CLINICAL INVESTIGATION PLAN (CIP)

CIP Number:	TP.102.17.22.PAR
ClinicalTrials.gov ID:	NCT05757427
Title of CIP:	An open-label, single site, pilot clinical investigation to assess the detectability and sizing of invasive breast cancers, the detectability of benign breast lesions, as well as the differentiation between malignant and benign breast lesions using the Wavelia#2 Microwave Breast Imaging system
Clinical Investigation Sponsor/Funder:	MVG Industries SAS, 13 Rue du Zéphyr, Parc d'Activités de l'Océane, 91140 Villejust, FRANCE

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
3D	3 dimensional
AAL	Anterior Axillary Line
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
BIRADS	Breast Imaging Reporting and Database System
BP line	line perpendicular to the Anterior Axillary Line and passing from the nipple of the breast
CI	Confidence Interval
CIP	Clinical Investigation Plan
C-N line	line connecting the midpoint of the clavicle (C) and the nipple of the breast (N)
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computerized Tomography
DICOM	Digital Imaging and Communications in Medicine
EC	Ethical Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FiH	First in Human
FPI	First Patient In
GCP	Good Clinical Practice

GDPR	General Data Protection Regulations
GP	General Practitioner
HPRA	Health Products Regulatory Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICNIRP	International Commission on Non-Ionizing Radiation Protection
ID	Identifier
IDC	Invasive Ductal Carcinoma
IEC	Independent Ethical Committee and International Electrotechnical Commission
ILC	Invasive Lobular Carcinoma
IRB	Institutional Review Board
ISO	International Organization for Standardization
IVDR	In Vitro Diagnostic Regulation
LPLV	Last Patient Last Visit
MWBI	Microwave Breast Imaging
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulation
MRI	Magnetic Resonance Imaging
MVG	Microwave Vision Group Industries
NB	Naïve Bayesian
NCA	National Competent Authority
OBCD	Optical Breast Contour Detection

PDF	Portable Document Format
PI	Principal Investigator
PIL	Patient Information Leaflet
REC	Research Ethics Committee
RF	Radio-Frequency
RMF	Risk Management File
ROI	Region-Of-Interest
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAR	Specific Absorption Rate
SAS	Statistical Analysis System
SOP	Standard Operating Procedure
TL	Transition Liquid
TMF	Trial Master File
UAT	User Acceptance Testing
USADE	Unanticipated Serious Adverse Device Effect
VBD	Volumetric Breast Density
VDG	Volpara Density Grade
VDM	Volumetric Density Measurement

SYNOPSIS

Short Title of Clinical Investigation	An open-label, single site, pilot clinical investigation to assess the detectability and sizing of invasive breast cancers, the detectability of benign breast lesions, as well as the differentiation between malignant and benign breast lesions using the Wavelia#2 Microwave Breast Imaging system
Name of sponsor/company	MVG Industries SAS, 13 Rue du Zéphyr, Parc d'Activités de l'Océane, 91140 Villejust, FRANCE
Stage of development	Stage 2 – Preliminary Technical/Analytical Performance in accordance with the Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software (MDCG 2020-1).
Clinical Investigation Design/population	The study is designed as a single arm two-stage adaptive trial following Simon's two-stage design. Female patients who present to the symptomatic clinics with a breast abnormality will be reviewed for suitability and assessed for participation.
Study Objectives	The objectives of the clinical investigation are to assess the detectability and sizing of invasive breast cancers, the detectability of benign breast lesions, as well as the differentiation between malignant and benign breast lesions using the Wavelia#2 Microwave Breast Imaging System.
Key inclusion and exclusion criteria	**Inclusion Criteria** Female subjects attending the symptomatic breast units **with an investigator assessed discrete breast abnormality of size >1cm** who: • Have provided personal explicit written informed consent prior to any study related procedures. • Are 18 years or older. • Are able and willing to comply with the requirements of this study protocol.

	• Have investigator confirmed intact breast skin (i.e., without bleeding lesion, no evidence of inflammation, oedema and/or erythema of the breast). • Subjects whose breast size is adapted to the cylindrical container of the MWBI system. **Exclusion Criteria** To be eligible for inclusion in this study the subjects must **NOT** meet any of the following criteria: Female subjects who: • Have a cup size of A or whose breast is deemed too small to allow MWBI assessment in the opinion of the investigator. • Are pregnant or breast-feeding. • Have had surgery on either breast within the past 12 months. • Have any aesthetic breast implant. • Have any active or metallic implant (e.g., cardiac pacemaker, stents, internal cardiac defibrillator, cardiac resynchronisation device, nerve stimulator, etc.), or subjects bearing any non-removable metallic object (e.g., piercing) on their torso. • Have significant co-morbidities or medical conditions which, in the opinion of the investigator, may cause unacceptable risk to the patient or compromise the integrity of the data. • Would be unsuitable for an MWBI scan or unlikely to follow the protocol in the opinion of the Investigator.
Study Endpoints	Primary Endpoints - Detectability rate – defined as the percentage of breast lesions (benign or malignant) that were detected by the Wavelia#2 Microwave Breast Imaging System - Discrimination between malignant and benign breast lesions

	Secondary Endpoints - Correct sizing of invasive breast cancers - Discrimination among different cancer types
Number of subjects scanned	73

1 INTRODUCTION

1.1 Rationale for the Clinical Investigation

Microwave breast imaging (MWBI) has been investigated as a novel modality for the detection of breast disease, offering a non-ionising, non-compressive approach [1] and as a potential diagnostic management strategy in the monitoring of neoadjuvant chemotherapy [2]. Despite extensive efforts to harness the potential of this modality, spanning 40 years, a pertinent clinical application for this modality has yet to be identified [3,4]

To date, a total of ten (10) MWBI system prototypes have been employed in human subject tests, to investigate the clinical utility of MWBI [3,5,6]. While some studies to date have been too small to determine clinical efficacy, larger-scale trials have been conducted with three (3) state-of-the-art MWBI system prototypes, with favourable preliminary results [7-9]. Despite encouraging clinical results being reported, several recurrent limitations, detailed in Table 1 remain unresolved across most studies, likely hindering the translation of this modality to the clinical setting.

Table 1: Current unresolved limitations of the MWBI technology

A non-negligible false positive rate.
The challenges of managing a wide range of breast sizes with the same MWBI system.
The automated and repeatable/consistent detection of breast pathologies of various types in breasts of various levels of density.
Factor analysis (breast density, breast size, age, cancer size, histological subtype and stage) in the absence of consistent datasets from larger-scale MWBI clinical trials
The identification of clinical cases where the addition of MWBI would be a useful clinical adjunct to detect or characterise breast pathology.
The detectability of small, non-palpable, breast pathologies.
The achievable accuracy of lesion localization in the breast has not been quantified with MWBI by any group.
The standardization of the patient positioning and scan process.

The above listed challenges justify further clinical research with alternative MWBI systems, such as Wavelia.

In the First-in-Human (FiH) study, conducted in 25 patients, the Wavelia#1 prototype system demonstrated the ability to detect and discriminate between palpable breast lumps, the imaging procedure had no safety issues and patients reported a favourable experience of the MWBI scan. The promising findings from this study, which provided initial data to support a valid clinical association in accordance with Stage 1 of the Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software (MDCG 2020-1), have warranted the preparation of further clinical investigations with an upgraded prototype version of the Wavelia system (Wavelia#2).

The clinical data that will be collected in this 2nd study with Wavelia is intended to build upon the outcomes of the First in Human (FiH) study (TN.32.1.17. SATF), as reported in [10], as well as further address the current limitations of the state-of-the-art MWBI technology applied to clinical trials by now, as listed in Table 1 above.

Considering the notable number of technical adaptations of the Wavelia MWBI system, a **multi-stage adaptive design will be implemented in this clinical study**, allowing to first assess the technical performance of the upgraded Wavelia#2 MWBI prototype on a small patient dataset.

Rationale / Specification for the Technical Go/No-Go

In the case of a technical No-Go at the end of Stage 1 of the study, modification/correction of the Wavelia#2 prototype will be assessed by MVG, to be followed by a repeat of Stage 1 and requiring a second technical Go/No-Go evaluation, before proceeding to Stage 2. The following aspects will be required:

- Any action required to address technical modification(s) must be performed by the MVG engineering team, directly at the clinical investigation site (i.e. without need to transfer the prototype back to the MVG factory in France).

- A maximal duration of 1 month of pause of the study, for the technical intervention to be implemented and tested, will be considered.

- A maximum of two Technical Go/No-Go assessments can be performed.

If any of the above criteria are **not met** at initial MVG and clinical investigator assessment, it will be considered as requiring a study termination by MVG.

If all of the above criteria **are met** the proposed modifications/corrections to be made to the device will be specified and justified by MVG in an amendment to be submitted to the HPRA for review and approval prior to implementation.

Lesion detectability assessment for the Technical Go/No-Go evaluation

Given the early phase of development of Wavelia and the lack of standardization of the lesion detection process, in the context of the technical go/no-go evaluation, the detectability of the dominant discrete lesion from a given MWBI scan dataset will be qualitatively assessed.

A review by independent radiologists who are not engaged in the study will be implemented as part of the final data analysis.

The potential benefit of the device is to avoid exposing the patient to ionizing radiation. Having both MWBI and standard of care reference images may benefit subjects by improving identification of suspicious findings. A benefit, however, cannot be guaranteed.

2 CLINICAL INVESTIGATION OBJECTIVES

Primary study objectives:

- **Primary Objective #1:** Assess the detectability rate of malignant and benign breast lesions. This analysis can be completed per cancer type if sufficient data is available.
- **Primary Objective #2:** Assess the potential for differentiation between malignant and benign breast lesions, using Wavelia MWBI.

Secondary study objectives:

- **Secondary Objective #1:** Assess the lesion sizing for patients who have undergone surgery post MWBI scan and for whom post-surgery histology data is available.
- **Secondary Objective #2:** Assess the potential for differentiation between ILC and IDC cancer types, or other cancer types (if sufficient data is available) using Wavelia MWBI.

Exploratory Objective: evaluate the Wavelia MWBI breast lesion detectability rate (either malignant or benign) on patients with no biopsy clip, marking the lesion position in the breast.

Safety objective: provide further data to support the establishment of the safety profile of the investigational medical imaging device and associated procedures.

3 DESIGN OF THE CLINICAL INVESTIGATION

This second clinical investigation of the Wavelia MWBI modality, is intended to progress to Stage 2 of MDCG 2020-1 in an adaptive manner.

The adaptive method for clinical investigation design is described below.

- **Step #1: Preliminary Technical Performance Assessment / Interim Data Analysis**

Clinical data collection on an initial 30 patients with a dominant discrete lesion attributed to aggregates 1 and 2 for verification and approval of the technical evolutions that have been integrated in the Wavelia#2 prototype with a decision on a Technical Go/No-Go. Offline MWBI data processing will be performed by MVG, to form the images and extract the features for clinical analysis with access to reference clinical data provided, per patient case. In the case of a technical No-Go after an initial 30 patients a maximum of one additional technical assessment will be conducted in a second 30 patients.

  - No-Go - Pilot #1 paused: Prototype adaptation followed by a second and final technical re-evaluation will be performed as described above.

  - Go - Continue clinical data collection.

- **Step #2: Build up on the clinical findings of the FiH study**

If the technical status of the Wavelia#2 device is verified, continue to gather clinical data from an additional 32 patients for a clinical and technical assessment of Wavelia# 2, to build upon the findings of the FiH clinical investigation.

Offline MWBI data processing will be performed by MVG, to form the images and extract the features for clinical analysis with access to reference clinical data provided, per patient case.

The sample sizes have been formally computed, based on Simon's 2-stage adaptive study design.

- **Final Data Analysis**

The final data analysis will include all patients who have received an MWBI scan for the safety analysis. The full clinical and technical analysis will be performed on all patients who have been scanned with the technically validated MWBI to build upon the findings of the previous, FiH, study of Wavelia. The patient groups and clinical features of interest will be determined by the clinical and technical team based on the clinical and technical assessments of the datasets from all patients.

Ongoing data reviews are planned to be performed with the clinical and radiology site investigators **for every 15 patients,** all along the study.

A schematic description of the adaptive study design is provided in the Figure 1 below:

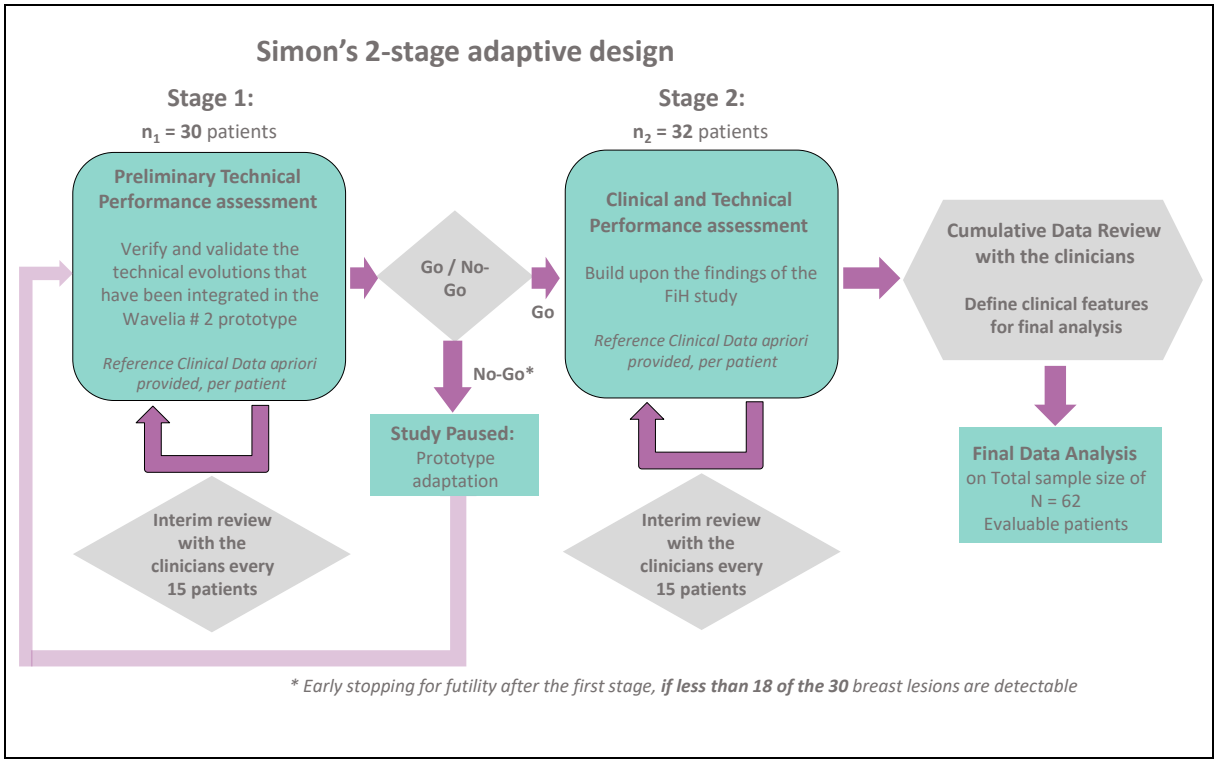

Figure 1: Schematic description of the adaptative study design

4 SELECTION OF STUDY POPULATION

4.1 Overall Description of Trial Subjects

Patients will be approached for inclusion in this clinical investigation from a single site University Hospital Galway. The study will be introduced to patients presenting to the symptomatic breast unit with a breast abnormality.

5 CLINICAL INVESTIGATION PROCEDURES

All patients with an investigator assessed discrete breast abnormality of size >1cm and who are called to attend the symptomatic breast unit for assessment as per standard of care protocol will be considered for participation in this clinical investigation.

Consenting Process:

Potentially suitable patients, presenting with a discrete breast abnormality at the symptomatic breast unit will be invited to discuss the study and any study procedures in detail. The Patient Information leaflet will also be provided to the patient.

After having sufficient time to read and understand all information provided, patients who confirm interest in participation and are willing to participate will be asked to provide written informed consent by the research nurse prior to any study activities taking place.

If eligibility is confirmed the patient will be enrolled into the study and will be scheduled for an MWBI scan either before or after standard of care assessments (See Table 2 and Table 3).

Table 2: Schedule of events for patients having MWBI on the day of presentation to the symptomatic breast unit

Procedures	**[†]Visit 1**	**[∞]Telephone Safety Assessment**	**[α]On-Site Safety Follow-up Visit**	**[§]End of Study FU Visit**
Written informed consent	**X**			
Demographics	**X**			
Medical History	**X**			
Targeted Physical examination	**X**			
Confirmation of Inclusion/Exclusion Criteria	**X**			
Urine Pregnancy Test (prior to MWBI procedure, on day of MWBI scan)	**X**[+]			
Enrolment	**X**			
Microwave Breast Investigation including patient breast marking procedure, as defined in Appendix A (OBCD scan and MWBI scan)	**X**			
Patient Experience Questionnaire	**X**			
Adverse Event Review	**X**	[∞]**X**	[α]**X**	**X**

Procedures	**†Visit 1**	**∞Telephone Safety Assessment**	**αOn-Site Safety Follow-up Visit**	**§End of Study FU Visit**
On-Site Safety Clinical Breast / Skin Assessment		**∞X**	**αX**	
End of Study Follow-up Patient Clinical Breast / Skin Assessment				**§X**

Adverse Event Review will only occur once the patient is consented

† On the day of presentation to symptomatic breast unit assessment clinic

+ Urine Pregnancy test to be conducted on the day of the MWBI scan, prior to the scan procedure (if patient is of childbearing potential)

∞ 24 to 72 hours post MWBI Telephone Safety Assessment – Breast Skin Questionnaire and Adverse Event check

α On-Site Safety Follow-up Visit will be performed as soon as possible **only** for patients who report breast/skin abnormalities or adverse events at the Telephone Safety Assessment

§ Up to 21 days post MWBI, or before surgery, whichever occurs first.

Table 3: Schedule of events for patients having MWBI AFTER standard of care assessments

Procedures	**†Visit 1**	**‡Visit 2**	**±Telephone Safety Assessment**	**αOn-Site Safety Follow-up Visit**	**§End of Study FU Visit**
Written informed consent	**X**				
Demographics	**X**				
Medical History	**X**	**X**			
Targeted Physical examination	**X**	**X**			
Confirmation of Inclusion/Exclusion Criteria	**X**	**X**			

Procedures	**†Visit 1**	**‡Visit 2**	**±Telephone Safety Assessment**	**αOn-Site Safety Follow-up Visit**	**§End of Study FU Visit**
Urine Pregnancy Test (prior to MWBI procedure, on day of MWBI scan)		**X+**			
Enrolment		**X**			
Microwave Breast Investigation including patient breast marking procedure, as defined in Appendix A (OBCD scan and MWBI scan)		**X**			
Patient Experience Questionnaire		**X**			
Adverse Event Review		**X**	**∞X**	**αX**	**X**
On-Site Safety Clinical Breast / Skin Assessment			**∞X**	**αX**	
End of Study Follow-up Patient Clinical Breast / Skin Assessment					**§X**

Adverse Event Review will only occur once the patient is consented.

† On the day the patient receives their biopsy results or at a subsequent scheduled visit before treatment

+ Urine Pregnancy test to be conducted on the day of the MWBI scan, prior to scan procedure (if patient is of childbearing potential)

‡ ≥14 days (not including day of biopsy) post biopsy and ≤ 12 weeks post standard of care reference imaging

∞ 24 to 72 hours post MWBI Telephone Safety Assessment – Breast Skin Questionnaire and Adverse Event check

α On Site Safety Follow-up Visit will be performed as soon as possible **only** for patients who report breast/skin abnormalities or adverse events at the Telephone Safety Assessment

§ Up to 21 days post MWBI, or before surgery, whichever occurs first.

Standard of Care Data/Reference Imaging:

In this clinical investigation, the MWBI scan will not be used for patient diagnosis and will be conducted in addition to standard of care assessments. Standard of care assessments performed

by the physician, as per normal practice in the symptomatic breast unit of University Hospital Galway include:

- Conventional medical history
- Clinical assessment, breast examinations and standard of care reference imaging (e.g. Mammogram and / or Ultrasound/and or MRI/and/or CT scan)
- Biopsy (if applicable)

The written radiology reports from standard of care reference imaging, as well as the core biopsy reports if applicable, will be acquired and used to evaluate the performance of the MWBI subsystem in terms of detecting and estimating size and consistency of the discrete breast abnormality.

Relevant data from Multi-Disciplinary Team (MDT) meetings in relation to the therapeutic strategy for the patient and if surgery is planned will be obtained.

In the case of patients who are scheduled for surgery, key reference data from their post-surgery histology report and post-surgery MDT meeting will also be collected for the evaluation of the MWBI imaging results in relation to the estimated tumour size.

6 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS, DEVICE DEFICIENCIES

Adverse Event Review will only occur once the patient is consented and continues until the End of Study Follow Up Visit. The End of Study Follow-up Visit will occur up to 21 days post MWBI or prior to surgery, whichever happens first.

6.1 Definitions

The following definitions have been sourced from the International Standard for Clinical investigation of medical devices for human subjects - Good clinical practice, ISO 14155:2020(E), with the exception of 6.1.9 the definition for ‘reportable device deficiency’ which is sourced from the Medical device Coordination Group (MDCG) guidance document MDCG 2020-10/1 Rev 1 ‘Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745’, Oct 2022.

6.1.1 Adverse Event (AE)

Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

6.1.2 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from **use error** or from intentional misuse of the investigational medical device.

Use Error

User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user. Use error includes the inability of the user to complete a task. Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment. Users might be aware or unaware that a use error has occurred. An unexpected physiological response of the patient is not by itself considered a use error. A malfunction of a medical device that causes an unexpected result is not considered a use error.

6.1.3 Serious Adverse Event (SAE)

Adverse events that led to any of the following:

- Death
- serious deterioration in health of the subject, users, or other persons as defined by one or more of the following:
    - a life-threatening* illness or injury, or
    - a permanent impairment of a body structure or a body function including chronic diseases, or

- in-patient hospitalization** or prolongation of existing hospitalization, or
- medical or surgical intervention to prevent life threatening illness or injury, or permanent impairment to a body structure or a body function,

- foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment.

* Life-threatening refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Planned hospitalization for a pre-existing condition, or a procedure required by the CIP without serious deterioration in health, is not considered a serious adverse event.

6.1.4 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

6.1.5 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment.

6.1.6 Anticipated Serious Adverse Device Effect (ASADE)

An Anticipated Serious Adverse Device Effect is defined as an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

6.1.7 Serious Health Threat

Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

6.1.8 Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. This definition includes device deficiencies related to the investigational medical device or the comparator.

A device malfunction is defined as the failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB.

6.1.9 Reportable Device Deficiency (as per MDCG 2020-10/1)

A Device Deficiency is considered a reportable event if it might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

6.2 Eliciting Adverse Events

Comprehensive assessments of any adverse event experienced by the subject will be performed throughout the course of the study from the time of subject's signature of informed consent. Study site personnel will report any adverse event, whether observed by the Investigator or reported by the subject.

Data on adverse events will be obtained at scheduled or unscheduled study visits, based on information spontaneously provided by the subject and/or through non leading questioning of the subject.

6.3 Evaluation of Adverse Events/Adverse Device Effects

The investigator or delegate will report all AE's/SAE's/ADE's/SADE's/device deficiencies to the sponsor as outlined in **Section 6.4**.

All safety reporting must be carried out in compliance with the current version of the Medical Device Coordination Group (MDCG) guidance document 'Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745'and the International Standard for Clinical investigation of medical devices for human subjects - Good clinical practice, ISO 14155:2020(E).

Assessment of Seriousness

The investigator or appropriately qualified member of the site team should assess the seriousness of an event as per the SAE definition in the CIP.

6.3.1 Assessment of Severity

The investigator will assess the severity for each AE, ADE, SAE and SADE and record this on the CRF according to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe or medically important: An event that prevents normal everyday activities.

Life threatening: An event that has life-threatening consequences.

Note: the term 'severe', should not be confused with 'serious' which is a regulatory definition based on subject/event outcome or action criteria.

6.3.2 Assessment of Causality

All AEs will be evaluated by both the investigator and the sponsor to determine the causal relationship to the investigational medical device or procedures.

The relationship between the use of the medical device (including the associated medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

During causality assessment activity, clinical judgement shall be used and the relevant documents containing the foreseeable serious adverse events and the potential risks are listed such as the Investigator's Brochure, the Clinical Investigation Plan or the Risk Management File shall be consulted. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality:

(1) Not related (2) Possible (3) Probable (4) Causal relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational device, the comparator or the investigation procedure.

Not related: relationship to the device or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
- the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

Possible: The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

Probable: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

Causal relationship: the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures; the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Any AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possible, probable or causal relationship) to the investigational medical device or procedures will be classified as an ADE/SADE.

6.3.3 Assessment of Expectedness

A list of all foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation, or treatment, have been included in the Risk Management File, after the completion of the Risk Analysis of the investigational medical imaging device.

An expectedness assessment will be carried out by the Sponsor for each SADE according to the current versions of the risk management file.

6.3.4 Exemptions from Safety Reporting

The following event would be commonly experienced in this cohort of participants and is therefore exempt from safety reporting:

i. Admission to hospital for surgery to the affected breast as part of their standard of care treatment

However, if any additional seriousness criteria are met during this hospitalisation, they are subject to SAE reporting.

6.4 Recording of Adverse Events in the CRF

The investigator or delegate will record every Adverse Event (AE), Adverse Device Effect (ADE), Serious Adverse Event (SAE), Serious Adverse Device Effect (SADE) or observed device deficiency (DD) and report it to the sponsor together with an assessment. All AEs, ADEs, SAEs, SADEs and DDs will be reported to the Sponsor as per the timelines in **Section 6.5** of the CIP.

As the quality and precision of acquired AE data are critical, Investigators must use the adverse event definitions provided in **Section 6.1** of the CIP.

- Whenever possible, recognised medical terms should be used to describe AEs (for example, 'influenza' rather than 'flu'), and abbreviations should be avoided.

- AEs should be described using a specific clinical diagnosis, if this is available, rather than a list of component signs or symptoms (for example, 'congestive heart failure' rather than 'dyspnoea, rales and cyanosis.')

- Signs and symptoms that are not linked (as "co-manifestations") to an identified disease or syndrome, or for which an overall diagnosis is not available, should be reported as individual AEs in separate CRF AE page(s).

- Provisional diagnosis (e.g., "suspected Myocardial Infarction") are acceptable but should be followed up to a definite diagnosis, if finally available.

6.5 Study Specific Reporting Procedure

6.5.1 Reporting by the investigator to the Sponsor

All AEs, ADEs and device deficiencies (that do not meet the definition of reportable device deficiencies) should be reported to the sponsor in a timely manner.

In compliance with the current version of the Medical device Coordination Group (MDCG) guidance document 'Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745' and the ISO guidelines 14155:2020(E) all SAEs, SADEs and device deficiencies that meet the criteria of a reportable event will be fully recorded and reported to

the Sponsor by the investigator immediately but no later than 3 calendar days after investigational site personnel's awareness of the event.

Site personnel are considered aware of an adverse event/DD from the time of first notification of the first member of the investigator site team, as per the site delegation log. All SAE's/SADE's and reportable device deficiencies will be submitted by site by completing the required fields on the AE/device deficiency CRF. A valid report must include all of the following:

- Adverse event/device deficiency term (based on what is known at time of reporting)
- Seriousness criteria (SAE form only)
- Date of procedure/first use of investigational device
- Date of event onset
- Severity assessment (SAE form only)
- Causality assessment (SAE form only)
- Investigator signature

The immediate report will be followed by detailed, written reports. The immediate and follow up reports will identify participants by unique code numbers.

All SAE/reportable DD information must be recorded on a SAE/reportable DD form submitted to sponsor. Additional information received for an event (follow-up or corrections to the original event) should be detailed and submitted to the sponsor in an expedited manner and within 3 days of site awareness of additional information. The Site Investigator or delegate will follow AEs reported during participation in the trial until resolved, considered stable or completion of participation in the Clinical Investigation. Follow up information will be sought and submitted as it becomes available. All SAEs should be followed up until resolution or they are clearly determined to be due to a participants stable or chronic condition or intercurrent illness(es).

If the eCRF is unavailable, a paper copy of the eCRF SAE/DD reporting form and supporting documentation (if applicable) should be completed and submitted to saereport@universityofgalway.ie within the required timelines for the event. Events submitted to the Sponsor in this manner should be entered in the eCRF as soon as it becomes available.

6.5.2 Reporting to the National Competent Authority and Ethics Committee

The sponsor will be responsible for the classification of the adverse events, after reviewing the principal investigator's assessment.

The Sponsor (or delegate) is responsible for the submission of reportable events to the NCA and Ethics Committee. The summary reporting form as provided in the current version of the

MDCG guideline 'Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745', shall be filled in/updated for each reportable event. This will be submitted to the NCA and EC each time a new reportable event or new findings/updates in relation to already reported events are reported to the Sponsor (or delegate).

Timelines for reporting to the NCA

The sponsor must adhere to the following timelines in the submission of reportable events to the NCA:

The sponsor (or delegate) must report to all NCAs where the clinical investigation is authorised to start:

- For all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it should be reported to the NCA **immediately, but not later than 2 calendar days** after awareness by sponsor of a new reportable event or of new information in relation to an already reported event. This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals.

- Any other reportable events or a new finding/update to it should be reported to the NCA **immediately, but not later than 7 calendar days** following the date of awareness by the sponsor of the new reportable event or of new information in relation to an already reported event.

Timelines for reporting to the EC

The sponsor (or delegate) must report to the EC where the clinical investigation is authorised to start:

- For all reportable events, as soon as possible after first becoming aware of them.

The sponsor (or delegate) will submit upon request a safety report to the NCA.

The sponsor (or delegate) will submit annual safety reports to the EC, if required.

6.6 Data Safety Monitoring Board (DSMB) Procedure

A DSMB will not be utilised for this Clinical Investigation.

7 STUDY ADMINISTRATION

7.1 Informed Consent Process

Before a subject can participate in the study, he or she must give explicit written informed consent. The informed consent process will be in accordance with ICH GCP, the Declaration of Helsinki and local regulatory requirements. Informed Consent Forms must be signed and personally dated by the subject and the research nurse who conducted the informed consent discussion.

Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed, signed and dated by the subject, and by the site team member who administered the informed consent process. A copy of the informed consent form will be given to the subject. The informed consent process will be clearly documented in the participant notes as per the requirements of ICH-GCP, ISO 14155 and MDR. No participant will be enrolled without signing the informed consent.

Any new information or protocol amendment that substantially alters the scientific validity of the study or affects the subjects' rights, safety, welfare, or their willingness to continue participation in the study, will result in the re-consenting of currently active patients on an updated and approved (as required by local law and regulation) patient information sheet and consent form.

7.2 Regulatory Authority and Ethical Approval

Before the study is initiated at a site, the Sponsor (or its delegate) will obtain approval to conduct the study from the appropriate regulatory authority in accordance with any applicable country-specific regulatory requirements.

The sponsor will submit and obtain approval from the above parties for substantial amendments to the original approved documents.

Before initiation of the study at a given centre, written approval of the protocol, Informed Consent Form and any information presented to potential subjects must be obtained from the appropriate Institutional Review Board or Independent Ethics Committee. If any amendments to any of these documents occur during the study, notification or written approval, as appropriate, must be obtained prior to their implementation.

Where required by local regulations, the Sponsor (or its delegate) is responsible for ensuring IRB/IEC approval of the study.

7.3 Study Organisation

7.3.1 Data Management

The sponsor or designee is responsible for the data management of this study including assurance of data integrity.

The Investigator or designee will be responsible for the study data in the electronic CRF provided by the Sponsor. It is the Investigator's responsibility to ensure the accuracy of the data entered in the CRFs. Prior to the start of the study, the Investigator will complete a delegation log which will record the signature and initials of all persons in charge of eCRF completion. Each person involved in eCRF completion, review, correction and/or validation will be trained and then will have an individual login and access code to the eCRF. An eCRF user guide will be available for investigators/on-site personnel involved in eCRF completion including the CRA who is reviewing the eCRF data as well as vigilance officers and the medical monitor(s). All data must be electronically submitted and signed by the responsible investigator or one of his/her authorized staff members.

The data will be entered into a validated EDC system compliant with the 21CFR part 11 and ICH-GCP guidelines. Only authorised personnel will have access to the EDC system. For each enrolled participant, an eCRF record will be maintained. eCRFs must be kept current to reflect participant status at each phase during the course of the investigation. The EDC system will keep track of all user actions via an audit trail functionality. The configuration of EDC and any study-specific implementation will be subject to internal User Acceptance Testing (UAT) before go-live for data entry.

eCRF entries must be completed by appropriately trained site staff only. A log of trained and authorised staff able to complete the eCRF will be maintained by data management.

The data and imaging material obtained in this study will be pseudonymized. Participants will be identified by a unique, EDC-generated patient ID. Any clinical report or medical image will be de-identified by the Investigator before submission onto participant's electronic record. The subject identification log, linking the identifiers to the participant's name, will be kept in the site's regulatory binder. This log will allow proper monitoring of the clinical records and by the appointed monitors in order to assure completeness, accuracy and correctness of the data collected at site.

During trial conduct, data will be reviewed to verify the completeness, consistency, plausibility and relevance of the data in accordance with the approved Data Validation Plan. In the event

that inconsistent data is captured, queries may be issued electronically to the site and answered electronically by that site personnel.

Database lock will occur once quality assurance procedures have been completed. The database will not be locked before all data clarifications have been resolved and monitored and the decision on subject evaluation has been completed. PDF files of the electronic CRFs will be sent to the Investigator at the completion of the study. Further details of the data management procedures will be included in the approved Data Management Plan.

7.3.2 Study Monitoring

Participating sites will be monitored to ensure compliance with the trial protocol, adherence to applicable regulations, accuracy of trial data and to ensure the safety and well-being of the subjects is preserved.

The Investigator must ensure that CRFs are completed in a timely manner and must allow a Sponsor representative (CRA or study monitor) periodic access to CRFs, subject records and all study-related materials. Trial data submitted will be reviewed against subject charts and other sources containing original records of subject data. Source document verification will occur as detailed in the Monitoring Plan.

The monitoring requirements for this this trial are detailed in the current version of the Monitoring Plan. The frequency of monitoring visits will be determined on a risk based approach taking into consideration factors such as the design of the study, the frequency of subject visits and the site enrollment rate. In order to verify that the study is conducted in accordance with ICH GCP, regulatory requirements, and the study protocol and that the data are authentic, accurate and complete, the study monitor will review CRFs and other study documents and will conduct source data verification.

On-site monitoring visits will be conducted in accordance with the clinical investigation Monitoring Plan. On-site monitoring will be an ongoing activity from the time of initiation until clinical investigation close-out and will comply with the principles of GCP, ISO 14155 and MDR. The frequency and type of monitoring will be detailed in the Monitoring Plan and agreed by the trial Sponsor.

Before the clinical investigation commences a Site initiation visit will take place to ensure that all relevant essential documents and supplies are in place and that site staff are fully aware of the clinical investigation protocol and procedures. On site monitoring visits during the clinical investigation will check the consenting procedures, completeness of patient records, the accuracy of entries in the CRFs, the adherence to the protocol, procedures and GCP, and the

progress of patient recruitment. Monitoring will also ensure that the investigational device and Transition Liquid is being stored and maintained according to specifications.

Monitoring activities will be documented in a monitoring report and will include a summary of items the monitor reviewed and observations regarding the completion of previous action items, significant findings, facts, deviations, conclusions, and recommended actions to be taken to secure compliance.

The Principal Investigator will ensure that access to all investigation related documents including source documents (to confirm their consistency with CRF entries) are available during monitoring visits.

Upon study completion, the Sponsor CRA or monitor will conduct a Site Closeout visit as outlined in the Monitoring Plan. This will involve collection of any outstanding documentation and resolution of all outstanding issues.

7.3.3 Subject Confidentiality

All information and data sent to parties involved in trial conduct concerning subjects or their participation in this trial will be considered confidential. The Investigator and the CRA (monitor) representing the Sponsor must ensure that the subjects' anonymity is maintained. All participant identifiers must be redacted from all documentation prior to submission to the Sponsor. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

All documents will be stored safely in a confidential and secure environment. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification number/code.

The data will be stored in encrypted software only accessible to those directly involved in the study. Subjects will be identified by a study specific subject number and/or code in the database. The name and any other identifying detail will not be included in any study data electronic file.

The Investigator will keep a separate log of subjects' identification numbers, names, addresses, telephone numbers and hospital numbers (if applicable). Documents which will not be submitted to the Sponsor, such as signed Informed Consent Forms, should be maintained in strict confidence by the Investigator.

The study will comply with the Data Protection Act and the General Data Protection Regulations (GDPR).

7.3.4 Direct Access to Source Data/Study Documentation

The agreement with the Principal Investigator will include permission for investigation related monitoring, audits and regulatory inspections, by providing direct access to source data and investigation related documentation. Consent from patients for direct access to data by sponsor or sponsor representatives, auditors and regulatory inspectors will also be obtained. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Source documents for this study may include hospital records e.g. procedure reports, imaging reports and data collection forms. These documents may be used to enter data on the case report form (CRF).

7.3.5 Quality Assurance

In compliance with ICH GCP and regulatory requirements, the Sponsor, a third party acting on behalf of the Sponsor, regulatory agencies or IRB/IECs may conduct quality assurance audits at any time during or following a study. The Investigator must agree to allow auditors and regulatory inspectors direct access to all study-related documents including source documents and must agree to allocate his or her time and the time of his or her study staff to the auditors in order to discuss findings and issues.

In addition to the monitoring activities noted in 7.3.2, a quality management plan will be implemented by MVG which will include the establishment of metrics to be reported and reviewed at regular teleconferences with the Study Coordination team throughout the study e.g. protocol and device issues, adverse events, monitoring findings, deviations from protocol and agreed study procedures to ensure any remedial action is taken in a timely fashion and to ensure appropriate reporting in accordance with regulated requirements.

7.3.6 Retention of Essential Study Documents

The sponsor and principal investigator shall maintain the clinical investigation documents. They shall take measures to prevent accidental or premature destruction of these documents. The principal investigator or sponsor may transfer custody of records to another person/party and document the transfer at the investigation site or at the sponsor's facility.

Essential documents as defined by ICH GCP include the signed protocol and any amendment(s), copies of the completed CRFs, signed Informed Consent Forms from all subjects who consented, hospital records, diary cards and other source documents, IRB/IEC approvals and

all related correspondence including approved documents, device accountability records, study correspondence and a list of the subjects' names and addresses.

The Investigator must retain copies of the essential documents for the period specified by ICH GCP and by applicable regulatory requirements.

Essential documents will be retained for 25 years. The documents may be retained for a longer period if requested by the Sponsor.

The Investigator will inform the Sponsor of the storage location of the essential documents and must contact the Sponsor for approval before destruction of any documents related to the study. The Investigator should take measures to prevent accidental or premature destruction of these documents.

8 SUSPENSION OR PREMATURE TERMINATION OF CLINICAL INVESTIGATION

The Sponsor may temporarily or permanently discontinue the study for safety, ethical, compliance or other reasons. If this is necessary, the Sponsor will endeavour to provide advance notification to the site. If the site or study is suspended or discontinued, the Investigator will be responsible for promptly informing the IRB/IEC.

Where required by local regulations, the Sponsor (or delegate) will be responsible for informing the IRB/IEC of study or site discontinuation.

In such cases, all study data and the Investigational Device must be returned to the Sponsor.

9 FINANCING INSURANCE AND INDEMNITY

MVG holds Public Liability ('negligent harm') and Clinical Trial ('non-negligent harm') insurance policies which apply to this trial. MVG is funding this trial.

10 REFERENCES

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