Intelligent Monitoring to Predict Atrial Fibrillation [NOTE-AF]: Clinical study 1 for the "Health virtual twins for the personalised management of stroke related to atrial fibrillation (TARGET)" project

IRAS ID: 342528

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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 GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.
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 clinical investigation without the prior written consent of the Sponsor.
I also confirm that I will make the findings of the study publicly 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 and serious breaches of GCP from the trial as planned in this protocol will be explained.

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2. WARD24/7, Copenhagen, Denmark (Full funding for work package 2, WARD 24 implementation study)

Study Synopsis

Title	INTELLIGENT MONITORING TO PREDICT ATRIAL FIBRILLATION [NOTE-AF]: CLINICAL STUDY 1 FOR THE "HEALTH VIRTUAL TWINS FOR THE PERSONALISED MANAGEMENT OF STROKE RELATED TO ATRIAL FIBRILLATION (TARGET)" PROJECT
Short title/Acronym	THE NOTE-AF STUDY
Protocol Version number and Date	V0.96_19/06/2024
IRAS	342528
Study Phase if not mentioned in title	N/A, observational study
Is the study a Pilot?	No
Study Duration	48 months
Methodology	Single centre mixed methods prospective observational study
Sponsor	Liverpool University Hospital Foundation Trust
UK legal representative	Liverpool University Hospital Foundation Trust
Chief Investigator	Prof. Ingeborg Welters
REC number	
Medical condition under investigation	Atrial fibrillation, abnormalities of vital signs
Purpose of clinical study	To determine 1. the incidence, the pattern and the recurrence rate of episodes of atrial fibrillation recorded as part of standard clinical care compared to data obtained through extended remote wireless patch-based monitoring for development and validation of health virtual twins and intelligent clinical decision support tools. 2. the occurrence, incidence and character of alerts registered by wCVSM devices and connected applications. 3. the acceptability and usability of post operative continuous real time physiological monitoring according to patients' and health care professionals' experiences and views.
Primary objective	To determine the incidence of clinical and subclinical episodes of AF in acutely unwell patients and to generate data for the development and validation of virtual twins and clinical decision support tools.
Secondary objectives	To describe the incidence and character of alerts registered by wireless continuous vital signs monitoring (wCVSM) devices and connected applications (WARD24). To determine patient acceptability and usability for health care professionals of a

	novel remote monitoring device with automated alert function
Number of Subjects	1200 patients of whom 25 participate in both work packages (1 and 2) of the study, and 25 health care professionals who participate in work package 2
Study Design	Single centre mixed methods prospective observational study
Outcomes	Primary endpoint: • Occurrence of clinical and subclinical episodes of atrial fibrillation (AF) Secondary endpoints: • ECG characteristics (p-wave duration, amplitude and dispersion, heart rate variability, QTc, incidence of premature atrial complexes) • Serum concentrations of troponin • Echocardiographic markers of atrial function (RWMA score, atrial size and volume, left ventricular strain rate, standard echocardiographic measurements as per BSE recommendations) • Length of stay • Hospital and 90-day Mortality • MAUQ score • Number of AF episodes • Recurrence of AF episodes • Time spent in AF • Time (in hours) wCVSM is attached • Number of cardiovascular alerts • Number of non-cardiovascular alerts • Change in inflammatory markers (white cell count, C-reactive protein and procalcitonin over time)
Main inclusion and Exclusion Criteria	<u>Inclusion criteria:</u> • Adult patients ≥50 years • Estimated risk of developing new episodes of AF>5% • Sinus rhythm at presentation • One of the following acute conditions: o Patients admitted or referred to Critical Care (NOTE-AF ICU) o Patients admitted to hospital with acute heart failure (NOTE-AF HF) o Patients admitted to Emergency Services with sepsis or infection (NOTE-AF Sepsis) o Patients post upper gastrointestinal surgery (NOTE-AF PULSE-GI) o Patients post vascular interventions (NOTE-AF Vasc) o Patients with acute respiratory failure (NOTE-AF Resp) o Patients admitted after acute stroke (NOTE-AF stroke) <u>Exclusion criteria:</u> • Atrial fibrillation or atrial flutter at the time of screening • Patients in atrial fibrillation or atrial flutter at time of preoperative assessment or admission to hospital

	• Paced cardiac rhythm • Inability to obtain consent • Allergy to plaster or silicone • Expected hospital stay <48h
Randomization	Randomisation is not applicable
Study procedure	The study comprises two work packages: Work package 1 (Monitoring for episodes of new onset AF): Over 48-month, period patients with one of the above acute conditions will have vital signs monitored continuously for seven days during their hospital stay using a remote wireless monitoring system (Isansys Lifecare Ltd, Patient Status Engine). Where deemed clinically indicated, routine standard vital signs via stationary monitors will be continued. Surplus blood samples will be collected at the beginning of the monitoring period and then in line with routine blood sampling as clinically indicated. When clinically indicated, extra blood samples will be collected for cardiac biomarkers. Echocardiography will be performed by qualified sonographers where clinically indicated. Data collection will include demographics, routine blood results, diagnoses, past medical history, drug history, interventions, length of hospital stay, anaesthetic risk profiles, quality of life, clinical symptoms. Work package 2 (Assessment of acceptability of and experience with a remote wireless monitoring system connected to an app by patients and health care professionals) Patients in Work Package 2 will be asked to complete a questionnaire to explore their experiences with a remote wireless monitoring system. Health care professionals will participate in semi-structured interviews and complete the mHealth App Usability Questionnaire (MAUQ) for Standalone mHealth Apps Used by Healthcare Providers a standard questionnaire designed by the University of Pittsburgh.
Statistical Methodology and Analysis	Descriptive statistics (mean, median, frequency of occurrences) will be used to summarise the data, univariable and multivariable analysis will be conducted for comparisons between groups, cluster analysis, generalised linear mixed effects models and survival analysis will be used (see statistical analysis plan). A two-sided p-value of <0.05 will be considered clinically significant. Data will be used further for the application and development of machine learning algorithms, aiming at developing and establishing dynamic clinical decision support tools and virtual twins.
Rationale	Among acutely unwell patients' arrhythmias and myocardial injury are common and associated with increased mortality, morbidity, and healthcare costs. Cardiovascular comorbidities in these high-risk patients commonly include hypertension (47%), dyslipidaemia (29%) and ischaemic heart disease (11%). We aim to detect clinical and subclinical episodes of atrial fibrillation lasting >30 seconds to develop risk prediction models to identify patients at high risk for ischaemic stroke. Data will serve to develop and validate bedside clinical decision support tools and virtual twins. Patients who develop episodes of AF as part of acute illness, will suffer further episodes of AF within one year in over 20% of cases with 27% progressing

	to paroxysmal/permanent AF [1]. The true incidence of AF is unknown in acutely unwell patients as a significant percentage of AF episodes remain undetected with conventional intermittent monitoring. Patients experiencing short self-terminating episodes of AF carry a 5-fold risk of developing continuous AF and double the risk of stroke and thromboembolic events. Patients suffering episodes of AF often remain asymptomatic but are at increased risk of heart failure and death at one year. Compared to routine intermittent manual measurement of vital signs, wireless continuous vital sign monitoring systems (wCVSM) detect deviations instantaneously with the option of alerting clinical staff in real time via mobile phone applications. Accurate categorisation of alerts into false and true events is essential for developing intelligent software that can be embedded into monitoring systems. Continuous ECG and vital signs monitoring can detect AF episodes more reliable, trigger timely investigations and support longer term treatment plans. Changes in patient pathways and introduction of novel devices to alert healthcare staff on the potential of clinical events require buy-in from all stakeholders. It is therefore essential to evaluate user acceptance and to determine perceptions of users before rolling out a novel patient pathways or implementation of a new device within an organisation. We therefore wish to explore users' views of the device, wearing the device and potential areas for improvement using questionnaires for patients and health care staff and by conducting semi-structured interviews with healthcare staff.

Abbreviations used in study protocol

AE	Adverse Event
AF	Atrial Fibrillation
AFRS	AF related stroke
AI	Artificial Intelligence
AR	Adverse Reaction
AKI	Acute kidney injury
APACHE II	Acute Physiology and Chronic Health Evaluation II
CI	Chief Investigator
CO	Cardiac Output
CRF	Case report form
CV	Cardiovascular
CVE	Cardiovascular Event
CVP	Central venous pressure
DMC	Data Monitoring Committee
eCRF	Electronic case report form
ICF	Informed Consent Form
LIDCO	Lithium indicator dilution cardiac output
MAP	Mean arterial pressure
ML	Machine learning
MUAQ	mHealth App Usability Questionnaire
NHS R&D	National Health Service Research & Development
NOAF	New onset atrial fibrillation
PI	Principal Investigator
POAF	Postoperative Atrial Fibrillation
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
RRT	Renal replacement therapy
SAE	Serious Adverse Event
SOFA Score	Sequential Organ Failure Assessment Score

SSA	Site Specific Assessment
TARGET	Health virtual twins for the personalised management of stroke related to atrial fibrillation
wCVSM	wireless continuous vital signs monitoring

Introduction

The Europe Horizon 2023 TARGET project

Atrial Fibrillation (AF) as a widespread irregular and often very rapid heart rhythm (arrhythmia) significantly increases the risk of complications such as stroke and heart failure. TARGET, a research project led by a consortium of 19 partners in various European countries, aims at reshaping risk prediction, diagnosis, and management of AF and AF related stroke, and accelerating the translation of research into practical applications. Artificial Intelligence (AI) solutions are being increasingly used in clinical practice. Coupled with AI, virtual twins aim to improve patient outcomes by enabling more accurate diagnoses, more personalised treatment plans, and more efficient resource allocation. TARGET will develop integrated, multi-scale computational models (virtual twins) and tools for personalised risk prediction of AF, optimised management and treatment of stroke, and enhanced rehabilitation.
TARGET focuses on patients at risk of AF and associated AF related stroke (AFRS), bringing together pathophysiological mechanisms and clinical evidence, and assessing their journey (dynamic, longitudinal monitoring) as they go through the acute phase of ischaemic stroke and rehabilitation, targeting the three key areas below:
Pillar I - Risk prediction and dynamic, longitudinal monitoring of AF and the subsequent risk of developing AFRS.
Pillar II - Diagnosis and management of AFRS, including early identification of stroke aetiology, prediction of 3-month outcomes and risk of stroke recurrence.
Pillar III - Rehabilitation focusing on identifying predictors of functional independence and quality of life in AFRS survivors and facilitating personalisation of rehabilitation.
The NOTE-AF clinical study is based in the risk prediction pillar (Pillar I) of TARGET and aims to collect high granularity data to develop virtual twins to dynamically predict the risk of developing AF for each patient individually. More information about TARGET can be found at https://target-horizon.eu.

The Clinical Problem and the Research Need

Atrial Fibrillation (AF) is the commonest arrhythmia worldwide, affects 5% of people over the age of 65 and increases the risk of stroke and heart failure [2]. AF is characterised by irregular atrial electric activity and ventricular response. In the general population, diabetes mellitus, high blood pressure and coronary artery disease are main risk factors. AF is a heterogeneous condition caused by various underlying pathophysiological disorders. AF risk increases with age, with ~18m AF patients estimated by 2060 [3]. It imposes a high financial, economic and human burden. Taking the UK as an example, the estimated cost of AF to the National Health Service (NHS) in 2020 ranged from £1,435-£2,548m (0.9-1.6% of expenditure) [4], with total direct NHS costs estimated to increase up to 4.27% by 2040. Patients with AF have a fivefold increased risk for ischaemic stroke. In Europe, stroke is the 2nd most common cause of death and the leading cause of disability (associated cost estimated at €45 billion [4], with more than 1m new stroke cases in 2017 and ~10m stroke survivors. These numbers are expected to increase by 27% due to ageing and improved survival rates. AF-related stroke (AFRS) accounts for 20% of

ischaemic strokes. The pathophysiology of AFRS is associated with severe neurological deficits due to larger clots, infarction of substantial cerebral areas and haemorrhagic transformation, a complication that significantly worsens prognosis. Functional recovery from AFRS is often unsatisfactory, leading to longer hospital stays, severe disability and high mortality.

AF can be paroxysmal or permanent, with varying symptoms (~25% of AF sufferers have no symptoms), ranging from subclinical forms of AF to permanent irregular heart rhythm. Notwithstanding the amount of research produced on AF and its complications, full detail of the pathophysiology linking AF and stroke remains elusive. This knowledge gap results in important drawbacks in clinical practice.

Traditionally, AFRS is predicted using clinical risk scores, e.g., CHA2DS2-VASc, which are limited by their modest predictive performance. However, risk factors such as renal impairment, inflammation, atrial remodelling and cardiac and cerebrovascular biomarkers, are not considered in these routine risk scores. Artificial Intelligence (AI) solutions are increasingly used in clinical practice for the prediction and detection of diseases and events, optimisation of treatments, etc. significantly outperforming more traditional techniques based on signal processing [5].

Personalised AI-based prognostication and decision support tools taking account of the patient individual characteristics, and medical and health status history will enhance risk prediction, leading to ultra-early AF identification, guide treatment decisions and prognosticate outcomes. The inclusion of biomarkers related to cardiac damage and automated analysis of ECG characteristics, add further pathophysiological information to the AI modelling. With rapid changes in such biomarkers and vital signs, a dynamic and personalised risk assessment approach taking into account individual pathophysiological risk factors for AF is required to reliably predict outcomes. Currently, risk assessment tools mostly focus on static risk factors and do not account for the dynamic nature of risk, which changes during acute illness, with ageing, and depends on comorbidities.

Patients admitted to hospital either for elective surgery or because they are acutely unwell, represent an opportunity to obtain continuous monitoring data. The data obtained in NOTE-AF will feed into the Horizon European TARGET project (TARGET: https://target-horizon.eu) which aims to develop multi-scale and multi-organ, dynamic, and interoperable virtual twins of AF patients to accelerate translational research, enabling personalised and cost-effective management. Within TARGET, personalised virtual twin models for dynamic risk prediction of AF and AFRS that take into account the patient individual characteristics and medical and health status history will be developed.

Atrial fibrillation in acute illness

AF is common in patients suffering from acute conditions such as infection, stroke, acute heart failure, acute respiratory failure or following major surgery, in particular vascular and upper gastrointestinal surgery [6-8]. Many of these episodes occur in patients without a history of atrial fibrillation. Episodes of AF during acute conditions represents a clinical deterioration in acutely unwell patients and lead to increased short and long-term morbidity and mortality [9]. Infections and in particular sepsis, are major triggers for AF, especially in patients without a history of this arrhythmia. The term “new-onset atrial fibrillation” has been coined specifically to describe the condition. The incidence of NOAF is estimated

to be between 5-15% in all patients with sepsis [10-15] with some studies reporting even higher incidences of up to 40% in patients admitted with septic shock [14, 16, 17]. Risk factors for the development of NOAF during admission to intensive care include increasing age, male sex, pre-existing cardiovascular disease, acute renal failure, and acute respiratory failure, with sepsis itself conferring a moderate risk for NOAF [18, 19]. NOAF in patients with sepsis carries an increased risk of both in-hospital and ICU mortality [10, 20].

Postoperative atrial fibrillation (POAF)

POAF is the most frequently reported cardiac arrhythmia following non-cardiac surgery. The incidence of POAF is highly variable but estimated to be between 0.5% to 15% in all non-cardiac procedures [21]. There is significant variability in reported incidences, likely caused by discrepancies in the definition of POAF as well as variation in risk depending on the surgical procedures performed. Upper GI surgery has a particularly high incidence of POAF, it occurs in up to 45.5% in patients undergoing oesophageal resections [1, 22] and is associated with increased 30-day mortality, stroke and hospitalisation. In 18% of cases patients suffer further episodes of AF within one year with 27% of these patients progressing to paroxysmal or persistent AF [1]. The true incidence of POAF after oesophagectomy is unknown, but 31.4% of patients meet hs-cTn criteria diagnostic of perioperative myocardial injury (PMI) [23]. Even patients experiencing only short self-terminating episodes of POAF carry a 5-fold risk of developing continuous POAF and double the risk of stroke and thromboembolic events [24]. POAF is also associated with increased all-cause mortality at 30 days, a 3-fold increased risk of stroke within one-month, a 4-fold increased risk of stroke at one-year, a 4-fold increased risk of myocardial infarction and increased risk of hospitalisation with heart failure.

Following non-cardiac surgery, the incidence of POAF is greatest within the first 72 hours postoperatively [25]. However, occurrence beyond 72 hours is less well defined, likely due to a lack of ECG monitoring and the clinically asymptomatic nature of POAF. AF is conventionally diagnosed by 12-lead ECG recordings demonstrating irregular RR intervals without recognisable p-wave activity with a duration of >30 sec. Recordings from implantable and patch-based cardiac monitoring devices suggest that that many patients experience episodes of AF which are not diagnosed clinically [26]. Such episodes are not benign entities: Multiple systematic reviews have demonstrated a 5-fold increased risk of developing clinically relevant forms of AF and a 2-3-fold increased risk of stroke and thromboembolic events [25, 27]. This population of postoperative patients at significant risk of complications will remain unidentified without wCVSM. In this study we will use continuous ECG monitoring integrated into wCVSM systems to identify episodes of AF >30s, independent of their clinical recognition.

Measurement of serum concentrations of high-sensitivity troponin T (hs troponin T)

In acute care illness, a positive troponin result is associated with a clinically important increased mortality even if levels are only slightly elevated [28]. Consequently, troponin measurements have been used in patients with and without Acute Coronary Syndromes to stratify between high and low mortality risk for all age groups.
Preoperative measurement of cardiac Troponins (cTn) adds additional value to existing cardiovascular risk prediction scores and may identify patients at risk of cardiovascular events. Measurement of cTn provides better preoperative risk stratification and may identify patients in whom increased perioperative monitoring (e.g., continuous, or advanced haemodynamic monitoring) and increased post operative vigilance (e.g., admission to ICU or higher care area) is indicated. In the perioperative setting, the potential for cTn to identify patients at risk of complications has led to recommendations from the European Society of Cardiology (ESC), Canadian Cardiovascular Society and the American Heart Association (AHA) that cTn should be reported as part of a comprehensive preoperative cardiovascular assessment beyond established tools such as the Revised Cardiac Risk Index. Similarly, the measurement of cTn and identification of myocardial injury has been identified as one of the standardised cardiovascular endpoints to be reported in perioperative studies as highlighted by the (StEP) initiative [29].

Echocardiography to assess atrial morphology and function

See Appendix H: Echocardiographic protocol.

Wireless continuous vital signs monitoring (wCVSM)

The technological advances of medical devices for vital signs measurements have led to the development of wireless continuous vital sign monitoring systems (wCVSM) with real-time data presentation to healthcare professionals. These systems can identify vital sign deviations that are not found with intermittent manual monitoring [30, 31], potentially identifying patients at risk earlier. This population of postoperative and acutely unwell patients at significant risk of complications will remain unidentified without wCVSM. In this study we will use continuous ECG monitoring integrated into wCVSM systems to identify episodes of AF >30s, independent of their clinical recognition.

However, the shift from intermittent measurements to continuous monitoring will result in an increase in alarms, unless a dedicated software is used. Alerts based on machine learning algorithms may reduce the total number of alerts and potentially decrease alert fatigue which in turn will allow staff to direct resources to patients at need.

The risk of alarm fatigue caused by high alert rates and high rates of so-called false alarms, requires that algorithms can reliably distinguish between “true” and “false cardiovascular events. It remains unclear

to date if sole monitoring of vital signs, in particular cardiovascular parameters, can be utilised sufficiently to achieve automated discrimination between true and false alerts.

Introducing wCVSM will pose major changes to the routines of nurses and doctors in hospitals. The manual measurement of vital signs is a very structured, standardised and routine task for nurses. Implementing wCVSM will change the entire afferent limb of the track-and-trigger system, affecting how nurses respond to patients and how they call for action. Introducing wCVSM will allow nurses to optimize the prioritization of resources, since patients will be monitored continuously and real-time with the software letting the nurses know when a patient needs response. This will allow for nurses to focus on non-patient related assignments, without compromising patient safety by leaving patients unattended. Introducing a new software can be challenging. We will test the usability of our wCVSM software on patients and nurses and quantify vital sign deviations in patients using the system. We will develop a thorough implementation guide for the software based on these findings.
Monitoring practices may differ substantially within and across healthcare organisations. Organisational culture may also affect implementation and adaptations of wCVSM, an aspect which to date has not yet been fully explored. After data sharing between this study and the international WARD24 pilot study (See separate protocol in Appendix 5) we will investigate how current monitoring practices differ across countries and different systems.

In this study we will monitor vital signs with a novel wireless remote monitoring system, determine the incidence of episodes of AF and assess the usability and acceptability of wCVSM in high-risk patients in various acute conditions. We will conduct two work packages to 1. Obtain data for the generation of virtual digital twins and to quantitively assess the incidence and pattern distribution of episodes of AF and to 2. Explore user acceptability of the monitoring system and experience of health care professionals in questionnaires and semi-structured interviews.

1. WP1: (Monitoring of vital signs to obtain data for virtual twins to predict clinical and subclinical episodes of AF):

The primary objective of this work package is to determine the incidence of clinical and subclinical episodes of AF in acutely unwell patients and to generate data for the development and validation of virtual twins and clinical decision support tools.

Secondary objectives include:

1. To determine the correlation between number of alerts and occurrence of AF
2. To identify differences in age, gender, length of stay, 30-day mortality, hs-cTn levels, RWMA scores and average National Early Warning (NEWS2) scores in acutely unwell patients
3. To determine the pattern and distribution of AF episodes in acutely unwell patients
4. To identify risk factors for the occurrence of AF episodes
5. To describe the occurrence, incidence and character of alerts registered by wCVSM devices and connected applications (WARD 24).

6. To describe the clinical response to non-cardiovascular alerts and cardiovascular alerts

2. WP2:

We will test the acceptability and usability of wCVSM by conducting questionnaires with patients and health care professionals. We will also conduct semi-structured interviews with health care professionals involved in the care of the study patients to explore their experience with the wCVSM system and the connected software and app. We will develop a thorough implementation guide for the software based on these findings.

Patients admitted to wards where the WARD247 application is being tested, will be asked to participate. Patients will be asked to complete a questionnaire (Appendix C) to explore their experiences with a remote wireless monitoring system. Health care professionals will participate in semi-structured interviews (Appendix A) and complete the mHealth App Usability Questionnaire (MAUQ) for Standalone mHealth Apps Used by Healthcare Providers a standard questionnaire designed by the University of Pittsburgh (Appendix B). The results and data obtained in this work package will be shared with the WARD24/7 international study team as described in a separate data sharing agreement.

Outcomes for this work package include:

- Number of false alerts
- Number of correct alerts
- MAUQ score
- Semi-quantitative assessment of patient acceptability
- Semi-quantitative assessment of acceptability for nursing and healthcare staff
- Time wCVSM is attached

Study Objectives, Design and Statistics

Research questions and objectives

The **primary research objective** is:

To determine the incidence of clinical and subclinical episodes of AF in acutely unwell patients and to generate data for the development and validation of virtual twins and clinical decision support tools.

The **secondary research objective** is:

To determine patient acceptability and usability for health care professionals of a novel remote monitoring device with automated alert function.

Primary outcome:

The incidence of episodes of AF lasting >30 seconds in acutely unwell and postoperative patients recorded as part of standard clinical care through extended remote wireless patch-based monitoring with or without the use of an alert system (Application).

Secondary outcomes:

Work package 1:

- Length of stay
- Hospital readmissions within 90 days
- Hospital and 90-day Mortality
- Recurrence of AF episodes
- Time spent in AF
- Number of AF episodes
- Complications of AF, e. g. stroke, thromboembolic events
- High sensitivity Troponin concentrations in patients with AF episodes
- Echocardiographic changes in patients with AF episodes

Work package 2:

- MAUQ score
- Percentage change of troponin concentrations in patients with and without episodes of AF
- Time (in hours) wCVSM is attached
- Number of cardiovascular alerts

- Number of non-cardiovascular alerts
- Number of alerts reflecting clinical changes
- Number of alerts reflecting artefacts or non-clinical events
- RWMA score, atrial size and volume, left ventricular strain rate, standard echocardiographic measurements as per BSE recommendations
- Change in inflammatory markers white cell count, C-reactive protein and procalcitonin over time

Study Design

This is a single centre mixed methods prospective observational study

Statistics

A detailed statistical analysis plan will be developed for the project in line with the objectives for TARGET to achieve the development and validation of dynamic risk prediction tools and virtual health twins.

Sample size considerations:

The primary aim for this study is to generate data for the development of Health Virtual twins as part of the EU Horizon 2023 TARGET project. We will therefore collect a convenience sample of at 1200 patients with a risk of developing episodes of AF of at least 5%. Given evidence from the literature that subclinical episodes that remain undetected may be as high as 30% or more, we expect that in a cohort of 1200 patients at least 60-120 patients will be diagnosed with episodes of AF of at least 30 seconds.

Although the primary aim of the study is to obtain data for the generation of dynamic risk prediction tools and virtual health twins, we will perform a conventional statistical analysis as part of this work:

The primary outcome (incidence of AF episodes >30 sec in acute illness) will be described as ratio of episodes/patient and as percentage of patients having episodes of AF. We will also analyse time spent in AF a percentage of time monitoring was in place, distribution pattern of AF, duration of AF episodes. Occurrence and frequency of premature atrial complexes as precursors of AF episodes.

We will use conventional logistic regression models to establish the correlation and weight between risk factors for AF 8e. g. age, cardiovascular comorbidities, organ dysfunction and support, blood pressure, infection status etc.) and occurrence of AF.

Outcomes will be compared in univariate analyses, using parametric or non-parametric test depending on sample distribution.

Descriptive statistics will be used to describe demographics, frequency of alerts and blood results in patients with and without episodes of AF. Group comparisons will include parametric (T-Test for independent samples) and non-parametric tests (Mann-Whitney-U-Test), depending on sample distributions. For categorical data, Fisher's exact test will be used to examine associations between variables. Monotonic relationships between two numerical variables will be defined using Spearman's rank correlation coefficient.

Where applicable, univariate analysis will be followed by multivariate logistic regression analysis to identify risk factors for the development of AF episodes postoperatively. Cochran–Mantel–Haenszel test (CMH) will be used for the analysis of stratified categorical data, using occurrence of AF >30 seconds as the binary outcome.

Data will be transferred to the data science group at LJMU (SOM, IOC) for development and validation of health virtual twins and dynamic risk prediction models in line with the TARGET proposal Work Packages 4 and 5 specific objective (pages 3, SO3 and 34-35, part B of the TARGET proposal): "Development of personalised virtual twin models for dynamic risk prediction of AF and AFRS that consider the patient individual characteristics and medical and health status history. These models are based on novel predisposing factors and will out-perform currently used clinical scores and models." The novel dynamic prediction tools will be compared against conventionally generated logistic regression models.

Sample Size, Selection and Withdrawal of Subjects

Sample size

The primary outcome will be described as ratio of AF episodes/patients. We aim to recruit at least 1200 patients over 40 month with the following characteristics:

- Patients admitted or referred to Critical Care (NOTE-AF ICU)
- Patients admitted to hospital with acute heart failure (NOTE-AF HF)
- Patients admitted to Emergency Services with sepsis or infection (NOTE-AF Sepsis)
- Patients post upper gastrointestinal surgery (NOTE-AF PULSE-GI)
- Patients after surgical vascular interventions (NOTE-AF Vasc)
- Patients with acute respiratory failure (NOTE-AF Resp)
- Patients admitted after acute stroke (NOTE-AF stroke)

We expect to recruit at least 150 patients in each of the above patient groups.

Inclusion criteria for enrolment

- Adult patients ≥50 years undergoing major upper gastrointestinal or vascular surgery or admitted to hospital with at least one of the following acute conditions associated with an estimated risk of developing episodes of AF>5%:
  - Acute respiratory failure
  - Any acute illness referred or admitted for higher level of care (level 2 or 3)
  - Patients with acute stroke
  - Patients with acute heart failure
  - Patients admitted to the emergency department with clinical suspicion of severe acute infection or sepsis requiring hospitalisation
- Sinus rhythm at preoperative assessment

Exclusion criteria for enrolment

- Atrial fibrillation or atrial flutter at the time of screening
- Patients in atrial fibrillation or atrial flutter at time of preoperative assessment or admission to hospital
- Paced cardiac rhythm
- Inability to obtain consent (patient and/or consultees decline study participation)
- Allergy to plaster or silicone
- Expected hospital stay <48h

Criteria for Premature Withdrawal

- Withdrawal of consent
- Intolerance of monitoring patch
- Persisting skin irritation at patch site

Study procedures

Screening Procedures

Patients with acute conditions listed above or who are scheduled to have vascular or major upper GI surgery will be screened against the inclusion and exclusion criteria.

Consent and Enrolment Procedures

We wish to include a wide range of patients admitted to various to acute care wards, e. g. emergency departments, acute medical wards, surgical wards and higher level of care units (level 2 and level 3) within the hospital. Thus, we expect patients with a wide range of cognitive function, reaching from normal mental capacity to confusion to severely impaired cognitive function to be included: While patients with planned surgery, e. g. major elective abdominal or vascular surgery, will be able to consent for themselves before the operation, patients undergoing emergency surgery, may have altered cognitive function, which will impair their capacity to consent for themselves. Similarly, patients with severe acute medical disease, e. g. sepsis may be acutely confused and therefore not able to consent for themselves. We will assess capacity for each patient before approaching them for consent, adhering to the principles outlined in the British Medical Association Ethics Toolkit (https://www.bma.org.uk/media/4z1l3khg/mental-capacity-act-england-and-wales.pdf?_gl=1*146j826*_up*MQ..*_ga*NDAxMDc0MTE1LjE3MTg4MzA1OTU.*_ga_F8G3Q36DDR*MTcxODgzMDU5NC4xLjAuMTcxODgzMDU5NC4wLjAuMA..). Therefore, for this study, different approaches of obtaining consent, depending on the mental situation of a patient, need to be applied. This tiered approach will be applied independent from the care setting by trained research staff. Where applicable, will use the CAM-ICU tool to assess mental capacity.

We aim to recruit patients before they undergo either elective or emergency surgery or as soon as possible after admission with an acute condition as listed above. When elective surgery is planned, we

will approach patients before their surgery, i. e. either during their outpatient visit, following their outpatient visitor on the day of admission to hospital. At this point, we will inform them about the purpose of the study via the participant information sheet, and through explaining the study procedures and the associated risks and potential benefits. We will also explain that they will continue to receive standard routine care in addition to wCVSM. Patients can be informed about the study via telephone, email, or face to face, and depending on patient preferences further discussions will take place via phone or in person.
In situations requiring urgent or emergency interventions and when patients lack capacity due to the nature of their illness, a personal or legal representative will be consulted before or after the intervention, but before any study interventions are performed. This process is described in more detail below. For patients with acute medical conditions a similar approach will be taken.

If there is no opportunity to recruit the patient before surgery or shortly after hospital admission, e. g. in emergency situations, we will approach a personal consultee, usually the next of kin. Provided the patient still meets the inclusion criteria and has no exclusion criteria but lacks the capacity to consent for themselves, we aim to consult the personal consultee. This will be necessary since patients commonly have impaired capacity after return from surgery or as part of acute illness. If a personal consultee is not immediately available, a professional consultee will be approached, and the study and potential recruitment of the respective patient will be discussed with them. For patients with acute medical disease (e. g. heart failure, stroke or sepsis/infection) who are unable to consent for themselves , the same approach will be taken. The person taking consent will emphasize that the potential benefits and risks are similar between standard monitoring and wCVSM.

We consider it necessary to include patients in emergency situations as these patients have a particularly high risk to develop episodes of AF. There is a possibility that they benefit most from the study, e. g. by identifying subclinical episodes of AF. Similarly, it is possible that they experience more complications of AF than patients who are not receiving wCVSM.

As such, there will be three routes by which a patient may be enrolled in the study.

i) Standard approach: Patient with capacity:

- The patient will be provided with a written ‘Patient Information Sheet’.

- A member of the research team with relevant GCP training will provide verbal information and answer any questions.
- If the patient chooses to be enrolled in the study, they will be invited to sign a 'Patient Consent Form'.
- The patient may withdraw consent as outlined above (as explicitly stated in the 'Patient Information Sheet').

ii) Patient without capacity where a Personal Consultee is immediately available:

- When a patient does not have capacity the research team will attempt to identify a personal consultee (in accordance with section 32 of the Mental Capacity Act).
- The personal consultee will be provided with a written 'Personal Consultee Information Sheet'.
- A member of the research team with relevant GCP training will provide verbal information and answer any questions.
- The personal consultee will be asked to use their knowledge of the patient's beliefs to advise the research team as to whether they feel the patient would have had any objections to participating in the study.
- If the personal consultee is not aware of any objections the patient may have and would have chosen to participate in the study, they will be asked to sign a Personal Consultee Declaration Form'.
- The personal consultee may withdraw the patient as outlined above (as explicitly stated in the 'Personal Consultee Information Sheet').
- When the patient regains capacity, the research team will speak to the patient at the earliest opportunity and invite the patient to give consent to continue participation; if the patient chooses to continue to participate in the study they will sign a 'Consent Form (Continuation)'; if the patient gives consent, they are free to withdraw their consent later as outlined above; if the patient does not wish to consent, they will be withdrawn from the study.
- If the patient never regains capacity or dies, he/she will remain in the study. In this case we plan to include their outcome data until day of death and biological samples in the final analysis.

iii) Patient without capacity where a Personal Consultee is not immediately available, and no appropriate person can be identified:

- When a patient does not have capacity and the research team are unable to identify or contact an appropriate personal consultee, we will contact a Professional Consultee.
- The Professional Consultee will be a senior medical doctor (>5years of experience) who understands the patient's medical problems and has been informed about the study. The Professional Consultee is a medical doctor who is not directly involved in the conduct of the study.
- The Professional Consultee will not be a member of the study team and will have no connection to the research, to the funder or to the Research Ethics Committee.
- The Professional Consultee will be provided with a 'Professional Consultee Information Sheet' and a member of the research team with relevant GCP training will provide verbal information and answer any questions.
- When the Professional Consultee believes that there is no reason why the patient would not have chosen to enrol in the study, they will be asked to sign a 'Professional Consultee Declaration Form'.
- The Professional Consultee may request that the patient is withdrawn at any stage as outlined above (as explicitly stated in the 'Professional Consultee Information Sheet').
- When the patient regains capacity, the research team will speak to the patient at the earliest opportunity and invite the patient to give consent to continue participation; if the patient chooses to continue to participate in the study they will sign a 'Consent Form (Continuation)'; if the patient gives consent, they are free to withdraw their consent at a later stage as outlined above; if the patient does not wish to consent, they will be withdrawn from the study.
- If the patient never regains capacity or dies, he/she will remain in the study. In this case we plan to include their outcome data until day of death and biological samples in the final analysis.

If patients do not have capacity to consent and a personal consultee is not immediately available, we will consult with a professional consultee (as outlined above) according to the emergency provision of the Mental Capacity Act. If the patient has capacity or a personal consultee is available, it is hoped that they will not need longer than 3 hours to make a decision regarding participation in the study. However, if patients or their personal consultees need longer to make an informed decision, this will be acknowledged. If participation is still possible within the limited time period, this will be facilitated. Otherwise, the patient will not be included.

Having consented, a patient can change their mind and withdraw from the study at any time between consent and completion of the study. Patients can withdraw consent at any time during the intervention period and later. If they withdraw during the intervention period, they will be asked if the withdrawal should apply to study data collected, and/or samples collected and/or sample analysis and if data and samples obtained so far can be used for study purposes.

A patient who decides to withdraw from the study can do so for any reason, without prejudice and without an impact on their clinical care.

A patient who was enrolled into the study following consultation with a personal or professional consultee may also be withdrawn from the study at the request of his/her legal representative or the professional consultee, for any reason and without prejudice. For patients who withdraw consent, the following options will be offered

- Data and/or blood samples obtained so far can be used for the research purposes, but no further samples or data will be collected.
- On patient request all data obtained so far will be deleted from the research database in REDCap and all paper documents containing patient data obtained as part of the study will be destroyed. All blood samples obtained will be destroyed.
- The above options will be available on the retrospective consent form.

For patients who were unable to consent for themselves when enrolled in the study, retrospective consent will be sought in written form for them to remain in the study, once they regain capacity (retrospective consent).

Monitoring

Alongside standard care, vital signs will be monitored continuously for seven days after recruitment using the Isansys Lifecare Patient Status Engine (PSE), a CE-marked class 2a medical device, with wireless wearable biosensors recording single-lead continuous ECG, heart rate, heart rate variability, respiratory rate, temperature, oxygen saturation and non-invasive blood pressure, which are displayed on a tablet (Patient Gateway) in real time and securely stored on a server. Alerts can be sent directly to healthcare professionals using authorized mobile devices.

Alternative systems, e. g. Smartcardia platform (SCaAI patch and cloud platform, a CE Class IIa approved system with monitoring of 7-lead ECG, respiration, SpO2, activity and cloud-based arrhythmia detection, may be used.

Blood sampling

Surplus serum blood samples will be collected on the day of recruitment (day 1), until day7 and within 24h before hospital discharge. Where a blood sample has been requested for clinical reasons, a serum blood sample will be added to the request if not yet included. Pseudonymized samples will be centrifuged, plasma or serum will be aliquoted, frozen and stored at -80°C for subsequent analysis. Serum samples will be transferred to the Liverpool Biobank at regular intervals to be available for future research. Serum samples will be used to determine cardiac biomarkers, including but not limited to troponins and natriuretic peptides and inflammatory markers, including but not limited to cytokines and interleukins. Samples of patients who decline use in future research will remain stored at freezers within the Liverpool University Hospitals NHS Foundation Trust and destroyed after this project has finished. A detailed flow diagram of blood sampling is provided in Appendix I.

Biomarker testing

The main biomarker analysed as part of clinical care is hs-cTn, which will be measured as deemed clinically indicated by the treating physician. In addition, surplus samples collected as part of this research will be used to determine further cardiovascular biomarkers, including but not limited to troponins and B-natriuretic peptides.

Echocardiography

Echocardiography will be performed by qualified sonographers in all patients where ultrasonic imaging of the heart is clinically indicated.

ECG analysis

ECG waveforms obtained from wCVSM devices will be analysed using previously described analysis techniques (pointcare plots, automated image analysis, convoluted neuronal networks). Where obtained as part of routine clinical care, 12-lead ECG recordings will be used to supplement information obtained from single lead continuous ECG recordings.

Follow up

Patients will be followed up for 3 months (90 days) to determine recurrence of AF, development of thromboembolic complications (ischemic stroke, limb or splanchnic ischemia, pulmonary embolism) and mortality.

End of Study Definition

The expected study duration is 48 months, including setup, recruitment, 6-months follow-up period for data cleaning and analysis and writeup of results. The study will close after data are analysed and a final report has been submitted to the funder.

Assessment of Safety

Safety outcomes

Safety laboratory tests will be performed routinely in these patients as acute illness is associated with complications. Adverse events related to the performance of wCVSM will be explicitly documented and recorded for both arms of the study. Serious adverse events (SAE) will be identified by daily review of the medical notes. If the SAE is related (i. e. the result of any of the research procedures), to the study procedures or is an unexpected occurrence (that is, the type of event is not listed in the protocol as an expected occurrence), it must be reported immediately upon knowledge of the event to the sponsor (LUHFT R&D) within 24 hours. For all other adverse events, these must be reported to LUHFT and as part of the Annual Progress Report. The Chief Investigator is responsible for reporting events to LUHFT R&D.

The definition of “serious” may be defined differently within the protocol and it is the responsibility of the research team to adhere to the protocol definition in terms of SAE reporting. Additionally, the protocol and other documentation may identify SAEs that do not need immediate reporting and SAEs falling under these categories should be recorded and reported according to the protocol. If an SAE occurs that does not require immediate reporting, this SAE should be reported in the Annual Progress Report and copied to R&D. All adverse events that are to be reported to R&D Directorate must be signed and dated and completed by the Investigator.

Ethics Reporting

Reports of related and unexpected SAEs will be submitted to the Main REC within 15 days of the Chief Investigator becoming aware of the event, using the NRES template. The form will be completed in typescript and signed by the chief investigator. The coordinator of the main REC will acknowledge receipt of safety reports within 30 days. A copy of the SAE notification and acknowledgement receipt will be sent to the R&D Directorate.

Data safety and study monitoring

Members of the TARGET executive board, at least two clinicians and a statistician will oversee data safety and monitoring, in line with the regulations stated in the EU consortium agreement. The task of the committee is to oversee the safety of the study subjects in the clinical study and to monitor the integrity and validity of the collected data and the conduct of the clinical study.

The TARGET executive board has the right to terminate the study prematurely if there are any relevant medical or ethical concerns, or if completion of the study is no longer practical. Members have access to all data and should assess them on a regular basis. They have the right to terminate the study in case of serious scientific or ethical concerns about continuation of the study. If such action is taken, the reasons for terminating the study must be documented in detail. All study subjects still under treatment at the time of termination must undergo a final examination which need to be documented. The TARGET executive board must be informed without delay if any investigator has ethical concerns about continuation of the study.

Premature termination of the study will be considered if:

- The risk-benefit balance for the study subject changes markedly.
- It is no longer ethical to continue the study.
- The Chief Investigator considers that the study must be discontinued for safety reasons.
- It is no longer practical to complete the study.

Ethics & Regulatory Approvals

The study documents will be submitted centrally for consideration by a NRES approved Research Ethics Committee as part of the Health Research Authority approval process within the NHS. The study will not be classified as a device study as all components of the monitoring system are CE marked (class IIa medical device) and have been tested in clinical studies before. Work package 2 represents and implementation study.

Data Handling

Data collection will include demographics, diagnoses, past medical history, drug history, clinical and surgical interventions, length of hospital stay, anaesthetic risk profiles, Quality of Life (EQ-5D-5L), mortality at 90-days.

Confidentiality

- All enrolled patients will have their hospital identification number and name recorded on a master list which will be stored in the investigator site file in a locked office at the investigator's site. Only members of the study team will have access to the master list.
- All enrolled patients will be allocated a unique study number which will be used for referencing.
- The Chief Investigator will act as 'Custodian' for all data collected.
- No patient identifiable details will be transferred outside of the UK.
- No patient identifiable details will be included in the published study reports.
- Data sharing will occur with partners of the TARGET consortium in line with the negotiated data sharing agreement. Only fully anonymised data will be transferred.

Information provided to General Practitioners

- If any relevant clinical findings occur (e. g. cardiovascular events, postoperative complications), the patient's general practitioner (GP) will be informed provided the patient or personal consultee have given consent to inform them (as described in the relevant patient, personal consultee and professional consultee information sheets, as well as in the relevant consent and declaration forms). Information of the GP will occur either in form of a separate letter or by adding relevant information to the clinical discharge letter.
- Patients, their personal consultees and professional consultees may elect to opt-out of having the patient's GP informed of their enrolment in the study.

Case Report Form

All data relevant to the study will be documented on electronic CRFs created using REDCap application (hosted at the University of Liverpool). The electronic CRFs will be held on password-secure NHS

computers. in a locked room and accessed by researchers only. All data will be anonymised using a unique study number.

Record Retention and Archiving:

- During the course of the study, all records are the responsibility of the Chief Investigator.
- When the research study is complete the records will be kept for a further 15 years (a requirement of the Research Governance Framework and Health Board Policy).

Compliance:

- The study will be conducted in compliance with the principles of the Declaration of Helsinki (2013), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

Clinical Governance Issues

The study may be selected for audit by any method listed below:

- The project may be identified via the risk assessment process.
- An individual investigator or department may request an audit.
- A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
- Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
- Projects may be randomly selected for audit by an external organisation.
- Internal audits will be conducted by a sponsor's representative.

Non-Compliance

Non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the R&D Office will agree an appropriate action, including an on-site audit.

Data Management Plan

It is a requirement for Europe Horizon funded projects to develop a Data Management Plan to ensure that data is handled efficiently, ethically, legally and sustainably throughout the project lifecycle, taking into account the FAIR principles (Findability, Accessibility, Interoperability, and Reusability). This plan will ensure systematic organisation and easy accessibility of data, maintain consistency and quality through standardised procedures, and ensure compliance with legal, ethical, and EU requirements. Additionally, it outlines strategies for data storage, backup, and long-term preservation to prevent data loss and ensure future usability.

The DMP outlines the data that will be used and generated throughout the project, including retrospective and prospective data. As a crucial aspect of sustainable data management, the DMP delineates the types of data to be collected, processed, and generated, along with the methods and standards to be employed. It addresses data sharing and open access and outlines plans for long-term preservation beyond the project's conclusion. It also provides guidance and details on the approach taken in TARGET to manage and safeguard its data. Additionally, TARGET's DMP is conceived as a living, dynamic document, which will be updated as the project evolves to ensure it remains relevant and useful, adapting to any arising change or circumstance.

Legal and technical aspects of collecting and processing personal data within the project are identified and thoroughly considered. This includes various data collection methods such as interviews, online surveys, workshops, and questionnaires. Data need to be shared with partners of the consortium after

anonymisation at the site where the data are being produced. TUW (TARGET partner) will develop a data platform for this purpose. From this data platform TARGET partners tasked with the development of virtual twins will access the data and process them further as required. Data sharing will occur via credentialised access in compliance with European legislation. AI models and outputs will also be stored on the Centralised Data Platform for further use in sharing.

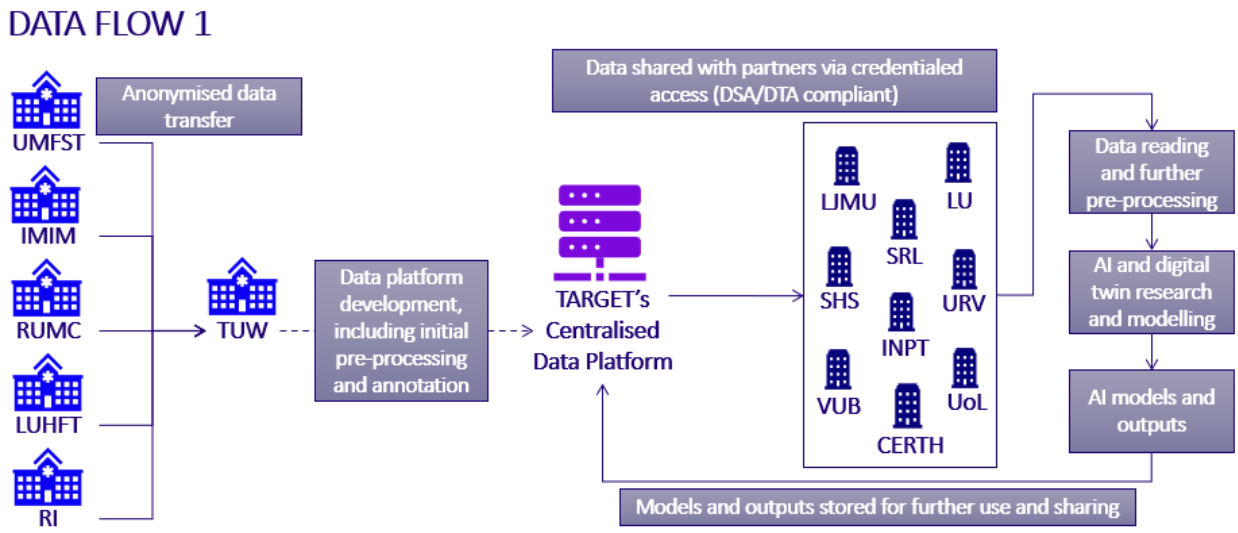


Figure 1: Details of TARGET's Data Flow. Data are anonymised at site. Also represented are the main activities performed on the data, such as initial pre-processing and annotation and transfer of the data which will be hosted in TARGET's centralised data platform. Data sharing will occur via credentialised access in compliance with The European Union Digital Services Act (DSA) and the Digital Transformation Accelerator (DTA) contract. Abbreviations: LUHFT: Liverpool University Hospitals NHS Foundation Trust, UMFST: Universitatea De Medicina, Farmacie, Stiinte Si Tehnologie "George Emil Palade" Din Targu Mures (TARGET partner), Hospital del Mar, Consorci Mar Parc De Salut e Barcelona (TARGET partner), RUMC: Radboud Universitair Medisch Centrum (TARGET partner), RI: Revalidatieziekenhuis Inkendaal (TARGET partner), TUW: Technische Universitaet Wien (TARGET partner), LJMU: Liverpool John Moores University (TARGET partner), LU: Lunds Universitet (TARGET partner), UoL: University of Liverpool (TARGET partner), SHS: Siemens Healthineers AG (TARGET partner), SRL: Siemens SRL (TARGET partner), INPT: Institut National Polytechnique de Toulouse (TARGET partner), CERTH: Center For Research and Technology Hellas (TARGET partner), VUB: Vrije Universiteit Brussel (TARGET partner)

Finance and Publication Policy

Finance

Funding has been secured from WARD24/7, Denmark and from EU Horizon 2023 as part of the TARGET project in open competition through an investigator-led funding scheme. The European Commission as funder of the TARGET Horizon 2023 project will have no involvement in the conduct of the study.

Dr. Katja Groenbaek is employee of WARD 24/7 and has overseen the design of WP 2 of the study. The results will remain intellectual property of the Sponsor. WARD 24 is a company registered in Copenhagen, Denmark. WARD 24/7 will have no involvement in conducting the study.

Publication policy

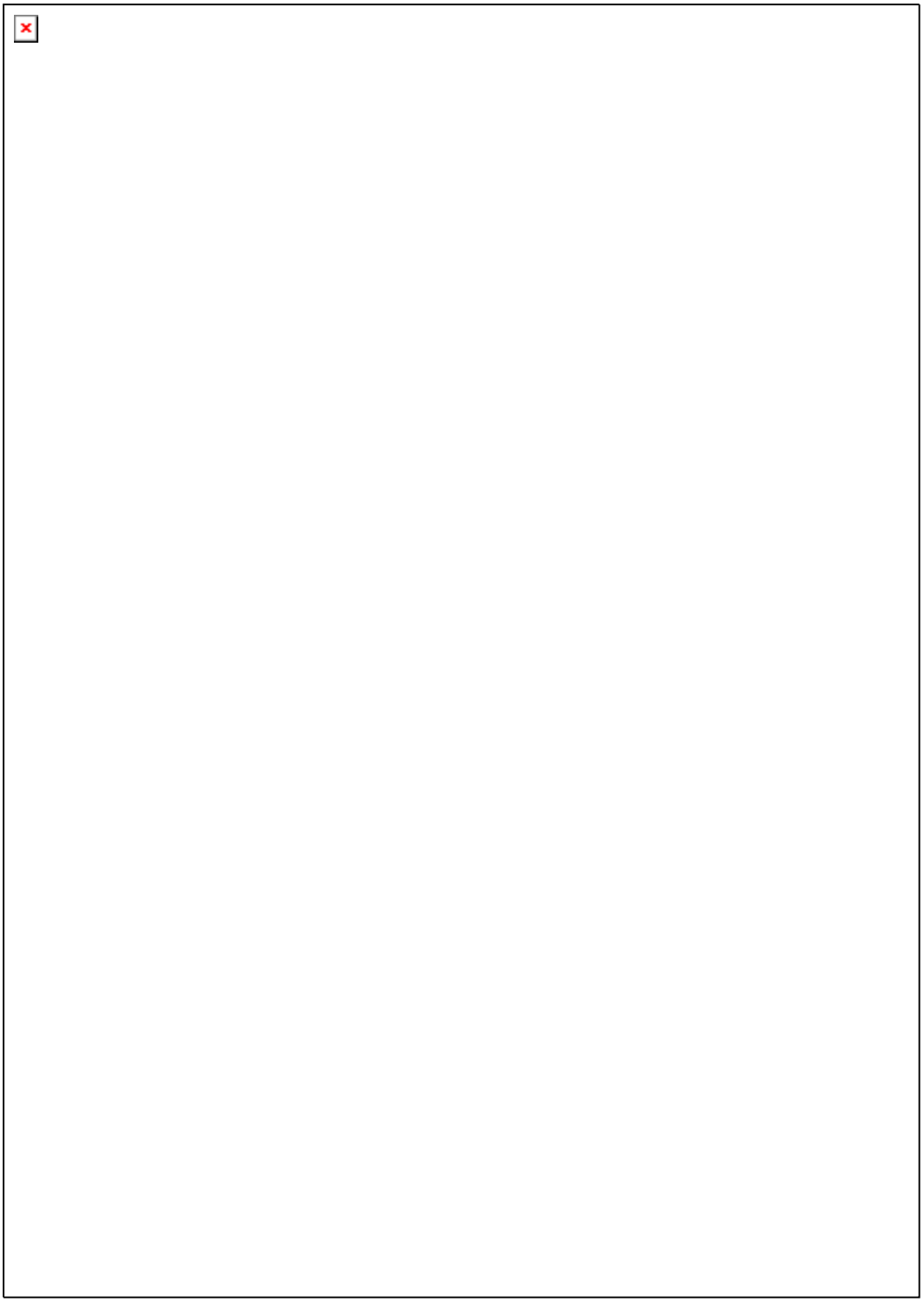
It is planned to publish the study results, in mutual agreement with the investigator team, in a scientific journal and at international congresses. Publication of the results of the two work packages in separate publications is intended. Requirements for authorship will follow AMA guidelines. Any publication will take account of the International Committee of Medical Journal Editors (ICMJE).

The study will also be registered in a public register in accordance with the recommendations of the ICMJE. Any published data will observe data protection legislation covering the study subject and investigators.

Publications or lectures on the findings of the present clinical study either as a whole or at individual investigation sites must be approved by the investigator team in advance, and the responsible institution reserves the right to review and comment on such documentation before publication.

Appendices

Appendix A: Semi-structured interview guide for health care professionals



Guidelines/Escalation protocol

Q: What do you do if vital signs deviate?

Q: Are there guidelines on specific interventions?

Q: Is there an algorithm for when you should contact a physician or the rapid response team (does it exist in your hospital)?

Q: Are you allowed to deviate from the guidelines?

(Questions for follow-up questions: do you ever deviate from guidelines, are there periods where is more difficult to follow guidelines, are there patients where you don't think its relevant to follow guidelines)

Q: Do you believe that this way of monitoring helps the patients?

Q: do you think patient monitoring could be improved?

The interviewer demonstrates the app for the participant

Q: Do you see any challenges using this app for vital signs monitoring in your WARD?

Q: do you have anything else to add?

Appendix B: mHealth PP Usability Questionnaire (MAUQ)

University of Pittsburgh

School of Health and Rehabilitation Sciences
Department of Health Information Management

6021 Forbes Tower
Pittsburgh, Pennsylvania 15260
Phone: 412-383-6653
Fax: 412-383-6655
HIM: http://www.shrs.pitt.edu/him
SHRS: http://www.shrs.pitt.edu

mHealth App Usability Questionnaire (MAUQ)
for Standalone mHealth Apps Used by Healthcare Providers

#	Statements	N/A	1	2	3	4	5	6	7
1.	The app was easy to use.	☐	DISAGREE ☐	☐	☐	☐	☐	☐	☐ AGREE
2.	It was easy for me to learn to use the app.	☐	DISAGREE ☐	☐	☐	☐	☐	☐	☐ AGREE
3.	The navigation was consistent when moving between screens.	☐	DISAGREE ☐	☐	☐	☐	☐	☐	☐ AGREE
4.	The interface of the app allowed me to use all the functions (such as entering information, responding to reminders, viewing information) offered by the app.	☐	DISAGREE ☐	☐	☐	☐	☐	☐	☐ AGREE
5.	Whenever I made a mistake using the app, I could recover easily and quickly.	☐	DISAGREE ☐	☐	☐	☐	☐	☐	☐ AGREE
6.	I like the interface of the app.	☐	DISAGREE ☐	☐	☐	☐	☐	☐	☐ AGREE
7.	The information in the app was well organized, so I could easily find the information I needed.	☐	DISAGREE ☐	☐	☐	☐	☐	☐	☐ AGREE
8.	The app adequately acknowledged and provided information to let me know the progress of my action.	☐	DISAGREE ☐	☐	☐	☐	☐	☐	☐ AGREE
9.	I feel comfortable using this app in social settings.	☐	DISAGREE ☐	☐	☐	☐	☐	☐	☐ AGREE
10.	The amount of time involved in using this app has been fitting for me.	☐	DISAGREE ☐	☐	☐	☐	☐	☐	☐ AGREE
11.	I would use this app again.	☐	DISAGREE ☐	☐	☐	☐	☐	☐	☐ AGREE
12.	Overall, I am satisfied with this app.	☐	DISAGREE ☐	☐	☐	☐	☐	☐	☐ AGREE
13.	The app would be useful for my healthcare practice.	☐	DISAGREE ☐	☐	☐	☐	☐	☐	☐ AGREE

14.	The app improved my access to delivering healthcare services.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
15.	The app helped me manage my patients' health effectively.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
16.	This app has all the functions and capabilities I expected it to have.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
17.	I could use the app even when the Internet connection was poor or not available.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
18.	This mHealth app provides an acceptable way to deliver healthcare services, such as accessing educational materials, tracking my own activities, and performing self-assessment.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE

In this questionnaire, 1 - strongly disagree, 2 – disagree, 3 – somewhat disagree, 4 – neither agree nor disagree, 5 – somewhat agree, 6 – agree, 7 – strongly agree

To determine the usability of an app, calculate the total and determine the average of the responses to all statements. The higher the overall average, the higher the usability of the app.

Please cite: Zhou L, Bao J, Setiawan A, Saptono A, Parmanto B, (2019), "The mHealth App Usability Questionnaire (MAUQ): Development and Validation Study", *JMIR mHealth and uHealth*, 7(4):e11500. DOI: 10.2196/11500. PMID: 30973342

Appendix C: Patient experience questionnaire

Questionnaire

Patient experience with wireless vital sign monitoring (WARD)

Date: _____ Patient ID: _____

Please answer every statement

How many days have the system been used: _____

Where did you have patch(es)/device(s) on you:

☐ Upper chest

☐ Shoulder

☐ Around your arm

☐ Under armpit

☐ Lower stomach

☐ Wrist

This section is about the patches/devices that were used for this specific study

I did not mind wearing the patches/devices while being in the hospital:

☐Strongly agree

Questionnaire

Patient experience with wireless vital sign monitoring (WARD)

☐agree

☐neither agree nor disagree

☐disagree

☐strongly disagree

The patches/devices restrained my movements:

☐Strongly agree

☐agree

☐neither agree nor disagree

☐disagree

☐strongly disagree

The patches/devices disturbed my sleep at night:

☐Strongly agree

☐agree

☐neither agree nor disagree

☐disagree

☐strongly disagree

Questionnaire

Patient experience with wireless vital sign monitoring (WARD)

My experience with the patches/devices were overall good:

☐Strongly agree

☐agree

☐neither agree nor disagree

☐disagree

☐strongly disagree

This section is about the methods of continuously monitoring patients and how this feel. In this section we will ask you to think less about the patches/devices and more about the monitoring as a concept

Being monitored continuously made me feel safe:

☐Strongly agree

☐agree

☐neither agree nor disagree

☐disagree

☐strongly disagree

Questionnaire

Patient experience with wireless vital sign monitoring (WARD)

I was happy to know that the nurse would be notified if my condition worsened:

☐Strongly agree

☐agree

☐neither agree nor disagree

☐disagree

☐strongly disagree

I felt left alone because the nurse did not measure my vital signs manually:

☐Strongly agree

☐agree

☐neither agree nor disagree

☐disagree

☐strongly disagree

I think the continuous monitoring resulted in less contact with the nurses:

☐Strongly agree

☐agree

Questionnaire

Patient experience with wireless vital sign monitoring (WARD)

☐neither agree nor disagree

☐disagree

☐strongly disagree

The continuous monitoring gave me more privacy:

☐Strongly agree

☐agree

☐neither agree nor disagree

☐disagree

☐strongly disagree

Additional thoughts about your experience:

_____
_____
_____
_____
_____
_____

THANK YOU FOR YOUR PARTICIPATION

Appendix D. Timeline of study activities

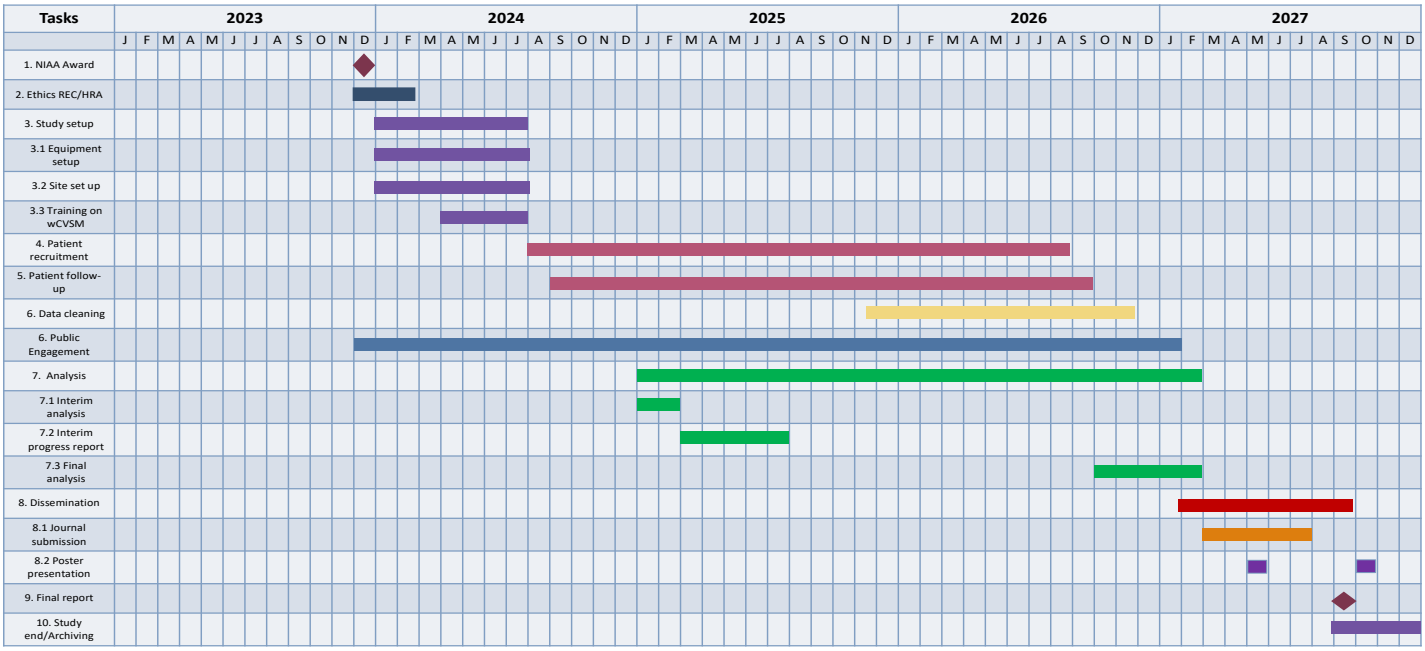


Figure 1. Provisional WARD-UK/PULSE-GI study timeline

Appendix E. Study procedures

	Screening / Pre-study	1	2	3	Day 3-7	Discharge	Day 90
Inclusion and Exclusion criteria	X						
Medical history (preexisting condition, premedication)	X						
Consent	X						
Demographic data	X						
Admission diagnosis, Category of admission (elective, emergency)		X					
Surgical parameters (type & duration of procedure, intraoperative transfusion)		X					
APACHE II		X					
SOFA Score		X	X	X			
Standard vital signs (SBP, DBP, MAP, HR, RR, SpO2, if indicated CVP, CO)	X	X	X	X			
Continuous Vital Signs monitoring		X	X	X	X		
Laboratory parameters (if clinically indicated)		X	X	X	X	X	
Collection of surplus routine blood samples (when available)	X	X	X	X	X	X	
Transthoracic Echocardiography (if clinically indicated and available)	X	X	X	X			
Vasopressor and inotrope use	X	X	X	X	X		
Documented episodes of AF (in clinical notes and on wCVSM)		X	X	X	X	X	X
Concomitant cardiac Medication (antiarrhythmics, diuretics, statins, antihypertensives)	X	X	X	X	X	X	X
Mortality						X	X
EQ-5D-5L						x	x
Duration of organ support (Begin and end of RRT, mechanical ventilation, oxygen therapy)	X	X	X	X	X	X	X
Length of stay (ICU, Hospital)					X	X	X
Cardiac Recovery							X
Cardiac diagnoses / complications (episodes of AF; congestive heart failure, thromboembolic event, stroke)	X	X	X	X	X	X	X
Non-cardiac diagnoses / complications (sepsis, pneumonia, wound infection, anastomotic leak, bleeds)		X	X	X	X	X	X

Appendix F. Scores

SOFA-Score

SOFA Score	0	1	2	3	4
Respiration PaO_2/FiO_2	>400	<400	<300	<200	<100
Platelet count ($10^3/\mu l$)	>150	<150	<100	<50	<20
Bilirubin (mg/dl)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12
Cardiovascular	No hypotension	MAP <70 mmHg	Dobutamine (any dose)	Norepinephrine/ epinephrine ≤0.1µg/kg/min	Norepinephrine/ epinephrine > 0.1µg/kg/min
GCS	15	13-14	10-12	6-9	<6
Creatinine (mg/dl) or UO (ml/d)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 ≤500	>5.0 <200

ASA-Score

ASA I	Normal healthy patients
ASA II	Patients with mild systemic disease
ASA III	Patients with severe systemic disease that is limiting but not incapacitating
ASA IV	Patients with incapacitating disease which is a constant threat to life
ASA V	Moribund patients not expected to live more than 24 hours
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes

APACHE-Score

Points	+4	+3	+2	+1	0	+1	+2	+3	+4
Temp. °C	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
MAP (mmHg)	≥160	130-159	110-129		70-109		50-69		≤49
HF/min	≥180	140-179	110-139		70-109		55-69	40-54	≤39
AF/min*1	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation	≥500	350-499	200-349		71-199	61-70		55-60	<55
pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Na^+ (mmol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
K^+ (mmol/L)	≥7	6.6-6.69		5.5-5.59	3.5-5.4	1.0-3.4	2.5-2.9		≤2.5
Creatinine (mg/dl) *2	≥3.5	2.0-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)	≥60		50-59.9	46-49.9	30 -45.9		20-29.9		<20
Leukocytes (x1000)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
GCS	Points= 15-current GCS								

*1 spontaneous breathing or mechanical ventilation

*2 AKI receives double points

Appendix G. Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	Report to sponsor within 24 hours of learning of the event Report to the MREC within 15 days of learning of the event	SAE report form for non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the sponsor and MREC immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual progress report form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of study declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the research	No standard format However, the following Information should be included: Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor

Appendix H: Echocardiographic analysis:

NOTE-AF Transthoracic Echocardiography Protocol

Introduction

The proposed Transthoracic Echocardiography (TTE) protocol for the NOTE-AF study strictly adheres to the outlined minimum data set presented by the British Society of Echocardiography (BSE) [32] with the addition of a number of novel advanced TTE metrics. The BSE minimum dataset ensures that a full and comprehensive assessment of cardiac anatomy, function and haemodynamics can be assessed on each patient enrolled within the study. When pathologies are present, additional TTE analysis can be performed (e.g., significant mitral regurgitation) on a case-by-case basis.

The TTE protocol outlined below aims to include the use of novel speckle tracking strain imaging on all four cardiac chambers. Left ventricular (LV) global longitudinal strain (GLS) is now an increasingly popular technique used to assess LV systolic function and regional wall motion abnormalities (RWMA's). Both LV GLS and strain rate have been associated with detections of subclinical cardiac disease and alterations in LV systolic function before detectable changes in ejection fraction (EF) [33]. Similarly, speckle tracking strain of the right ventricle is emerging as an increasingly popular method of assessing regional RV deformation, as it has shown to be reproducible and prognostic in a variety of conditions [34]. More recently in both research and clinical settings, speckle tracking imaging has been applied to the atria in order to better understand atrial mechanics and in efforts to detected subclinical changes. Atrial strain examines the three functions of the atria (reservoir, conduit and booster/pump). In a number of pathologies, atrial strain has shown to be impaired prior to any structural changes in LA volume, which has traditionally be used as a marker of atrial impairment [35]. Interestingly, emergency evidence is highlighting associations between strain measurements and detection of atrial arrythmias [36-39]. In addition to this, the proposed protocol outlined below aims to assess the electromechanical delay within the atria. Studies have previously identified that the time delay between the onset of the P wave on ECG, to the beginning of the A' wave of the Tissue Doppler Imaging (TDI's) has been independently associated with atrial arrythmia occurrence in both cardiac and non-cardiac pathologies [40-42].

In summary, the proposed protocol aims to utilise all standard TTE views outlined by a full and comprehensive level 2 study *(see Table 1)* with the addition of novel and emerging analysis techniques in order to detected subclinical, yet meaningful changes. All additional analysis outside of the minimum dataset with be performed off-line.

TTE Protocol Workflow

Image Acquisition and Analysis

It is anticipated that all TTE studies with be performed by BSE accredited echocardiographers. The TTE studies will be requested, performed and reported on as apart of the usual care pathway for patients. Reports will be to the standard set out by the Cardio-Respiratory Department of the Royal Liverpool Hospital, a BSE accredited department. TTE studies will be performed using a GE S70 Vivid (GE Vingmed Ultrasound) ultrasound machine, which is the standard clinical machine used for bedside full level 2 TTE studies. TTE Additional analysis, which is outside of the outlined minimum dataset will be performed off-line using EchoPac Analysis Software (GE Vingmed Ultrasound).

Data Storage

Images obtained will be storage onto IntelliSpace Cardiovascular (Phillips Medical) alongside the formal clinical report. Additional TTE parameters which are being examined (outside that of the BSE minimum dataset) will be analysed and stored on EchoPac Analysis Software (GE Vingmed Ultrasound). All images and reports are only accessible using Liverpool NHS Foundation login credentials, as well as those granted access to IntelliSpace and EchoPac (password protection). Raw data will be extracted from images and stored in a passport protected Microsoft Excel spreadsheet (Microsoft Office), accessible only my research team members.

Table 1. Summary of TTE protocol

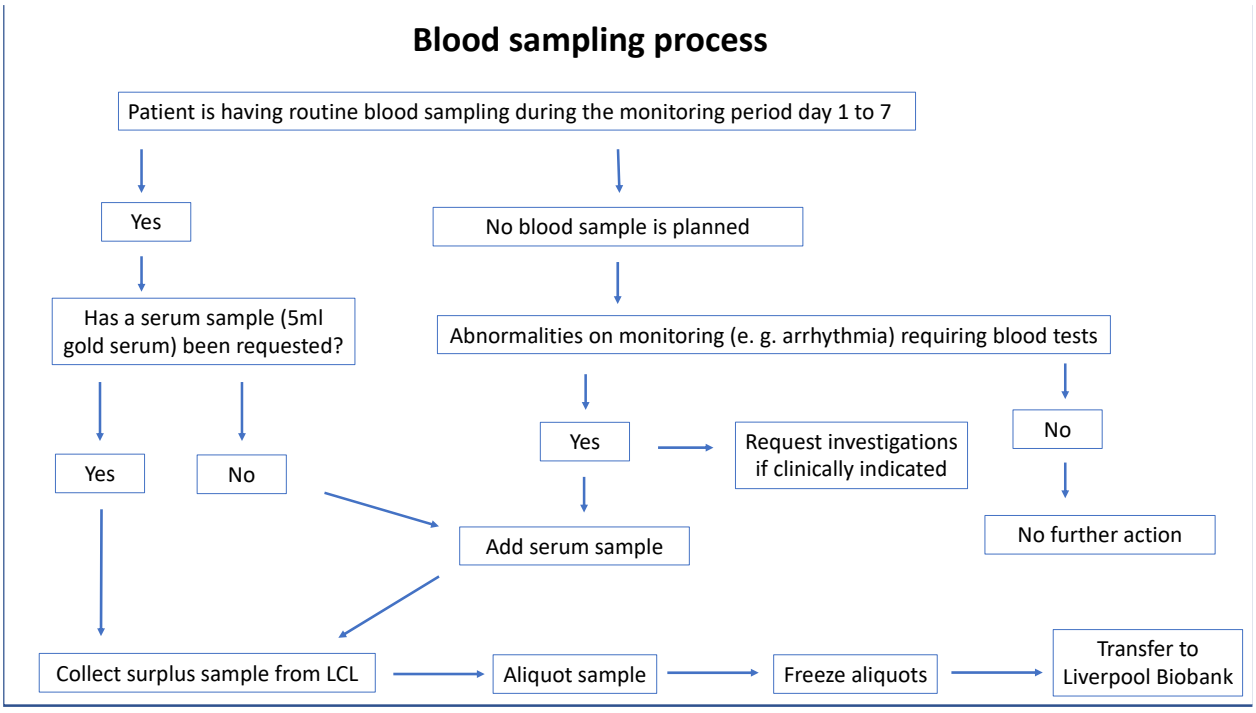
TTE View	***Measurements/assessments***
PLAX zoom out	Visual assessment of plural and pericardial space
PLAX	LV dimensions (LVEDd, LVESd, IVSd and PWDd). Visual assessment of LV and RV radial function. Left atrium dimension (Anterior-Posterior on PLAX zoom in). RVOT dimension. Visual assessment of MV structure

	(focused), colour assessment of MV. Visual assessment of AV structure (focused), colour assessment of AV. LVOT dimension. Aortic root dimensions (SOV, STJ and Prox Asc Aorta)
PLAX RV Inflow	Visual assessment of RV, TV and RA. Colour flow assessment of TV. CW Doppler assessment of TR Vmax.
PLAX RV Outflow	Visual assessment of RVOT, PV , main PA and bifurcation. Colour flow assessment of PV with CW Doppler. CW Doppler to assess PV Vmax. PW Doppler assessment in RVOT for Pulmonary acceleration time.
PSAX (aortic level)	AV Morphology. AV colour assessment. Colour assessment of IAS. Visual TV assessment and colour assessment. CW Doppler of TR (if present and measurable). RVOT 1 and RVOT 2 dimensions. PV visual assessment and colour assessment. CW Doppler of PR (if present) and PV Vmax). Main PA dimension.
PSAX (MV level)	Visual assessment of MV structure. Colour flow assessment of MV for origin of MR jet (if present). Visual assessment of RWMA's. . Colour flow assessment for VSD.
PSAX (Mid level)	Visual assessment of RWMA's. Colour flow assessment for VSD. Visual assessment of RV function.
PSAX (Apical level)	Visual assessment of RWMA's. Colour flow assessment for VSD.
A4C View.	Overall visual assessment of gross cardiac anatomy – focused (zoomed in) view used for assessment.
A4C view LA focus.	LA Biplane volume assessment. LA speckle tracking strain (reservoir, conduit and pump function). Visual MV structure assessment. Colour flow of MV assessment. Full comprehensive quantifiable MR assessment (if applicable). PW Doppler of Pulmonary veins. Colour flow assessment of IAS.
A4C view LV focus	Visual assessment of LV systolic function and RWMA's. EDV, ESV and EF

	assessment by Simpson's Biplane method. Global Longitudinal LV strain assessment. TDI assessment of lateral and medial annulus. PW Doppler of LV inflow velocities (electromechanical delay). Colour flow assessment of septum.
A4C view LV/RV focus	LV/RV basal diameter ratio
A4C view RV focus	RV basal, mid and length dimension. TDI and M mode assessment of RV longitudinal function. RV fractional area change. Global Longitudinal RV strain assessment. PW Doppler of RV inflow.
A4C view RA focus	RA area. Visual assessment of TV structure. Colour flow assessment of TR with full comprehensive quantifiable TR assessment (if applicable). CW Doppler of TR Vmax (if applicable).
A5C view.	Visual assessment of AV and LVOT. Colour flow assessment of AV. CW Doppler assessment of AR (if present) and transaortic velocities. PW Doppler assessment of LVOT.
A2C view	Overall visual assessment of gross cardiac anatomy – focused (zoomed in) view used for assessment.
A2C view LA focus	Visual assessment of LA and appendage (if visible). LA volume assessment with Biplane method. LA speckle tracking strain (reservoir, conduit and pump function). Visual MV structure assessment. Colour flow of MV assessment. Full comprehensive quantifiable MR assessment (if applicable).
A2C view LV focus	Visual assessment of LV systolic function and RWMA's. EDV, ESV and EF assessment by Simpson's Biplane method. Global Longitudinal LV strain assessment.
A3C view	Overall visual assessment of gross cardiac anatomy – focused (zoomed in) view used for assessment.
A3C view LA focus	Visual assessment of LA. Visual MV structure assessment. Colour flow of MV assessment. Full comprehensive quantifiable MR assessment (if applicable).
A3C view LV focus	Visual assessment of LV systolic function

	and RWMA's. Global Longitudinal LV strain assessment. Colour flow assessment of IVS.
A3C view AV focus	Visual assessment of AV and LVOT. Colour flow assessment of AV. CW Doppler assessment of AR (if present) and transaortic velocities.
A3C View TV tilt	Further visual assessment of TV structure. Colour flow assessment of TR. CW Doppler for assessment of TR Vmax (if applicable).
Subcostal view	Visual assessment of pericardial space, RV and LV radial function, TV and MV structure. Colour flow assessment of IAS. IVC diameter and change during inspiration (M-mode or 2D). Subcostal short axis view can be used to assessment structures outlined in PSAX view if image acquisition has been suboptimal.
Suprasternal view	Visual assessment of aortic arch structure. Dimensions of arch. Colour flow assessment. CW Doppler of descending aorta. PW Doppler of arch/descending aorta if significant gradient detected.

Appendix I: Blood sampling process



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