DUO-EF-19

Diagnosis of Heart Failure in the Post-COVID-19 Clinic, Primary Care and Hospital Setting Using a Digital Stethoscope with AI ECG

v2.0 04/02/2021

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STUDY COORDINATION CENTRE: Connected Care Bureau, 4th Floor ICTEM Building, Hammersmith Hospital , London, W12 0HS

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Protocol authorised by:

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Dr Daniel Keene		5.10.20
Dr Alex Fragoyannis		5.10.20
Dr Patrik Bachtiger		4.10.20

Version Control

Version Number	Purpose/Change	Author	Date
1.0	First version	Bachtiger et. al	18/10/2020
2.0	Second version updating with REC feedback.	Bachtiger et. al	04/02/2021

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Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Research Governance and Integrity at:

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Funder

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This protocol describes the DUO-EF-19 study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

COVID-19	coronavirus disease caused by SARS-CoV-2
DUO-EF	**the prediction of ejection fraction above or below 40% based on the interpretation of a single-lead electrocardiogram using a machine learning algorithm**
ECG	electrocardiogram
LVEF	left ventricular ejection fraction; the pumping function (in %) of the left ventricle of the heart, where >50% is normal (preserved); 40-49% is moderately reduced; and <40% is reduced
Echo	echocardiogram
HF	heart failure
HFpEF	heart failure with preserved ejection fraction (above 50%)
HFmEF	heart failure with moderately reduced ejection fraction (between 41 - 50%)
HFrEF	heart failure with reduced ejection fraction (below 40%)
LVEF	left ventricular ejection fraction
cMRI	cardiac magnetic resonance imaging

KEYWORDS

- COVID-19
- Heart failure
- Ejection fraction
- Machine learning

STUDY SUMMARY

TITLE **DUO-EF-19: Diagnosis of Heart Failure in the Post-COVID-19 Clinic, Primary Care and Hospital Setting Using a Digital Stethoscope with AI ECG**

DESIGN Prospective cross-sectional study

AIMS

1. **To validate detection of left ventricular ejection fraction (LVEF) above or below 40% using single-lead ECG interpreted by machine learning algorithm (DUO-EF) compared to gold-standard investigations for calculating LVEF (echocardiography [echo], and a subgroup in cardiac MRI [cMRI])**
2. To conduct a real-world evaluation of DUO-EF detection of LVEF above or below 40% in the primary care and COVID-19 follow up clinic setting; validated against subsequent gold standard investigations
3. To evaluate the positive and negative-predictive value of DUO-EF at 24 months

Methods

1. Head-to-head comparison of DUO-EF against gold standard investigation (echo and cMRI) for classifying LVEF<40%; in unselected patients attending for routine echocardiography (main study group) and cardiac MRI (subgroup) as part of their routine clinical care
2. Point-of-care DUO-EF in patients where GP suspects new heart failure and comparison with:
    a. Subsequent DUO-EF at time of gold-standard investigation (if indicated as standard of care)
    b. Ejection fraction as calculated by gold-standard investigation
3. Point-of-care DUO-EF in patients attending COVID-19 follow up clinic where clinician suspects new heart failure and comparison with:
    a. Subsequent DUO-EF at time of gold-standard investigation for HF
    b. Ejection fraction as calculated by gold-standard investigation

Telephone call follow-up at 24 months for all patients with DUO-EF suggestive of HFrEF but normal gold standard investigations

OUTCOME MEASURES

- **1.) Primary: Sensitivity and specificity of DUO-EF for detecting LVEF above or below 40%**
- 2.) Secondary:
  - DUO-EF performance against subgroup LVEF calculated by cardiac MRI
  - Consistency of DUO-EF result at point-of-care in GP practice ('real world' use where GP suspects new heart failure) against repeat DUO-EF at time of gold-standard investigation
  - Consistency of DUO-EF result at point-of-care in Covid-19 follow up clinic ('real world' use where clinician suspects new heart failure) against repeat DUO-EF at time of gold-standard investigation
  - Development of LVEF <40% at 24 months in participants with initial DUO-EF suggestive of LVEF <40% but gold standard investigations LVEF >40% i.e., can DUO-EF predict future development of LVEF <40%
  - DUO-EF point-of-care determination of LVEF<40% in comparison with the components of the established NICE pathway (BNP result)

POPULATION

- **Group 1**: All-comers to **echocardiography** and cardiac MRI departments across Imperial College Healthcare NHS Trust (**echo n = 1,500**, cMRI n = 100)
- **Group 2**: Patients seen in primary care (GP) with symptoms newly suggestive of heart failure (n = 400); contributing to Group 1 if standard of care indicates need for referral to echo/cMRI
- **Group 3**: Patients seen in the COVID-19 follow-up clinic with symptoms newly suggestive of heart failure (n = 400); contributing to Group 1 if standard of care indicates need for referral to echo/cMRI

ELIGIBILITY

Inclusion criteria for all	- Age 18 years or above - Able to give informed consent		
	Group 1	**Group 2**	**Group 3**
Additional inclusion criteria	- Patient attending for departmental echo or cardiac MRI	- Attending for GP appointment; GP concerned about heart failure diagnosis and initiates patient onto routine NICE pathway	- Attending COVID-19 follow-up clinic; clinician concerned about heart failure diagnosis and initiates patient onto routine NICE pathway

Exclusion criteria	Any chest wound, skin pathology or other feature that would prohibit routine stethoscope examination

DURATION Start date 01/02/2021, duration 36 months

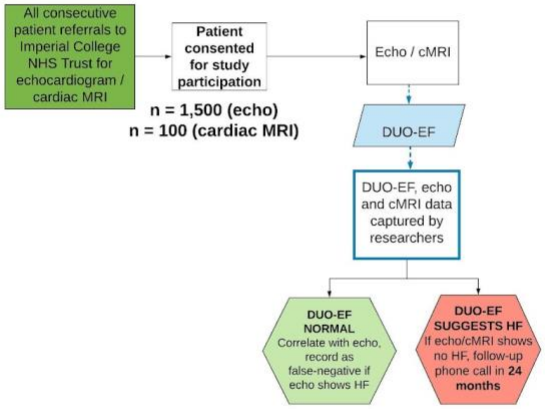
STUDY WORKFLOW SUMMARY DIAGRAM ON NEXT PAGE

DUO-EF-19: Diagnosis of Heart Failure in the Post-COVID-19 Clinic, Primary Care and Hospital Setting Using a Digital Stethoscope with AI ECG

Study Workflow

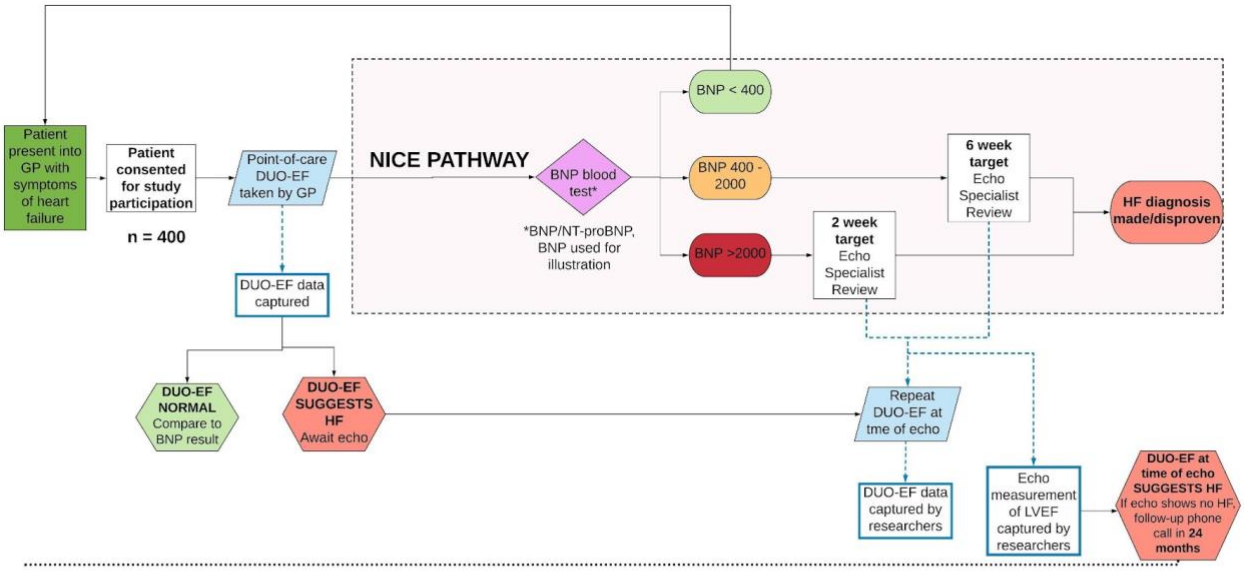
Imperial NHS Trust Echocardiography and Cardiac MRI Departments

St Mary's, Hammersmith & Charing Cross Hospitals and Community Cardiology Centres



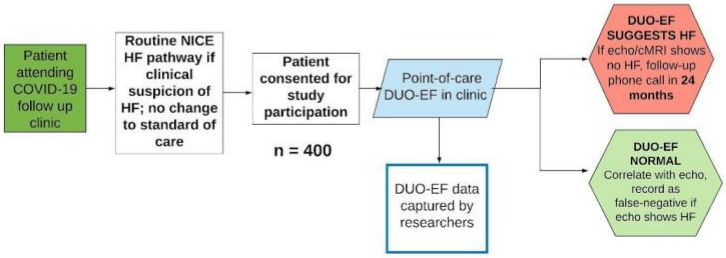
GP Practices

NIHR North West London Clinical Research Network portfolio support



COVID-19 Clinic

All-comers to COVID-19 follow up clinic at St Mary's Hospital



1. INTRODUCTION

1.1 BACKGROUND

Heart Failure

One million people in the UK are living with heart failure (HF), with more than 60,000 new cases annually. Consuming 2% of the entire NHS budget, HF has a worse prognosis — 50% mortality within five years — than most cancers. Furthermore, hospital admissions and demand for social care related to HF is expected to increase by 50% by 2040.[1] Given this massively increasing prevalence of HF, the evidence for the benefits of early diagnosis and treatment coupled with the importance of accuracy and difficulty in diagnosis, HF is one of the biggest challenges facing the NHS, for which better, early diagnostic and management strategies are urgently needed.

HF is a clinical syndrome with a wide spectrum. The majority of patients with HF have heart failure with reduced ejection fraction (HFrEF), characterised by a reduction in blood pumped out of the left ventricle with each heartbeat, as seen on an echocardiogram (an ultrasound-based medical imaging tool, where above 50% is considered normal ejection fraction). **HFrEF is defined as a left ventricular ejection fraction (LVEF) below 40%**. The clinical syndrome of heart failure with preserved ejection fraction (HFpEF) features similar clinical symptoms (e.g. breathlessness, fatigue, ankle swelling) to HFrEF. However, it is difficult to diagnose and no treatment has been proven in pivotal clinical trials to be effective for HFpEF,[2] the mortality from which is lower than treated HFrEF, even when optimally managed.

There is strong and abundant evidence that early effective drug therapy can improve symptoms and prognosis in patients with HFrEF (LVEF <40%), where a substantial portion of increased morbidity and mortality is attributable to late initiation of therapies — caused by delayed diagnosis.[3]

HF is poorly served in primary care, as it can be difficult to diagnose from non-specific symptoms. Delays in diagnosis lead to late initiation of life-prolonging therapies. Current clinical management guidelines from the National Institute for Health and Care Excellence (NICE) suggest performing a brain natriuretic peptide blood test (BNP) when HF is suspected. According to the NICE guidelines, if BNP is elevated, the GP makes a referral for specialist tests (echocardiogram) and assessments within six weeks - two weeks if BNP is especially high.[1]

Only 4% of patients complete these NICE-recommended investigations in the recommended time frame,[3] largely reflecting this unwieldy diagnostic pathway, limited resources, and HF being a common condition that is inherently difficult to diagnose.

Consequently, although 40% of patients might previously have seen their GP with HF symptoms (including breathlessness, ankle swelling, fatigue), the diagnosis of HF is made in 80% of cases

when patients have advanced, severe (and life-threatening) worsening of symptoms, requiring hospital admission.[4] HF is now the most common reason for acute hospital admission in those aged over 65 and and improving diagnosis in the community is listed as an explicit priority for the NHS Long Term plan.[5]

Heart Failure and COVID-19

It is now indisputable that patients with COVID-19 are at increased risk of cardiovascular complications, in many cases culminating in heart failure.[6] As our understanding continues to develop, some studies have suggested myocardial involvement is present in as many as 78% of patients.[7] Importantly, a substantial proportion of heart failure in need of treatment to prolong life is initially asymptomatic. Guidance from the British Thoracic Society[8] recommends all patients who attended hospital with clinico-radiological findings of COVID-19 should be followed up as an outpatient within six weeks -- a huge challenge given the high volume of patients.

Part of this care involves measurement of blood oxygen saturations and testing to screen for chronic lung disease. At present, despite the known cardiovascular complications, no routine screening for heart failure is being done for patients in this setting. This is partly due to the gold standard diagnostic for heart failure -- echocardiography -- being a limited, expensive and specialist resource.[9]

Eko DUO Digital Stethoscope with Artificial Intelligence Electrocardiogram (ECG)

The Eko DUO, is a stethoscope with an expanded acoustic “bell” with which heart sounds can be heard either through conventional rubber tubing (removable) with conventional ear pieces or via a connected mobile phone speaker. Eko DUO is also unique among stethoscopes in featuring a single-lead electrocardiogram (ECG). The Eko DUO and ECG capability are fully CE marked.

With just 15 seconds of Eko DUO ECG data, a deep neural network (a form of artificial intelligence), developed at the Mayo Clinic in the US, can accurately **predict low ejection fraction, abbreviated for this study as DUO-EF.** Previous studies (n = 100) have shown DUO-EF has high accuracy for achieving this (AUC 0.906 [CI: 0.831-0.955] for EF <=35%; 0.841 [CI: 0.754 - 0.906] for EF<50%).[10]

Single-lead ECG requires only two contact points, as in the case of the two stainless steel electrodes on the body of the Eko DUO device, touched to the skin of the patient’s chest wall for instantaneous acquisition of ECG signal. Single-lead ECG is already well established to be

adequate for a machine learning algorithm that detects atrial fibrillation, now a standard feature of some of the biggest consumer wearable technologies (e.g. Apple Watch Series 4). The Eko DUO is able to give a DUO-EF reading at the clinically significant threshold of 40% using single-lead ECG alone -- a study of 100 patients at the Mayo Clinic showed an AUC of 0.89 for detection of LVEF above or below 40%.[11]

Eko DUO Device Regulatory Approvals

The Eko DUO device with ECG has full Conformite European (CE) marking. This study will seek approval both from the Health Research Authority research ethics committee for use of the **DUO-EF algorithm as a 'medical device'**..

In the US, the Food and Drug Administration (FDA) has cleared Eko DUO and its AI-algorithms for heart sound interpretation and ECG detection of atrial fibrillation. The algorithm for detecting low EF recently received FDA Breakthrough Status and fast-track approval in the US. The 12-lead ECG algorithm has recently (May 2020) received Emergency Use Authorization for use during the COVID-19 pandemic.

2. STUDY OBJECTIVES

Primary objective:

1. **To test if the DUO-EF algorithm can achieve a sensitivity and specificity above 80% for detection of LVEF above or below 40% in comparison to gold-standard echocardiography**

Secondary Objectives:

- To perform a subgroup analysis of DUO-EF against LVEF calculated by cardiac MRI (another gold standard investigation for calculating LVEF <40%)
- To validate consistency of DUO-EF result at point-of-care in GP practice ('real world' use where GP suspects new heart failure) against repeat DUO-EF at time of gold-standard investigation
- To validate consistency of DUO-EF result at point-of-care in Covid-19 follow up clinic ('real world' use where clinicians suspect new heart failure) against repeat DUO-EF at time of gold-standard investigation
- To measure if participants with DUO-EF suggestive of LVEF <40% but with gold standard investigations where LVEF >40% are at increased risk of developing heart failure at 24 months i.e. can DUO-EF predict future development of LVEF <40% at 24 months
- To evaluate DUO-EF point-of-care determination of LVEF<40% in comparison with the components of the established NICE primary care pathway (e.g. BNP result)

3. STUDY DESIGN & METHODS

Statistical Considerations

Type of study: Prospective cross-sectional study comparing identification of LVEF above or below 40% by DUO-EF algorithm versus gold-standard methods.

Duration: Start date 01/02/2021, duration 36 months

Number and type of participants: across all settings 2,400 total

Sample Size

Imperial College Healthcare NHS Trust performs over 20,000 echocardiograms per year across its three hospital and community sites, serving the most ethnically and socioeconomically diverse population in the UK.

Based on established data and extensive clinical expertise of the investigators, around half of all patients who attend for echocardiography at the Trust are found to have LVEF <40%. **The sample size calculation below addresses the primary objective: evaluating if the DUO-EF algorithm can achieve a performance of sensitivity and specificity above 80% for detection of LVEF above or below 40% – compared to gold-standard echocardiography.**

SAMPLE SIZE CALCULATION

Primary Variable: Left Ventricular Ejection Fraction >/< 40%

Null Hypothesis: DUO-EF **DOES NOT** detect with sensitivity and specificity exceeding 80% a LVEF greater or less than 40%

Alternate Hypothesis: DUO-EF **CAN** detect with sensitivity and specificity exceeding 80% a LVEF greater or less than 40%

Type 1 error 5% (5% 2 sided test)

Type 2 error 20% (80% power)

Based on the above parameters for sample size calculation (Ref: G*Power, proportion, difference from a constant [binomial test 1 sample test]) to address the primary objective, this study will recruit participants until at least 500 have been recruited with an LVEF above 40% and 500 with a LVEF below 40% i.e the minimum total required is 1000 patients.

This will provide us with an ability to estimate sensitivity and specificity with a 95% CI ±3.3%, and assuming the underlying sensitivity and specificity are at least 85% provide us with 80% power at the 5 % significance level to detect that they exceed the pre-specified criterion of a sensitivity and specificity of 80%.

Dropouts: Dropouts are unlikely within the context of the primary objective since consent and the entire data collection will occur within a short space of time during a single clinical visit (standard-of-care attendance for echocardiography).

Protocol Allowances: Although we require 466 patients with EF >40% and 466 patients with EF <40% we have rounded these up to 500 patients. Furthermore, we will likely need to recruit up to 1,500 patients in total since it is unlikely that the first 1,000 patients will fulfil the exact breakdown of required LVEF above and below 40%.

Controls: The ‘control’ population in this study are participants with LVEF>40%. Indications for referral to echocardiography are broad and include but are not limited to: suspected or known

ischaemic heart disease, suspected cardiomyopathy, pericardial disease, murmurs, assessment of valve disease, assessment of prosthetic valves, assessing chronic lung disease, neurological disease (stroke or transient ischaemic attack), arrhythmia (palpitations and/or loss of consciousness), high blood pressure (common) and as a standard investigation considered before surgery. Many of these referred patients are found to have no abnormalities on echo and are otherwise healthy. Therefore, the unselected approach of this study to include all-comers to echo will generate a population sample that can be evaluated for alignment with the type of population in whom a screening programme for heart failure may be beneficial.

Performance characteristics: Eko Health (the 'manufacturer' of the algorithm) indicate a performance of 80% sensitivity and 80% specificity for the identification of LVEF above or below 40%

Confounders: our study design precludes confounders

Avoidance of bias for primary objective

To avoid any biases in both the recording of DUO-EF readings by the member of the research team and this influencing calculation of %LVEF by the echocardiography team (sonographer), the following steps will be taken:

- The member of the research team approaching patients in the echo department for consent will not be aware of the indication for referral at time-of-consent
- DUO-EF readings can happen before or after the echo, with the member of the research team unaware of the echo-derived %LVEF until they check the electronic health record (after DUO-EF has already been recorded).
- The sonographer will not be made aware of the results of DUO-EF, therefore not biasing any interpretation of %LVEF if borderline around 40%

Study Participant Population

All study participants will be approached to take part and have a DUO-EF reading during the course of their routine care (minimal disruption) in the echo or cardiac MRI setting, during their GP appointment, or while attending COVID-19 follow up clinic. This will result in a large, representative study population to meet the objectives of testing the hypothesis for DUO-EF as a screening tool.

Group 1: Departmental Echocardiography and Cardiac MRI, Imperial College Healthcare NHS Trust

Unselected patients attending for departmental echocardiography (n = 1,500) and subgroup in cardiac MRI (n = 100). Patients will be consented by a member of the research team while they wait for an echocardiogram/cMRI. Patients from group 2 (GP referrals) will also be attending for an echo as part of their routine care on the heart failure pathway; they will be re-consented by a member of the research team upon arrival in the department.

Researchers will perform and record DUO-EF readings on participants and subsequently review echocardiography and cardiac MRI reports and document the LVEF calculated by these modalities.

If echocardiography does not suggest heart failure with LVEF<40% but DUO-EF does, patients will be followed-up with a **24 month phone call** (early evidence indicates the algorithm can identify low ejection fraction before being detectable on echo[8]).

Group 2: Patients in Primary care ('real world' evaluation)

NIHR North West London Primary Care **Clinical Research Network** (n = 10 GP practices). Patients attending GP with signs/symptoms of heart failure (n = 400 in total across all sites) will proceed with standard-of-care NICE heart failure pathway, with no change to standard of care through participation in study. GP's will be asked to record DUO-EF in any patient where heart failure is suspected.

Researchers will capture the point-of-care DUO-EF prediction from the GP:

- Comparing this to repeat DUO-EF ('agreement' between two time points) at time of (group 1) echocardiography (if indicated by standard of care investigations: BNP and 12-lead ECG)
- And comparing both of these DUO-EF measurements to echocardiography derived LVEF

Group 3: COVID-19 Clinic, Imperial College Healthcare NHS Trust

Patients attending COVID-19 follow up clinic (n = 400). Only patients who are being routinely referred onto the heart failure pathway for investigations will be invited to participate i.e. patients **with clinical symptoms of heart failure**, who would/should be referred onto routine NICE pathway. Researchers will capture the point-of-care DUO-EF prediction from the Covid-19 follow up clinic setting:

- Comparing this to repeat DUO-EF ('agreement' between two time points) at time of (group 1) echocardiography
- And comparing point-of-care and time-of-echo DUO-EF results

Method for Single-Lead ECG Collection for DUO-EF

For echo and cMRI, DUO-EF recordings will be made after these gold standard investigations so as not to bias interpretation of results. The protocol for DUO-EF recording for all patients in the COVID-19 follow up clinic, GP, echo and cMRI setting will be as follows:

1. Clinical user turns on Eko DUO device and confirms connection to secure app
2. Participants sitting upright will have 15 second single-lead ECGs recorded by the Eko DUO from five different locations:
    a. Lead I position (holding the device's electrodes between two hands)
    b. Clavicle
    c. Angled
    d. V2 position
    e. V5 position
3. Five recordings of DUO-EF recorded by researchers

The participant will be categorised as having a DUO-EF <40% if any of the five DUO-EF readings suggest this.

Data point collection: %LVEF echo, %LVEF cMRI, BNP

Recording %LVEF from echocardiography

EF is routinely measured or estimated using well-established standardized methodologies. For the purpose of this study we draw on previous work by Attia et al (2019) to record the %LVEF value on echocardiography using the first available model in a standard hierarchical sequence:

- EF determined using 3-D echocardiography[12]
- Biplane approach using the Simpson method[13] a 2-D method, or M-mode
- In the absence of any of the preceding, the reported visually estimated EF

If the estimation is a range, the midpoint as a single LVEF value will be used. LVEF will also be classified as low (≤40%), moderately depressed (41–49%), or normal (≥50%).

Recording %LVEF from cardiac MRI

As with echo, standard approaches to calculating EF also exist for cMRI. Calculated %LVEF (reported as standard) will be recorded alongside classification as low (≤40%), moderately depressed (41–49%), or normal (≥50%).

Brain Natriuretic Peptide

Where available, particularly in patients initiated onto the routine diagnostic heart failure pathway in the primary care and COVID-19 follow up clinic setting, BNP will also be recorded by researchers as an additional comparator to DUO-EF. BNP recorded longer than two months before or after DUO-EF will be excluded.

3.1 STUDY OUTCOME MEASURES

The study will end after 36 months or at the point where the predetermined number of participants have been recruited; and 24-month follow up phone call has been completed for those with DUO-EF suggestive of LVEF<40% but gold-standard LVEF >40%.

Primary outcome measure:

- **Sensitivity, specificity for DUO-EF detecting LVEF above or below 40%**

Secondary outcome measures:

- DUO-EF performance against subgroup %LVEF calculated by cardiac MRI
- Consistency of DUO-EF result at point-of-care in GP practice ('real world' use where GP suspects new heart failure) against repeat DUO-EF at time of gold-standard investigation; similarly with patients attending Covid-19 follow up clinic with symptoms of LVEF <40%
- Development of LVEF <40% at 24 months in participants with initial DUO-EF suggestive of LVEF <40% but gold standard investigations LVEF >40% i.e. can DUO-EF predict future development of LVEF <40%
- DUO-EF point-of-care determination of LVEF<40% in comparison with the components of the established NICE pathway (BNP result)

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

No pre-registration screening or tests are required.

4.2 INCLUSION CRITERIA & EXCLUSION CRITERIA

Inclusion criteria for all	- Age 18 years or above - Able to give informed consent		
	Group 1	**Group 2**	**Group 3**
Additional inclusion criteria	- Patient attending for departmental echo or cardiac MRI	- GP concerned about heart failure diagnosis and initiates patient onto routine NICE pathway	- Attending COVID-19 follow-up clinic and clinician concerned about heart failure diagnosis and initiates patient onto routine NICE pathway
Exclusion criteria	- Any chest wound, skin pathology or other feature that would prohibit routine stethoscope examination		

4.4 WITHDRAWAL CRITERIA

Participants are free to withdraw their consent from the study at any point.

5. ADVERSE EVENTS AND RISK

False negative & False Positive Results

This study poses minimal to no risk to participants. The Eko DUO device's capability to record ECG is fully CE marked and is already in mainstream clinical use. There are no ‘side-effects’ or contact hazards. There is a risk of a ‘false negative’ DUO-EF reading in those who in fact do have LVEF <40; however this is already accounted for in this study since DUO-EF is not interfering with the standard of care (e.g. echocardiography to definitively determine LVEF).

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
CI email (and contact details below)
Fax: xxx, attention xxx
Please send SAE forms to: xxx
Tel: xxx (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

Please see table below describing follow up procedures for different groups of the study. Describe how incidental findings will be identified, reviewed and reported, and to which individuals they will be reported to (i.e. GP, clinical care team).

	Group 1: All-comers to echo/cardiac MRI	**Group 2: GP patients**	**Group 3: COVID-19 follow-up clinic**
Follow-up	Follow-up phone call at 24 months for all patients with positive DUO-EF but negative gold standard investigations for LVEF <40% (to evaluate if positive DUO-EF is an indicator of future risk for developing LVEF <40%)		

The recruitment for the study will end when the requisite number of participants has been achieved. For some groups, there will be a long-term follow up period as described above. The study will end upon completion of these follow up periods.

In those patients where a 24 month follow up phone call is indicated, we will first attempt to confirm whether or not the participant is deceased by review of the NHS Spine, thereby avoiding unnecessary distress for relatives.

Incidental Findings

Incidental findings are highly unlikely in the course of this study since the process of having DUO-EF would not identify anything additional to what would be found during standard of care. In the unlikely event of the study team making an incidental finding they will notify the team in charge of the patient's care at the time-of-appointment.

7. STATISTICS, DATA ANALYSIS, DATA SECURITY

Data Analysis

Data will be analysed using a statistical package and platform (R Studio). Analysis will be completed by a clinical research fellow with appropriate access privileges (including honorary Imperial NHS contract) to study data.

Data Protection, Security and Compliance

This study has been reviewed and approved by the Imperial College Healthcare NHS Trust Data Protection Office (reference 20HH6360). Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

All study data will be collected using a REDCap (Research Electronic Data Capture) database, with a unique study ID for each participant (only identifiable by the principal investigator using an encrypted master key held in a password protected file on NHS servers) Patients will be allocated a de-identified study ID number, derived from a key that processes NHS numbers algorithmically. This key will be kept secure in a password encrypted file (accessible only to principal investigator). Study participant data will therefore not be identifiable unless researchers revert study ID's to NHS number.

The following data (where available) will be captured by researchers from the electronic health record (EHR):

- Encrypted NHS number (master key held in password protected file on NHS server, only accessible to principal investigator)
- Age
- Ethnicity
- Comorbidities
- Classification into study group 1-3
- BNP blood test result
- Echocardiography calculated %LVEF and categorisation
- Cardiac MRI calculated EF and categorisation

Eko DUO Data Security

The only data received by Eko Health will be digital ECG data. This will not be identifiable to the patient (i.e. not associated with an NHS number, date of birth or other identifier and Eko will not have access to the key for linkage with NHS numbers). This digital ECG data is uploaded to the Eko cloud via the mobile phone app (connected to the Eko DUO by bluetooth, no data stored on the device).

The data can be freely retrieved and will only be accessed through and securely stored within Imperial College London computers and servers. At the end of the study, all digital ECG data will be retrieved from Eko's servers and stored in accordance with Imperial College London policy on secure College computers.

No ECG or other data is stored on the mobile phone/on the app.

Interim Analysis

An interim analysis will be conducted (anticipated at 3 months) when the study has recruited n = 400 patients with paired DUO-EF and echocardiography results. Based on the previous power calculation this should be sufficient to indicate with 90% power if we can reject a null hypothesis that the AUC <0.7 at the 0.05 level of significance.

Missing Data

The study design and nature of the variables collected makes missing data unlikely. In order to avoid introducing bias into the dataset by removal of participants with any missing data, all participants will be retained; missing of any variable will entail the affected participant not being included only in the analyses specifically relevant to that variable. Access to shared primary and secondary care electronic health records should make missing data retrievable in most cases. Details of any missing data will be explicitly described in any reports or publications.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the xxx Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. The right of the participant to refuse to participate without giving reasons will be respected.

Consent will either be in the form of a standard paper consent form or, for those with access to the Imperial NHS Care Information Exchange electronic patient record, using a digital consent form that conforms to the HRA and MHRA's joint statement on e-consent for research.

After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

NIHR is funding this study. Participants will not be paid for joining the study. Investigators will receive no direct or indirect payments for conducting the study.

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the Imperial College & Trust Connected Care Bureau, 4th Floor ICTEM, Hammersmith Hospital, London, W12 0HS.

10. PUBLICATION POLICY

Results from this study will be published in peer-reviewed journals and presented at relevant conferences with all named lead and co-investigators as authors.

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Appendix 1. Summary of investigations, treatment and assessments

Exam		**Week of Treatment**		
	Pre-treatment	**Group 1**	**Group 2**	**Group 3**
Initial/repeat (for GP and COVID-19 follow up patients) DUO-EF reading at echocardiography/cMRI	Nil	X	X	X

Initial DUO-EF reading in COVID-19 clinic or with GP	Nil		X	X
24 month follow-up phone call for DUO-EF positive but gold standard negative	Nil	X	X	X