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Statistical Analysis Plan

Protocol ID: **IGT_IGD_ICE Registry Study_2019_10745 Version 2.0**

Protocol Title: **ICE-Guided Cardiac Interventional Percutaneous Procedures**

Project: **The Philips ICE Registry**

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ADE	Adverse Device Effect
ANOVA	Analysis of Variance
ASD	Atrial Septal Defect
CFR	Code of Federal Regulation
CRF	Case Report Form
CRO	Contract Research Organization
DDE	Direct Data Entry
DICOM	Digital Imaging and Communications in Medicine
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
ICE	Intracardiac echocardiography
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISO	International Organization for Standardization
PACS	Picture Archiving and Communication System
PFO	Patent Foramen Ovale
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
TAVR	Transcatheter Aortic Valve Replacement
TEE	Transesophageal Echocardiography
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VSD	Ventricular Septal Defect

2 INTRODUCTION

Philips Image Guided Therapy Devices has recently developed and received FDA clearance for an intracardiac echocardiography (ICE) catheter (VeriSight/ VeriSight Pro, henceforth referred to as VeriSight in this plan) that has 2D and/or 3D imaging capabilities. These catheters are for use with Philips EPIQ series ultrasound system. VeriSight is intended (indication for use, IFU) for intracardiac and intra-luminal visualization of cardiac and great vessel anatomy and physiology as well as visualization of other devices in the heart. The catheter is intended for imaging guidance only, not treatment delivery, during cardiac interventional percutaneous procedures. A detailed description of VeriSight can be found in the products' IFU.

The current benchmark/ standard of care for image guidance in percutaneous cardiac intervention procedure is transesophageal echocardiography. The major advantage of ICE over TEE is its unique imaging from within the heart, providing shorter image distances to target anatomy or device, and higher resolution. In addition, ICE can be used under conscious sedation thus avoiding the need for esophageal intubation and eliminating the risk for esophageal trauma. Further, ICE may also reduce fluoroscopy exposure to both the patient and the operator.

3 STUDY OBJECTIVES

The overall purpose of this observational multi-center registry is to report real-world performance and safety of VeriSight ultrasound guided ICE imaging in percutaneous cardiac intervention procedures when used in standard clinical practice.

3.1 Primary Objectives

The primary objectives will include the following:

a) **Technical success** – defined by successful delivery of VeriSight to the target intracardiac position and sustained device operation during the procedure

   Successful device delivery is defined as ability of the VeriSight catheter to reach the target intracardiac anatomical position. Sustained operation of VeriSight is absence of technical complications or procedural delays/ disruption.

b) **Imaging success** – Adequate image quality as determined by the investigator using a Likert scale assessment.

c) **Clinical success** - Adequacy of VeriSight imaging for visualization of major cardiac structures, and guiding procedural intervention, and ability to detect/ assess intra-procedural complications.

Clinical success will be measured by ability of VeriSight to adequately guide procedural intervention using the following parameters:

i. number of great vessels imaged, number of chambers imaged, including angle of views, axis, and modality
ii. assessment of key cardiac structures and sizing relevant anatomy
iii. verification of delivery and/or placement of interventional device (e.g. transeptal puncture devices, closure devices, Left Atrial Appendage Occlusion (LAAO), Patent Foramen Ovale (PFO), Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), valves (e.g for TAVR), clip devices (e.g. MitraClip), annuloplasty devices (e.g. Cardioband), ablation devices (e.g cryoballoon, RF ablation catheter), leads (leads extraction), etc.)
iv. assessment of procedural related complication (e.g. cardiac tamponade, pericardial effusion, thrombus) will be documented for each patient based on the procedure type.

d) **Safety** - Device related adverse events periprocedural through discharge or 48 hours post-procedure, whichever is earlier.

3.2 Secondary Objectives

Secondary objectives will include the following:

a) Procedural characterization when using VeriSight measured by

v. type of procedure utilizing ICE imaging
vi. total procedural room time (door-in to door-out, mins), total procedure time (skin to skin, mins)
vii. total fluoroscopy time (mins)
viii. total contrast volume used (cc), fluoroscopic dosage (mGy)
ix. ability to image from the right side of the heart for a left sided intervention
x. TEE usage rate and avoidance of TEE procedure
xi. Other imaging modality used during the procedure
xii. Change in management from use of VeriSight – need for high risk patient and/or procedure management
xiii. Duration and type of anesthesia
xiv. Freedom from general anesthesia

b) Device characterization when using VeriSight based on a scoring scale for the physical attributes of the VeriSight catheter

c) Physician survey regarding the Philips ICE using a five-point ordinal Likert-type rating scale

d) Staff survey regarding the Philips ICE using a five-point ordinal Likert-type rating scale

4 INVESTIGATION PLAN

4.1 Overall Study Design

This is a prospective, multi-center, observational, single-arm registry intended to gather real-world data to report VeriSight ICE catheter performance and safety. It will be conducted in the United States under the approval of one or more recognized institutional review boards and in compliance with GCP guidelines defined in ISO:14155, the Declaration of Helsinki, and all applicable federal and local laws and regulations. Only on label uses of the VeriSight ICE catheter will be allowed. No specific claims are being validated during this registry, though data analyzed from this registry are intended to inform future claims regarding the performance and safety of the VeriSight catheter.

Enrolled subjects will be imaged with VeriSight for various types of percutaneous cardiac interventional procedures. Enrolled subjects will be followed until discharge or ≤48 hrs post-procedure. The registry has a planned duration of approximately 24-36 months with interim analysis planned at 100 subjects to conduct safety and performance analysis for data submission toward CE mark application. Therefore, the initial analysis (n=100) may be limited in scope and it is anticipated that enrollment will continue beyond 100 patients. Statistical hypotheses are not intended for this registry and descriptive analysis will be conducted.

Data from all clinical sites are intended to be pooled for analysis. It is possible that sub-analyses may be conducted to demonstrate VeriSight guidance for target intervention types in structural heart and electrophysiology procedures (see section 8.9 for examples).

4.2 Discussion of Study Design

Please refer to section 4.1

4.3 Selection of Study Population

All subjects age 18 and older that are scheduled for and will undergo a planned cardiac interventional percutaneous procedure in which the guidance of ICE is indicated, eligible and willing to sign an informed consent form without meeting any of the exclusion criteria set and

meeting all the inclusion criteria set forth in the protocol will be included in the population for analyses. Those who sign consent but do not undergo a cardiac procedure utilizing the Philips ICE catheter will be excluded from the analyses (screen failures).

4.4 Treatments

This is a single-arm registry study, so there are no treatments groups

4.4.1 Treatment Groups

This is not applicable for the single arm observational study.

4.4.2 Randomization

This is not applicable for the single arm observational study.

4.5 Control to Minimize Bias

The following measures will be taken to minimize and/or avoid bias in this registry:

a) A multi-center observational registry design is used to help ensure a representative sample of physicians performing the procedure and to provide a reasonable enrollment period.

b) Sites will have the ability to represent all-comers in various percutaneous cardiac intervention procedures.

c) Subjects will be screened to confirm study eligibility with defined inclusion/exclusion criteria prior to inclusion. Sites are required to maintain a log of all subjects screened and enrolled for the study.

d) Data collection requirements and study procedures will be standardized across all sites. All sites will follow the same version of the protocol and eCRFs.

e) Collection and archiving of image data will be managed adequately to reduce the impact of data loss and error in analysis.

f) Standardized protocol training will be developed and distributed to all participating sites to ensure data of uniform quality are obtained from all subjects

g) Regular monitoring will be conducted to verify source data and adherence to the protocol

5 EFFICACY AND SAFETY VARIABLES

The overall purpose of this observational multi-center registry is to report real-world performance (efficacy) and safety of VeriSight ultrasound guided ICE imaging in percutaneous cardiac intervention procedures when used in standard clinical practice.

5.1 Efficacy and Safety Measurements

See Sections 5.3 below.

5.2 Appropriateness of Measurements

Please refer to section 5.3 and 5.4 below .....

5.3 Efficacy Variables

5.3.1 Primary Efficacy Variables

a) **Technical success** – defined by successful delivery of VeriSight to the target intracardiac position and sustained device operation during the procedure

   Successful device delivery is defined as ability of the VeriSight catheter to reach the target intracardiac anatomical position. Sustained operation of VeriSight is absence of technical complications or procedural delays/ disruption.

b) **Imaging success** – Adequate image quality as determined by the investigator using a Likert scale assessment.

c) **Clinical success** - Adequacy of VeriSight imaging for visualization of major cardiac structures, and guiding procedural intervention, and ability to detect/ assess intra-procedural complications. Clinical success will be measured by ability of VeriSight to adequately guide procedural intervention using the 4 parameters listed below:

   - number of great vessels imaged, number of chambers imaged, including angle of views, axis, and modality
   - assessment of key cardiac structures and sizing relevant anatomy
   - verification of delivery and/or placement of interventional device (e.g. trans septal puncture devices, closure devices (LAAO, PFO, ASD, VSD), valves (e.g for TAVR), clip devices (e.g. mitral clip), annuloplasty devices (e.g. Cardioband), ablation devices (e.g cryoballoon, RF ablation catheter), leads (leads extraction), etc.)

- assessment of procedural related complication (e.g. cardiac tamponade, pericardial effusion, thrombus) will be documented for each patient based on the procedure type.

5.3.2 Secondary Efficacy Variables

Secondary analyses will include the following:

a) Procedural characterization when using VeriSight measured by
   i. type of procedure utilizing ICE imaging
   ii. total procedural room time (door-in to door-out, mins), total procedure time (skin to skin, mins)
   iii. total fluoroscopy time (mins)
   iv. total contrast volume used (cc), fluoroscopic dosage (mGy)
   v. ability to image from the right side of the heart for a left sided intervention
   vi. TEE usage rate and avoidance of TEE procedure
   vii. Other imaging modality used during the procedure
   viii. Change in management from use of VeriSight – need for high risk patient and/or procedure management
   ix. Duration and type of anesthesia
   x. Freedom from general anesthesia

b) Device characterization when using VeriSight based on a scoring scale for the physical attributes of the VeriSight catheter

c) Physician survey regarding the Philips ICE using a five-point ordinal Likert-type rating scale

d) Staff survey regarding the Philips ICE using a five-point ordinal Likert-type rating scale

5.4 Safety Variables

Device related adverse events periprocedural through discharge or 48 hours post-procedure, whichever is earlier.

6 ENDPOINT DEFINITION

The statistical endpoint is a registry trial outcome value that is measured for each subject, for example subject is a success for binary endpoint.

The four key endpoints are:

1. Binary end points are yes/no type of measurements.
2. Categorical endpoints are categorized measurements such as race, gender. Typical summary measures are frequencies and percentages.
3. Continuous endpoints are measured on a numerical scale such as age in years and heights in inches. Typical summary measures are N, mean, median, standard deviation.
4. Time to event endpoints.

7 DATA QUALITY ASSURANCE

Each site, both clinical and laboratory (if applicable), should have SOPs for quality management that describe:

- How data will be evaluated for compliance with the protocol, ethical standards, regulatory compliance, and accuracy in relation to source documents.
- The documents to be reviewed (e.g., CRFs, clinic notes, questionnaires, audio or video recordings), who is responsible, and the frequency for reviews.
- Who will be responsible for addressing QA issues (e.g., correcting procedures that are not in compliance with protocol) and QC issues (e.g., correcting errors in data entry).
- Staff training methods and how such training will be tracked.
- If applicable, calibration exercises conducted prior to and during the study to train examiners and maintain acceptable intra- and inter-examiner agreement.

Regular monitoring and an independent audit, if conducted, must be performed according to International Conference on Harmonisation-Good Clinical Practice (ICH GCP).

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

8 STATISTICAL METHODS

8.1 Sample Size

A sample size of up to 200 subjects who are scheduled to undergo cardiac interventional percutaneous procedures are planned for the ICE registry and is considered adequate.

No formal statistical hypothesis test is to be performed and the primary and secondary endpoints will also be summarized by descriptive statistics only.

8.2 General Consideration

No formal statistical hypothesis tests are planned. The primarily all data are to be summarized using descriptive statistics only.

The categorical data will be summarized by frequencies and associated percentages. The continuous data will be summarized by appropriates descriptive statistics such as mean, median, mode, standard deviation, and appropriate percentiles.

The response categories, particularly Physician and Staff Survey data, in Likert scales have a rank order, but the intervals between values cannot be presumed equal. Therefore, the mean (and standard deviation) is inappropriate for ordinal data. So, this type of data will be summarized by Percentiles, such as median, proportions, and mode. Display the distribution of data observations in a bar chart.

The exact (Clopper-Pearson) two-sided 95% confidence interval for each of the 3 primary parameters, namely technical success, imaging success, and clinical success will be reported.

The Clopper-Pearson exact method is chosen since it uses exact binomial distribution to provide at least 95% confidence level for the interval for proportions (p) of the three primary efficacy parameters.

8.2.1 Analysis Population

Since registry study is an observational study, no per protocol nor intent-to-treat population analyses is to be performed.

8.2.2 Handling of Dropouts or Missing Data

Since this is an observational study, only descriptive statistics are reported, and therefore impact of missing data will not be evaluated.

8.2.3 Efficacy Subset

No subset of efficacy data summarization is planned. Consequently, subset analyses will not be performed.

8.3 Patient Disposition

Enrolled subjects will be followed until discharge or ≤48 hrs post-procedure. A subject is considered to have completed and exited the registry if he or she has completed all phases of the study including the last visit or the last scheduled procedure.

A protocol deviation is defined as an event where the clinical Investigator or site personnel deviate from the registry protocol or study procedures.

8.4 Demographics and Baseline Characteristics

The categorical data will be summarized by frequencies and associated percentages. The continuous data will be summarized by appropriates descriptive statistics such as mean, median, mode, standard deviation, and appropriate percentiles.

8.5 Compliance

This study will be monitored using a risk-based monitoring approach, consistent with the FDA guidance Oversight of Clinical Investigations.

8.6 Concomitant Therapy

Not applicable

8.7 Efficacy Analysis

The categorical data will be summarized by frequencies and associated percentages. The continuous data will be summarized by appropriates descriptive statistics such as mean, median, mode, standard deviation, and appropriate percentiles.

8.7.1 Primary Efficacy Analysis

The exact (Clopper-Pearson) two-sided 95% confidence interval for each of the 3 primary parameters, namely technical success, imaging success, and clinical success will be reported.

The Clopper-Pearson exact method is chosen since it uses exact binomial distribution to provide at least 95% confidence level for the interval for proportions (p) of the three primary efficacy parameters.

8.7.2 Secondary Efficacy Analysis

The categorical data such as race, gender, age categorized as old vs young will be summarized by frequencies and associated percentages. The continuous data will be summarized by appropriates descriptive statistics such as mean, median, mode, standard deviation, and appropriate percentiles.

8.7.3 Supplementary Efficacy Analysis

Refer to Section 8.2 above for the details on assessment for Physician and Staff survey data.

8.8 Safety Analysis

Due to the nature of this observational real-world registry, a safety oversight/data safety monitoring committee is unnecessary and not planned.

Summary of Adverse Events will consist of reporting Total Number of Events, Subjects with at Least One AE, Subjects with at Least One SAE, Subjects with at Least One UADE, Subjects with at Least one Procedure or Study device related, and Subjects with at Least One ongoing AE.

Incidence of AE with Relationship to study intervention will be summarized by frequencies associated percentages.

8.9 Subgroup Analysis

Subgroup analyses reporting of descriptive statistics for demographic, safety and efficacy parameters as requested may be performed for the procedure types obtained from the registry.

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8.10 Adjustment for Covariates

Not applicable.

8.11 Multiple Comparison and Multiplicity

Not applicable

9 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

9.1 Changes in the Conduct of the Study

None

9.2 Changes in the Planned Analysis

None

10 REFERENCES

All statistical analyses will be performed using the SAS® software version 9.4

11 FIGURES

Appropriate histogram or bar charts will be reported.

12 TABLES

Statistical summary of analyses will be reported as by appropriate tables which will be provided as a separate document.

13 INDIVIDUAL SUBJECT DATA LISTINGS

Data listing supporting statistical tables will be generated.

Document Revision History

Version	Date	Author	Description of Change	Reason for Change
1.0	02SEP2022	Bob Patel	N/A	Initial release

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Document Approval History

Approved by	Role / Function	Signature & Date
Bob BabaBhai Patel	Project Statistician (SAP author)	Bababhai Patel *Electronically signed by: Bababhai Patel* *Reason: "I Approve"* *Date: Sep 2, 2022 19:40 EDT*
Rashmi Ram, PhD	Project Manager or Business Leader	Rashmi Ram *Electronically signed by: Rashmi Ram* *Reason: "I Approve"* *Date: Sep 2, 2022 17:50 MDT*
Janice Ambers	Clinical Study Manager or Clinical Operations Lead	 *Electronically signed by: Janice Ambers* *Reason: "I Approve"* *Date: Sep 2, 2022 12:18 PDT*
Kevin Najarian	Director of Biostatistics	Kevin Najarian *Electronically signed by: Kevin Najarian* *Reason: "I Approve"* *Date: Sep 2, 2022 15:25 EDT*
Sheri Halverson	Associate Director of Clinical Operations	Sheri L. Halverson *Electronically signed by: Sheri Halverson* *Reason: "I Approve"* *Date: Sep 2, 2022 19:57 CDT*

ICE VeriSight Registry SAP

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