Prospective Cardiac Ultrasound Imaging Study With Demonstrator

Type of Research Project:	Research project involving human subjects
Risk Categorisation:	Limited patient risk
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PROTOCOL SIGNATURE FORM

Study Title Prospective Cardiac Ultrasound Imaging Study With Demonstrator

The project leader has approved the protocol Version 1, 31-mar-2021, and confirms hereby to conduct the project according to the protocol, the local legal requirements, current version of the World Medical Association Declaration of Helsinki [1] and the principles and procedures for integrity in scientific research involving human beings.

Project leader:

Site IRCCS Policlinico S. Matteo, Pavia
Name: Dr. Roberto Rordorf

Date: _____ Signature: _____

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GLOSSARY OF ABBREVATIONS

CRF	*Case report form*
CT scan	*Computed Tomography scan*

1 BACKGROUND AND PROJECT RATIONALE

Echocardiography is an established specialty with dedicated tools, which require a lot of know-how both in manipulation and interpretation [1, 2]. Most cardiac patients who are prescribed a Computed Tomography scan (CT scan), or a Magnetic Resonance Imaging exam will undergo transthoracic echocardiography in the first place. The Prospective Cardiac Ultrasound Imaging Study aims at collecting cardiac ultrasound data from patients diagnosed with ventricular tachycardia. The research will analyse the ultrasound image data quality and establish if it is appropriate to develop a new medical device supporting automated cardiac ultrasound image interpretation during non-invasive cardiac procedures, i.e. ventricular tachycardia stereotactic radioablation. Such device would allow for a new way of monitoring patients during hospital procedures.

This early research protocol will collect data from volunteer patients. The data will not be used for diagnostic nor treatment purposes and the protocol's procedure duration is limited, hence the research is of very limited risk for the participants. The research has the potential to enable the creation of a medical device that will benefit patients with ventricular tachycardia and other cardiac pathologies in the future.

2 PROJECT OBJECTIVES AND DESIGN

2.1 Primary objective

The primary objective of the research is to evaluate the ultrasound image quality for arrythmia patients, to investigate potential echogenicity and artefact issues, which may arise from age, body composition, mechanical valves, leads from implanted devices, etc. in order to have a representative sample of the variety of ventricular tachycardia patients.

2.2 Primary and additional endpoints

Objectives
The primary research objective is the proportion of subjects who have a positive evaluation in image interpretation metric and positive visual inspection of the ultrasound images.

Secondary objective; Additionally, for patients for whom a full field of view CT scan is available, the theoretical impact of probe positioning during a CT scan is analysed for hypothetical treatment planning.

Endpoints
Primary
The objective will be quantitatively assessed by scoring each patient as follows:

- A) Cardiac motion analysis performance:
  - Score 1 if analysis of the ultrasound images with the EBAMed software gives a cardiac phase error (within R-R interval) < 0.1
  - Score 0 otherwise
- B) Respiratory motion analysis performance:
  - Score 1 if analysis of the ultrasound images with the EBAMed software gives a motion amplitude lower than 30 mm and if the number of breathing cycles matches the one observed from the motion of the chest.
  - Score 0 otherwise

- C) Image quality performance:
    - Score 1 if visual inspection by a member of San Matteo team can identify in the ultrasound images at least one of these structures: left ventricular wall, interventricular septum, or heart valve.
    - Score 0 otherwise
- D) Image quality performance :
    - Score 0 if visual inspection by a member of San Matteo team identifies that the heart becomes invisible for part of the time due to tissue motion linked to respiration.
    - Score 1 otherwise

For each patient, scoring will be done for each imaging view (parasternal and apical). If the score is 2 (at least 1 point in A or B and 1 point in C or D)or higher for at least one of the imaging views, the outcome will be considered as positive. The final result will be the proportion (in %) of patients with a positive outcome defined as the number of patients with a positive evaluation divided by the total number of patients x 100.

Secondary
The objective will be quantitatively assessed by scoring each patient (only those with a CT available):

- with Score 1: if a successful radio-ablation treatment plan respecting dose constraints can be created using a clinical treatment planning software (see details below) and,
- with Score 0: if it is not possible to create such a treatment plan .

The final result will be the proportion of patients (in %) with a 1 Score: number of patients with score 1 divided by the number of patients with Score 0 or 1 x 100.

The treatment plan is performed with the Raystation clinical treatment planning software by a Medical Physicist from the EBAMed team. An electrophysiologist from the San Matteo team will draw on the CT the contours of a realistic ventricular tachycardia ablation treatment target and the contours of relevant organs-at-risk (including e.g. adjacent cardiac substructures, oesophagus, stomach and trachea). An additional virtual structure will be contoured on the CT, representing the position of the ultrasound probe (based on the best probe view as assessed by scoring for the primary endpoint). A successful treatment plan will need to accomplish all of the following:

- radiation beams do not go through the ultrasound probe
- treatment target receives at least 25 Gy (typical treatment dose)
- organs at risk receive a dose below the thresholdsgiven in Table 1

Table 1: OARs and their relevant metrics (some taken from literature[1], others from consultations with early implementers).

OAR	Relevant Metric	Limit
Whole heart – PTV	*D(50%Volume)	< 5 Gy
Non-involved myocardium = Left ventricular wall + right ventricular wall – PTV	V(20Gy)	Low as possible
Left Atrium	*Dmax	< 4.4 Gy
Mitral valve	Dmax	< 14 Gy
Aortic valve	Dmax	< 14 Gy
Left-anterior-descending coronary artery	*Dmax	< 14 Gy
Aorta	*Dmax	< 20 Gy
Superior Vena Cava	*D(50%Volume)	< 0.6 Gy
Whole Lungs	*V(total) – V(7Gy), D(5%Volume)	> 1500 cc
Spinal Canal	*Dmax	< 7 Gy
	V(6Gy)	< 0.1cc
Oesophagus	*Dmax	< 14.5 Gy
	V(9Gy)	< 1cc
Skin	*Dmax	< 14.4 Gy
	V(10Gy)	< 10 cc
Trachea	*Dmax	< 15 Gy
	V(10Gy)	< 1 cc
ICD (electronics)	*Dmax	< 0.5 Gy

Data that may influence the results will be collected such as patient's demographics and cardiovascular history.

2.3 Project design

This is a single center, one arm, feasibility study. The patients will undergo one Cardiac motion monitoring procedure to collect ultrasound imaging data via the Demonstrator 2 developed by EBAMed SA, Switzerland and there is no follow-up planned.

2.4 System in use

For this study, Demonstrator 2 and related components provide monitoring of the cardiac motion in all its components: cyclical heart-beat motion, cyclical respiratory motion and non-cyclical heart position changes with the patient lying in supine position.

[1] Radiosurgery for ventricular tachycardia: preclinical and clinical evidence and study design for a German multi-center multi-platform feasibility trial (RAVENTA). Oliver Blanck et al. Clinical Research in Cardiology (2020) https://doi.org/10.1007/s00392-020-01650-9

The system encompasses Demonstrator 2 for ultrasound imaging and optical localization. The system offers non-invasive means for accurate and precise real-time monitoring of the patient's heart position and cardiac motion management (see ***Figure 1*** below).

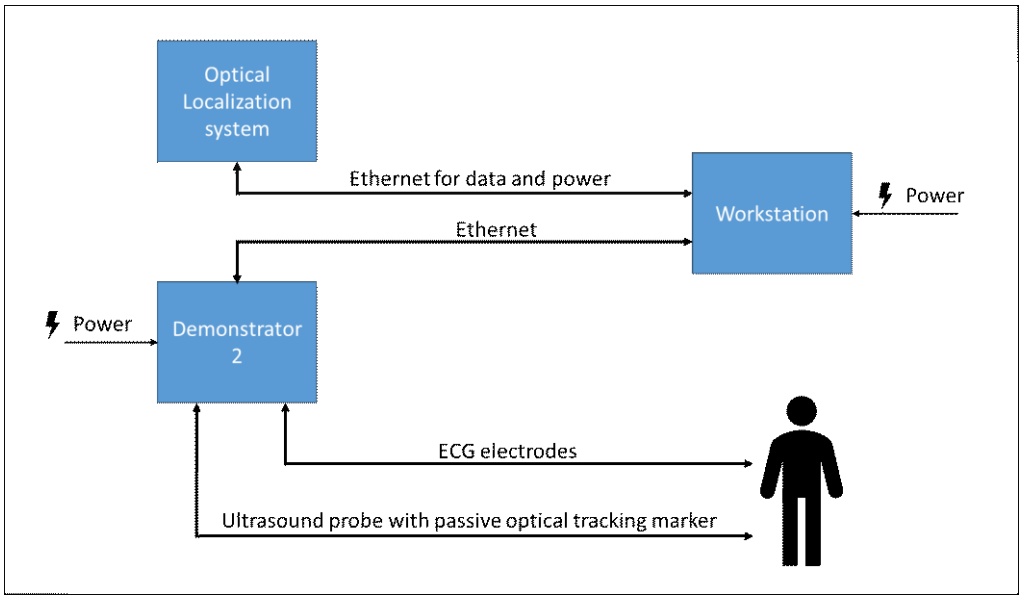

Figure 1 Schematic view of study system

The system is comprised of the following functional components:

- The Workstation, which integrates:
  - Consumer grade computer
  - Consumer grade screen
  - Consumer grade keyboard and mouse

  The Workstation is used for:
  - Communication with Optical localization system
  - Communication with Demonstrator 2
  - Graphical User Interface
- The real-time data acquisition module of Demonstrator 2 (Appendix A - Demonstrator IFU), which controls data acquisition from:
  - ECG system (Appendix B – ECG Operator's Guide)
  - Ultrasound imaging system (beamformer and probe)
- The Optical localization system (Appendix C - Optical Localization System User Guide)

The following additional components are provided to the users:

- Disposable ECG electrodes
- Re-usable reflective markers for optical localization
- Disposable ultrasound probe holder strap
- Re-usable ultrasound probe holder
- Patient positioning board with grab bar and arm support (EagleBoard)

The system provides the following output information:

- User Interface with live ultrasound images, ECG signals including ECG R-waves, ultrasound probe localization data and metrics calculated during the data acquisition, as well as warnings.
- Session records including ultrasound images, ECG data and ultrasound probe localization data.
- Metrics calculated during the data acquisition, including warnings

3 STUDY POPULATION AND PROCEDURES

3.1 Study population, inclusion and exclusion criteria

The study will enrol up to 24 adult patients diagnosed with ventricular tachycardia.

Patients with cardiac or non-cardiac implants in the thorax area are of interest for the research. Patients of all relevant ages and gender should be represented in the final study population.

Inclusion criteria:

1. Patient with history of ventricular tachycardia
2. Over 18 years old
3. Ability and willingness to provide written informed consent

Exclusion criteria:

1. Patient in arrhythmic storm

3.2 Recruitment, screening and informed consent procedure

All consecutive adult patients diagnosed with ventricular tachycardia and visiting the site will be screened for the study by the study leader and his study team.

After reviewing the information sheet, patients will be offered the opportunity to ask questions and they will be offered enough reflexion time before they sign the informed consent form. Two copies of the informed consent will be signed. One copy is for the patient, one copy will be maintained at the site. The data collection and study procedure will start after the signature of the informed consent by both parties and within a maximum of 30 days after the signature. Above 30 days, a new consent form needs to be collected before proceeding with the protocol.

The patients will not receive compensation for their participation in the study.

3.3 Study procedures

Patient's participation starts at informed consent signature and ends after completion of the study's Cardiac Motion Monitoring procedure.

The study will start as soon as the protocol is approved by ethics. The recruitment period is expected to last from May 2021 to August 2021.

The table below describes the data collection and study procedures:

Data Collection	**Information and informed consent form**	**Procedure** (within 30 days of consent)
Signature	X	
Demographics and cardiovascular history		X
Cardiac Motion Monitoring with Demonstrator 2		X
CTscan (if available)		(X)
Adverse Event		X
Deviations, technical issues		X

3.1.1 Demographics and cardiovascular history

The patient will be asked to confirm his/her demographics and cardiovascular history.

3.1.2 Cardiac Motion monitoring

The following procedure steps will take place:

- The study system is installed in the room before patient arrival
- The patient needs to *fully* undress the upper body before lying on the bed
- The 3 ECG electrodes are placed
- Ultrasound gel is applied on the ultrasound probe

A – Apical view

- The ultrasound probe is positioned for apical viewing and fixed with the probe holder and the probe holder strap around patient's chest. Probe position is recorded on case report form. The relative position of the probe is automatically recorded via is optical localization system.
- The cardiac motion monitoring can start. During data acquisition, the image quality of the ultrasound images is visually monitored. The following data sequences are acquired successively:
    1. Patient in free breathing, 5 minutes
    2. Next 5 minutes, the patient starts holding breath for 10 seconds, repeated every minute (total: 5 breath holds in 5 minutes)
- Ultrasound probe, probe holder and strap are removed

B – Parasternal view

- The ultrasound probe is positioned for parasternal viewing and fixed with the probe holder – when available and stable - or held manually.
- The following data sequences are acquired successively:
    1. Patient in free breathing, minimum 1 minute, goal: 5 minutes with fixed probe position
    2. Next 5 minutes, the patient starts holding breath for 10 seconds, repeated every minute (total: 5 breath holds in 5 minutes), with fixed probe position. Note: this step is required when probe holder is in use, and optional when probe is manually held.
- The patient is offered tissues to remove ultrasound gel before dressing up
- The patient is asked whether he/she experienced any discomfort during the procedure

The procedure is performed by a trained investigator. The Cardiac Motion monitoring procedure will last for up to one (1) hour.

3.4 Withdrawal and discontinuation

Patient will be withdrawn from the study if they do not pertain the enrollment criteria, or in case of absence of a Cardiac Motion monitoring procedure by the time the study ends.

Patients can withdraw their consent at any time. No additional data will be collected after patient withdrawal. As much as possible, the reason for patient withdrawal shall be collected.

In case of a patient withdrawal before any data is collected, a new enrollment may take place to ensure enough data is collected in the study.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

Sample Size. This is a feasibility study at early research stage. We plan to enroll 24 patients. We aim at a feasibility of 90% for the primary endpoint (success in 22/24 pts). With 24 patients and an expected proportion of 90%, the lower limit of the 95% confidence interval (95%CI) will be 73% (precision 17%); with an expected proportion of 95% (success in 23/24 pts), the lower limit of the 95%CI would be 79% (precision 11%).

Data Analysis. The number and proportion of success for the primary and secondary endpoint will be reported with their 95%CI. The proportion of success and 95%CI will also be reported by patients characteristics (for instance, but not limited to: age <=/>65; BMI overweight/normo-underweight), gender, VT etiology)

Descriptive statistics (mean and standard deviation/median and quartiles or counts and percent) will be reported for the population description.

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4.2. Handling of missing data

Patients with major deviation to the protocol, i.e. lack of ultrasound imaging data, will not be analyzed.

4.3 Core laboratory

The data will be shared with EBAMed SA to perform the analysis of the records upon their anonimization.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, and local relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

5.2 Notification of safety and protective measures

Although not expected, the project leader will promptly notify the Ethics Committee (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project.

5.3 Serious events

If a serious adverse event occurs, the research project will be interrupted, and the Ethics Committee notified on the circumstances.

5.4 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.5 End of project

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days.

5.6 Insurance

For any damage caused by the trial, the IRCCS Policlinico San Matteo Foundation insurance policy is active to cover the civil liability of its employees.

6 BENEFIT-RISK ASSESSMENT

The study is set-up in order to minimize the burden on the patient, with a single non-invasive, short and simple Cardiac Motion monitoring procedure. The procedure bears no risk for the study participant. The participant will not get direct benefit from her/his participation in the study, but, as mentioned in *1 Background and project rationale*, the research has the potential to enable the creation of a medical device, that will eventually benefit patients with ventricular tachycardia and other cardiac pathologies in the future.

7 QUALITY CONTROL DATA PROTECTION

7.1 Quality measures

Data will be collected on site and maintained in dedicated study files. Training and support will be provided by EBAMed SA on the use of the system (Demonstrator 2 and related components).

For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2 Data recording and source data

The source data is collected on paper Case Report Forms (CRF) and retained at study site. Any error or correction will be marked in a legible format, with initials and date of input by the corrector. CRF data is transferred to electronic format in a single database for further analysis. The Demonstrator 2 system session records are saved on the Workstation in electronic format. Demonstrator 2 system data is saved in an external hard drive for archiving.

7.3 Confidentiality and coding

Study data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other study specific documents, participants are only identified by a unique participant number.

7.4 Retention of study data

The source data will be maintained at the site and stored for a minimum of 5 years.
The data may be pooled with additional future studies of similar interest to increase study power.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

The site receives funding by EBAMed to undertake the study. The site and EBAMed have a contract in place that covers study data sharing.

The investigators have no personal interest, financial or otherwise, in the conduct of the study.

In the event of a publication, both the study leader, the study team and EBAMed will collectively participate.

9 REFERENCES

1. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography, 2018 (https://www.asecho.org/wp-content/uploads/2019/01/2019_Comprehensive-TTE.pdf)
2. Malik et al, Transthoracic Echocardiography: Pitfalls and Limitations as Delineated at Cardiac CT and MR Imaging, RadioGraphics 2017; 37:383–406 (https://pubs.rsna.org/doi/pdf/10.1148/rg.2017160105)
3. Declaration of Helsinki
   (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects)

10 APPENDIX

Appendix A - Demonstrator IFU

IFU_2021MAR23_OperationManualDemonstrator2IOCabinet_v1.0

Appendix B – ECG Operator's Guide

Accusync42_OperatorGuide

Appendix C - Optical Localization System User Guide

20200811_EXP_HWB_NDI-PolarisVega-User-Guide