Use of Artificial intelligence-Guided echocardiography to assIst cardiovascuLar patient managEment (AGILE-Echo)

PROTOCOL
(Version: 1.1, June 2022**)**

AGILE-Echo INVESTIGATORS

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CLINICAL TRIAL REGISTRATION
Pending.

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ETHICS AND GOOD CLINICAL PRACTICE STATEMENT

The AGILE-Echo Study has been designed and will be performed according to the principles of the International Conference on Harmonisation (ICH) and the guidelines of Good Clinical Practice (GCP) enunciated within the Declaration of Helsinki. Specifically, this study will follow the *National Statement on Ethical Conduct in Research Involving Humans* written by the National Health and Medical Research Council (NHMRC) and the *Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)* produced by the Therapeutic Goods Administration (TGA), both of which are the Australian ethical standards against which all research involving humans, including clinical trials, are reviewed.

The study will not commence without written approval from appropriate Human Research Ethics Committees (HRECs) that comply with the NHMRC National Statement. Primary ethics approval will be sought and obtained from each participating site. All participants will provide written informed consent prior to study commencement. The Protocol and Participant Information and Consent Form will be reviewed and approved by a properly constituted HREC before study start as acknowledged by a signed and dated Ethics Approval Certificate.

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1. BACKGROUND

Desired outcome. This application seeks to accelerate equitable patient access to best care that results in best possible outcomes, by use of novel technologies to enhance and accelerate diagnosis.

Echocardiography access – A wicked problem. Transthoracic echocardiography (TTE) is a cardiac imaging technique that involves moving an ultrasound probe across the chest. The images, showing structure, function and blood flow, are a cornerstone of modern cardiology, and over 1 million studies/y are reimbursed by the Medical Benefits Scheme (MBS) (1). TTE are especially important for the detection of heart valve disease (HVD) and cardiac dysfunction – the drivers of the epidemic of CVD in the elderly (2). However, although inexpensive and portable, and amenable to remote interpretation, the use of TTE is limited by the fact that an echocardiogram is technically challenging to acquire. Even in hospital inpatients, it can be difficult to obtain prompt testing, with the consequence that echo imaging is delayed until patients are discharged from the hospital, delaying appropriate management decisions (eg initiation of cardioprotective medications) and leading to the possibility that diagnoses are missed because a test or follow-up are missed.

AI-guided echocardiography. We may be on the brink of a solution to this technical challenge. This has two components – image processing, which can be done remote to point of care and can be mainly automated,(3) and acquisition. The latter may be solved by artificial intelligence (AI)-guided TTE and our proposed study will test the utility of a newly available echo machine and software, which has been shown to be feasible.(4) The planned study will be the next step in the process of miniaturization and automation will put the test in the hands of health practitioners. Combined with upload of the required images to the cloud, remote expertise in measurement, automated off-line quantitation and interpretation can be provided. This strategy has never previously been tried in Australia or elsewhere. Proof of concept is necessary in order to incorporate AI-based TTE in the health system – current regulations in the Diagnostic Imaging Accreditation Scheme stipulate accreditation of sonographers. AI-based echo performed by a non-sonographer cannot be reimbursed in this scheme, making such a service non-viable.
The current AI equipment obtains 2D and colour-flow images but not spectral Doppler. CI-Marwick is a leader in the development of **2-dimensional strain**, which has been validated as a clinical imaging tool for assessment of LVD(5) and incorporated in guidelines.(6) The simplest and most robust parameter is **GLS**, an automated and quantitative technique for assessment of function (**Figure 1**). We have validated this on the AI machine (**Figure 2**), and developed an approach to the assessment of diastolic dysfunction (DD),(7) so this can be done independent of spectral Doppler, which is not yet available on the AI equipment

Figure 1. Calculation of LV-GLS. Tracking the image provides strain curves denoting longitudinal deformation in all segments, compiled in a strain map to provide GLS.

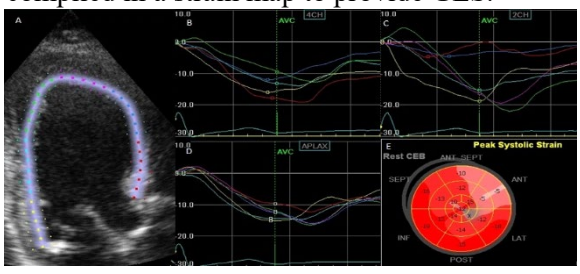
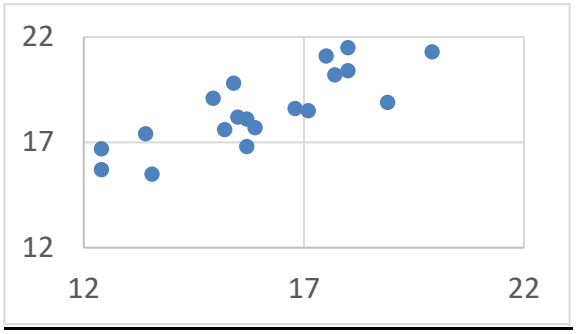


Figure 2. Validation of AI-based strain.



Significance. Both heart failure (HF) and heart valve disease (HVD) have a long pre-symptomatic phase and are often diagnosed late in the course, when a crisis is provoked – most often by acute HF or atrial fibrillation (AF). Abnormal results will lead to follow-up of HVD and provision of cardio-protection based on self-care promotion and intensified risk management with ACEi/ARB, BB and SGLT2i to asymptomatic persons at increased risk of clinical HF.
This project will build on the experience of investigators to show that use of AI-TTE is a route to early diagnosis of HF and HVD than traditional TTE in RRA. Over the last 8 years, CIs-Marwick and Wright have recruited nearly 1000 subjects >65 years with HF risk factors in Tasmania **(TasELF)** and Victoria **(VicELF).** These studies showed i) Undetected HVD, ii) Abnormal diastolic function (20%) and abnormal strain (25%); iii) Development of HF in >10%/year in patients with abnormal scans(8). Thus, we know that screening is feasible and acceptable, without psychological distress, excessive invasive testing and over-treatment.(9) In

the longer term, and supported by this study, we intend to use AI-Echo to improve access to echo in rural and remote Australia.

2. STUDY RATIONALE

The goal of the AGILE-Echo study is to identify the feasibility and value of AI-guided echocardiography in inpatient and outpatient care.
The equipoise in this study is based around better access to echo with AI-echo (which should shorten the time to diagnosis) vs less complete examinations (which may lengthen the time to diagnosis because of the need for repeat testing).
The objectives are to show that compared to usual care, the use of AI-based TTE will identify more HVD and cardiac dysfunction than usual care by 12 months, because of better access to testing.

3. STUDY HYPOTHESES & STUDY ENDPOINTS

3.1 Hypothesis

The **primary hypothesis** of the AGILE-Echo study is that use of AI-TTE in inpatients >65 years (>45 years in Central Australia) provides better recognition of HF or HVD at 1 year than usual care because of better access to testing.

3.2 Primary End-Point

The primary outcome is a composite of diagnosed HVD and HF at 12 month follow-up.

3.3 Secondary End-Points

Secondary endpoints (from baseline to 12 months) are: i) numbers of patients on cardioprotective treatment and/or cardiac valve review, ii) functional capacity, iii) symptoms, iv) health related quality of life, v) resource utilization at 24 months.

4. METHODOLOGY

4.1 Study Design. Multicentre observational study in urban, suburban and rural/remote health care facilities, comparing AI-TTE with usual care in people at risk of HVD or HF.

4.2 Study Centers and Recruitment.

Participants will be recruited from study sites – Baker Heart And Diabetes Institute, Dubbo Base Hospital, Alice Springs Hospital, Princess Alexandra Hospital, Royal Perth Hospital inpatients and outpatients**.**
The coordinating site will be the Baker Institute, with responsibility for data management and core imaging laboratory for primary endpoint determination. Data entry will be completed by each site through REDCap.

4.3 Study Timelines and Follow-up

Participant recruitment utilising this current protocol is planned to commence in mid-2022 and conclude in mid 2024 (24 months in total). The follow-up will be completed in 2025.
Outcome data will be gathered 12 months after the recruitment of the last patients (at conclusion of the trial).

4.4 Participants

This study will be conducted in patients at risk of HVD or HF;
Inclusion criteria: Age ≥65 years, eligible for Medicare, with exercise intolerance and cardiovascular (CV) risk factors,
Exclusion criteria: Known HF or HVD, situations where cardio-protection is already indicated (eg. known CAD), comorbid conditions with life expectancy <2 years, inability to provide written informed consent.

4.5 Screening and Recruitment Procedures

Based on our previous experience, we seek 612 patients who will be subject to the following screening and recruitment process:

STEP 1:
a) Identification of potentially eligible participants
At each referral site, a range of recruitment strategies targeting potentially eligible subjects will be applied. These reflect the different institutional settings and will include:

i) Informing the General Medicine and cardiology teams (doctors, nurses, allied health staff) about the study
ii) Posters and information brochures about exercise intolerance.

b) Screening of potential participants

After potential participants are identified, hospital or clinic staff will contact participants in person, to provide information regarding the project. The research staff will confirm eligibility and offer the opportunity to participate.

STEP 2: Consent

Interested patients will be provided patient information and consent forms by the study co-ordinator in person. Potential participants can take whatever time they need to consider participation. Consent will be obtained after the potential participant has had the opportunity to have questions answered.

STEP 3: Randomisation

After informed consent is obtained, the participant will be randomised to usual care (decision by clinician as to whether an echo is needed now, referral to usual pathway to obtain echo), or AI-Echo (done as soon as machine is available, usually at the time of clinical evaluation). Randomisation will be done using a computerized protocol at a ratio of 1:1. We will use block randomisation stratified by centre. Randomisation will take place through RedCAP, on the Baker Institute secure website.

4.6 Baseline Participant profiling. Baseline data will be collected via validated and reliable methods comprising self-administered questionnaire and clinical assessment:

i) **Demographic factors** – age, sex, marital status, education.
ii) **Health behaviour** – questionnaire on physical activity.
iii) **Clinical assessment**: height, weight, cardiovascular abnormalities;
iv) **General health: personal and family medical history**; ARIC HF risk questionnaire(10); co-morbidities (Charlson comorbidity index); and overall health and wellbeing (AQOL).

Those with abnormal TTE results will have valve review, cardioprotective therapy, and lifestyle intervention if warranted.

4.7 Echo evaluation. AI-guided echo acquisition will be performed using a desktop echo machine (uSmart 3300, Terason, Burlington, MA) with AI software (Caption Health, Brisbane, CA) currently in use at the Baker Institute. The images will be uploaded onto a secure cloud and downloaded at the core lab (AccessPoint, Freeland Systems, Carmel, IN), and LVEF and left atrial (LA) volume(11) measured. The three apical views will be used to obtain average global peak systolic longitudinal strain, using offline semi-automated speckle tracking techniques (Tomtec, Munich, Germany).(12) Segments unable to be adequately tracked will be excluded – GLS can be calculated in >90% of subjects; GLS >-16% will be considered abnormal. The class of diastolic dysfunction will be determined using LA strain,(13) as validated in our recent work.

4.8 Follow-up. Randomized subjects will have a follow-up in person or by telehealth at 1 year. Patients will be diagnosed with clinical HF based on Framingham HF diagnostic criteria (14). Further phone contact and/or chart review will be obtained at 3 years.

4.9 Data management. Data collection will be overseen by the study co-ordinator. Data are entered online through RedCap survey software and managed by the Baker Institute (see section 5).

4.10 Intervention strategy. Patients with abnormal findings (in either group) will be treated as they would in Usual Care of HVD or LV dysfunction.

For HVD, this will include clinical evaluation, and may involve detailed echocardiography, cardiac catheterisation, valve intervention or prescription of regular penicillin.

For LV dysfunction, this will involve **cardio-protective therapy** (lifestyle intervention and dose-optimized ACE inhibitors, angiotensin receptor blockade, beta-blockers, and if appropriate, SGLT2 inhibitors. The guidance that we will give the clinical teams will be;

i) ACEi/ARB. Patients already taking ACEi/ARB will be uptitrated to the maximum dose. Those not taking ACEi/ARB will be initially treated at low dose and uptitrated to peak dose.

ii) Beta Blockers. Patients already taking BB will be titrated to obtain a resting HR <60/minute. Treatment-

naive patients will be initiated on ACEi/ARB first, and then BB up-titrated.
iii) SGLT2i. Patients with diabetes, eligible for SGLT2i will have these agents started.
Clinical assessment in the sites and prescribing will be overseen by each site co-ordinator.
All medical treatments are given at the discretion of the treating physician and are recommended in the setting of cardiac dysfunction, not part of the trial. Information about side-effects will be gathered during follow-up.

4.11 Clinical Trial Endpoints. The clinical trial **primary end-point** will be diagnosed HF (Framingham criteria) or moderate or worse HVD at 12 months. **Secondary endpoints** will be; : i) numbers of patients on cardioprotective treatment and/or cardiac valve review, ii) functional capacity, iii) symptoms, iv) health related quality of life, v) resource utilization.

4.12 Sample size calculation and analysis plan.
Sample size calculation –We anticipate that 60% of patients with cardiac dysfunction or HVD are identified within 12 months by current measures (referral for echocardiography). Randomization of 406 subjects (203 per treatment arm) will provide 90% power to show a 25% increment in diagnosis by AI-TTE (to 75% positivity). We anticipate 406 subjects with HVD or cardiac dysfunction will be identified from 612 patients with reduced functional capacity.

Analysis plan – The analysis of this trial will be led by CI-Huynh, who has content knowledge through work on the previous TasELF and VicELF studies.
The main analysis will be intention-to-manage (by AI-TTE vs usual care), comparing diagnoses at 12 months between treatment arms. Chi-square analysis will be supplemented using logistic regression models to adjust for confounders. Secondary binary outcomes will be analysed similarly, with the mean difference in continuous outcomes compared between groups using linear regression models additionally adjusted for baseline values. Standard diagnostic plots will be used to assess validity of assumptions, and multiple imputation will be applied to deal with missing data in a secondary analysis.

4.13 Feasibility: Over the last 10 years, CI-Marwick's group have recruited nearly 1000 patients into two trials (TasELF and VicELF) similar to the planned study. Over a similar time-frame, the Baker's facility in Alice Springs has collaborated with Alice Springs Hospital and regional health services in a variety of interventions targeted at the prevention of cardiometabolic disease. Thus, this study brings together groups with a track record of success in CVD detection and prevention.

5. DATA

5.1 Data Collection/Gathering

Baseline data will include:

- Baseline profiling data (clinical and functional)
- Echocardiogram parameters

As detailed in section 4, data are collected using questionnaires and echocardiogram.
Follow-up data will include

- Titration data
- Follow-up visit data (clinical, and echocardiogram)
- Safety data
- Discontinuation data - Participant withdrawal is permitted. At the time of withdrawal, clarification will be sought as to whether the participant a) does not wish to undertake an intervention but will return for follow-up, b) doesn't want further contact but will allow use of baseline data, c) wishes to remove baseline data.

5.2 Data Management

Data will be stored in electronic format (RedCap) on a secure, password-protected server, accessed through the Baker. Access will be limited to the investigators. Disclosure to external parties will be permitted only if mandated by law. Re-use will be permitted if approved by a HREC. Data will be archived for 15 years and then destroyed.

6. SAFETY

6.1 Risk of discomfort and harm

Participants will undergo the following investigations, which may cause discomfort, which may be mitigated as follows;

Procedure	Discomfort/harm	Mitigation
Screening questionnaires to gather information about general health and wellbeing	Disclosure of sensitive personal information	Protocols for confidential handling of data
Cardiac ultrasound	Chest wall discomfort, time (~15 mins)	Reassurance

6.2 Clinical Safety

Safety evaluations will be performed by recording adverse events (AEs), serious adverse events (SAEs), and by monitoring laboratory parameters, physical examinations, ECGs and vital signs. The following cardiac events will be considered:

1) Sudden death;
2) Cardiac death;
3) Overt HF requiring hospitalization, including acute pulmonary oedema;
4) Serious arrhythmias requiring treatment; and
5) Conduction disturbances requiring a permanent pacemaker implantation.

Study data capture, analyses and archiving will be coordinated via the Baker Institute using well established resources. Investigators and/or research nurses will enter the information required by the protocol into REDCap. Non-obvious errors or omissions will be recorded on data query forms which will be returned to the investigational site for resolution. Study monitors will verify randomly selected study data against source documents via a systematic auditing program. Site data will be submitted via Redcap. The only aspect kept on site will be the linked study ID and patient details. This will be kept on the PI's secure network at the site.

7. SIGNIFICANCE AND OUTCOMES

Better recognition of HF and HVD represents an opportunity, because HF risks are treatable. We anticipate that this study will show undiagnosed HVD and LVD. These results may lead to a change in guidelines regarding echo use, as well as how the test is delivered.

10. TIMELINES

Phase 1 - Preparatory (HREC and governance review, trial registration) will start in Q3 '22.
Phase 2 – Study performance: Enrolments will commence in Q3/2022 and end in Q2/2024. Program delivery will conclude in Q2/2025. Data cleaning and analysis will run concurrently.
Phase 3 – Analysis and dissemination: Results will be reported in leading international Oncology and CV journals (eg. JACC, Circulation) will follow.

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