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PROTEUS: Evaluating the use of artificial intelligence to support stress echocardiography testing for heart disease

Submission date 06/07/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 09/07/2021	**Overall study status** Completed	
Last Edited 18/12/2023	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
Coronary Artery Disease (CAD) is a leading cause of death in the UK. Stress echocardiography (SE) remains the only imaging method available widely in the UK to diagnose CAD, however its accuracy varies for a number of reasons – for example image quality and the expertise of the clinician assessing it. A reliable, automated method to analyse scans is therefore required to reduce variability and improve the accuracy of diagnosis. Ultromics (a spin out company from the University of Oxford), has developed software called EchoGo. EchoGo processes echocardiographic images using Artificial Intelligence (AI), aiming to aid CAD diagnosis by taking more detailed measurements. The AI model was developed by processing images from patients who previously underwent SE exam. Analysis of its performance shows higher accuracy than clinical practice. Having tested EchoGo performance on retrospective echocardiogram images, it now requires testing in clinical practice. We propose a prospective Randomised Controlled Trial evaluating the use of EchoGo to aid clinical decision making.

Who can participate?
Adult patients who have been referred for a stress echocardiogram for the assessment of CAD.

What does the study involve?
The trial will recruit 2500 adults referred for SE examination in up to 20 NHS units in the UK. Participants will be randomised (1:1) to receive either: -Standard care -Standard care with EchoGo report Participants will be followed-up at 3 months and 6 months after SE scan, via medical notes review and a short quality of life and symptom questionnaire. The trial will assess if using EchoGo improves patients' clinical outcomes and improves accuracy of diagnosis. A health economic analysis will also be conducted, and a qualitative sub-study will investigate attitudes of NHS stakeholders to the adoption of AI within the NHS.

What are the possible benefits and risks of participating?
There are no direct benefits or risks. The data collected in this study could benefit future patients if:
EchoGo could help future patients receive the best possible care,

If EchoGo could save the health service money,
If clinicians are confident in the EchoGo reports,
If EchoGo reduces the numbers of patients undergoing serious cardiac events,
If EchoGo reduces the variation normally seen in Stress Echocardiography.

Where is the study run from?
Ultromics Ltd (Oxford)

When is the study starting and how long is it expected to run for?
July 2021 to December 2023

Who is funding the study?
National Institute for Health Research (NIHR) (UK).

Who is the main contact?
Dr Ben Thompson
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Study website
https://www.ultromics.com/proteus-trial

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
293515

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
COL-69, IRAS 293515, CPMS 49805

Study information

Scientific Title
A PROspective Randomised Controlled Trial Evaluating the Use of Artificial Intelligence in Stress Echocardiology (PROTEUS)

Acronym
PROTEUS

Study objectives
Null hypothesis: The intervention (EchoGo plus standard care) is inferior to the comparator (standard care), with the difference in AUROC between comparator and intervention greater or equal to the non-inferiority margin of 0.05 (C-I ≥ 0.05)

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 22/07/2021, North West - Preston Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)2071048290; preston.rec@hra.nhs.uk), ref: 21/NW/0199

Study design
Multicentre two arm randomized controlled trial

Primary study design
Interventional

Secondary study design

Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet.

Health condition(s) or problem(s) studied
AI assessment of patients with suspected Coronary Artery Disease (CAD)

Interventions
Eligible patients will be randomised using a secure online randomisation tool. Participants will be randomised 1:1 to receive 1) standard care (comparator) or 2) AI supported standard care (intervention). Participants in both arms will have a stress echocardiographic (SE) examination undertaken according to local trust practice. For the intervention group, images taken during the SE exam will be securely transferred to Ultromics and analysed by the EchoGo Pro AI tool. The AI software will generate a report containing a binary classification of the risk of cardiovascular disease for the patient. The EchoGo Pro report will be returned to the treating clinician in real time. The clinician may use the report to inform their treatment plan for the participant at their discretion. Participants will be follow-up for 6 months following the SE. Notes reviews will be conducted at 3 and 6 months. Patient reported health economic and symptom outcome data will be collected at 3 and 6 months.

Intervention Type
Device

Phase
Phase III

Drug/device/biological/vaccine name(s)
EchoGo (Ultromics LTD)

Primary outcome measure
Current primary outcome measure as of 26/05/2022:
AUROC for the ability to make an appropriate referral to coronary angiogram measured using medical record review at 3 and 6 months

Previous primary outcome measure:
Assessment of whether appropriate clinical management has been achieved at 6 months post visit through medical record review at 3 and 6 months.

Secondary outcome measures
Current secondary outcome measures as of 26/05/2022:
1. Appropriate clinical management at 6 months following stress echocardiogram (SE) measured using medical record review at 3 and 6 months. Appropriate management will be defined as a composite of:

1.1. If, following a stress echo, the decision was made to refer the patient for a coronary angiogram, the outcome will be positive if the coronary angiography demonstrates severe coronary disease fulfilling clinical care guidelines for revascularisation, or
1.2. If, following a stress echo, the decision was made not to refer the patient for coronary angiography, but rather, the patient to have medical management, the outcome will be positive if the follow up of participant health provides reassurance without unanticipated serious adverse cardiac events
2. Number of acute coronary events not related to elective cardiac procedures occurring up to 6 months following SE measured using medical record review at 6 months. Acute coronary events are defined as:
2.1. Myocardial Infarction Type 3 (ECS universal definition), and
2.2. Hospital admission with Myocardial Infarction Type 1 (ESC universal definition)
3. Change in clinical management decision following review of the EchoGo report measured using clinician self-report at baseline, 3 months, and the end of study at each participating site
4. Clinician diagnostic confidence in their interpretation of the stress echo report measured using clinician self-report at baseline, 3 months, and the end of study at each participating site
5. Inter-clinician and in-site variability measured at baseline, 3 months, and at end of study
6. Incidences of the following (occurring up to 6 months following stress echo) measured using medical record review at 3 and 6 months:
6.1. Myocardial Perfusion Scan
6.2. CT coronary angiogram
6.3. Stress echo
6.4. Invasive coronary angiogram
6.5. Stress CMR
6.6. Exercise tolerance test
6.7. Initiation of anti-anginal medication/medical management of angina
7. Coronary artery disease symptoms and impact on participant health status as measured using patient-reported short Seattle Angina Questionnaire (SAQ-7) at trial entry, 3 months and 6 months
8. Intervention cost benefit as defined by individual-level data conducted from the health system perspective from randomisation to follow-up at 6 months
9. Change in health-related Quality of Life measured using patient-reported EQ-5D-5L at trial entry, 3 months and 6 months

Previous secondary outcome measures:
1. Assessment of whether appropriate clinical management has been achieved at 6 months post visit through medical record review at 3 and 6 months.
2. Numbers of unanticipated acute cardiac events (not related to elective procedures) in NHS sites collected at 6 months post baseline visit.
3. Impact on clinical management decision making by review of the EchoGo report measured through comparison of the trial arm and comparator arm at 6 months post baseline visit.
4. Clinician diagnostic confidence in their interpretation of the stress echo report measured by clinician self-report at baseline, 3 months and end of study at each participating site.
5. Inter-clinician and in-site variability in measured at baseline, 3 months and at end of study.
6. Data on incidences of further diagnostic testing (Myocardial Perfusion Scan, CT coronary angiogram, Stress echo, Invasive coronary angiogram, Stress CMR, Exercise tolerance test, Initiation of anti-anginal medication/medical management of angina) occurring up to 6 months following stress echo collected from participants medical records at 3 and 6 months.
7. Coronary artery disease symptoms and impact on participant health status measured by patient-reported short Seattle Angina Questionnaire (SAQ-7) at trial entry, 3 months and 6 months.
8. Health economic impact of EchoGo implementation assessed through cost benefit analysis (as

defined by individual-level data conducted from the health system perspective), and changes in health-related quality of life (EQ-5D-5L) at baseline, 3 and 6 months.

Overall study start date
06/07/2021

Completion date
31/12/2023

Eligibility

Key inclusion criteria
1. Willing and able to provide informed consent
2. Male or female, ≥18 years of age at study entry
3. Referred to an NHS Trust for stress echocardiography for investigation of ischaemic heart disease

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
2,500

Key exclusion criteria
1. More than moderate valvular heart disease
2. Left ventricular outflow tract obstruction defined as a gradient > 30mmHg (fixed or dynamic; supravalvular, valvular or sub-valvular)
3. Significant co-morbidities (e.g. cancer) with an expected life-expectancy of under 12 months in the investigator's opinion
4. Previous coronary artery bypass graft or other cardiac surgery
5. Congenital or inherited myocardial disease

Date of first enrolment
08/11/2021

Date of final enrolment
30/06/2023

Locations

Countries of recruitment

England

United Kingdom

Study participating centre
Cardiac Clinical Research Facility (Oxford University)
Cardiovascular Clinical Research Facility
Level 1 Oxford Heart Centre
John Radcliffe Hospital
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Sponsor type
Industry

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.
Trial findings will be credited to collaborators and investigators who have taken part in carrying out the trial, the PROTEUS study team at Ultromics, the CCRF, OxCATTS, King's College London and Oxford AHSN. Authorship of principle results papers will follow the format "[name], [name], on behalf of the PROTEUS investigators' group", and authorship will be carried out by a writing committee. Authorship criteria will follow ICMJE guidelines, and other contributors will be acknowledged.
Members of the research team conducting other elements of the study, including health economics, qualitative assessment, will determine authorship criteria as necessary. All decisions regarding secondary publications using data generated from the study will be discussed and agreed by the trial management team and Trial Steering Committee.

Intention to publish date
31/12/2023

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No
Other publications	A qualitative study using semistructured interviews	11/12/2023	18/12/2023	Yes	No