Statistical analysis plan title	PROSPECTIVE EVALUATION OF HEARTFOCUS: A SOFTWARE SUPPORTING THE ACQUISITION OF CARDIAC ULTRASOUND EXAMS
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Abbreviations

Abbreviation	Definition of terms
A2C	Apical 2-chamber
A3C	Apical 3-chamber
A4C	Apical 4-chamber
A5C	Apical 5-chamber
AE	Adverse event
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DD	Device deficiency
Expert	Experienced sonographer or cardiologist
FAS	Full analysis set
FDA	Food and Drug Administration
HeartFocus software	Software to assist healthcare professionals in the acquisition and interpretation of cardiac ultrasound images
HeartEF	Algorithm to automatically calculate the ejection fraction from the ultrasound
ICC	intraclass correlation coefficient
ICD	Implantable cardioverter-defibrillator
IVC	Inferior vena cava
IVSd	Inter-ventricular septum thickness at end-diastole
LAA	Left atrial appendage
Limited ultrasound exam	Video clip acquisition of the 10 reference views
LV	Left ventricle
LVEDD	Left ventricular diameter at end-diastole
LVESD	Left ventricular diameter at end-systole
(LV) EDV	(Left ventricular) End-diastolic volume
(LV) EF	(Left ventricular) Ejection fraction
(LV) ESV	(Left ventricular) End-systolic volume
MRMC	Multi-reader multi-case
Novice	Nurse without prior ultrasound experience
PLAX	Parasternal long-axis
PSAX-AV	Parasternal short-axis at the aortic valve
PSAX-MV	Parasternal short-axis at the mitral valve
PSAX-PM	Parasternal short-axis at the papillary muscles
PWd	Posterior wall thickness at end-diastole
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC-4C	Subcostal 4-chamber
SC-IVC	Subcostal inferior vena cava

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1. Introduction

This document presents the statistical analysis plan (SAP) for the clinical trial “Prospective Evaluation Of Heartfocus: A Software Supporting The Acquisition Of Cardiac Ultrasound Exams” (HF-01) to evaluate the effectiveness of the HeartFocus application.

This analysis plan is based on the protocols version 4.2 (approved by the IRB for the US) and 2.0 (approved by the CPP for France). The statistical analyses described in these protocols are identical; the modifications between version 2.0 and 4.2 do not impact the statistical analyses.

2. Study Design and Procedures

2.1 Study Design

This prospective multicentric international non-inferiority pivotal investigation will evaluate the ability of the Heartfocus software to support novices for the acquisition of 10 reference views of cardiac ultrasound. The 10 reference views are the following:

- apical 2-chamber (A2C),
- apical 3-chamber (A3C),
- apical 4-chamber (A4C),
- apical 5-chamber (A5C),
- parasternal long axis (PLAX),
- parasternal short axis at the aortic valve (PSAX-AV),
- parasternal short axis at the mitral valve (PSAX-MV),
- parasternal short axis at the papillary muscles (PSAX-PM),
- subcostal 4-chamber (SC-4C),
- subcostal inferior vena cava (SC-IVC).

Novices will be nurses without prior ultrasound experience who have received dedicated training on cardiac ultrasound and Heartfocus software.

Patients included in the study will be adult patients scheduled for an echocardiogram at one of the two investigating centers. Each patient included in the study will receive a standard cardiac ultrasound exam performed in the standard way with the regular ultrasound system used in the cardiologic service.

Patients will receive 2 additional limited exams to their standard exam, which consist of the acquisition of ultrasound clips for each of the 10 reference views:

- one by a novice, *i.e.* nurses having received a dedicated training of 2 days, with the Clarius phased array probe and the HeartFocus software with the guidance system,
- one by an expert (experienced sonographer/cardiologist) with the Clarius phased array probe and the HeartFocus software without the guidance system.

A total of 8 novices will perform the acquisition on 30 different patients each. In total 240 patients will be included in the analysis, half in each investigator center. The exams (240 acquired by novices, 240 by experts) will be assessed by an independent review committee, composed of 5 different cardiologists. Each exam will be reviewed by all 5 cardiologists from this committee. Cardiologists will not know if the exam was performed by a novice or an expert. Cardiologists will be blinded to the investigating center in which the acquisition has been performed.

2.2 Collected Data

The following data will be collected for both the exam acquired by the expert and the exam acquired by the novice:

- Whether the exam was acquired by the expert/novice,
- Reason for not acquiring the exam,
- Whether the exam has successfully been exported for review by the cardiologists,
- Number of clips acquired by the expert/novice,
- Novice acquisition duration in minutes,
- Report of Adverse event (AE) with details, start and end date, severity, relationship, action taken and outcome,
- Report of Device deficiency (DD) with details, date, type, and reason of deficiency, action taken and outcome,
- Report of Serious adverse event (SAE) with details, start and end date, severity, relationship, action taken, and outcome.

The following data will be collected for each review performed by each cardiologist on each exam for qualitative assessment:

- Qualitative assessments
- For the 10 reference views of cardiac ultrasound (PLAX, PSAX-PM, PSAX-MV, PSAX-AV, A4C, A5C, A2C, A3C, SC-4C and SC-IVC), quality of diagnostic (Yes/No/No clip),
- Qualitative visual assessment of left ventricular size (Yes/No) and type* (if Yes),
- Qualitative visual assessment of left ventricular function (Yes/No) and type* (if Yes),
- Qualitative visual assessment of right ventricular size (Yes/No) and type* (if Yes),
- Qualitative visual assessment of right ventricular function (Yes/No) and type* (if Yes),
- Qualitative visual assessment of non-trivial pericardial effusion (Yes/No) and type* (if Yes),
- Qualitative visual assessment of left atrial size (Yes/No) and type* (if Yes),
- Qualitative visual assessment of right atrial size (Yes/No) and type* (if Yes),
- Qualitative visual assessment of segmental kinetics of the left ventricle (Yes/No) and type* (if Yes),
- Qualitative visual assessment of aortic valve (Yes/No) and type* (if Yes),
- Qualitative visual assessment of mitral valve (Yes/No) and type* (if Yes),
- Qualitative visual assessment of tricuspid valve (Yes/No) and type* (if Yes),
- Qualitative visual assessment of inferior vena cava size (Yes/No) and type* (if Yes).

* For each assessment, the type will be described in section 3.4.1.

The following data will be collected for each review performed by each cardiologist on each exam for quantitative assessment:

- For PLAX clip:
  - If measurement = Yes, IVSd, LVEDD, and PWd measurement (in mm),
  - If measurement = Yes, LVESD measurement (in mm),
  - If measurement = Yes, Aortic root measurement (in mm),
- For A4C clip:
  - If measurement = Yes, A4C single-plane LV EDV and LV ESV measurement (in mL) and LV EF measurement (in %),
- For A2C clip:
  - If measurement = Yes, A2C single-plane LV EDV and LV ESV measurement (in mL), LV EF measurement (in %),
- For A4C and A2C clips:
  - If measurement = Yes, Biplane LV EDV and LV ESV measurement (in mL) and Biplane LV EF measurement (in %),
- For SC-IVC clip:
  - If measurement = Yes, Diameter of the IVC measurement (in mm).

The following data will be collected for each patient:

- Information regarding consent form and eligibility criteria,
- Information regarding premature discontinuation (date of end of study and reason for study exit),
- Demographics (age, sex, height, weight, BMI, ethnicity*, race*),
- Indication for cardiac ultrasound exam,
- Prior cardiac diagnoses (hypertension, hyperlipidemia, diabetes, heart failure, atrial fibrillation, other arrhythmias, coronary artery disease, prior heart attack, valvular heart disease, pulmonary hypertension, heart transplant, cardiomyopathies, congenital heart disease, other and specification of other prior cardiac diagnoses, none, not reported),
- Prior non-cardiac diagnoses (renal disease, COPD/emphysema, pulmonary embolus, systemic infiltrative disease like amyloid or hemochromatosis, cancer, underwent chemotherapy, underwent radiation, other and specification of other prior non-cardiac diagnoses, none, not reported),
- Implanted medical devices (pacemaker/ICD, leadless pacemaker, prosthetic heart valve, LAA closure device, atrial septal defect closure device, ventricular septal defect closure device, patent foramen ovale closure device, valve repair device, other and specification of other implanted medical devices, none, not reported),
- Cardiac abnormalities (abnormal left ventricular size or function, abnormal right ventricular size or function, abnormal left atrial size, abnormal right atrial size, septal defect, abnormal mitral valve, abnormal tricuspid valve, abnormal aortic valve, non-trivial pericardial effusion, abnormal inferior vena cava size, patent foramen ovale, other and specification of other cardiac abnormalities, none, not reported).

* Only collected for US patients.

2.3 Eligibility Criteria

2.3.1 Inclusion Criteria

The inclusion criteria are:

- patient (male or female) over 18 years old,
- patient having an echocardiography exam scheduled in an investigated center,
- patient who has given his consent to participate in the research and signed consent form,
- patient affiliated with social security (for France only).

2.3.2 Exclusion Criteria

The exclusion criteria are:

- patient subject to a measure of legal protection (safeguard of justice, guardianship, or curatorship),
- patient deprived of liberty by judicial or administrative decision,
- patient unable to give his consent,
- pregnant or breastfeeding women (declarative),
- patient with cardiac anatomy that does not allow reference electrocardiographic sections to be made (situs inversus, single ventricle, congenital anomalies, etc.),
- patient having benefited from prior echocardiographic exams whose reports mention poor or weak echogenicity,
- patient having known chest deformity that has already been mentioned in previous reports or has been the subject of investigations (*pectum excavatum*),
- patient who has undergone total or partial pneumonectomy.

3. Study Objectives

The primary hypothesis is that novices without previous experience in ultrasound examination could obtain diagnostic-quality acquisitions with the software HeartFocus.

3.1 Primary Objective

The primary objective of the study is to evaluate if ultrasound exams, performed with the HeartFocus software by novices (nurses without prior ultrasound experience), allow the qualitative visual assessment of

- left ventricular size,
- global left ventricular function,
- right ventricular size,
- non-trivial pericardial effusion.

3.2 Secondary Objectives

The secondary objectives are:

- to evaluate the agreement between the acquisitions obtained by experts and those obtained by novices in terms of quality and echocardiographic parameters,
- to evaluate the impact of the investigating centers, prior cardiac diagnoses, and obese patients on the quality of ultrasound exams,
- to evaluate the time to acquire a limited ultrasound exam for a novice with the HeartFocus software,
- to evaluate the performance of HeartEF to automatically calculate the ejection fraction.

3.3 Primary Endpoints

The entire exam allows the qualitative visual assessment of

- left ventricular size (yes, no),
- global left ventricular function (yes, no),
- right ventricle size (yes, no),
- non-trivial pericardial effusion (yes, no).

All endpoints will be assessed by 5 different cardiologists, from the independent review committee. The criteria will be assessed on the exams obtained by novices and those obtained by experts, for each patient.

Success Criteria

The lower limit of the 95% confidence interval (CI) around the percentage of exams that have sufficient quality to allow the qualitative visual assessment of

- left ventricular size,
- global left ventricular function,
- right ventricle size,
- and non-trivial pericardial effusion

are all strictly above 80%.

3.4 Secondary Endpoints

3.4.1 Quality Endpoints

These endpoints will assess the quality of the exams. They complement the primary endpoints.

The entire exam allows the qualitative visual assessment of

- right ventricular function (yes, no),
- left atrial size (yes, no),
- right atrial size (yes, no),
- segmental kinetics of the left ventricle (yes, no),
- aortic valve (yes, no),
- mitral valve (yes, no),
- tricuspid valve (yes, no),
- inferior vena cava size (yes, no).

Diagnostic quality clip for

- apical 2-chamber (yes, no, no clip),
- apical 3-chamber (yes, no, no clip),
- apical 4-chamber (yes, no, no clip),
- apical 5-chamber (yes, no, no clip),
- parasternal long axis (yes, no, no clip),
- parasternal short axis at the aortic valve (yes, no, no clip),
- parasternal short axis at the mitral valve (yes, no, no clip),
- parasternal short axis at the papillary muscles (yes, no, no clip),
- subcostal 4-chamber (yes, no, no clip),
- subcostal inferior vena cava (yes, no, no clip).

3.4.2 Clinical Endpoints

3.4.2.1 Qualitative Endpoints

Indicate the evaluation when the entire exam allows the qualitative visual assessment of

- left ventricular size (normal or borderline, hypertrophy, dilation, hypertrophy and dilation),
- global left ventricular function (normal or borderline, reduced (EF ≤ 50 %)),
- right ventricular size (normal or borderline, hypertrophy, dilation, hypertrophy and dilation),
- non-trivial pericardial effusion (absent, present),
- right ventricular function (normal or borderline, reduced),
- left atrial size (normal or borderline, abnormal (enlarged)),
- right atrial size (normal or borderline, abnormal (enlarged)),
- segmental kinetics of the left ventricle (normal or borderline, abnormal),
- mitral valve (structurally normal, structurally abnormal, suspected device),
- tricuspid valve (structurally normal, structurally abnormal, suspected device),
- aortic valve (structurally normal, structurally abnormal, suspected device),
- inferior vena cava size (normal, dilated),

Any other abnormalities (free text) that can be visually assessed will be described in listings.

NB: For visual assessment of left ventricular size and right ventricular size, the choices “hypertrophy,” “dilation,” and “hypertrophy and dilation” can be grouped in a more general category: “abnormal (enlarged).”

3.4.2.2 Quantitative Endpoints

The exam allows the quantitative evaluation of

- the septal wall thickness (in mm), the posterior wall thickness (in mm), the internal end-systolic and end-diastolic diameter of the left ventricle (in mm), and the diameter of the aortic root (in mm),
- the left ventricular end-systolic and end-diastolic volumes (in mL), and the left ventricular function (ejection fraction in %) *via* both the Simpson Biplane method using the cardiologists’ segmentations and the HeartEF algorithm developed by DESKi,
- the diameter of the inferior vena cava (in mm).

3.4.3 Duration Endpoint

Acquisition time (in minutes) required to obtain the acquisitions of the 10 reference views for the novices.

3.5 Sample Size Justification

The main hypothesis for the sample size calculation is based on the sequential testing of the four primary endpoints (the left ventricular size, the left ventricular function, the size of the right ventricle, and the presence of non-trivial pericardial effusion) with the performance goal of 80% (each lower 2-sided 95% CI limit for each parameter should be greater than 80%).

As the study design is like the pivotal trial, conducted by a US team, which led to FDA certification of our competitor software to assist novices in performing cardiac ultrasound acquisitions, we based our sample size calculation on the sample size calculation of the pivotal trial. This pivotal trial included 240 patients and 8 different operators. Each operator performed the acquisitions on 30 patients.

The elements for the sample size calculation of the pivotal study are described below:

- the pivotal study was powered to detect the primary endpoint's exceeding the performance goal of 80% (alpha = 0.05, beta = 0.2),
- the statistical power was estimated using iMRMC 4.0 software developed by the FDA, which provides the 95% CI around the point estimate for a given parameter and was used for the primary endpoint analysis,
- the sample size (240 patients and 8 different operators who performed the acquisitions on 30 patients) would have a statistical power of 0.98 for each parameter or greater than 0.92 for 4 sequentially tested parameters.

4. Statistical Methodology

4.1 Definitions and Conventions

Statistical analyses will be carried out by a qualified biostatistician using SAS® software (V9.4 or later), R (CRAN), or specific software for multi-reader multi-case (MRMC) study analysis.

Qualitative variables will be described using the number of filled and missing data and, for each modality, the frequency and percentage (referring to filled data). Proportions will be estimated with their exact (binomial) 95% CIs when appropriate.

Quantitative variables will be described using the number of filled and missing data, arithmetic mean, standard deviation, median, 1st and 3rd quartiles, minimum, and maximum. Means will be further described with 95% CIs when appropriate. They can also be presented in class (*e.g.* age groups) and described in the form of categorical variables, based on quartiles and medians or known clinical thresholds.

Statistical tests will be two-sided at a level of type I error alpha set to 5%. All confidence intervals will be two-sided and presented at the 95% confidence level.

Comparisons of two or more qualitative variables are made using the $\chi 2$ test or Fisher exact test, according to the expected values under the assumption of independence. Comparison of quantitative variables according to 2 groups are made using a Student test or Mann-Whitney-Wilcoxon test (nonparametric test comparing ranks) depending on the distribution of the variable of interest. Transformations to normalize the distribution of the variable can be performed if necessary.

Correlations are made using the Pearson/Spearman correlation coefficient depending on the type of correlation.

4.2 Analysis Populations

4.2.1 Screened Population

All patients who signed an informed consent form.

4.2.2 Eligible Population

All patients from the screened population who met the eligibility criteria.

4.2.3 Full Analysis Set (FAS) Population

All patients from the eligible population with at least the exam performed by the novice. This population will be used for the analyses of primary and secondary endpoints.

NB: Only patients from the FAS population who have both exams will be used for the comparison of primary and secondary endpoints between novices and experts.

4.2.4 Safety Analysis Set (SAF) Population

All patients from the eligible population with at least one exam performed. This population will only be used for the safety analysis.

4.2.5 Subgroups

Analyses will be performed on the following subgroups:

- Investigator center (France, US)
- Known cardiac abnormality (with, without)
- Body mass index (< 25, [25, 30[, ≥ +30)
- Exam sequence number ([1-10], [11-20], [21-30])

4.3 Handling of Missing Data

Missing data will not be replaced in the statistical analysis. The number of missing data will be specified in the analysis.

5. Analysis Plan

5.1 Patient Enrollment and Disposition

Participant enrollment and follow-up are described based on the study profile as defined in the CONSORT recommendations. A summary table and a flowchart will present for each population the number of participants at each assessment.

The following analysis will be performed:

- Number of patients in the screened population (total, and for each site).
- Number of patients in the eligible population (total, and for each site) and reasons for non-eligibility will be described for patients excluded from the eligible population.
- Number of patients in the FAS population (total, and for each site) and reasons for non-eligibility will be described for patients excluded from the FAS population.
- Number of patients in the SAF population (total, and for each site).
- Number of patients (total, and for each site) who have the exam performed by:
    - a novice and the 5 reviews,
    - an expert and the 5 reviews,
    - both novice and expert and the 5 reviews.

The number and percentage of patients who withdrew from the study and the reasons for withdrawal will be presented overall and by site. The time between inclusion and withdrawal (in days) will also be presented.

5.2 Demographics and Anthropometric Characteristics

All demographics and anthropometric characteristics will be performed on the FAS population and according to the site. A comparison of demographics and anthropometric characteristics between sites will be performed.

Quantitative analyses will be performed on the following variables:

- Age (in years),
- Height (in cm),
- Weight (in kg),
- BMI (in kg/m^2).

Qualitative analyses will be performed on the following variables:

- Sex with the following categories:
  - Male
  - Female
  - Other
- BMI with the following categories:
  - BMI < 25 kg/m²
  - 25 ≤ BMI < 30 kg/m² (overweight)
  - BMI ≥ 30 kg/m² (obese)
- Ethnicity with the following categories:
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Unknown / Not Reported
- Race with the following categories:
  - White
  - Black / African American
  - Asian
  - American Indian / Alaska Native
  - Unknown / Not Reported
  - Other

5.3 Medical History

On the FAS population, the following qualitative analyses will be performed:

- Indications, classified in the following categories: respiratory pathology, pulmonary hypertension, pericardial effusion, cardiotoxic drugs, endocarditis, hypertrophic cardiomyopathy, rhythm disorders, valvulopathy, dilated cardiomyopathy, cardiovascular risks/symptoms, valve prosthesis/valvuloplasty, ischemic heart disease, heart transplant follow up, other, not reported,
- Prior cardiac diagnoses,
- Prior non-cardiac diagnoses,
- Implemented medical devices,
- Cardiac abnormalities.

Other prior cardiac diagnoses, other prior non-cardiac diagnoses, other implemented medical devices, and other cardiac abnormalities will be described in listings (and translated into English when required).

See section 2.1 to see the categories for each variable.

5.4 Primary and Secondary Endpoints Analyses

5.4.1 Primary Endpoints Analysis

The analyses will be performed on the FAS population.

For the 4 primary endpoints, the number and percentage of achievement of qualitative visual assessment according to cardiologist review (at least 3 of 5 cardiologists answer “yes”, that is to say, the majority) and its 95% CI will be evaluated for the novice and the expert. The 95% CI will be computed *via* an MRMC analysis.

For comparison, the difference between the percentage of success for the novices’ exams and the percentage of success for the experts’ exams will be computed, in patients from the FAS population who have exams performed by both novices and experts.

In secondary analyses of primary endpoints, the same analysis will be performed on each subgroup (investigator center, known cardiac abnormality, body mass index, and exam sequence number), depending on the number of patients in each subgroup.

5.4.2 Secondary Endpoints Analysis

The analyses will be performed on the FAS population.

5.4.2.1 Quality Endpoints Analysis

For the quality endpoints (enumerated in section 3.4.1), the number and percentage of achievement of qualitative visual assessment according to cardiologist review (at least 3 of 5 cardiologists answer “yes”, that is to say, the majority) and its 95% CI will be evaluated for the novice and the expert. The 95% CI will be computed *via* an MRMC analysis.

For comparison, the difference between the percentage of success for the novices’ exams and the percentage of success for the experts’ exams will be computed, in patients from the FAS population who have exams performed by both novices and experts.

In secondary analyses of quality endpoints, the same analysis will be performed on each subgroup (investigator center, known cardiac abnormality, body mass index, and exam sequence number), depending on the number of patients in each subgroup.

5.4.2.2 Clinical Qualitative Endpoints Analysis

For clinical qualitative endpoints, at least 3 of 5 cardiologists had to answer the endpoint. The value chosen by most cardiologists who answer the endpoint on the experts’ exam will be considered as the reference value. Similarly, the value chosen by most cardiologists who answer the endpoint on the novices’ exam will be considered as the tested value. For both exams, it is possible not to have a majority assessment among cardiologists, as only 4 cardiologists may answer the question.

For each clinical qualitative endpoint, the number of patients for whom both the reference and tested values are the same and are different will be computed. These figures will be presented in a confusion matrix similar to Table 1 (the categories will change according to the endpoint, see categories according to the endpoint in section 3.4.2.1). The percentage of the overall agreement will be calculated for each qualitative endpoint as the corresponding confidence interval.

		Experts' exams				% Overall Agreement and C.I.
		Normal or borderline	Reduced	No majority assessment among cardiologists	Total	
Novices' exams	Normal or borderline					-
	Reduced					-
	No majority assessment among cardiologists					-
	Total					

Table 1: Confusion matrix to compare novices' exams to experts' exams for the endpoint "qualitative visual assessment of right ventricular function".

It is expected that not many exams will be counted in the "No majority assessment among cardiologists" category, either novice or expert exams. If this is not the case, a sensitive analysis will be conducted.

For each endpoint, the endpoint will be converted into a binary issue, answering the question "Is the structure normal?", according to the following rules:

- "yes" if the answer to the endpoint is:
  - "normal or borderline" or "structurally normal" or "normal"
  - "absent"
- "no" if the answer to the endpoint is:
  - "hypertrophy"
  - "dilation"
  - "hypertrophy and dilation"
  - "reduced (EF ≤ 50 %)" or "reduced"
  - "present"
  - "abnormal" or "structurally abnormal" or "abnormal (enlarged)"
  - "suspected device"
  - "dilated"

Then, for each endpoint, and on the exams where there is a majority assessment among cardiologists, the following figures will be computed:

- Number of true positives (TP) when both the reference and tested values are positive,
- Number of false positives (FP) when the reference value is negative and the tested value is positive,
- Number of false negatives (FN) when the reference value is positive and the tested value is negative,
- Number of true negatives (TN) when both the reference and tested values are negative.

In addition, based on these figures, the following metrics will be computed:

- Accuracy, calculated using the formula: (TP + TN) / (TP + FP + FN + TN),
- Sensitivity (= recall), calculated using the formula: TP / (TP + FN),
- Specificity, calculated using the formula: TN / (TN + FP),
- Precision, calculated using the formula: TP / (TP + FP),
- F1-score, calculated using the formula: 2 × (precision × recall) / (precision + recall).

5.4.2.3 Clinical Quantitative Endpoints Analysis

For quantitative endpoints, the average of the values obtained by at least 3 cardiologists on the experts' exams will be considered as the reference value. Similarly, the average of the values obtained by at least 3 cardiologists on the novices' exams will be considered as the tested value.

The following metrics will be computed for each endpoint:

- The number and proportion of novices' and experts' exams on which at least 3 cardiologists were able to make the quantitative assessment.
- The mean and standard deviation of the distribution of the reference and tested values.
- The mean, standard deviation, and 95% CI of the difference will be calculated between the measurements made on the acquisitions obtained by the novices and those obtained by the experts.
- The concordance of measurements will be assessed using the intraclass correlation coefficient (ICC), and its 95% CI.
- The Pearson or Spearman correlation coefficient will be computed depending on the distribution.
- Bland-Altman and correlation plots will be performed.

5.4.2.4 Duration Endpoint Analysis

A quantitative analysis will be performed for the duration endpoint.

5.5 Other Analyses

5.5.1 Intra-Observer Study

The purpose of the intra-observer study is to check the reproducibility of a review by the same cardiologist. The intra-observer study will be performed randomly on 10% of the exams from the FAS population. A balance between experts' and novices' exams and between both centers will be performed. 2 reviews of the same exam, at least 3 weeks apart, will be performed by each cardiologist. No comparisons will be made between the novices' exams and the experts' exams.

For each cardiologist and all 5 cardiologists together, the agreement rate and the intraclass correlation coefficient (ICC) with their 95% CI will be computed for qualitative (primary, quality, and clinical qualitative) and quantitative (clinical quantitative) endpoints respectively, on the 10% of exams between the first and second review.

Those comparisons will be made for each cardiologist to evaluate individually if the cardiologist makes reproducible reviews, and for all 5 cardiologists together to evaluate globally if the 5 cardiologists make reproducible reviews.

5.5.2 Inter-Observer Study

The purpose of the inter-observer study is to check the reproducibility of a review by different cardiologists. The inter-observer study will be performed twice, in the FAS population:

- on novices' exams,
- on experts' exams.

For each qualitative (primary, quality, and clinical qualitative) endpoint:

- The number and proportion of exams where at least 3, 4, and 5 cardiologists agree will be computed.
- The agreement between each pair of cardiologists will be assessed using the agreement rate, and its 95% CI.

For each quantitative (clinical quantitative) endpoint:

- The mean, standard deviation, and 95% CI of the difference between the assessments of each pair of cardiologists will be calculated.
- The concordance of measurements will be assessed using the ICC, and its 95% CI.

5.5.3 HeartEF Analysis

For each exam, the biplane left ventricular end-systolic volume, end-diastolic volume, and ejection fraction calculated from the HeartEF algorithm will be compared respectively to the average of the end-systolic volumes, end-diastolic volumes, and ejection fractions assessed by at least 3 different cardiologists on the novices' exams and experts' exams from the FAS population.

- The number and proportion of novices' and experts' exams on which HeartEF was able to make the quantitative assessment.
- The mean and standard deviation of the distribution of the left ventricle measurements on novices' and experts' exams.
- The mean, standard deviation, and 95% CI of the difference between the left ventricle assessment with HeartEF and the average of the assessments made by at least 3 cardiologists will be calculated.
- The concordance of the measurements will be assessed using the ICC and its 95% CI.
- The Pearson or Spearman correlation coefficient will be computed depending on the distribution.
- Bland-Altman and correlation plots will be performed.

These errors will be compared to the inter-observer variabilities assessed in the study (see section 5.5.2) and the inter-observer variabilities assessed in the literature.

5.5.4 Comparison to Competitors

The performance of HeartFocus software will be compared to the ones of our competitors. The purpose of this analysis is to check whether our results are similar to theirs.

This comparison will be performed in the clinical report. It will summarize and explain the results, taking into account the results of the different studies.

5.6 Safety Analyses

All safety analyses will be performed using the safety analysis set.

A listing will be provided for

- all adverse events,
- all device deficiencies,
- all serious adverse events.

A separate listing will be provided for

- events leading to study discontinuation,
- events leading to death.

5.6.1 Adverse Events

Adverse events will be summarized in terms (number and proportion) of

- expectation,
- severity,
- relationship to the exam,
- taken action,
- outcome.

Among these AEs, the number and proportion of AEs due to DDs will be computed. In addition, the number and proportion of SAEs among these AEs will be computed.

5.6.2 Device Deficiencies

Device deficiencies will be summarized (number and proportion) in terms of causes and taken actions. In addition, the number and proportion of DDs that lead to SAEs will be computed.

5.6.3 Serious Adverse Events

Serious adverse events will be summarized in terms (number and proportion) of

- expectation,
- severity,
- relationship to the procedure,
- relationship to the device,
- taken action,
- outcome.

5.7 Sequence of Planned Analyses

The analyses will be performed when all patients of both the French and the USA sites have their ultrasound exams (performed by novices, experts, or both), the latter being reviewed by all 5 cardiologists.