medications as a first-line therapy for AF to restore and maintain normal sinus rhythm and reduce disease related symptoms .[11]

January et al. reported that amiodarone has been shown to be effective compared to other antiarrhythmic medication for maintaining normal sinus rhythm and reduce the risk of stroke. However, it can cause adverse effects including multiorgan toxicity and sinus node dysfunction.[16] In addition, hospital admission is needed for some cases to monitor the safety during initiation of other antiarrhythmic therapy which is inconvenient for some patients.[17]

Radiofrequency catheter ablation is an invasive procedure recommended to be used as a second-line treatment if antiarrhythmic medication failed to restore and maintain normal sinus rhythm, or if patient couldn't tolerate using pharmacological therapy.[11,18] A systematic

review published by Chen et al. indicated that catheter ablation had a better impact on preventing recurrence of AF and improve disease related symptoms compared to other medical treatments. However, a limited evidences supported the long term effect of ablation on maintaining normal sinus rhythm.[19] Another study published by M. Kalla et al. indicated that ablation is a safe procedure and successful in reducing recurrence of AF by 80% in patients with symptomatic paroxysmal AF if they don't have structural heart disease. However, the evidences is limited in those with persistent AF due to the heterogenous mechanisms of arrhythmia in this population.[20]

Although the positive effect of current AF treatments in managing heart arrhythmia, reducing risk of stroke and disease related symptoms, they haven't focused on patients exercise capacity and health related quality of life which are common to be reduced in patients with AF.[21,22]

Rehabilitation programme is a multidisciplinary comprehensive programme targeting patients with pulmonary, cardiovascular and chronic diseases. The programme includes patient assessment, education, exercise training, behavior modification and risk factor management.[23] The duration of this programme usually lasts between 6 to 12 weeks, and patients attend two to three sessions per week. A qualitative work done by Risom et al. demonstrated that rehabilitation programme had a beneficial effect on improving physical capacity and disease related anxiety and stress for post-ablated AF patients.[24] A meta-analysis published by Raisom et al. from six randomised clinical trials, found that exercise training programme had a positive impact on physical capacity in AF patients measured by $VO_2$ peak or six minute walk test (6MWT) compared to those with no exercise. However, it was not possible to describe the impact upon mortality, and the evidence was limited in terms of improving health related quality of life (HRQoL).[18] Another meta-analysis published in 2018 by Smart et al. indicated that there were a significant improvement in physical and mental components of HRQoL using SF-36 in exercise group compared to control group. Also, there were a significant improvement in exercise capacity measured by $VO_2$ max or six minutes walking distance (6MWD). Moreover, there were a reduction in maximal and resting heart rate and AF symptoms following exercise-based programme. However, there were insufficient data due to low number of studies and participants.[25]

In addition, most of the studies included by Raisom et al. and Smart et al. were not sufficiently well powered, or inappropriately designed, and only included hospital based rehabilitation.

Corona virus disease 2019 (COVID-19) is a respiratory viral infection that can affect multiple body organs including the heart which may lead to cardiac rhythm disturbance.[26]

The main symptoms of COVID-19 are palpitation, fatigue and dizziness which give an indication for cardiac involvement.

Recent observational studies reported that the incidence rate of cardiac arrhythmias in patients admitted to hospital with COVID-19 were between 17% to 23.5%, with atrial fibrillation being the most common type of arrhythmia.[27-29]
In addition, the observed cardiac arrhythmias in patients with COVID-19 might be a result of immune system response to virus which has a negative effect on the Autonomic Nervous System (ANS) that regulates the heart rhythm.[30,31]
Studies showed that rehabilitation programme could improve and restore autonomic function balance in patients with different conditions. Cheng et al. reported in his study that rehabilitation programme had a significant impact on reversing the cardiac autonomic functions in patients with COPD which represented by a significant improvement in Heart Rate Variability (HRV) parameters, besides improvement in other outcome measures including exercise capacity and HRQoL.[32] A meta-analysis conducted by Pearson et al. in 2018 from 16 randomised controlled trials, indicated that exercise-based programme improved the autonomic function parameters including heart rate variability in patients with heart failure (HF), which reduced the risk of mortality and morbidity in this population.[33]
Another study conducted by Sandercock et al. in patients with coronary artery disease (CAD) with altered autonomic functions following myocardial infraction (MI), they reported a significant improvement in HRV domains, exercise capacity measured by ISWT, hospital anxiety and depression scores after eight weeks of rehabilitation programme.[34]
There is a concern that COVID-19 related symptoms can cause an increase in morbidity and significant burden on healthcare services. Therefore, we aim to explore the potential benefits of rehabilitation programme in reversing the abnormal autonomic function and heart rhythm disturbances in this population.

## 9.2 RESEARCH AIM(S)\ OBJECTIVE(S)\ QUESTION(S)

### 9.2.1 Research aim

The aim of this project is to explore the impact of rehabilitation on autonomic nervous system and cardiac functions in patients with COVID-19.

### 9.2.2 Research objectives

***Primary objective***

- To conduct an observational cohort study to explore the impact of rehabilitation programme on autonomic functions and cardiac disturbance in COVID-19 patients. We will also assess other outcome measures including: Exercise capacity, health related quality of life, disease symptoms, fatigue, physical activity, anxiety and depression.

***Secondary objectives***

- To conduct a qualitative interviews and surveys to better understand patients experience with AF, attitude and expectation toward rehabilitation, their facilitator and barriers to the programme.
- To conduct a qualitative interviews and surveys to understand the attitude of health care professionals who are involved in the care for patients with AF toward disease management , exercise for AF patients and facilitators and barriers to rehabilitation programme.

### 9.2.3 Research questions

1. What are the patients attitude and expectation toward rehabilitation programme ?
2. What are the staff attitude and expectation toward rehabilitation programme ?
3. What is the effect of rehabilitation programme on autonomic function in COVID-19 patients ?

## 10.STUDY DESIGN

This study will have 3 stages and will adopt a variety of different approaches.

### 10.1 Stage 1

**Understand patients attitude and expectation toward rehabilitation programme**

This study will be conducted using surveys and semi-structured interviews.
**a)** The surveys will be conducted through the phone, the initial approach will be made by the cardiac arrhythmia team. Eligible patients will be contacted by the arrhythmia team asking the patients if they are happy for the research team to contact them about the study. Patients expressing willingness to take part will then be contacted by the research team. A member of the research team will contact the patient and provide a clear verbal description about the study and will send a copy of the study information sheet and consent form, allowing them at least 24 hours to read the information before participating in the study. They will then be contacted for consent prior to study initiation.
Due to the nature of this study where there is no intervention, the informed consent will be obtained through the phone by the research team. The aim of the survey is to understand patients experience with AF symptoms, preference of rehabilitation programme delivery,

internet usage survey contains questions about patients experience with AF symptoms, preference of rehabilitation programme delivery, internet usage and their exercise habits.

**b)** An Audio-recorded semi-structured qualitative interview will be conducted through the phone. The initial approach will be made by the cardiac arrhythmia team. Eligible patients will be contacted by the arrhythmia team asking the patients if they are happy for the research team to contact them about the study. Patients expressing willingness to take part will then be contacted by the research team. A member of the research team will contact the patient and provide a clear verbal description about the study and will send a copy of the study information sheet and consent form, allowing them at least 24 hours to read the information before participating in the study. They will then be contacted for consent prior to study initiation.
Due to the nature of this study where there is no intervention, the informed consent will be obtained through the phone by the research team prior to the interview. The interview will be led by an indicative topic guide to explore their views and experience with the disease, their barriers and facilitators to rehabilitation programme.
This will be audio-recorded and transcribed for analysis using qualitative methods.[35] The purpose of this qualitative work is to better understand patients experience with the disease, how it affected their life and their activity levels. Also, it will focus on understanding patient barriers and facilitators to rehabilitation programme.
Eligible participants will be recruited until both theoretical saturation and the diversity of the sample required has been met; a sample of approximately 20 participant is anticipated.

Interview questions and surveys have been devised based on relevant literature, experience of the team and consultation with patient representatives and were piloted before use to ensure validity.

### 10.1.1 Inclusion Criteria for stage 1

To be included, participants must meet the following criteria:

1) 18 year or older. 2) All genders.

3) Have a clinical diagnosis of AF and awaiting for ablation.

4) Able to exercise and understand exercise instructions.

5) Able to speak and read English.

6) Willing and able to provide informed consent for participation in the study.

### 10.1.2 Exclusion criteria

1) Aged < 18 years.

2) Unable to provide valid informed consent.

3) Unable to exercise due to significant musculoskeletal or neurological abnormalities.

4) Unable to speak and read English.

## 10.2 Stage 2

**Understand staff attitude and expectation toward rehabilitation programme**

This study will be conducted using semi-structured interviews. Health care professionals who are involved in the care of patients with AF will be recruited from Glenfield Hospital. Clinical leads of cardiac arrhythmia and cardiac rehabilitation will be approached and asked to disseminate the study information leaflet to participate in this study to their UHL colleagues.
An Audio-recorded qualitative interview will be conducted to better understand their general attitude toward AF management, implementation of rehabilitation contents, barriers and facilitators to rehabilitation programme.[36] An interview will be either face to face or by telephone privately between the interviewer and each staff who involved in the care of AF patients. A study information sheet and consent form will be received by participants. Participants will be recruited until both theoretical saturation and the diversity of the sample required has been met.
Methodology of analysing qualitative data will be as stage 1.

### 10.2.1 Inclusion Criteria for stage 2

To be included, participants must meet the following criteria:

1) 18 year or older. 2) All genders.

3) Health care professionals who are involved in the care for patients with AF.

4) Willing and able to provide informed consent for participation in the study.

### 10.2.2 Exclusion criteria

1) Aged < 18 years.

2) Unable to provide valid informed consent.

3) Health care professionals who are not involved in the care for patients with AF.

### 10.3 Stage 3

**An Observational Cohort Study to Explore the Impact of Rehabilitation Programme on Autonomic Function in COVID-19 Patients**

An observational cohort study will be conducted to assess the effect of rehabilitation programme on autonomic function in COVID-19 patients. We will be using a 12- lead ECG Holter device beside the assessment of patient's physical activity before and after rehabilitation programme.

We will also assess the effect of rehabilitation on other outcomes which are routinely collected:

1. Health-related quality of life, 2. Exercise capacity, 3. Disease symptoms,
4. Fatigue, 5. Anxiety and depression.

We aim to recruit eligible patients who are scheduled to attend post covid rehabilitation programme. An Informed consent will be obtained from all patients prior to study initiation. The initial approach will be made by clinical team running the rehabilitation programme and any patients expressing an interest in taking part will be provided with a written information leaflet. patients expressing willingness to take part will then be introduced to the research team. The research team will contact the patient to explain the study and explain the benefits of conducting this study. At this stage, any interested patient who agrees to participate will be asked to sign a written consent form prior to study initiation.

#### 10.3.1 Description of the intervention

The post covid recovery programme comprised a twice-weekly supervised sessions of disease education and exercise training including aerobic activities, general physical mobility, muscle strength and resistance training for six weeks. The disease educational component comprised twelve sessions of discussions and practical demonstrations assessed by health care professional. Patients are encouraged to perform a regular physical activities five times a week for 30 minutes at home.

#### 10.3.2 Outcome measures to be used in the observational study

The clinical outcome measures to assess the intervention will be collected at baseline and 6 weeks. Baseline demographics including: Age, gender, ethnicity, BMI, smoking status, employment status, previous cardiac events and medications will be recorded.

The **primary outcome** of this study is to assess the impact of rehabilitation on autonomic functions in COVID-19 patients.

***Study Measures**

- **Autonomic function measures**

We will be using a non-invasive 12-lead ECG NORAV Holter device. The data will be collected continuously for 24 hours from patients before and after the rehabilitation period. In addition, a resting 12-lead ECG recordings will be collected for 10 minutes at baseline and again after rehabilitation. Biomarkers of interest include QT variability, signal averaging ECG (fragmented QRS complexes), temporal T wave morphology variability, and T wave alternans. This will provide a wide analysis of heart rates that are suitable for detailed assessment of the autonomic function before and after rehabilitation programme.

- **Physical Activity**

Daily physical activity (step count) will be assessed for seven days using the GT3x Actigraph device that is worn around the waist.[37] Prior to starting the programme, all participants will be asked to wear the activity monitor every day for the next week for at least 12 h a day (seven full days) and only remove the device for showering or bathing. Participants will then be asked to wear the monitor again for another seven days at week 6 of the programme.

***Routine Measures**

We will also assess other outcome measures which are routinely collected at baseline and after 6-weeks of rehabilitation:

1. **Health-related quality of life**

   by using The EuroQual 5 domain (EQ5D) health related quality of life which measures mobility, self-care, usual activity, pain/discomfort, anxiety and depression.[38]

2. **Exercise capacity**

   Will be measured by using the ISWT, which is a field test commonly used to assess cardiopulmonary fitness.[39]

3. **Disease symptoms**

   Using COPD Assessment Test (CAT) for the evaluation of COVID-19 symptoms.[40]

4. **Fatigue**

   Will also be measured by using Functional Assessment Chronic Illness Therapy Fatigue scale (FACIT-FS) which contains 13-items to measure the participant's fatigue level during their daily activity.[41]

5. **Anxiety and depression**

   Will be measured by using the Hospital Anxiety and Depression Scale (HADS).[42]

# 11. Eligibility criteria for the observational study (Stage 3)

## 11.1 Participants Inclusion and Exclusion Criteria

### 11.1.1 Inclusion Criteria

To be included, willing participants must meet the following criteria:

1) 18 year or older. 2) All genders.

3) Those who recovered from COVID-19.

4) Enrolling into post COVID-19 rehabilitation programme.

5) Able to speak and read English.

6) Willing and able to provide informed consent for participation in the study.

### 11.1.2 Exclusion criteria

1) Aged < 18 years. 2) Unable to provide valid informed consent.

3) Patients with known AF or any type of arrhythmia.

4) Patients using beta blockers.

5) Unable to read, speak and write English.

# 12. SAMPLE (Stage 3)

## 12.1 Size of sample

As this is an observational study, we aim to recruit 30 participants into this stage.

## 12.2 Sampling technique

Patients will be recruited from those attending their scheduled Post-Hospitalisation rehabilitation programme for COVID-19.

# 13. QUALITY ASSURANCE

The study will be conducted with correspondence to the rules of Good Clinical Practice (GCP).

# 14. DATA ANALYSIS

## 14.1 Quantitative statistical analysis

All quantitative data will be analysed using SPSS software.[43] For the patients survey, all the data will be entered into SPSS spreadsheet. A descriptive statistics will be used for the analysis. The data will be presented by percentages, means and standard deviations. For the observational study, analysis will be primarily descriptive statistics, the baseline characteristics of participants will be represented using mean, standard deviation and percentages as appropriate. measurements will be compared, paired t-test statistical analysis will be used for normally distributed data and Wilcoxon statistical test will be used if the data were not normally distributed.[44,45]

For the Autonomic Function assessment, The data will be analysed using robust signal processing approaches by the biomedical engineering research associate (RA). Advanced HRV analysis will be performed with the Holter ECGs. Biomarkers of interest include QT variability, signal averaging ECG (fragmented QRS complexes), temporal T wave morphology variability, and T wave alternans. These features will be compared and combined to be further correlated with patient-specific characteristics.

## 14.2 Qualitative data analysis

Audio-recorded interviews will be conducted privately face to face or via telephone between the participant and an interviewer after informed consent. The interviews would be anticipated to be between 30 minutes and one hour duration and will be professionally transcribed verbatim, with identifiable information removed. The transcription will be performed by an external company and a confidentiality agreement will be in place. Interview prompts will be devised based upon relevant literature and experience of the team.

The interviews will be reviewed using thematic analysis supported by NVivo software. This approach follows six distinct stages: familiarisation with data; generating initial codes; searching for themes; reviewing themes; defining and naming themes and producing the report. Initial coding will be carried out and a sample of interviews will be coded. Throughout the data analysis, meetings will be undertaken with the research team to discuss and review emerging themes.

## 14.3 Data entry

Data entry will be conducted by the study delivery team at site. Source documentation will be on files stored in a locked office at BRC. Electronic files will be kept on a password protected , UHL computers.

Data validation and cleaning will be carried out throughout the study by the research team at site. Data management will be conducted by the study Co-ordinator. Access to the data will be provided to the study team only. The data and CRFs will be archived for five years in line with Sponsor SOPs.

Identifiable information will be kept in a locked office and not be removed from the clinical centres or made available in any form to those outside the study.

## 15. INFORMED CONSENT

The Informed consent of subjects to participate in the study must be obtained before any study specific procedures are undertaken. The participant information sheet supplied to potential study subjects and the consent form will be in accordance with the requirements in ICH GCP and will have been approved by an Ethics Committee. Written and verbal versions of the participant information and informed consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Stage 1: The study will be explained over the phone and the patient information sheet and consent will be sent to their home to be read if they wish to go ahead. Due to the nature of this studies where there are no intervention or clinical management and due to distancing measures, participants will be able to consent over the phone and talked through PIS. The completed consent form will include personally dated signatures of the person taking consent over the phone on behalf of the individual taking part in the study.

Stage 2: Participants will have the choice to conduct the interview by phone or face to face depending on their preference. The study will be explained either in person or over the phone and the participants information sheet and consent will be given to the participant or sent to their mail to be read if they wish to go ahead. If attending face to face, the consent form will be completed on site.

Stage 3: A written informed consent will be obtained face to face by means of participant dated signature and dated signature of the person who presented and obtained the informed consent.

The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the PI as detailed on the Delegation of Authority and Signature log for the study.

The original signed form will be retained at the study site within the TMF or Investigator Site File (ISF). A copy of the signed Informed Consent will be given to participants and a copy retained in the participant medical notes.

Patients will be asked to provide consent to enable access their future health status through records maintained by NHS Digital, together with other central UK NHS bodies. This data will be used to measure long-term morbidity and mortality outcomes.

## 16. ETHICAL AND REGULATORY CONSIDERATIONS

### 16.1 Participants confidentiality

The study team will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participant ID number on the CRF and any electronic database. All study documentation containing identifiable patient data will be managed in accordance with ICH GCP, the UK Policy Framework for Health and Social Care, the Data Protection Act and the EU General Data Protection Regulation (GDPR).

### 16.2 Others

The sponsor will ensure that the investigators and study team are adequately qualified by education, experience and/or training to perform the study procedures and duties in accordance with ICH GCP. The qualifications, experience and training of all members of the study team will be detailed in signed curriculum vitae and training certificates, which will be retained with the other ICH GCP essential documents in the trial master file.

### 16.3 Assessment and management of risk

The study is considered to be low risk. Patients will be asked to complete several simple physical tests at the study visits. They may feel breathless at the end of the walking tests but this normally settles within a few minutes. It would be very unusual for symptoms to persist. However, in this unlikely situation medical staff are on hand at the hospital.

Some patients may find the ECG electrodes uncomfortable to keep on for 24 hours, but this is rare.

We will abide by the safeguarding policy of the University Hospitals of Leicester NHS Trust and ensure that all staff working with patients on the study have undertaken safeguarding training.

## 17. PEER REVIEW

A full review of the protocol was completed by a member of Centre for Exercise and Rehabilitation Science (CERS) team who can provide a review that is independent, expert and proportionate.

## 18. PATIENT & PUBLIC INVOLVEMENT

The research topic and study stages were presented to patients within our local PPI cardiorespiratory group where we had discussions about the benefits of rehabilitation for patients with AF and recent evidences about arrhythmia in COVID-19 patients. The research protocol, PIS , surveys and interviews have been reviewed by patients and a public representative with an interest in cardiorespiratory rehabilitation. We anticipate that the PPI members will be involved in developing and reviewing patient documents to ensure they are written in lay language . They helped us to adapt the protocol in in terms of agreeing the participant inclusion criteria and how the project stages should be delivered.
We will have at least two patient and public representatives as part of the steering group and who will help as needed throughout the study duration.

## 19. DATA PROTECTION AND PATIENT CONFIDENTIALITY

### 19.1 Source data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records or GP records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, activity monitor data downloads, laboratory results and participant-completed questionnaires.
CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). In this study the CRF will be used as the source document in addition to participant-completed questionnaires.
All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by their initials and the study participant number, not by name.

### 19.1.1 Study records

During the study, records will be kept in a secure area accessible to study site and sponsor staff. The PI at site will be provided with a study specific Investigator Site File to assist with the storage and archiving of essential documents. Records of study subject data will be made on study specific CRFs. All external documents required by ICH GCP will be made available when requested for inspection by trial monitors, auditors or the regulatory authorities.

### 19.1.2 Data confidentiality

Data will be collected and stored in accordance with the 2018 UK (GDPR). We will need to use information collected from the individual and their medical records for this research project. If ineligible for the trial, anonymised data (initials and year of birth) will be added to a screening log along with the details for the reason of your ineligibility, with the permission of the participant. This information will include initials, NHS/ hospital number, name and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know personal details will not have access and data will have a code number instead. This will prevent personal data from being viewed by all members of the trial team. In general, the CI/ PI will have access to individual data in circumstances of Serious Adverse Events (SAEs), patient withdrawal and trial end.

We will keep all information safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out who took part in the study.

Participants are able to withdraw from the study at any time, without giving a reason, but we will keep information about them that we already have. Participants will also have the option to take part in future research using data saved from this study (by signing up to our research database).

### 19.1.3 Data handling

Access to the database will be permission based. Permissions will be allocated by the CI or delegate. Data will be validated using electronic and manual checks detailed in a pre-approved validation specification document. The participants will be identified by a trial specific participant number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file. Data will be entered by the clinical team into an electronic database using a secure hospital computer system.

### 19.1.4 Archiving

Following completion of the trial data analysis, data and essential trial records, including the final trial report, will be archived in a secure location, for at least five years after the completion of the trial, in accordance with Sponsor SOPs. No trial-related records, including hospital medical notes, will be destroyed unless or until the Sponsor gives authorisation to do so.

### 19.1.5 Access to the final study dataset

The full dataset will be available to the CI, trial co-ordinators on each site, the trial statistician and the trial steering committee. Anyone outside of these roles will need to write to the trial steering committee for approval to access the data. No secondary analysis of the data is planned.

## 20. INDEMNITY

The University Hospitals of Leicester holds an insurance policy to compensate study subjects for any study-related injury. The UHL insurance cover routinely provides for negligent harm. If a patient is harmed due to negligence this would be covered by the sponsor indemnity arrangements for all participants in clinical trials. If a study participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, the standard National Health Service complaint system will be available to them.

## 21. DISSEMINATION OF FINDINGS

### 21.1 Dissemination policy

The aim will be to publish the main outputs from the study in general medical peer reviewed journals to reach the largest audience . The final dissemination newsletter for patients will be developed with the PPI representatives.

The findings from the study will be disseminated by usual academic channels, i.e. presentations at meetings, as well as by peer-reviewed publications and though patient presentations and newsletters to patients, where available. Publication or presentation of the results will be in line with the funder agreement and intellectual property guidelines and with the permission of the PI. The PI is responsible for the final reporting and will determine the authorship of any publication, which will also conform to the CONSORT guidelines. All those contributing to the study but not eligible for authorship will be acknowledged.

The funder will be notified of any publications, presentations etc. prior to issue by the PI, in a timely manner. A summary of the final report will be provided to the main Research Ethics Committee within 12 months of the end of study declaration.

### 21.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship for any publications arising from this trial will rest with members of the trial steering committee who meet the following criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work.
- Drafting the work or revising it critically for important intellectual content.
- Final approval of the version to be published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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