	<b>Study Title</b>	An Interventional, Post-Market Study to Evaluate the Performance of a Custom-made Medical Device, "Breast Cancer Locator Guidance (BCL)" System, in Breast-conserving Surgery (BCS)		
	<b>Study ID</b>	CS-BCL-EU2021	<b>Sponsor</b>	CairnSurgical Inc.
	<b>Date</b>	25Nov2022	<b>Version</b>	1.0 Substantial Amendment 1_GERMANY

## An Interventional, Post-Market Study to Evaluate the Performance of a Custom-made Medical Device, "Breast Cancer Locator Guidance (BCL)" System, in Breast-conserving Surgery (BCS)

### CLINICAL INVESTIGATION PLAN


**Study ID:** CS-BCL-EU2021  
NCT06461663

**25 November 2022**

**CONFIDENTIAL**

**Study Sponsor:** CairnSurgical, Inc.

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## PROTOCOL APPROVAL

**SPONSOR:** CairnSurgical, Inc.

Address: 16 Cavendish Court, Lebanon NH 03766

E-Mail: info@cairnsurgical.com

Sponsor Representative:

**Name:** David Danielsen

**Role:** CEO


E-Mail: danielsen@cairnsurgical.com

**Signature:** \_\_\_\_\_

**Date:** \_\_\_\_\_

## REVISION HISTORY

REVISION	DATE	DESCRIPTION
Rev 00	18 October 2021	First submission to EC
Rev 01	25 November 2022	Substantial Amendment 1_GERMANY

	<b>Study Title</b>	An Interventional, Post-Market Study to Evaluate the Performance of a Custom-made Medical Device, "Breast Cancer Locator Guidance (BCL)" System, in Breast-conserving Surgery (BCS)		
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### INVESTIGATOR'S SIGNATURE PAGE

I have read and understood the content of the "CS-BCL-EU2021" Clinical Investigation Plan (CIP) and agree to abide by the requirements set forth in this document.

I understand that all the information retained in the Study Protocol, Case Report Form, in any other study document and all information related to the patients, are and shall be kept as confidential.

I confirm that I will conduct the study according to this protocol, the Declaration of Helsinki, Good Clinical Practice, and other applicable laws and regulations in the Country where the study is to be conducted and ensure that all study personnel are appropriately trained prior to any study activities.

I confirm that I am aware of the need to retain the study records and that no data can be destroyed without the written consent of the Sponsor.


N° site: \_\_\_\_\_

Investigator: \_\_\_\_\_

Institution: \_\_\_\_\_  
\_\_\_\_\_

Signature \_\_\_\_\_

Date \_\_\_\_\_

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## Protocol Summary of Changes

### Version 1.0 – 25 November 2022, Substantial Amendment n.1\_GERMANY

#### Rationale

All the changes to the Clinical Investigational Plan, summarized below have been made to facilitate and speed up the enrollment of patients in Germany.

For this reason, the exclusion criteria N. 15 has been modified as follow:


"Simultaneous participation in an interventional study or participation in an interventional study in the last 1 month before study inclusion, ***that, in the opinion of the Investigator, could impact patient's safety or the study endpoints***".

Therefore, if, according to the Investigator's judgment, the participation of a patient already enrolled in another study does not affect the safety of the patient nor the CS-BCL-EU2021 study endpoints, that patient can be enrolled in the CS-BCL-EU2021.

## SUMMARY OF CHANGES

(Changes by *italics* and **bold**)

### HEADER

	<b>Study Title</b>	An Interventional, Post-Market Study to Evaluate the Performance of a Custom-made Medical Device, "Breast Cancer Locator Guidance (BCL)" System, in Breast-conserving Surgery (BCS)		
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	<b>Date</b>	<del>18 Oct 2021</del> <b>25 Nov 2022</b>	<b>Version</b>	1.0 <b>Substantial Amendment</b> <b>1_GERMANY</b>

## STUDY PROTOCOL COVER PAGE


~~18 October 2021~~ **25 November 2022**

## PROTOCOL APPROVAL PAGE

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<b>Rev 01</b>	<b>25 November 2022</b>	<b>Substantial Amendment 1_GERMANY</b>

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## SYNOPSIS

### Exclusion criteria

[...]


"Simultaneous participation in an interventional study or participation in an interventional study in the last 1 month before study inclusion, ***that, in the opinion of the Investigator, could impact patient's safety or the study endpoints***".

## CIP

### Section 2.6.2 Exclusion criteria

[...]


"Simultaneous participation in an interventional study or participation in an interventional study in the last 1 month before study inclusion, ***that, in the opinion of the Investigator, could impact patient's safety or the study endpoints***".

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### PROTOCOL SYNOPSIS


<b>Study Title:</b>	An Interventional, Post-Market Study to Evaluate the Performance of a Custom-made Medical Device, "Breast Cancer Locator Guidance (BCL)" System, in Breast-conserving Surgery (BCS).		
<b>Study Sites:</b>	Subjects will be enrolled at up to 3 centers. For the information regarding the participant sites and the Principal Investigators, please refer to the separate specific document.		
<b>Countries:</b>	Germany, Italy, Switzerland.		
<b>Study Design:</b>	This interventional, post-market, multicenter clinical investigation is designed to evaluate the performance of a custom-made medical device, "the Breast Cancer Locator (BCL) in Subjects with non-palpable breast cancer, in Europe.		
<b>Study Period:</b>	Date of first enrolled patient (FPI): Q1 2022 Date of last completed patient (LPO): Q3 2022 Total study duration: approximatively 9 months.		
<b>Enrollment Period:</b>	4-5 months.		
<b>Investigational Product (IP):</b>	<b>Description:</b>	<p>The Breast Cancer Locator (BCL) is a custom-made medical device developed by CairnSurgical Inc.</p> <p>BCL is a patient-specific surgical guide designed to reduce positive margins during breast cancer tumor removal. The BCL is created using an additive manufacturing (3D printing) process involving a digital model that is derived from the subject's supine magnetic resonance imaging (MRI) data. The BCL is constructed from a biocompatible, semi translucent, UV-cured, photopolymer resin material using the stereolithography (SLA) additive manufacturing process.</p> <p>The BCL provides information regarding tumor size, shape, and margin boundary to assist surgeons in the excision of cancer and preserves normal breast tissue.</p>	
	<b>Intended use:</b>	The BCL System is intended to be used to guide the surgeon when performing partial mastectomy for breast cancer and to minimize positive margins.	
	<b>Procedure:</b>	Investigators will be provided with a three dimensional (3D) image of the cancer in the breast which allows them to visualize the closest distance from the tumor to the skin and the chest wall and quantifies those distances. Investigators will also use a BCL, which is a patient specific, plastic, bra-like form that is transiently placed on the breast prior to surgery and allows the Investigator to mark the projected edges of the tumor on the breast skin and to place bracketing wires inside	

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		the breast which define the center of the cancer and distances 1 cm from the tumor edges defined by pre-operative supine MRI.
<b>Background and Rationale:</b>	<p>Breast cancer (BC) is the most commonly diagnosed cancer and leading cause of cancer-related death among women. Breast cancer screening programs and improved imaging techniques have contributed to an increased incidence of early-diagnosed (non-palpable) invasive breast cancer (IBC) or ductal carcinoma in situ (DCIS).</p> <p>Breast conserving surgery (BCS), also known as lumpectomy or partial mastectomy, can be considered the gold standard of early stage invasive breast cancer treatment. The primary aims of BCS are 1) to resect the tumor with a surrounding margin of tissue free of cancer cells and 2) to minimize the volume of tissue removed, thereby preserving the overall shape and appearance of the breast. Consequently, BCS results in better physical and psychological well-being when compared to mastectomy procedure. One of the challenges of BCS in non-palpable breast cancer is precise localization of the tumor. The standard method for localization of non-palpable breast lesions is wire-guided localization (WGL) which consists of ultrasound or mammography assisted introduction of the guide wire allowing accurate location of the tumor. Despite the safety and cost-effectiveness of WGL, several complications have been reported included vasovagal reactions, cutting, moving, or loss of the wire, and patient discomfort. Furthermore, WGL may result in excessive removal of breast tissue (therefore, inferior cosmetic outcomes) and high positive margin rates leading to re-operation or an increased risk of local recurrence.</p> <p>CairnSurgical has developed the Breast Cancer Locator (BCL) System. Within the BCL procedure, a supine MRI image is first performed with the breast positioned in its surgical position providing precise detail on the size, shape, depth, edges and 1 centimeter margin for the tumor. These data are then used to analyze the tumor and construct a three-dimensional (3D) tumor model that serves as the basis for two surgical tools. The MRI is also used to manufacture the BCL, a 3D-printed bra-like plastic form that matches the breast surface and designed to guide the surgeon to the precise tumor boundaries and margins. The BCL is constructed pre-operatively, sterilized, packaged and shipped to the hospital of the surgeon prior to the day of the procedure.</p> <p>Dartmouth-Hitchcock Medical Center investigators have recently completed a randomized prospective clinical trial comparing supine MRI, intraoperative scanning and tracking technique to wire localization. One hundred thirty eight (138) subjects were randomly assigned in a 1:1 ratio to partial mastectomy guided by supine MRI or wire localization. The proportion of subjects with positive margins in the MRI guided surgery group was half that observed in wire localization group (9% vs. 19%, <math>p = 0.08</math>).</p>	

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	<p>CairnSurgical has tested the BCL system in a small cohort of 19 subjects. First, the BCL accurately localized the cancers. Second, all subjects had their tumors resected with negative margins. Third, no adverse events occurred.</p> <p>An ongoing multicenter clinical trial in the United States, is investigating the safety and effectiveness of the BCL System in more than 400 subjects with non-palpable breast cancer.</p> <p>The aim of this interventional, post-market, multicenter clinical investigation is to evaluate the performance of a custom-made medical device, the BCL system, in subjects with non-palpable breast cancer. The study will be conducted in European countries.</p>
<b>Study Objectives:</b>	<p><b>Primary</b></p> <p>To evaluate the performance of the BCL in reducing the positive margin rate when the BCL system is used to guide a surgeon performing partial mastectomy.</p> <p><b>Secondary</b></p> <ul style="list-style-type: none"> <li>To calculate the specimen volume after BCL guided partial mastectomy;</li> <li>To evaluate the surgeon's perception of ease of use of the BCL system;</li> <li>To evaluate the safety and tolerability of BCL;</li> <li>To evaluate the patient's satisfaction.</li> </ul>
<b>Study Endpoints:</b>	<p><b>Primary</b></p> <p>To evaluate the performance of BCL in reducing the positive margin rate, the proportion of patients with positive margins after partial mastectomy with the BCL will be obtained (results will be available within 14 days from the day of sample arrival at the pathological lab).</p> <p><b>Secondary</b></p> <ul style="list-style-type: none"> <li>To calculate the specimen volume after BCL guided partial mastectomy, the water displacement method (WDM) will be used (results will be obtained within the same day of surgery).</li> <li>To evaluate the surgeon's perception of ease of use of the BCL system, a 5 Likert scale will be used at V2;</li> <li>To evaluate the safety and tolerability of BCL through physical examination and AEs assessment including the relationship of the AE to the BCL system at V1, V2, V3, V4;</li> <li>To evaluate the patient's satisfaction, the BREAST-Q will be used at EOS/V4.</li> </ul>
<b>Study Procedures:</b>	This is an interventional, post-market, multicenter clinical investigation aimed to

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	<p>enroll patients who require the tumor to be localized in order for the surgeon to perform BCS. The investigation will be useful to collect Investigational Product (IP)' performance/safety evidence in Europe.</p> <p>Each Subject, after signing the Informed Consent Form (ICF), will enter into a screening phase (V0) during which several assessments (e.g., demographics, medical history, evaluation of available prone MRI and core biopsy pathological results) will be conducted. Blood samples will be collected at V0.</p> <p>At visit 1 (V1), the Subject will undergo supine MRI (10-40 days prior to surgery), from which the 3D breast image and BCL will be made. At visit 2 (V2) the patient will undergo BCS using the BCL system.</p> <p>Soon after surgery and prior discharge, potential AEs will be assessed. On the same day, the specimen volume will be determined. The excised specimen will be sent to the pathological lab for analysis. The results, including the positive margin rate (PMR) and specimen mammogram, will be obtained within 14 days.</p> <p>At visit 3 (V3), follow-up assessments (including physical examination, and AEs review) will be performed. At the End Of Study (EOS/V4), AEs events will be assessed and patients will be asked to express their satisfaction with the BREAST-Q.</p>		
<b>Study Population:</b>	Adult women with a diagnosis by pre-operative biopsy of non-palpable breast cancer.		
<b>Number of subjects (planned and analysed):</b>	Planned:	35 subjects will be enrolled.	
	Sample size justification:	<p>The positive margin rate (PMR) rate with the use of BCL is expected to be &lt; 5%. If we assume a true PMR rate of 3% and applying the exact or Clopper-Pearson method for a single binomial proportion then a sample size of N=35 will achieve a confidence interval with total width of 15%.</p> <p>We will calculate an exact binomial confidence interval using the actual PMR.</p>	
	Safety Set	The "Safety Set" included all enrolled patients undergoing surgery with the BCL system.	
	Full Analysis Set (FAS)	The "Full Analysis Set" (FAS): this set included all enrolled patients undergoing surgery with the BCL system.	
	Per protocol Set (PPS)	The "Per-Protocol Set (PPS)" would include all the FAS patients who (a) met all inclusion/exclusion criteria liable to affect the performance assessment, (b) did not present serious deviations of the protocol that may affect efficacy.	
<b>Diagnosis and main criteria for inclusion:</b>	Inclusion criteria:	<ul style="list-style-type: none"> <li>• Patient Informed consent form (ICF) signed;</li> <li>• Female Aged <math>\geq 18</math> years at the time of the signature of ICF;</li> <li>• Histologic diagnosis of IBC or DCIS;</li> </ul>	


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		<ul style="list-style-type: none"> <li>• Tumor excision that will require localization because it cannot be definitively defined by palpation;</li> <li>• The tumor is unifocal; possible satellite lesions &lt; 2 cm from primary are eligible;</li> <li>• The tumor enhances and is greater than or equal to 5mm on prone breast MRI imaging;</li> <li>• Subject and surgeon agree to perform BCS;</li> <li>• Willingness to follow all study procedures, including attending all site visits, tests and examinations.</li> </ul>
	Exclusion criteria:	<ul style="list-style-type: none"> <li>• Absolute contraindication to MRI, including presence of implanted electrical device (e.g., pacemaker or neurostimulator), aneurysm clip, or metallic foreign body in or near eyes;</li> <li>• Severe claustrophobia;</li> <li>• Contraindication to use of gadolinium-based intravenous contrast, including life-threatening allergy;</li> <li>• Uncontrolled cardiac, renal, or pulmonary disease;</li> <li>• Uncontrolled systemic disease (e.g., lupus erythematosus or scleroderma);</li> <li>• Compromised renal function including chronic, severe kidney disease (GFR &lt; 30 ml/min/1.73m<sup>2</sup>), or acute kidney injury;</li> <li>• Pregnancy or breast-feeding;</li> <li>• Subjects who have received or plan to receive neoadjuvant chemotherapy;</li> <li>• Sternal notch to nipple distance of &gt; 32 cm as measured in a sitting or standing position;</li> <li>• Measurement of widest circumference around breasts and arms &gt; 135 cm;</li> <li>• Known allergy to device components;</li> <li>• Multicentric tumors (additional tumors &gt; 2 cm from primary);</li> <li>• Infectious or inflammatory processes near the area of intervention;</li> <li>• Planned surgery with localization devices including WGL, intraoperative ultrasound guidance, radiofrequency emitting implants, magnetic seeds, radioactive seeds, and tissue inspection devices;</li> </ul>

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		<ul style="list-style-type: none"> <li>• Simultaneous participation in an interventional study or participation in an interventional study in the last 1 month before study inclusion, that, in the opinion of the Investigator, could impact patient's safety or the study endpoints;</li> <li>• Known drug and/or alcohol abuse;</li> <li>• Mental incapacity that precludes adequate understanding or cooperation.</li> </ul>
<b>Safety:</b>		<p>Safety will be monitored through vital signs, physical examination, and adverse events monitoring including assessment of relationship to the IP.</p> <p>Subjects will be assessed at V1, soon after surgery and at discharge for AEs (V2).</p> <p>Subjects will undergo a physical examination and will be assessed for AEs at V3 (2 weeks post-surgery) and V4 (6 weeks post-surgery).</p>
<b>Statistical methods:</b>		<p>In general, all the variables will be descriptively analyzed by treatment groups and visit (mean, median, standard deviation, minimum and maximum for continuous variables after normality check of distribution with Kolmogorov-Smirnov test, frequency distribution for categorical variables). All the analysis will be detailed in the Statistical Analysis Plan (SAP) which will be finalized in Version 1.0 before the Data Base Lock (DBL).</p> <p>In details, the safety data will include (at least) vital signs, and adverse events will be analyzed.</p>

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## LIST OF ABBREVIATIONS AND ACRONYMS


<b>ADE</b>	Adverse Device Effect
<b>AE</b>	Adverse Event
<b>ASADE</b>	Anticipated Serious Adverse Device Effect
<b>BC</b>	Breast Cancer
<b>BCL</b>	Breast Cancer Locator
<b>BCS</b>	Breast Conserving Surgery
<b>BMI</b>	Body Mass Index
<b>BP</b>	Blood Pressure
<b>CDMS</b>	Clinical Data Management System
<b>CI</b>	Confidence Interval
<b>CIP</b>	Clinical Investigation Plan
<b>COTS</b>	Commercial Off The Shelf
<b>CRA</b>	Clinical Research Associate
<b>CRO</b>	Contract Research Organization
<b>DBL</b>	Database Lock
<b>DCIS</b>	Ductal Carcinoma In Situ
<b>EC</b>	Ethics Committee
<b>eCRF</b>	Electronic Case Report Form
<b>EDC</b>	Electronic Data Capture
<b>EOS</b>	End Of Study
<b>FAS</b>	Full Analysis Set
<b>GCP</b>	Good Clinical Practice
<b>GLP</b>	Good Laboratory Practice
<b>GMP</b>	Good Manufacturing Practice
<b>HR</b>	Heart Rate

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<b><sup>125</sup>I</b>	Iodine-125
<b>IBC</b>	Invasive Breast Cancer
<b>ICF</b>	Informed Consent Form
<b>IFU</b>	Instruction For Use
<b>IP</b>	Investigational Product
<b>IRB</b>	Institutional Review Board
<b>ISF</b>	Investigator Site File
<b>MD</b>	Medical Device
<b>MRI</b>	Magnetic Resonance Imaging
<b>OR</b>	Operating Room
<b>PMR</b>	Positive Margin Rate
<b>PPS</b>	Per Protocol Set
<b>ROLL</b>	Radio-guided Occult Lesion Localization
<b>RSL</b>	Radioactive Seed Localization
<b>SADE</b>	Serious Adverse Device Effect
<b>SAE</b>	Serious Adverse Event
<b>SAP</b>	Statistical Analysis Plan
<b>SAS</b>	Safety Analysis Set
<b>SLA</b>	Stereolithography
<b>SNB</b>	Sentinel Node Biopsy
<b>SOP</b>	Standard Operation Procedure
<b>TF</b>	Technical File
<b>US</b>	Ultrasound
<b>USADE</b>	Unanticipated Serious Adverse Device Effect
<b>USP</b>	United States Pharmacopeia
<b>UV</b>	Ultraviolet

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<b>WDM</b>	Water Displacement Method
<b>WGL</b>	Wire-guided localization (WGL)

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## 1. INTRODUCTION

### 1.1 BACKGROUND INFORMATION

#### 1.1.1 Non-palpable Breast Cancer

Breast cancer (BC) is a heterogeneous disease encompassing multiple subgroups with differing molecular signatures, prognoses, and responses to therapies [1]. BC is the most common cancer in women. In 2020, there were 2.3 million women diagnosed with BC and 685.000 deaths globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years [2]. In 2018, the predicted number of new breast cancers in 28 European Union (EU) countries was 404.920, with estimated age-adjusted annual incidence of breast cancer of 144.9/100.000 and mortality of 32.9/100.000, with 98.755 predicted deaths [3].

Breast cancers are considered palpable if they can be appreciated on physical examination by a physician. Early detection of nonpalpable tumors can only be achieved through imaging analysis [4]. The introduction of national mammographic screening programs has led to an increased number of identified nonpalpable breast lesions, and, accordingly, an increased need for preoperative localization of the lesions. The increase reflects detection of small invasive breast cancers (IBCs) and detection of ductal carcinoma in situ (DCIS), which were rarely detected before the introduction of mammographic screening owing to lack of clinical symptoms [5].


In Western countries, non-palpable DCIS comprises 15–30% of all newly diagnosed breast neoplasms [6]. DCIS is generally accepted as a nonobligate precursor of IBC. DCIS shares many of the epidemiological risk factors as invasive breast cancer (IBC) including age, family history, and some other hormonal factors and high mammographic density [7], [8]. There are several theoretical models for the development of DCIS and its progression to invasive disease, based on molecular profiling and animal studies. However, as in IBC, DCIS is not a single disease, but varies based on hormonal status, growth factor receptor status, proliferation rate, and genetic features. In particular, the interaction of all these factors with the microenvironment in the initiation of neoplasia and progression to invasive disease needs to be better elucidated [8].

To prevent progression to invasive disease, almost all DCIS lesions are treated by breast-conserving surgery (BCS) with or without adjuvant radiotherapy and/or endocrine therapy [7].

#### 1.1.2 Breast-Conserving Surgery (BCS)

The choice of breast-conserving surgery (BCS) vs mastectomy depends on the extent of the lesion, size of the breast, patient preference, and comorbidities. BCS, also called "lumpectomy," "wide local excision," "partial mastectomy", denotes the removal of a breast cancer with clear surgical margins [9].

Currently, BCS is the treatment of choice for non-palpable breast cancer. Various randomized trials have reported this approach to be safe and effective, thus determining a decrease in the adoption of mastectomy as the treatment of choice for early invasive breast cancer [10]. The goal of optimally

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performed BCS is to obtain tumor-free resection margins while maintaining the natural shape of the breast. Margins positive or focally positive for tumor cells are associated with a high risk of local recurrence, and in the case of tumor-positive margins, re-excision or even mastectomy are sometimes needed to achieve definite clear margins [11]. An important secondary goal of BCS is achievement of a satisfactory cosmetic outcome, which has received growing attention in recent years because of the close relation with patients' wellbeing and quality of life. The key factor in a poor cosmetic result after BCS is the volume of breast tissue resected; thus, surgeons should aim for complete excision of the carcinoma while sacrificing as little healthy breast tissue as possible [11].

Intraoperative localization represents one of the BCS challenges that faces every surgeon aiming to remove the mass and the adequate safety margins within one operation with no need to re-operate the patient [12].

### 1.1.3 BCS Localization Tools

Wire-guided localization (WGL) is considered the gold standard for localization of non-palpable breast lesions. This technique depends on mammographic, ultrasonic, or magnetic resonance imaging (MRI) guidance imaging to insert a wire into the lesion, enabling intraoperative localization and excision [13]. Despite the safety and cost-effectiveness of WGL, several complications have been reported such as wire dislocation, migration and even pneumothorax [14]. One of the most important disadvantages of WGL is the relatively large number of patients with positive microscopic margins detected at the final pathologic evaluation leading to re-operation [5].

These disadvantages have prompted the development and implementation of alternative approaches, such as radio-guided occult lesion localization (ROLL), ultrasound (US)-guided surgery and localization by radioactive seed localization (RSL) [13]. The ROLL technique utilizes the intralesion injected radiotracer that has already been used for the lymphatic mapping and sentinel node biopsy (SNB) to localize the primary lesion intraoperatively guided by a  $\gamma$ -probe. A disadvantage of the technique is the chance of radioactive substance flowing into the mammary tissue adjacent to the tumor.


US-guided excision uses real-time US guidance to direct the surgeon during tumor excision. One of the main problems is that US images often underestimate the size of the lesion.

The RSL technique uses the radio- activity of a seed containing  $^{125}\text{I}$  to localize the lesion. A major advantage of localization with a  $^{125}\text{I}$  seed is that this isotope has a half-life of 60 days, so, contrary to ROLL or WGL, there is no strict timing of this procedure, and it can take place weeks before surgery. A potential drawback in the use of RSL is the small chance of seed migration, causing the surgeon to perform an inadequate excision or even an excision without tumor tissue [13].

Currently, MRI of the breast has been shown to be more sensitive than ultrasound or mammography for the detection of cancer [15].

#### Supine MRI-guided BCS

Breast MRI is commonly performed in the *prone* position with the breast pendant into specialized coil arrays. This *prone* positioning minimizes breast motion due to respiration and reduces the potential interference with the beating heart. In addition, the coil coupling is improved [16]. While *prone* breast MRI is well suited for diagnosis, it is less suitable for use in combination with clinical applications such as surgery and US-guided biopsy where the patient is in supine position [16]. Sakakibara et al.

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demonstrated that *supine* MRI more accurately replicates the surgical position compared to *prone* MRI. The authors randomized patients with DCIS to undergo wire localized or *supine* MRI-guided BCS and found that the positive margin rate and resected tissue volume were lower in patients undergoing *supine* MRI-guided excision compared to conventional BCS [17]. In another study, Pallone et al., developed combined preoperative *supine* MRI and intraoperative optical scanning to define tumor size and position. This technique provided the surgeon with 3D views of tumor shape and position within the breast as it appeared during surgery. The authors demonstrated that *supine* MRI-guided BCS could define tumor size and location as accurately as palpation [15].

## 1.2 Breast Cancer Locator (BCL) System

### 1.2.1 Intended Use

As reported in the IFU, the Breast Cancer Locator (BCL) System manufactured by CairnSurgical Inc., is a custom-made medical device intended to be used to guide a surgeon when performing partial mastectomy for breast cancer and to minimize positive margins.

This BCL System should only be used by a physician trained in its indicated use.

### 1.2.2 General Description


The BCL System is a patient-matched Breast Conserving Surgery (BCS) guidance device derived from *supine* breast magnetic resonance imaging (MRI) data. The device allows the surgeon to transfer surgical cues associated with a patient's breast and breast cancer to help guide the surgeon with the tumor resection procedure.

The BCL is created using an additive manufacturing (3D printing) process involving a digital model that is derived from the Subject's *supine* MRI data.

The BCL model is constructed from a biocompatible, semi translucent, UV-cured, photopolymer resin material using the stereolithography (SLA) additive manufacturing process.

The BCL System is comprised of the following components and accessories:

- BCL Kit, including:
  - Sterile patient-specific BCL model
  - BARD® GHIATAS® Beaded Breast Localization Wires (up to 6, patient-specific sizes; sizes are limited to 5 cm, 7 cm, 9 cm, or 14 cm)
  - Medical grade permanent marking pen and ruler (Viscot Medical, LLC Sterile Reg/Fine Tip XL Prep Resistant Ink Marker)
- MR Kit, including:
  - Viscot Medical, LLC Sterile Reg/Fine Tip XL Prep Resistant Ink Marker (x1)
  - 3M™ Tegaderm™ Transparent Dressing (x3)
  - Izi Medical Products MRI fiducial markers (x5)
- MR Coil Pad Kit, including:
  - MRI Coil Cushion (pad) (x2)

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The BCL device itself doesn't contain any software. However, various software tools are used to design the BCL:

- Combination of commercial off the shelf (COTS) software and proprietary CairnSurgical software components to create digital anatomical models of the Subject's breast surface, tumor, chest wall, the BCL device model, and patient-specific reports of geometrical data to relevant to BCS.
- An optional web browser-based interactive surgical plan Visualizer will be provided. The Visualizer software displays the 3D model of the BCL, the tumor, and chest wall, with visual markers to show locations where the tumor is closest to the skin and closest to the underlying chest wall/muscle (including distances from tumor to skin and the tumor to the chest wall).

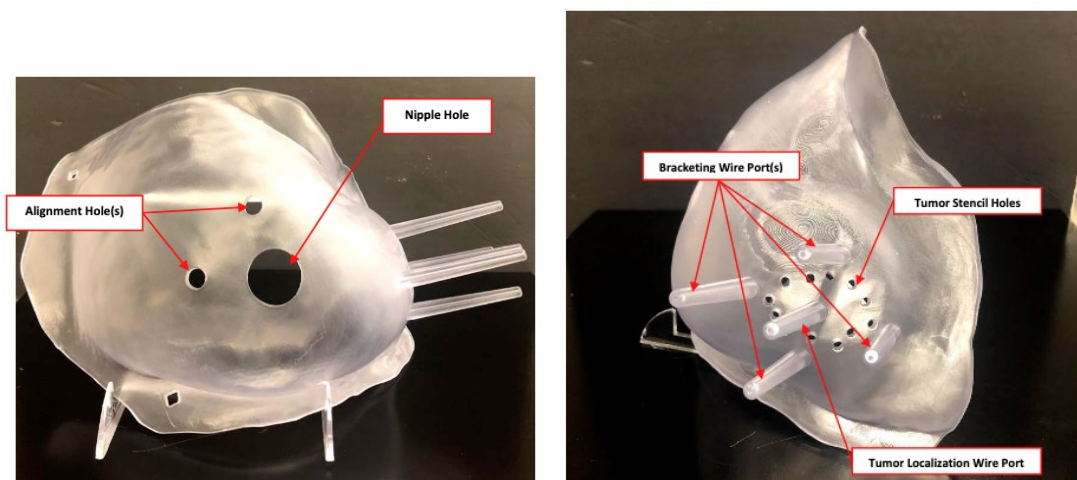
### Details of the BCL model

The BCL is manufactured using 3D printing to create a bra-like plastic form that matches the breast surface (**Figure 1**) when the Subject is in the *supine* MRI (and surgical) position.


The projected silhouette outline of the breast cancer on the breast surface at the point where the cancer is closest to the skin is built into the BCL as a stencil, so that the surgeon can apply the BCL to the Subject's breast and trace the tumor outline on the skin.

In most cases, there will be a central tumor localization port and four bracketing wire ports. However, in some cases, based on anatomical features including the location of the tumor in the breast and the distance from the breast surface to chest wall, the BCL may have 0-4 ports. In cases where the distance from the skin to the chest wall is < 2.5 cm, the BCL will not have any ports. In such cases, the surgeon would use the projected tumor edges on the breast surface, defined by the tumor stencil holes in the BCL, to guide surgery.

In cases where the tumor is close to the edge of the breast, such as near the inframammary fold, the BCL may have fewer than four bracketing wire ports.



**Figure 1. Patient-Specific BCL Model.** *Left:* front view showing key functional features including, a cut-out for the nipple and an alignment hole for intraoperative positioning. *Right:* showing key functional features, including

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stencil of the tumor extents/silhouette as viewed from the incision location, the central wire port to localize the tumor volume, and the surrounding auxiliary wire ports to bracket the surgical margins around the tumor in vivo. Pictures were taken from the IFU.

As shown in **Figure 1**, the BCL model consists of the following:

- Rigid bra-like breast shell that matches the surface of a Subject's breast in the supine position, as captured during MRI.
- Circular cutout to clear the nipple and a set of alignment holes to support device placement on the Subject's breast.
- Central needle port that allows the surgeon to deploy a localization wire that extends from the point of surgical incision (defined by the central wire port) to the distal or posterior edge of the tumor based upon the Subject's MRI and associated image data.
- Up to 4 bracketing ports that project outward from the BCL surface and allows the surgeon to deploy additional localization wires to provide landmarks for guiding the resection margin (1 cm away from MRI defined tumor edges) in multiple locations based on the Subject's MRI and associated image data. If the distance from the skin to the chest wall at a potential port site is <2.5 cm, the projected tumor edge margins on the skin surface will be sufficient to guide surgery, so the BCL will be constructed without that port for wire placement.
- Stencil of the tumor silhouette outline projected onto the breast surface along the direction of the tumor centroid to the defined incision location to allow the surgeon to mark the edges of the tumor on the breast surface, based upon the Subject's MRI and associated image data.

#### Details of the MRI kit and MRI procedure

The BCL System's MRI Procedure Kit consists of the following components packaged together. 10 MRI Procedure Kits will be packaged per box. They are for single use only.

##### Single use components:

- One (1) medical grade permanent marking pen with ruler
- Five (5) Multi-Modality Fiducial Markers, individually packaged
- Three (3) Tegaderm™ transparent dressings, individually packaged

##### Reusable components:


A separate MRI coil pad set is provided as part of the MRI Kit. The coil pads are supplied as re-usable components.

The *supine* breast MRI procedure requires the use of reusable coil support pads supplied in CairnSurgical MRI Kits and single use marking and marking protection aids. An overview of the procedure is described below:

#### 1) Scan Sequences.

The *supine* breast MRI consists of 2 key sequences:

- T1 pre-gadolinium, large field-of-view, without fat saturation: for skin surface extraction.
- T1 dynamic pre- & post-gadolinium, with fat saturation: to visualize the tumor and co-register to the surface rendering.

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2) Scanner.

The MRI may be performed on any approved 1.5T or 3T scanner and should strictly follow the guidelines in MRI Acquisition Procedure and the Supine Breast MRI protocol.

3) Data Transfer.

The MRI images should be transferred to CairnSurgical as per Data Transfer IFU. Data should also be backed up locally as per site protocols in case of transmission error/failure.

4) Visit Schedule.

The *supine* MRI should be performed after the patient's clinical *prone* MRI, and a minimum of 10 calendar days prior to surgery to allow time for the images to be processed and the BCL System to be manufactured and shipped.

5) MRI Incidental Findings.

Scans are evaluated only for surgical planning and to support BCL manufacturing. The evaluation of scans for incidental pathology is a local responsibility and should be handled according to local practice.

For the **MRI Acquisition Procedure** and the **Supine Breast MRI protocol**, please refer to IFU provided with these kits for additional information.

### Classification

According to Medical Device Regulation 2017/745, Article 2: "*custom-made* device means any device specifically made in accordance with a written prescription of any person authorised by national law by virtue of that person's professional qualifications which gives, under that person's responsibility, specific design characteristics, and is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs."


Therefore, the BCL is defined as custom-made medical device.

According to Medical Device Regulation 2017/745, Rule 6:

"All surgically invasive devices intended for transient use are classified as class IIa unless they:

- are intended specifically to control, diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with those parts of the body, in which case they are classified as class III;
- are reusable surgical instruments, in which case they are classified as class I;
- are intended specifically for use in direct contact with the heart or central circulatory system or the central nervous system, in which case they are classified as class III;
- are intended to supply energy in the form of ionising radiation in which case they are classified as class IIb;
- have a biological effect or are wholly or mainly absorbed in which case they are classified as class IIb; or
- are intended to administer medicinal products by means of a delivery system, if such administration of a medicinal product is done in a manner that is potentially hazardous taking account of the mode of application, in which case they are classified as class IIb."

Therefore, the BCL is classified as **Class IIa** medical device.

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### 1.2.3 Biocompatibility

As reported in the "Biocompatibility Test Report", the BCL is identified as follows.

*Body Contact Category:* Surface device  
*Contact type:* Breached or compromised surface  
*Contact duration:* Limited, less than 24 hours

Based on this information, the following tests were performed as part of the Biocompatibility testing at NAMSA test laboratories (Northwood, Ohio, USA 43619) using Good Laboratory Practice in accordance with FDA 21 CFR Part 58:

- Cytotoxicity Test (ISO Elution Method), in accordance with ISO 10993-5:2009;
- ISO Guinea Pig Maximization Sensitization Test, in accordance with ISO 10993-10:2010;
- ISO Intracutaneous Study in Rabbits, in accordance with ISO 10993-10:2010;
- USP Rabbit Pyrogen Study, Material Mediated, in accordance with ISO 10993-11:2017;
- ISO Acute Systemic Toxicity Study in Mice, in accordance with ISO 10993-11:2017.

Based on the test results, it is concluded that the sterilized BCL devices are: Non-Cytotoxic, Non-Irritating, Non-Sensitizing, Non-Pyrogenic, and have No signs of Systemic Toxicity.

### 1.2.4 Principles and Mode of Operation

The BCL System is a patient-matched Breast Conserving Surgery (BCS) guidance device derived from *supine* breast magnetic resonance imaging (MRI) data. The device allows the surgeon to transfer surgical cues associated with a patient's breast and breast cancer to help guide the surgeon with the tumor resection procedure. The BCL model is manufactured from a 3D printed patient specific model using biocompatible material via an additive manufacturing process. This BCL is constructed pre-operatively, sterilized, packaged, and shipped to the hospital of the surgeon Investigator prior to the day of the procedure.

The procedure consists of three main steps as described in the BCL System IFU:


#### STEP 1. PRE-SURGICAL IMAGING AND IMAGE TRANSFER

BCS is scheduled at least 10 days after the *supine* MRI. Patients undergo a contrast-enhanced *supine* MRI at their local facility using a body MRI coil, a CairnSurgical supplied MRI Pad Kit and the MRI Procedure Kit. Refer to IFU provided with these kits for additional information.

At the end of the pre-surgical imaging, the images are reviewed and transferred to CairnSurgical for manufacturing of the patient-specific BCL model. The user is involved again once the sterile packaged BCL Kit is obtained for surgery. See MRI Procedure IFU for transfer instruction.

#### STEP 2: BREAST TISSUE MARKING USING THE BCL


1. Place the patient in the supine position on the surgical table.

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2. Remove the two Tegaderm™ transparent dressings from the patient to expose the BCL model alignment markings made during MR imaging. Using a non-sterile skin prep resistant marker, reinforce these markings on the breast skin.
3. Place the patient under general anesthesia. Place the patient's arm on the side of the cancer on an arm board parallel to the table, approximately in the same position as it was during the MRI.
4. Prepare the breast surface for surgery using institutional protocol.
5. Using sterile technique, place the sterile BCL on the surface of the breast by aligning the nipple hole with the nipple and the alignment holes with the alignment markings present on the patient's skin (see an example of BCL in **Figure 1**).
6. Once the BCL model is aligned on the patient's breast, have an assistant firmly hold the BCL in place. Using the prep-resistant ink marker supplied in the kit and the tumor edge stencil holes present in the BCL model, mark the BCL-defined edges of the tumor on the breast skin through the stencil holes.
7. Place a GHIATAS® wire localization needle into the tumor using the central port. It is important that the surgeon "pops" the needle forcibly through the port and through the skin and breast tissue up to the hub of the needle. It commonly helps to employ a twisting movement to make sure that the needle hub does not recoil away from the end of the port. If it recoils away, then the tip of the wire will not be placed as deeply as planned into the breast, so repeat the needle placement. After deploying the wire, remove the needle. If no ports are present (as in the case of a patient with a very thin breast) then no wire placements are required.
8. Using the same technique, deploy additional localization wires through all bracketing wire ports to delineate 1 cm surgical margins around the MRI-derived tumor edges. At a minimum, there will always be one additional localization wire packaged with the BCL for the number of bracketed ports.
9. Trim the wires by cutting them at the top of the BCL ports.
10. Carefully remove the BCL, leaving the wires in place.
11. Connect the tumor edge markings using the supplied prep resistant marker to outline the projected edges of the tumor on the breast surface.
12. Re-prepare the breast surface for surgery per standard surgery protocols.

### STEP 3: SURGERY AND TUMOR REMOVAL

1. Perform a breast conserving tumor resection. The objective of the breast conserving resection will be to remove approximately 1 cm of breast tissue around all tumor edges. The site of the incision is at the surgeon's discretion.
  - a) Dissect down a distance 1 cm less than the distance from the skin to the tumor provided in the patient specific BCL information sheet.
  - b) Create skin flaps until the bracketing peripheral hook wires are reached, which will be located 1 cm past the tumor edges. The depth of these flaps underneath the skin will be determined by the distance from the skin to the anterior tumor edge.
    - i. If this distance is < 1 cm, make the flap just under the dermis.

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- ii. If this distance is > 1 cm, dissect down into the breast to 1 cm from the superficial tumor surface, then form the horizontal flaps.
- c) Knowing the location of the tumor center, as defined by the central hook wire, and cutting with a scalpel or cautery immediately outside of the peripheral hook wires, incise down into the breast tissue, thereby creating a specimen of breast tissue. The deep end of the specimen should be 1 cm below the deep tumor surface: knowledge of the distance from the deep tumor surface to the chest wall (as provided in the patient specific BCL Information sheet) will guide dissection of the deep specimen margin.
  - i. If the deep tumor surface is < 1 cm from the underlying muscle, then remove the fascia of the underlying muscle with the specimen.

The surgeon may also use the BCL Visualizer software to access the virtual 3D model of the breast, tumor, and the chest wall in the operating room (OR) to guide the dissection. Refer to BCL Visualizer Software Instructions for Use (IFU) for more information.

2. Remove peripheral hook wires from the specimen, if applicable.
3. Leave the central wire in place, if applicable.
4. Orient the excised specimen, mark the specimen for pathological analysis as per local institutional protocol, and send the specimen for radiography assessment per institutional protocol.
5. The specimen radiograph is used to confirm the excision of the biopsy clip and for evaluation of the surgical margins.

### 1.3 Investigational Device Packaging And Labelling


The Sponsor will be responsible for the packaging of the study products. The study product will be provided free of charge by CairnSurgical, Inc.

The study device is packaged in boxes, and it will be sent to the Investigational sites as follow:

- 1 BOX containing the BCL kit:
  - one (1) sterile BCL model;
  - up to six (6) BARD® GHIATAS® Beaded Breast Localization Wires (patient-specific sizes; sizes are limited to 5 cm, 7 cm, 9 cm, or 14 cm);
  - medical grade permanent marking pen and ruler (Viscot Medical, LLC Sterile Reg/Fine Tip XL Prep Resistant Ink Marker).

Due to the patient specific nature of the device, one additional BCL is provided should it be needed. The BCL model is for single use only. Do not reuse. Do not re-sterilize.

- 1 BOX containing the MRI Accessory Kit with ten (10) pouches, with each pouch containing:
  - one (1) medical grade permanent marking pen and ruler (Viscot Medical, LLC Sterile Reg/Fine Tip XL Prep Resistant Ink Marker)

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- three (3) 3M™ Tegaderm™ Transparent Dressing
- five (5) Izi Medical Products MRI fiducial markers

The MRI Accessory Kit is used to create the alignment reference points for the subsequent design of the BCL via MRI imaging. The marking pen, fiducial markers, and the Tegaderm™ transparent dressing are intended for single patient use.

Do not re-sterilize.

- 1 BOX containing the MRI Coil Pad with two (2) pouches, with each pouch containing:
  - MRI Coil Pad

The Coil Pad is used during MRI imaging process. Do not re-sterilize any part of the Kit.

The label on the primary and the secondary packaging respectively will contain all necessary information for the traceability of the investigational product, such as:

- patient identifier
- details identifying use, such as anatomical location
- final design iteration or version used to produce the device
- precaution that the patient should be surveyed for potential anatomical changes prior to the procedure
- batch number
- expiry date
- sponsor/manufacturer details
- storage conditions.


The label will also contain the instructions and statement that the IP is intended for clinical research only.

### **Patient-Specific Information Sheet**

Ensure the information on the patient-specific information sheet matches the Subject ID number on the BCL model, and the medical record for the patient undergoing the surgery. The patient-specific information sheet provided with this BCL System consists of the following information:

- Subject ID Number assigned by CairnSurgical. The identical Subject ID Number is printed on the physical BCL model. Ensure that the Subject ID Number on the patient-specific information sheet and BCL match.
- Closest distance from the breast skin to the tumor in millimeters (mm).
- Closest distance from the tumor to the chest wall in mm.
- Patient specific needle length (mm).
- Unique URL address to access and visualize the 3D BCL and anatomical models using CairnSurgical.
- Needle target depth for each port present on BCL.

#### **1.3.1 Product Accountability**

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Each site will be provided with MD inventory and accountability forms to maintain accurate written documentation of all products transfer processes between the Sponsor, the site, the Investigator, and the patient enrolled. The MD inventory form will be used to document when and how many MDs are delivered to the study site. Site staff has to countersign the form to confirm date of receipt and amount received.

The study product provided for this study will be used only as directed in this study protocol. The Principal Investigator (or delegates) will indicate the date of the surgical procedure and fill the information in the Subject IP Accountability Form for each patient. At the end of the clinical investigation and/or before the expiration date, any partially used/unused component must be returned to Sponsor for destruction. Dispose of used BCL System components in accordance with applicable local, state, and federal laws and regulations.

### 1.3.2 Blinding/Unblinding

Considering the design of the study a blinding/unblinding procedure is not required.

### 1.3.3 Randomization

Considering the design of the study a randomization procedure is not required.

### 1.3.4 Compliance

Considering the design of the study (i.e., the procedure will be performed by the Principal Investigator), a procedure for the evaluation of the compliance is not required.

### 1.3.5 Concomitant Pharmacological Therapies


All concomitant medications should be registered on the appropriate page in the electronic case report form (eCRF) with the dosage and the medication (active substance).

There are no contraindications to the use of any other concomitant medication during the study. Post-operative pain medications will be prescribed as per standard of care.

## 1.4 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

The introduction of national mammographic screening programs has led to an increased number of identified non-palpable breast lesions, and, accordingly, an increased need for preoperative localization of the lesions. The increase reflects detection of small invasive breast cancers (IBCs) and of ductal carcinoma in situ (DCIS), which were rarely detected before the introduction of mammographic screening owing to lack of clinical symptoms. Patients diagnosed with DCIS represent 15% to 20% of cancers detected via mammographic screening, with variations between countries [5]. These patients are often eligible for breast-conserving

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surgery (BCS) since it has been shown a disease-free survival rate equivalent to those of mastectomy, offering the advantages of cosmetic outcome preservation, a better quality of life and a decrease in psychological morbidities [18].

For non-palpable lesions, a precise preoperative localization technique for the detection of the lesions is needed. Various techniques have been used for identifying non-palpable breast tumors, but the most popular method is the wire-guided localization (WGL). This procedure can easily be performed under ultrasound or mammography guidance and provides real-time control of the wire-needle position, allowing accurate location of the lesion [19]. Over time, though, this procedure has faced several limitations: (i) wire dislodging, migration or wire fracture; (ii) higher patient discomfort and (iii) logistic difficulties, as the wire is to be placed no more than one day before surgery. Moreover, poor cosmetic outcomes have been described and high rates of a non-radical excision of the lesion due to wire dislodging and poor localization have been reported [18]. One of the most important disadvantages of WGL is the relatively large number of patients with positive margins detected at the final pathologic evaluation [5]. Reoperation with further resection is required when a positive margin is present; such a procedure can be both physically and mentally exhausting for the patient and can impair the cosmetic outcome. In addition, reoperation delays adjuvant treatment and is an extra financial expense [5].

In order to reduce the positive margin rate (and therefore the risk of reoperation) and to improve cosmesis (and therefore patient's satisfaction and psychological status), new precise localization tools are needed when performing BCS in patients with non-palpable BC.


CairnSurgical has developed the Breast Cancer Locator (BCL) System to address the limitations of intra-operative scanning and tracking method. In the BCL imaging system, a *supine* MRI is performed several days before surgery and the 3D interactive image of the tumor in the breast (including information on the closest distances from tumor to skin and chest wall) is available to the surgeon in the operating room. Instead of utilizing intra-operative optical scanning and tracking, 3D printing is used to manufacture a patient-specific plastic bra-like form (the BCL), which is placed on the breast. It has holes in its surface, which allow the surgeon to mark the projected tumor edges on the skin. The BCL also has ports, which allow the surgeon to place one hook wire in the center of the MRI-defined tumor and 4 additional bracketing wires to mark the tumor edges inside the breast. The central wire defines a vector from the skin surface to the tumor center, and the bracketing wires give the surgeon guidance within the breast (**Figure 1**).

CairnSurgical has already tested the BCL in a pilot study of 19 Subjects with palpable tumors [20].

No adverse events occurred, and all Subjects had their tumors resected with negative margins. The BCL System is currently under investigation in a prospective, multicenter, 1:1 randomized, controlled trial in 15 centers in the United States. The purpose of that study is to provide evidence that the positive margin rate following BCS using the BCL is not inferior to WGL for surgical guidance.

The BCL System is expected to improve surgical planning and to achieve precise tumor localization, which in turn would result in low re-excision rates, reduced specimen volume and improved cosmesis.

According to Regulation 2017/745 (MDR), manufacturers of medical devices (including custom-made medical devices) shall proactively collect and evaluate clinical data from the use in or on humans of a device which bears the CE marking and is placed on the market or put into service within its intended purpose with the aim

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of confirming the safety and performance throughout the expected lifetime of the device, of ensuring the continued acceptability of identified risks and of detecting emerging risks on the basis of factual evidence. Since the BCL system is a new custom-made device, the aim of this investigational, post-market clinical investigation is to collect clinical data to confirm the safety and performance of the device in patients eligible for BCS in European countries.

## 2. CLINICAL STUDY DESIGN METHODOLOGY

### 2.1 CLINICAL STUDY OVERVIEW

This is an interventional, post-market, multicentre clinical investigation aimed to enrol patients who require the tumor to be localized in order for the surgeon to perform BCS.

The study will include enrollment at 3 centers in Europe. The countries involved are Germany, Italy, Switzerland. The investigation will be useful to collect Investigational Product (IP)' performance/safety evidence in Europe.

Each Subject, after signing the Informed Consent Form (ICF), will enter into a screening phase (V0) during which several assessments (e.g., demographics, medical history, blood sample collection, evaluation of available prone MRI and core biopsy pathological results) will be conducted. At visit 1 (V1), the Subject will undergo *supine* MRI (10-40 days before surgery), from which the 3D breast image and BCL will be made. At visit 2 (V2) the patient will undergo BCS using the BCL System.

Soon after surgery and prior discharge, potential AEs will be assessed. On the same day, the specimen volume will be determined, and the specimen mammogram will be performed. The excised specimen will be sent to the Pathology lab for analysis. The results of the positive margin rate (PMR), will be obtained within 14 days. At visit 3 (V3), follow-up assessments (including physical examination, and AEs review) will be performed. At the End Of Study (EOS/V4), AEs events will be assessed and patients will be asked to express their satisfaction with the BREAST-Q.


### 2.2 STUDY OBJECTIVES

#### Primary

To evaluate the performance of the BCL in reducing the positive margin rate when the BCL System is used to guide a surgeon performing partial mastectomy.

#### Secondary

- To calculate the specimen volume after BCL guided partial mastectomy;
- To evaluate the surgeon's perception of ease of use of the BCL System;
- To evaluate the safety and tolerability of BCL;
- To evaluate the patient's satisfaction.

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## 2.3 STUDY ENDPOINTS

### 2.3.1 Primary Endpoints

To evaluate the performance of BCL in reducing the positive margin rate, the proportion of patients with positive margins after partial mastectomy with the BCL, will be obtained (results will be available within 14 days from the day of sample arrival at the pathological lab).

### 2.3.2 Secondary Endpoints

- To calculate the specimen volume after BCL guided partial mastectomy, the water displacement method (WDM) will be used (results will be obtained within the same day of surgery).
- To evaluate the surgeon's perception of ease of use of the BCL System, a 5 Likert scale will be used at V2;
- To evaluate the safety and tolerability of BCL through physical examination and AEs assessment including the relationship of the AE to the BCL System at V1, V2, V3, V4;
- To evaluate the patient's satisfaction, the BREAST-Q will be used at EOS/V4.

### 2.3.3 Study Early Termination

Early termination or suspension of the study is not anticipated. The Sponsor reserves the right to terminate an investigational site from the study for any of the following reasons:


- Failure to comply with investigational plan;
- Failure to obtain written informed consent from Subjects;
- Failure to provide case report forms and/or source documentation;

If the study is terminated early, the Investigator should consult with the Subjects enrolled to determine appropriate follow-up and subsequent treatment. After the end of the study the investigator will ensure the treatments and the support required as per clinical practices. All study data obtained prior to the study termination should be provided to the Sponsor.

## 2.4 BIOLOGICAL SAMPLES MANAGEMENT

All biological samples (blood samples and tumor specimens) collected according to the Laboratory Manual will be managed according to site internal procedures but ensuring the maintenance of the correspondence between samples and number assigned to the enrolled patient.

At the end of the study, after concluding all the analysis planned in the trial, all the biological samples stored as per Laboratory Manual will be destroyed, as per site procedure. They will be processed exclusively for the analysis described in this study and according to the trial procedures.

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## 2.5 STATISTICAL METHODS AND DATA ANALYSIS

### 2.5.1 Sample Size Justification

The positive margin rate (PMR) rate with the use of BCL is expected to be < 5% based on our previous study [20]. If we assume a true PMR rate of 3% and applying the exact or Clopper-Pearson method for a single binomial proportion then a sample size of N=35 will achieve a confidence interval with total width of 15%. The upper limit of this confidence interval (18%) is lower than the currently observed positive margin rate using the standard of care.

We will calculate an exact binomial confidence interval using the actual PMR.

### 2.5.2 Data Analysis

In general, all the variables will be descriptively analysed by visit (mean, median, standard deviation, minimum and maximum for continuous variables after normality check of distribution with Kolmogorov-Smirnov test, frequency distribution for categorical variables).

In particular, for the primary analysis PMR will be calculated when results of histopathological examination will be provided (results will be available within 14 days from the day of sample arrival at the pathological lab).

Moreover, 95% Confidence Interval (CI) of PMR will be presented.

All secondary endpoints will be evaluated in a descriptive way presenting the results by study visit, where appropriate.

All the analysis will be detailed in the Statistical Analysis Plan (SAP) which will be finalized in Version 1.0 before the Data Base Lock (DBL).

### 2.5.3 Safety Analyses


Safety will be monitored through vital signs, physical examination, laboratory parameters, and adverse events including assessment of relationship to the IP.

Summary table of AE details will also be reported including frequency, maximum intensity, relation to study treatment, seriousness, action taken, and outcome. Regarding relation: definite, probable, and possible is classified as "related" and unlikely and unrelated is classified as "unrelated" (see Section 3.6).

Safety data will only be handled descriptively.

### 2.5.4 Definition Of Datasets

For the statistical analysis the enrolled Subjects will be divided into the following datasets:

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Safety Analysis Set (SAS):	The "Safety Set" included all enrolled patients undergoing surgery with the BCL System.
Full Analysis Set (FAS):	The "Full Analysis Set" (FAS): this set included all enrolled patients undergoing surgery with the BCL System.
Per-Protocol Set (PPS):	The "Per-Protocol Set (PPS)" would include all the FAS patients who (a) met all inclusion/exclusion criteria liable to affect the performance assessment, (b) did not present serious deviations of the protocol that may affect efficacy.

Definition of major protocol deviations and selection of Subjects accordantly will be performed prior to database lock.

## 2.5.5 Handling Of Missing Values Including Withdrawals

Handling of missing data will be described in detail in the SAP. If nothing is described no imputation of data will be carried out in case of missing data, but all available data will be used to its full extent. Patients who withdraw from the study will not be replaced. The end of the study will occur when the last participating patient completes the last scheduled visit of the Investigational plan.

## 2.6 PATIENT SELECTION CRITERIA


All Patients shall be screened for initial study eligibility by the Principal Investigator or his/her designees at the investigational site. Potential candidates, that according to the Investigator judgment should undergo BCS with the BCL, will be identified, with the assessment of their eligibility criteria, by the study site Principal Investigator and research staff.

Patients will be considered to be enrolled in the study once they have met all of the inclusion and none of the exclusion criteria. Patients who do not meet the criteria will not be enrolled in the study.

The patient involvement in the study will last until the EOS visit.

### 2.6.1 Inclusion Criteria

- Patient Informed consent form (ICF) signed;
- Female Aged  $\geq 18$  years at the time of the signature of ICF;
- Histologic diagnosis of IBC or DCIS;
- Tumor excision that will require localization because it cannot be definitively defined by palpation;
- The tumor is unifocal; possible satellite lesions  $< 2$  cm from primary are eligible;
- The tumor enhances and is greater than or equal to 5mm on prone breast MRI imaging;
- Subject and surgeon agree to perform BCS;
- Willingness to follow all study procedures, including attending all site visits, tests and examinations.

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## 2.6.2 Exclusion Criteria

- Absolute contraindication to MRI, including presence of implanted electrical device (e.g., pacemaker or neurostimulator), aneurysm clip, or metallic foreign body in or near eyes;
- Severe claustrophobia;
- Contraindication to use of gadolinium-based intravenous contrast, including life-threatening allergy;
- Uncontrolled cardiac, renal, or pulmonary disease;
- Uncontrolled systemic disease (e.g., lupus erythematosus or scleroderma);
- Compromised renal function including chronic, severe kidney disease (GFR < 30 ml/min/1.73m<sup>2</sup>), or acute kidney injury;
- Pregnancy or breast-feeding (\*);
- Subjects who have received or plan to receive neoadjuvant chemotherapy;
- Sternal notch to nipple distance of > 32 cm as measured in a sitting or standing position;
- Measurement of widest circumference around breasts and arms > 135 cm;
- Known allergy to device components;
- Multicentric tumors (additional tumors > 2 cm from primary);
- Infectious or inflammatory processes near the area of intervention;
- Planned surgery with localization devices including WGL, intraoperative ultrasound guidance, radiofrequency emitting implants, magnetic seeds, radioactive seeds, and tissue inspection devices;
- Simultaneous participation in an interventional study or participation in an interventional study in the last 1 month before study inclusion, that, in the opinion of the Investigator, could impact patient's safety or the study endpoints;
- Known drug and/or alcohol abuse;
- Mental incapacity that precludes adequate understanding or cooperation.

*(\*) The pregnancy status will be assessed by performing urine pregnancy test (dipsticks will be provided by the Investigational site).*

*Women not of childbearing potential may have undergone menopause or permanent sterilization (hysterectomy, bilateral oophorectomy, or bilateral tubal ligation). Menopause is defined as ≥12 months of non-therapy-induced amenorrhea. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented.*

*Women of childbearing potential must agree to complete abstinence from sexual intercourse or to use single or combined contraceptive methods that result in a failure rate of <1% per year from 6 days prior to administration of the study product until completion of the study. Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Alternatively, established, proper use of combined oral or injected hormonal contraceptives, or double barrier method (condom used with spermicidal foam or occlusive cap used with spermicidal foam) from 6 days prior to administration of the study product until completion of the study are acceptable.*

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## 2.7 SITE SELECTION CRITERIA

As defined in the ISO 14155, prior to the initiation of the clinical investigation, the qualifications of the Principal Investigator and adequacy of the investigation site shall be verified and documented.

Sites must have adequate facilities and equipment to treat/evaluate the patients. The investigational staff must have adequate experience, commitment to safety and consistency in adherence to the protocol. For each enrolled patient, the IP' safety/performance evaluations will be monitored until the End Of Study Visit.

The Principal Investigator must understand and agree to this Protocol. The Principal Investigator and the study Sponsor (or its designee) will execute a clinical trial agreement. The investigational site is also required to execute said clinical trial agreement.

Statement addressing the financing of the clinical investigation, including a description of the agreement between the Sponsor and investigation site(s), will be available in a separated document.

## 2.8 SCREENING FAILURES

Subjects who will fail to meet the inclusion and exclusion criteria are defined as screening failures. Principal Investigator will maintain a Screen Failure Log for screening failures. The log will document at minimum the Subject number and the reason(s) for excluding the Subject from the study. This log will be kept as a source document in the Investigator's Study File. It will be used to determine systematic bias in selection of Subjects for entry into the study.


## 2.9 SUBJECT WITHDRAWAL AND DISCONTINUATION/STOPPING OF TREATMENT

All Subjects are expected to continue in the "CS-BCL-EU2021" study except in the event of death or upon a Subject's early withdrawal from the clinical study. Although every Subject is informed of her right to withdraw at any time from the clinical study, all measures should be taken by the Investigator to encourage Subjects to return for required follow-up visits. If a large number of Subjects are lost to follow-up, attaining clinical study objectives could be jeopardized. The Investigator may prematurely discontinue or withdraw any Subject from the study if any of the study procedures are deemed potentially harmful to the Subject.

Once a Subject has been enrolled in the study, she may withdraw her consent to participate in the study at any time without prejudice. Participation in this clinical investigation is entirely voluntary.

Any Subject receiving breast surgery with BCL who prematurely terminates participation, will undergo a final examination (end-of-study visit/early termination visit). For Subjects considered lost to follow-up, the eCRF will be completed up to the last visit.

The Investigator has the right to terminate participation of any Subject at any time if he/she deems it in the Subject's best interest. The discontinuation from the study may be foreseen in the following (but not limited to) conditions:

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- Subject withdraws consent for personal reasons;
- Significant non-compliance with study protocol or lack of cooperation;
- Pre-existing violation of eligibility criteria;
- Serious Adverse Event (SAE) or concomitant illness developed by the subject, which, in the opinion of the Investigator and/or the medical expert, does not recommend continuation in the trial;
- Concomitant assumption of prohibited products/medications during the study;
- Subject lost to follow-up;
- Other reasons as determined by the Investigator.

If a Subject is withdrawn, the Sponsor (or its designee monitor) should be informed as soon as possible (i.e., no later than 24 h after learning of the event).

## 2.10 STUDY PROCEDURES AND VISITS

### 2.10.1 Visit Scheduling

Following the evaluation of the inclusion/exclusion criteria and after signing the Informed Consent Form (ICF) criteria at the screening visit (V0), four additional visits will be planned.

At visit 1 (V1), the Subject will undergo *supine* MRI (10-40 days before surgery), from which the 3D breast image and BCL will be made.

At visit 2 (V2) the patient will undergo BCS using the BCL System. On the same day, the specimen volume will be determined. The excised specimen will be sent to the pathological lab for analysis. The surgeon will be asked to fill a 5-point Likert scale to express the ease of use of the BCL.

At visit 3 (V3), follow-up assessments (including physical examination, and AEs review) will be performed.


At the End Of Study (EOS/V4), AEs events will be assessed and patients will be asked to express their satisfaction with the BREAST-Q.

AEs, and concomitant medications, will be assessed from V0 until the EOS visit. Vital signs will be measured from V0 until V3. Any device deficiency/incident will be recorded at V1 and V2.

### 2.10.2 Description Of Visits And Assessment

Participants will be recruited from the Investigator' Subject population or through referrals. The Investigators will obtain signed Subject's informed consent prior to enrolling the Subject into the study.

After signing the ICF, Subjects will enter a **screening phase (V0)** during which evaluation of the inclusion/exclusion criteria will be performed. Demographic data and medical history will be recorded. All Subjects will have had a mammogram and *prone* MRI assessment prior to enrolment as per clinical practice. Results of imaging studies should be obtained within 3 months of study enrolment. The results from pathological analysis of diagnostic core biopsy specimens (including IBC vs. DCIS) will be documented. Physical examination will include weight, height, distance from sternal notch to the nipple, the circumference around the breast and arms, calculation of BMI, and specific documentation

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that the breast cancer cannot be palpated. At V0, vital signs will be measured, and blood samples will be collected.


For females of childbearing potential only, urine pregnancy test will be performed with dipsticks supplied by the Investigational site. Results must be available before any procedure.

**At visit 1 (V1; supine MRI)**, for each Subject, a *supine* MRI will be performed. Surgery will be scheduled 10-40 days after the *supine* MRI. A review of adverse events and concomitant medications will be performed on the day of MRI. Vital signs will be monitored during the MRI. Any device deficiencies/incidents will be recorded.

Subjects will undergo a contrast-enhanced supine MRI at their local facility using a body coil, applied on top of a specially designed foam support structure, with MRI sequences that are designed to obtain both breast surface contour and breast tumour signatures, as detailed in the [MRI Kit](#) and [MRI Acquisition Procedure Manual](#). The Subject's arm on the cancer side will be parallel to the body. Two marks will be placed on the breast using the marker provided with the investigational device for this purpose at exactly 4 cm directly medial and 4 cm directly cranial to the nipple. An MRI fiducial will be placed over each mark for the duration of the MRI. A fiducial will also be placed on the nipple, but no mark will be placed on the nipple. After the MRI is completed, the fiducials will be removed, marks will be reinforced by the MRI technician, and a transparent plastic dressing (Tegaderm™) will be placed over each mark. Patients with a documented Tegaderm™ allergy will be excluded from the study. For patients who develop a possible allergic reaction to the Tegaderm™, if the reaction is mild (e.g., mild redness with no or mild symptoms) the Tegaderm™ should be left in place. If the reaction is moderate to severe and symptomatic (e.g., very itchy or painful) the Tegaderm™ should be removed, the mark should be reinforced, and an alternative hypoallergenic plastic dressing should be placed. The Subject will be instructed that it is important to leave the Tegaderm™ dressings in place over the marks until surgery. If a Tegaderm™ dressing is removed for any reason, the Subject will be instructed to call her Investigator and have the Investigator remark and cover the site as soon as possible.

MRI images will be transmitted to CairnSurgical, Inc. where a study radiologist will outline the tumor edges on the supine MRI. The study Radiologist will have access to *prone* MRI, mammogram and ultrasound images (if performed) of the cancer containing breast. The *supine* MRI images will be used to fabricate a BCL using 3D printing. A prototype of the BCL design will be approved by a study surgeon at CairnSurgical. The printed product will include a surface which will fit over the breast, with an opening for the nipple and two additional 5 mm openings, corresponding to the fiducials placed 4 cm medial and cranial to the nipple (these 3 openings and the inferior mammary fold will allow the investigator to be sure the locator is positioned accurately on the breast). The BCL will also contain openings for the investigator to mark the tumor image on the breast surface, 4 peripheral cylindrical ports to guide hook wire placements to define the cancer edges, and a central port to place a hook wire into the center of the tumor. The BCL will be tested for quality, sterilized, packaged, and shipped to the Investigators.


**At visit 2 (V2; Surgery)**, the Investigators will receive both an email and a BCL Information Sheet with a unique on-line link to a 3D image of the tumor in the breast. When this link is opened on a computer in the operating room (OR), the Investigator will be able to see the MRI-defined tumor in the breast.

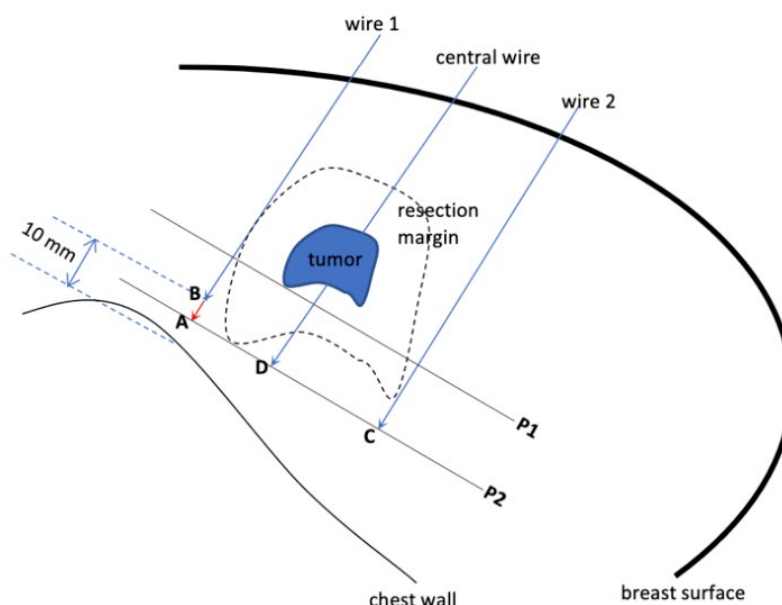
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The closest distances (in mm) from the tumor to the skin and from the tumor to the chest wall will be displayed.

Prior to anesthesia, the Tegaderm™ or hypoallergic plastic dressings will be removed. Since the ink spot may be partly removed with the dressing when it is removed, the inked spots will be reinforced with a marker. In the OR, the Subject will undergo general anesthesia. The Subject's arm on the side of the cancer will be placed on an arm board parallel to the OR table, in roughly the same position as it was during the MRI. The breast and axillary skin will be prepped with the Investigator's choice of solution. Using sterile technique, the surgeon will position the BCL on the Subject's breast, being sure to align the nipple and the two openings 4 cm from the nipple with the marks on the subject's skin. The Investigator will use a marker to mark the BCL-defined edges of the tumor on the breast skin using the marking holes in the BCL form once properly positioned on the Subject's breast. Four Breast Localization hook wires will be deployed using a 20-gauge needle by the Investigator through the 4 peripheral ports to delineate a distance of 1 cm from the cranial, caudal, medial and lateral tumor margins. The central needle port will also be used to place a Breast Localization hook wire in the center of the tumor. The depth of needle insertion is determined by the length of the port; the surgeon places the needle as far in as possible (up to the hub of the needle), and then deploys the wire at that depth. The wires will be trimmed by cutting them at the top of the BCL ports. The BCL will be removed. The Subject will be re-prepped and draped for the surgical procedure.

The Investigator will then perform a breast conserving tumor resection. The Investigator will attempt to resect all tissue inside of the 4 peripheral hook wires used to identify the 4 tumor edges. Specifically, an incision will be made at the Investigator's discretion. The Investigator will dissect into the breast tissue a distance 1 cm less than the distance from the skin to the tumor delineated by the virtual 3D model, then create flaps horizontal to the skin until reaching peripheral hook wires, which will be located 1 cm past the tumor edges. The depth of these flaps underneath the skin will be determined by the distance from the skin to the anterior tumor edge. If this distance is < 1 cm, the flap will be made just under the dermis. If this distance is > 1 cm, the Investigator will dissect into the breast until they are 1 cm from the superficial tumor surface, and then will form the horizontal flaps. Knowing the location of the tumor center, as defined by the central hook wire, and cutting with a scalpel or cautery immediately outside of the peripheral hook wires, the Investigator will incise into the breast tissue, thereby creating the specimen of breast tissue. The tips of the wires are targeted to be placed 1 cm below the deep edge of the tumor. However, the wire depths are not meant to mark the deep margin. The safety requirement, which ensures that the wire tips are placed at least 10 mm away from the chest wall, is still applicable to all wires placed. In the event that the tip of any of the localization wires (central or peripheral) lands closer than 10 mm to the chest wall, the manufacturing software will adjust the length of the respective port during the BCL manufacturing process to ensure that the minimum safety distance of 10 mm to the chest wall is maintained (see **Figure 2**).

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**Figure 2.** Illustration of needle depth adjustment made by the software to ensure a minimum of 10 mm safety margin from chest wall - In the case of Wire 1, the tip of the localization wire placed at the posterior edge of the tumor-margin happens to be closer than 10 mm to the chest wall (position A). In this case, as shown in the illustration, the manufacturing software adjusts the port length to ensure that the tip is pulled back sufficiently (to position B) to maintain the minimum 10 mm safety distance to the chest wall. However, in the case of the peripheral Wire 2 and the central wire, the tip of the localization wire placed at the posterior edge of the tumor-margin is >10 mm away from the chest wall and so no adjustments are made to their intended targeting locations (positions C and D respectively).

Once beyond the wire tips, the Investigator will curve the incision inward to form the deep edge of the specimen, with the goal of obtaining 1 cm of normal tissue deep to the tumor. The virtual 3D image of the cancer in the breast and knowledge of the distance from the deep tumor surface to the chest wall will guide dissection of the deep specimen margin. If the deep tumor surface is <1 cm from the underlying muscle, then the fascia of the underlying muscle will be removed with the specimen. All wires will be removed from the breast.

After the tumor specimen is removed, the Investigator will remove the 4 peripheral hook wires from the specimen. The central wire will be left in place. Specimen volume will be determined by water displacement into a marked transparent cylinder containing 200 ml water. Specimen surfaces will be patted dry and marked for margin orientation as per standard protocol of the local institution. A specimen mammogram will be obtained and then the specimen will be sent to Pathology.

No devices will be utilized to assess whether cancer cells may be present at the edges of the specimen or the lumpectomy cavity. Frozen section pathologic analysis of specimen margins will not be utilized. Additional shave biopsies may be taken after the initial tumor resection at the discretion of the Investigators. To minimize potential Investigator bias, additional shave biopsies can only be taken if the following criteria are met: 1) the Investigator palpates a margin of the specimen or the lumpectomy cavity which is suspicious for cancer or 2) the specimen mammogram indicates that the cancer is < 2 mm from a margin. If the Investigator decides to remove additional margins because of

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findings on specimen palpation or specimen mammography, the number of additional specimens will be recorded, their volume will be determined by water displacement, and they will be marked for margin orientation.

The Investigator should specifically request that Pathologist evaluates and records the distance from the invasive cancer (and separately, if present, from DCIS) to all 6 tumor edges. The consensus guidelines will be used to define positive margins (see **APPENDIX 1**).

To evaluate the surgeon's perception of ease of use of the BCL System, the Investigator will complete a 5-point Likert scale. If, for any reason, the PI is not able to fill the 5-point Likert Scale soon after surgery, the procedure must be completed prior discharge of the patient.

At **visit 2 (V2; Prior to discharge)**, the patient (including the surgical site) will be examined. Post-operative pain medications will be prescribed as per standard of care. The study Investigator will review adverse events and concomitant medications. Device deficiencies/incidents will be monitored.

At **visit 3 (V3; Follow-up)**, Subjects will be seen on-site for a post-operative evaluation. Subjects will have vital signs taken and a physical exam consisting of evaluation of the surgical site. A review of adverse events will also be performed.

At the **End of Study visit (EOS/V4)**, evaluation of adverse events and concomitant medications will be performed for each Subject. Furthermore, to evaluate the patient's satisfaction, the BREAST-Q (see **APPENDIX 2**) will be used at EOS/V4.

After the EOS visit, the patient will exit the study and data collection will be stopped. In case of need, the patient will continue to be treated according to her conditions and the Investigator will decide the best treatment strategy to be used.

#### **Laboratory examinations:**

##### Pathological analysis

Soon after surgery, tumor specimen handling is either performed directly by the surgeon (PI) or by the PI's delegate. In either case the PI oversees and is responsible for the process.


The tumor specimen will be analyzed locally, at hospital by the Investigator or designee. In details:

- the specimen volume will be determined on the same day of surgery;
- the specimen mammogram will be obtained on the same day of surgery;
- the positive margin rate (PMR) will be obtained within 14 days from the day of sample arrival at the Pathology laboratory.

Once the tumor specimen arrives at the Pathology laboratory:

- specimen surfaces are inked by the surgeon with different colors for orientation,
- the Pathologist performs microscopic evaluation of the margin status, measuring the distance from the edges of the tumor to the edges of the specimen.

See **APPENDIX 1** for additional information about the PMR.

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#### Blood samples (safety)

At the screening visit (V0) blood samples will be collected to check for laboratory parameters:


- serum creatinine levels to calculate the glomerular filtration rate (GFR), acid uric for renal dysfunction;
- complete blood count;
- electrolytes (sodium, potassium, chloride, bicarbonate).

### 2.10.3 Flowchart

The study visits, and related procedures are summarized in the flowchart below.

Determinations	Screening & Enrollment (V0) <sup>A</sup>	Visit 1 (V1) Supine MRI <sup>A</sup>	Visit 2 (V2) Surgery		Visit 3 (V3) Follow-Up	Visit 4 (V4) End Of Study (EOS)
	Within 15-30 days before V1	Day 0 <sup>A</sup>	Within 10-40 days from supine MRI	Prior to discharge	2 weeks ± 7 days post surgery	6 weeks ± 7 days post surgery
ICF <sup>A</sup>	X					
Inclusion/Exclusion criteria	X					
Medical history <sup>B</sup>	X					
Demographic data (including age, smoking habits and alcohol use)	X					
Vital signs (BP, HR, O <sub>2</sub> saturation)	X	X	X	X	X	
Physical examination <sup>C</sup>	X			X	X	
Blood samples (laboratory parameters) <sup>D</sup>	X					
Urine pregnancy test to all women of childbearing potential <sup>E</sup>	X					
Radiological assessment <sup>F</sup>	X					
Supine MRI		X <sup>A</sup>				

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Provide tumor specimen to pathological lab <sup>G</sup>			X			
BCS with BCL <sup>H</sup>			X			
5 Likert Scale (completed by PI) <sup>I</sup>			X			
BREAST-Q						X
Adverse events (AEs)	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Device deficiencies/incidents monitoring		X	X			

#### Notes:

<sup>A</sup> Informed Consent Form (ICF) signed and dated, before any trial procedure is performed. In order to provide the Investigator with an adequate time frame to organize and perform the clinical tests and assess the inclusion/exclusion criteria on the Subject, the screening phase was set up a maximum duration of 30 days (V0). After the ICF is signed, a supine MRI will be scheduled as soon as possible but according to local standard procedure.

<sup>B</sup> Medical history includes patient-reported bra cup size and documentation of any contraindications to MRI (e.g., implanted electrical devices exist), history of adverse reactions to gadolinium, breastfeeding or pregnancy.

<sup>C</sup> Physical examination includes weight, height, distance from sternal notch to the nipple, the circumference around the breast and arms, calculation of BMI, and specific documentation that the breast cancer cannot be palpated.

<sup>D</sup> Laboratory Tests include:

- serum creatinine levels to calculate the glomerular filtration rate (GFR), acid uric for renal dysfunction;
- complete blood count;
- electrolytes (sodium, potassium, chloride, bicarbonate).


<sup>E</sup> For females of childbearing potential only, urine pregnancy test will be performed with dipsticks supplied by the Investigator. Results must be available before any procedure.

<sup>F</sup> All Subjects will have had a mammogram and prone MRI assessment prior to enrollment. If breast ultrasound images are obtained, they will be available to the study team. The results from pathologic analysis of diagnostic core biopsy specimens, including IBC vs. DCIS, will be documented. Results of imaging studies should be obtained within 3 months of study enrollment.


<sup>G</sup> After the tumor specimen is removed:

- the specimen volume will be determined by water displacement,
- a specimen mammogram will be obtained and then the specimen will be sent to the pathologist for evaluation of the positive margins.

<sup>H</sup> Surgery will be scheduled 10-40 days after the supine MRI. Subjects will have a pre-surgical contrast-enhanced supine MRI. MRI images will be transmitted to CairnSurgical where a study radiologist will outline the tumor edges on the supine MRI. These supine MRI images will be used to fabricate a BCL using 3D printing. The Investigator will perform the BCS using the BCL device. Specimen volumes will be determined by water displacement. Specimen mammograms will be obtained. Additional shave biopsies may be taken after the initial tumor resection at the discretion of the investigator. The specimen will be sent to Pathology.

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<sup>1</sup> If, for any reason, the PI is not able to fill the 5-point Likert Scale soon after surgery, the procedure must be completed prior discharge of the patient.

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#### 2.10.4 Visit 0 (V0): Screening (within 15-30 days before V1)

- Signed and dated Informed Consent obtained prior to start any procedure scheduled for the study;
- Verification and confirmation of the inclusion/exclusion criteria;
- Medical history;
- Demographics (including age, smoking habits and alcohol use);
- Vital signs (BP, HR, O<sub>2</sub> saturation);
- Physical examination;
- Blood samples (laboratory parameters);
- Urine pregnancy test to all women of childbearing potential;
- Evaluation of radiological assessment;
- Adverse Events;
- Concomitant medications.

#### 2.10.5 Visit 1 (V1): Supine MRI (Day 0)


- Vital signs (BP, HR, O<sub>2</sub> saturation);
- Supine MRI;
- Adverse Events;
- Concomitant medications;
- Device deficiencies/incidents monitoring.

#### 2.10.6 Visit 2 (V2): Surgery (within 10-40 days from supine MRI)

- Vital signs (BP, HR, O<sub>2</sub> saturation);
- Breast-conserving surgery (BCS) with the Breast Cancer Locator (BCL);
- Provide tumor specimen to Pathology;
- 5 Likert Scale (completed by PI);
- Adverse Events;
- Concomitant medications;
- Device deficiencies/incidents monitoring.

#### Prior to discharge

- Vital signs (BP, HR, O<sub>2</sub> saturation);
- Physical examination;
- Adverse Events;
- Concomitant medications;

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#### 2.10.7 Visit 3 (V3): Follow-Up

- Vital signs (BP, HR, O<sub>2</sub> saturation);
- Physical examination;
- Adverse Events;
- Concomitant medications.

#### 2.10.8 Visit 4 (V4): End Of Study

- BREAST-Q;
- Adverse Events;
- Concomitant medications.

#### 2.10.9 Additional Visits

In the event that additional visit(s) are required other than those described in this Protocol, this information must be documented in any applicable Case Report Form. A copy of the visit form and clinical dictation should be placed in the Trial chart.

### 2.11 CLINICAL RISK BENEFIT ASSESSMENT


#### 2.11.1 Anticipated Clinical Benefits

The clinical benefits of using the BCL System can be deduced from available data in the literature and recent clinical trials.

##### Supine MRI-guided BCS.

Because the tumor-positive margin in BCS is highly correlated with the recurrence rate of breast cancer, it is important to have adequate margin resection. Therefore, the area of the tumor should be accurately predicted before surgery. To improve diagnostic accuracy, MRI is performed at the prone position (patient lying on her front side, with the breasts pendant in bilateral imaging coils) with a special breast coil. However, the surgical position is a supine, which is different from the position of the tumor observed in the prone position during an MRI scan [21]. It has been shown that *supine* MRI replicates the surgical position and has the potential to increase the precision of BCS by reducing the positive margin rate and the specimen volumes [17], [22].

In 2014, Pallone et al., developed a new method of MRI-guided BCS that incorporates preoperative *supine* MRI to define tumor extent and uses an intraoperative optical scan to co-register the MRI image to the breast position in the operating room [15]. This technique provides the surgeon with 3D views of tumor shape and position within the breast as it appears during surgery. When combined with intraoperative tracking technology, which allows the surgeon to mark the edges of the cancer on the breast and determine a directional vector to the MRI-defined tumor center. In a pilot study of 18

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women with palpable tumors, the authors demonstrated that this method localized breast cancer as accurately as by palpation [15].

Barth et al., have recently completed a randomized prospective clinical trial comparing *supine* MRI, intraoperative scanning and tracking technique to wire localization [23]. The study involved one hundred thirty-eight (138) subjects randomly assigned in a 1:1 ratio to partial mastectomy guided by *supine* MRI (group MRI) or wire localization (group WL). Sixty-six (66) percent had invasive breast cancer and DCIS, 22% had invasive cancer and 12% had DCIS. No differences in subject or tumor characteristics existed between groups. The proportion of subjects with positive margins in the MRI guided surgery group was half that observed in group WL: 12% vs. 23% ( $p = 0.08$ ). Mean specimen volumes in groups MRI and WL were not significantly different: 74 vs. 70 ml ( $p = 0.45$ ). Margins for invasive cancers were considered positive if invasive cancer or DCIS cells were present at the edge (on ink) or if DCIS was present  $< 1$  mm from the inked edge. Margins for specimens that contained only DCIS were considered positive if DCIS was present  $< 1$  mm from the inked edge. Consensus guidelines for positive margins were established after the study was initiated [24], [25]. The consensus guideline criteria for a positive margin for invasive cancer was invasive cancer or DCIS at the edge (on ink); the margin for cases that contained only DCIS was considered positive if DCIS was present  $< 2$  mm from the inked edge. Using the new consensus definition of positive margins, the positive margin rate in the MRI group (9%) was lower than those reported in any previously published RCT.


#### The BCL System

CairnSurgical has tested the BCL System in a pilot study of 19 subjects with palpable tumors [20]. Patients underwent partial mastectomy after placement of surgical cues using patient specific BCL devices. BCL cue placements (tumor edge markings, blue-dye injections, and wire placement) were completed in less than 5 minutes for all patients, and no adverse events occurred. The BCL accurately localized 18/19 cancers. The one inaccurate localization was in a patient with a tumor deep in the upper outer quadrant of a large breast. The breast was deformed by the circular coils placed on the breast during MRI and the BCL did not account for the breast deformation caused by the coil. However, construction of BCL directly from the MRI-defined breast surface solved this problem; any indentation from a coil was printed into the BCL, which reproduced the same indentation in the breast when used in the operating room (OR). No inaccurate localizations occurred in the 10 patients treated after this modification. No adverse events occurred during the study and all subjects had their tumors resected with negative margins. The mean specimen resection volumes ( $116 + 73$  ml) were similar to the optimal resection volumes ( $103 + 86$  ml) [20].

Ease-of-use of a device specifically designed to impart *supine* MRI imaging information to the surgeon in the OR was also tested. Results showed that the MRI-derived cues could be transferred quickly and easily.

In conclusion, the anticipated clinical benefits of using the BCL System developed by CairnSurgical are:

- 1) The BCL device is obtained from *supine* MRI images which replicate the surgical position resulting in increased precision of tumor localization.

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- 2) A pre-operative 3D visualization of the cancer combined with a patient specific BCL device is expected to decrease the positive margin rate. This will in turn reduce the need for re-excision [20], [23].
- 3) The BCL provides a localization cue (the hook wire) with which surgeons are familiar yet improves current practice because the wire placement does not require a separate procedure on the day of surgery, which can complicate surgical scheduling and cause patients pain [20].
- 4) The BCL is safe, quick, easy to use, and accurately localizes breast cancers [20].
- 5) The volume of breast tissue excised upon BCS with BCL is expected to be close or lower to the "ideal" resection volume [20].
- 6) As cosmetic outcome is negatively influenced by the percentage of breast volume excised, and by re-excision procedures [26], the BCL System is expected to improve cosmesis and patient satisfaction after breast-conserving surgery.

### 2.11.2 Anticipated ADE


Complications of breast-conserving surgery are unusual. However, the most common complications are hematoma or bleeding, infection and seroma (clinical detectable pocket of fluid developing after the surgical procedure in the operated breast) [27].

### 2.11.3 Risks Associated With The Participation In The Clinical Investigation

Potential risks associated with the procedures that will be performed during this clinical investigation are reported below.

#### Risks associated with the MRI

1. Anaphylactic allergic reaction from Gadolinium based intravenous contrast.  
*Likelihood:* 0.001-0.01% [28].  
*Clinical consequences:* hypotension.
2. Gadolinium based contrast adverse reactions (injection site pain, headache, nausea, paresthesia, dizziness).  
*Likelihood:* 0.07%-2.4% [28].  
*Clinical consequences:* most reactions are mild and do not require therapy.
3. Gadolinium based contrast induced nephrogenic systemic fibrosis.  
*Likelihood:* very rare if patients with kidney disease are excluded [28].
4. Gadolinium deposition in organs, including but not limited to brain, bone, skin, kidney, liver, and spleen.  
*Likelihood:* high  
*Clinical consequences:* in autopsy studies no histologic evidence of toxicity in the human brain has been demonstrated. No adverse clinical consequences of gadolinium retention in the brain and other organs have been proven [28], [29].  
While negative effects of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring

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multiple lifetime doses, pregnant and pediatric patients, and patients with inflammatory conditions [30].


#### Risks associated with the BCL device

5. The needles used to deploy the hook wires may be placed through the chest wall into the lung, causing a pneumothorax.  
*Likelihood:* the BCL is designed to prevent needle tips from getting close to the lung.  
*Clinical consequences:* Subjects who developed respiratory symptoms and had a pneumothorax diagnosed by chest x-ray would be treated with transient placement of a small diameter chest tube.
6. The BCL may introduce an additional infection risk.  
*Likelihood:* although the BCL could have the potential to introduce additional infection risk, the BCL is sterile and is used in a sterile field in the operating room.  
*Clinical consequences:* cellulitis would require antibiotic treatment; an abscess would require incision and drainage and antibiotics.
7. The BCL may inaccurately localize the cancer, causing the Investigator to miss the cancer or excise it with a higher-than-expected positive margin rate.  
*Likelihood:* in the Dartmouth clinical trial of *supine* MRI/intraoperative scanning and tracking technique, 66 of 67 (99%) tumors were successfully localized and removed. The BCL incorporates design features (central wire) that further mitigate this risk. In the pilot BCL study of 19 subjects, tumors were localized very accurately: the median distance from the central wire to the tumor center was < 5 mm and all tumors were excised with negative margins [20].  
*Clinical consequences:* the Subject would require a second surgery to identify the cancer or re-excise the positive margin.

#### Risks associated with BCS

8. Bleeding associated with BCS.  
*Likelihood:* risk of bleeding after partial mastectomy requiring that the subject return to the operating room ranges from 0.5-1% [31].  
*Clinical consequences:* the Subject would require a second surgery to identify the area of bleeding.
9. Postoperative nausea and vomiting are frequent after general anesthesia.  
*Likelihood:* the average rate in contemporary practice is thought to be ~20-30% or higher [32], [33].  
*Clinical consequences:* most episodes are mild and do not require therapy.
10. Postoperative pain requiring an opioid analgesic after discharge to home.  
*Likelihood:* approximately 15% of patients used an opioid after partial mastectomy and 25% after partial mastectomy with sentinel lymph node biopsy [34].  
*Clinical consequences:* post-operative pain may require opioid analgesic after discharge.

As reported in the Risk Management Report, it can be concluded that for the BCL System any risks that were identified from various risk analysis activities have been eliminated or reduced to an acceptable

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level. There are no unacceptable residual risks in the system. As part of the Risk Management activity, the Project / Risk Management leader has reviewed the risk management process to ensure that:

- the risk management plan has been properly implemented,
- the overall residual risk is acceptable,
- CairnSurgical has applicable procedures (Complaints, CAPA, PMS, PMCF, etc.) in place to obtain relevant production and post-production information.

#### 2.11.4 Interactions With Concomitant Medical Treatments As Considered Under The Risk Analysis

There are no contraindications to the use of any other concomitant medication during the study. Post-operative pain medications will be prescribed as per standard of care.

#### 2.11.5 Steps That Will Be Taken To Control Or Mitigate The Risks


The risks associated with the BCL System will be minimized by the clinical investigation design as follows:

- a) Risk of allergy or severe adverse reaction to gadolinium based intravenous contrast. All Subjects will have already undergone a standard of care *prone* contrast-enhanced MRI prior to study enrollment. Any Subject who had an allergic or severe adverse reaction to gadolinium will be excluded from this study.
- b) Risk of nephrogenic sclerosis secondary to gadolinium. Nephrogenic Systemic Fibrosis (NSF) risk appears highest for patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m<sup>2</sup>) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30 to 59 mL/min/1.73m<sup>2</sup>) and little, if any, for patients with chronic, mild kidney disease (GFR 60 to 89 mL/min/1.73m<sup>2</sup>). This complication is extremely rare in Subjects with normal renal function. Subjects with impaired renal function (GFRs <30 mL/min/1.73 m<sup>2</sup>) will be excluded from this study.
- c) Risk of infection due to the BCL. Any adverse event will be monitored during the study.
- d) The risk of pneumothorax from needles inserted using the BCL will be monitored during the study.
- e) The risk of inaccurate localization using the BCL, resulting in either missing the tumor or having a higher-than-expected positive margin rate, will be monitored during the study.

Furthermore, a list of warnings/precautions are reported on the IFU related to each kit.

Considering the design of the study, to collect the safety data, vital signs, physical examination will be assessed during the study. During scheduled visits, Subjects will be properly interviewed by Investigator or delegates to assess the adherence to the indications and protocol procedures, as well as to evaluate any adverse event or Concomitant Medication intake.

During the performance of all the procedures required and described in this protocol, the Principal Investigator and the involved collaborators will give high priority to the health and the well-being of each enrolled Subject until the end of the study.

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Investigators and site staff will be trained on how to use the BCL System.

Subjects will be also requested to immediately contact the Investigator in case of any adverse effect/adverse device effect, in order to allow the Investigator to take the best decision to ensure the safety and wellbeing of trial Subjects.

Subjects must be carefully selected in order to prevent any kind of risks not related to the investigational device, as living and working climate conditions.

#### 2.11.6 Rationale for the Benefit-Risk Ratio

Considering all the potential risks and risk reduction measures and the potential benefits of the BCL System, and the results of previous clinical studies regarding the use of the BCL, it is concluded that the potential benefits associated with the use of the BCL System outweigh the potential risks.

### 3. ADVERSE EVENTS

#### 3.1 ADVERSE EVENT DEFINITION

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other parties, 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 comparator).
- the procedure involved.

#### 3.2 SERIOUS ADVERSE EVENT


Serious Adverse Event (SAE) is defined, as per ISO 14155, adverse event that:

*a) led to death,*

*b) led to serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:*

- 1) a life-threatening illness or injury, or*
- 2) a permanent impairment of a body structure or a body function, or*
- 3) in-patient or prolonged hospitalization, or*
- 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,*

*c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment*

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

### 3.3 ADVERSE DEVICE EFFECT

Adverse Device Effect (ADE) is an 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 an error use or from intentional misuse of the investigational medical device (or comparator if available in the trial).

### 3.4 SERIOUS ADVERSE DEVICE EFFECT

A Serious Adverse Device Effect (SADE) is any adverse device event that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.


### 3.5 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT

An Unanticipated Serious Adverse Device Effect (USADE) is an effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. Procedures associated with the use of a device should be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAEs are Unanticipated Serious Adverse Device Effect or not. SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device should not be considered Serious Adverse Device Effects. Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

### 3.6 CAUSALITY ASSESSMENT

According the MDCG-2020-10/1 (Guidance on safety reporting in clinical investigations), the relationship between the use of the medical device (including the 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, such as the Investigator's Brochure, the Clinical Investigation Plan or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. 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. The above considerations apply also

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to the serious adverse events occurring in the comparison group. 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.

1. **Not related**: Relationship to the device, comparator 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.

2. **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.

3. **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.

4. **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
  - o the investigational device or procedures are applied to;
  - o 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);

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- 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 the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

The Sponsor and the Investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The Sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an Investigator assessment is not available and/or the Sponsor remains uncertain about classifying the serious adverse event, the Sponsor should not exclude the relatedness; the event should be classified as "possible" and the reporting not be delayed.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related could suggest that the clinical investigation places Subjects at increased risk of harm than was to be expected beforehand.


### 3.7 ADVERSE EVENT REPORTING

Timely and complete reporting of Adverse Events (AE) and safety assessments allows:

- Protection of safety and study Subjects;
- Greater understanding of the overall safety profile of the study treatment;
- Appropriate modification of study protocols and improvement in study design and procedures;
- Adherence to regulatory requirements;

The definitions and reporting requirements adopted in this study are derived from the current International standard on clinical investigations: ISO 14155:2020 and MDCG 2020-10.

Adverse event, adverse device effect and device deficiency/incident information will be collected throughout the study. The investigator or its delegates will record these events on the CRF. The event, date of onset, severity, duration, and relationship to the device will be recorded. Any adverse event will be monitored until it is adequately resolved or explained.

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The Investigator or its delegates will monitor the occurrence of adverse events for each Subject, including lead-in Subjects, during the course of the study. All Adverse Events (AEs) reported by the Subject, observed by the Investigator, or documented in medical records will be recorded on the adverse event CRF, whether believed by the Investigator to be related or unrelated to the investigational device. Starting with the study enrollment, any new event/experience that was not present at baseline, or worsening of an event present at baseline, is considered an adverse event. All adverse events and unanticipated adverse device effects will be collected and monitored throughout the entire course of the study.

Unchanged, chronic conditions are not adverse events and should not be recorded on the adverse event CRF.

If AE will persist after EOS visit, the Principal Investigator will be in touch with the Subject to support the best decision ensuring the safety/wellbeing of trial Subjects.

### 3.8 SERIOUS ADVERSE EVENT REPORTING TO SPONSOR AND EC

All serious adverse events, serious adverse device effects and device deficiency that might have led to a serious adverse effect should be reported via telephone or fax to the Sponsor within 24 hours after the Investigator first learns of the event. This report must be followed by full and complete written documentation.

All reports, with associated eCRFs' identification code and source documentation, should be sent via mail or fax to:


<b><i>Sponsor's Safety Responsible Person:</i></b>	<b><i>Sponsor's Study Coordinator</i></b>
<b>Name:</b> Dr. Richard Barth <b>Role:</b> Co-Founder, CMO and Professor of Surgery, Geisel School of Medicine at Dartmouth. <b>Address:</b> DHMC, 1 Medical Center Drive Lebanon NH 03756 <b>E-mail:</b> Richard.J.Barth.Jr@Hitchcock.ORG	<b>Name:</b> Gisella Lopez <b>Role:</b> Sr. Director, Clinical Affairs <b>Address:</b> 16 Cavendish Court, Lebanon NH 03766 <b>Mobile:</b> (978) 828-3752 <b>E-mail:</b> <a href="mailto:lopez@cairnsurgical.com">lopez@cairnsurgical.com</a>

All adverse events and adverse device effects will be reviewed with the clinical Investigator, and, where appropriate, reported to the relevant authorities and ethics committees.

As defined in the ISO 14155:2020, a Data and Safety Monitoring Board will be created to periodically review the adverse events reported in the study and make recommendations to the company regarding any actions to be taken.

### 3.9 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT REPORTING TO SPONSOR AND EC

*This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable Independent Ethics Committees National Competent Authorities or Institutional Review Boards. The contents of this document shall not be disclosed to others without written authorization from CairnSurgical, Inc.*

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If the Investigator believes that an adverse event meets the definition of unanticipated serious adverse device effect, the Investigator must report the event to the Sponsor, without unjustified delay (e.g., within 24 hours), of the Investigator's knowledge of the effect. The Sponsor will make the final determination if an adverse event meets the definition of unanticipated adverse device effect. The Principal Investigator must report any unanticipated serious adverse device effect to the reviewing EC/IRB according to the institution's EC/IRB reporting requirements. If the relationship of the unanticipated effect to the device is unknown, the Investigator is also required to follow these reporting obligations.

The Sponsor will ensure that all unanticipated serious adverse device effect reporting requirements are followed.

### 3.10 DEVICE DEFICIENCIES REPORTING TO SPONSOR AND EC

According to ISO 14155:2020, a device deficiency is any 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 (if applicable).

All device deficiencies of an investigational device shall be documented throughout the clinical investigation and managed by the Sponsor in accordance with written procedures for the control of a non-conforming product. The Sponsor shall take, where applicable, appropriate corrective and preventive actions to protect the safety of subjects, users, and other persons. Device deficiencies of the comparator, if applicable, shall be documented.

The Sponsor shall arrange for the safe return of the investigational device that is related to the device deficiency. Device deficiencies that did not lead to an adverse event but could have led to a serious adverse device effect

- a) if either suitable action had not been taken,
- b) if intervention had not been made, or
- c) if circumstances had been less fortunate,


shall be reported. Where applicable, the analysis of used investigational devices shall be included as supportive information.

The Sponsor is responsible for review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the Sponsor and the Principal Investigator, the Sponsor shall communicate both opinions to concerned parties.

All device deficiencies that could have led to a serious adverse device effect will be reported to the Sponsor without unjustified delay (according to the indications reported in *Section 3.8*) and reported to the EC and the regulatory authority, as required by local law.

### 3.11 REPORTING TO REGULATORY AUTHORITIES BY SPONSOR

The Sponsor or designee will be responsible for reporting adverse events as appropriate per local regulations to the Regulatory Authorities. Depending upon applicable national regulations and requirements, the

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Investigator is responsible for submitting the completed SAE Report Form to the regulatory authorities with the fullest possible details within 2 calendar days of knowledge of the SAE.

### 3.12 INCIDENTS

Incident means any malfunction or deterioration in the characteristics or performance of a device, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.

Incidents in medical devices may arise due to:

- shortcomings in the design or manufacture of the device itself
- inadequate instructions for use
- inadequate servicing and maintenance
- locally initiated modifications or adjustments
- inappropriate user practice
- inappropriate management procedures
- inappropriate environment in which a device is used or stored
- selection of the incorrect device for the purpose

Serious incident means any incident that directly or indirectly led, might have led or might lead to any of the following: (a) the death of a patient, user or other person, (b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health, (c) a serious public health threat.

The Principal Investigator should report to the Sponsor all incidents or suspected incidents using the contact details reported in *Section 3.8* without unjustified delay (e.g. within 24 hours).

The reporting of the incidents will be performed according to the requirements of the Regulation EU 2017/745 (MDR), and Manufacturer's Standard Operating Procedures.


The Manufacturer will report incidents to the Competent Authority (CA) complying with the following timings, in accordance with MEDDEV 2.12-1 rev. 8 (Guidelines on a Medical Devices Vigilance System):

- Serious public health threat: immediately, but not later than 2 calendar days after awareness of this threat;
- Death or unanticipated serious deterioration in state of health: immediately after establishing a link between the device and the event but not later than 10 calendar days following the date of awareness of the event;
- Others: immediately after establishing a link between the device and the event but not later than 30 elapsed calendar days following the date of awareness of the event.

## 4. CONDUCT OF THE STUDY

### 4.1 ETHICAL CONSIDERATIONS

This study will be conducted in conformity with the ethical principles set forth by the Declaration of Helsinki, Good Clinical Practice (GCP) principles, international harmonized standards for clinical investigation of

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medical devices (ISO 14155:2020), MDCG-2020-10 (Guidance on safety reporting in clinical investigations), Regulation EU 2017/745 (MDR), MEDDEV 2.12-1 rev. 8 (Guidelines on a Medical Devices Vigilance System), the laws and regulations of the countries where the study will take place, and indemnity / insurance requirements.

#### 4.2 ETHICS COMMITTEE REVIEW

This investigational plan and the informed consent must be reviewed and approved by the appropriate Ethics Committee where the trial will be conducted before enrollment of Subjects. Changes to the investigational plan that may increase the risk or present new risks to the Subject, or that may adversely affect the validity of the trial, must be approved in writing by the Sponsor and by the Ethics Committee.

Prior to the Subject enrollment, a signed copy of the Ethics Committee approval form or a signed copy of the Ethics Committee approval letter addressed to the investigator must be submitted to the Sponsor certifying this approval.

All correspondence with the Ethics Committee should be filed in the Investigator's Study File and a copy forwarded to the Sponsor and to the site monitor.

Modifications to the study Informed Consent must have approval from Sponsor, the Ethics Committee and Competent Authority/ Ministry of Health, as required.

#### 4.3 REGULATORY COMMUNICATIONS


All necessary arrangements for the registration and approval of this study with the appropriate regulatory authorities will be undertaken by the Sponsor. As appropriate, the Sponsor will submit amendments in the Investigational Plan to the appropriate Competent Authority and investigator to obtain Ethics Committee re-approval.

Depending upon applicable national regulations and requirements, the Sponsor will submit the required Competent Authority reports, including: unanticipated adverse device effects, withdrawal of Ethics Committee approval, current investigator list, annual progress reports, recall information, final reports, investigational plan deviations, any occurrence of withdrawing the investigational devices from the investigation site for reasons related to safety of the Subject or investigational device clinical performance.

#### 4.4 INVESTIGATOR'S RESPONSIBILITIES

The selected Principal Investigator will provide written agreement to the following Sponsor requests:

- to adapt the clinical routine if required by the protocol and local procedures to comply with the standardization required for the study;
- to comply with Good Clinical Practice (GCP) and ISO 14155:2020 for the conduct of clinical investigations of medical devices;

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- to collect clinical data as outlined in this protocol and complete all relevant documentation (such as the case report form) in a legible and timely condition;
- to permit authorized Sponsor representatives, monitors and auditors to inspect all records pertaining to the trial.

The Principal Investigator will be required to submit curriculum vitae for all participating clinicians. All participating clinicians will attend training to familiarize themselves with the protocol and GCP before the initiation of the study.

Participating investigators will be trained to use the BCL through written description of the training process, and from online video that demonstrates the details of BCL placement and BCL guided surgery. Investigators will be required to affirm that they have completed the training prior to enrolling patients in the study. A clinical specialist from the Sponsor will physically attend or will be virtually present for the first surgical case at each site to facilitate use of the BCL guidance system.


The Principal Investigator is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The Principal Investigator may delegate tasks to qualified members of the investigation site team but retains responsibility for the clinical investigation.

#### 4.5 SUBJECT INFORMATION SHEET AND INFORMED CONSENT

Written informed consent and Authorization to Use and Disclose Health Information must be obtained from a potential Subject prior to conducting the screening assessments. Once the Investigator has determined the Subject's potential eligibility for the study, the benefits and risks of the procedures and the study itself must be explained to the Subject.

Study Subjects must additionally be informed that:

- Participation in this study is voluntary, that they may withdraw from this study at any time for any reason and that withdrawal of consent will not affect their subsequent medical treatment or relationship with the treating physicians.
- They will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in this study.
- Alternative procedures or treatment that may be available and the important potential benefits and risks of these available procedures or treatments.
- Any compensation for additional costs and/or injury caused to a subject attributable to participation in the study.
- Financial expenses, if any, to the subject for participating in the study as well as prorated payments, if any, to the subject for participating in the study.
- Any foreseeable circumstances and/or reasons under which the subject's participation in the study may be determined.
- The person(s) to contact for further information regarding the study and whom to contact in the event of study related injury.

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All items discussed in the Subject Information and the Informed Consent Form (ICF) must be explained. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The opportunity to ask questions and time for consideration should be given to the potential study subject. The Subject must have ample time and opportunity to read and understand the informed consent form, to inquire about details of the study, and to decide whether or not to participate in the registry. All questions about the data collection should be answered to the satisfaction of the Subject.

Neither the Investigator, nor the investigation site staff shall coerce or unduly influence a Subject to participate or to continue to participate in the clinical study.

When the Subject decides to participate in the study, the Informed Consent Form must be signed and personally dated by the Subject and Investigator or authorized designee. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the Subject Information and Informed Consent Form was accurately explained and clearly understood by the subject, and that informed consent was freely given.

After all persons have signed and dated the Informed Consent Form, the Investigator must provide the Subject with a copy of the Subject Information and the signed and dated Informed Consent Form.

A copy of the informed consent form approved by the Ethics Committee must be maintained in the Investigator's study file. The original of each subject's signed consent form must be filed by the Investigator in the Investigator Site File (ISF) Binder.


#### 4.6 CONFIDENTIALITY AND STUDY DATA PROTECTION

All information and data concerning Subjects or their participation in this trial will be considered confidential. Only those working on the Sponsor behalf, the independent Ethics Committee and regulatory authorities will have access to subject medical records and other study documents for verification of study procedures and data without violating the confidentiality of the subject. All data used in the analysis and reporting of this evaluation will not bear identifiable reference to the Subjects.

The Investigator must ensure that the Subject's anonymity will be maintained and that the confidentiality of records and documents that could identify Subjects will be protected, respecting the privacy of and confidentiality rules in accordance with applicable regulatory requirements.

- Subjects must be identified only by their assigned study number and initial on eCRFs and other records and documents submitted to the Sponsor, the monitor, and other authorized parties.
- The Investigator will keep a Subject Identification List with complete identification information (name, address, contact number, IC#) on each Subject.
- Documents not for submission to the Sponsor, such as Subject's written informed consent, should be maintained by the investigator in strict confidence.

The Subject should also be informed about the use of her health information collected during the study (study data).

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#### 4.7 INSURANCE POLICY

All patients participating in the study will be insured by the Sponsor against injury caused by their participation in the study according to local legal requirements in where the study takes place.

#### 4.8 PROTOCOL DEVIATIONS

It is the Investigator's responsibility to ensure that there are no deviations from the protocol in full compliance with all established procedures of the EC/IRB.

The Investigator will not deviate from the investigational plan for any reason except in cases of medical emergencies when the deviation is necessary to protect the life or physical well-being of the Subject.

Investigators shall be required to obtain prior approval from Sponsor or its designee before initiating deviations from the investigational plan, except where necessary to protect the life or physical well-being of a Subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., Subject did not attend scheduled follow-up visit, etc.); however, the event is still considered a deviation.

The occurrence of protocol deviations will be monitored by the Sponsor or designee. Investigator will inform their EC/IRB of all protocol deviations in accordance with their specific EC/IRB reporting policies and procedures.


In the event that an Investigator does not comply with the Investigator Agreement or protocol, the Sponsor will notify the Investigator of the site's non-compliance. Continued non-compliance may result in further escalation in accordance with the Sponsor or designee's Standard Operation Procedure (SOP).

#### 4.9 STUDY DOCUMENTATION AND RECORD ARCHIVING

##### 4.9.1 Regulatory Documents

Regulatory documents are those documents that individually and collectively permit evaluation of the study compliance with applicable regulations and the quality of the data produced. These documents include:

- Signed protocol and amendments;
- Sample CRFs (eCRFs);
- EC/IRB Approval letter, including a dated list of EC membership and members' affiliation;
- Informed consent form;
- CV of investigator and co-investigator(s);
- Correspondences with EC/IRB and Sponsor;
- Interim reports to EC/IRB;

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- Site signature log;
- Monitor visit log;
- Other appropriate documents in accordance with GCP guidelines.

These documents will be filed in an Investigator Study File provided by the Sponsor. This file shall be used to facilitate and ensure filing of all relevant regulatory documents during and after the study. The Investigator will be responsible for keeping the Investigator's Study File updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

#### 4.9.2 Source Data

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which Subject data are recorded and documented for the first time.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in *Section 4.9.3*.

To facilitate source data verification, the Investigators and Institutions must provide the Sponsor direct access to applicable source documents and reports for trial related monitoring, Sponsor audits and EC/IRB review. The study Site must also allow inspection by applicable health authorities.


#### 4.9.3 Retention of Study Documents

Records and documents pertaining to the conduct of this study, including informed consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any record to another party or moving them to another location.

#### 4.10 CASE REPORT FORM (CRF)

The Clinical Data Management System (CDMS) is a validated software compliant to ICH/GCP guidelines and FDA 21 CFR Part 11. The CDMS allows to generate an e-CRF for electronic data capture (EDC) of data. The server/s hosting the CDMS (Microsoft Azure), are compliant to the guidelines of ISO 20000-1:2011, ISO 27001:2013, ISO 27017:2015, ISO 27018:2014, ISO 9001:2015, SOC 1 2 3, GxP (FDA 21 CFR Part 11), HIPAA BAA, EU GDPR. The Server/s are managed by 1MED SA (or a specialized delegated company) in order to guarantee maximum data protection with secure back-up hosting.

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1MED SA guarantees technical support dedicated to the users of eCRF, for any kind of problem or enquiry. All investigational centers must have a secure internet connection to comply with eCRF requirements.

#### 4.10.1 CRF Transmittal and Retention

The Sponsor and delegates will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via electronic data capture (EDC) through the use of eCRFs. The Site will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor or delegates will request data clarification from the Site, which the Site will resolve electronically in the EDC system.

eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored by Sponsor's delegates and records retention for the study data will be consistent with the Sponsor standard procedures.

#### 4.10.2 CRF Review and Query Generation

The study monitor or Clinical Research Associate (CRA) will review the eCRFs for completeness and accuracy. Periodically, edit check, based on data validation plan, will be run on the data. Errors detected or suspected will require clarification or correction of errors. Modified and/or corrected data elements must have data element identifiers that reflect the date, time, originator and reason for the change, and must not obscure previous entries (audit trail). A field should be provided allowing originators to describe the reason for the change (e.g., transcription error). Any data correction must be documented and approved by the investigator. Wherever possible the investigator should assist in clarification or correction of errors detected within 48 hours of their being brought to the attention of the Investigator.

### 4.11 CRF: STUDY MONITORING, AUDITS AND INSPECTIONS

The data must be recorded in an electronic CRF within 5 working days from each Subject study visit. The Investigator will enter data and perform corrections as per GCP requirements.


The Investigators will assign for each Subject a screening number, in an ascendant order according to the informed consent signature, and such number will be the only identification code used that will be also entered into the eCRF as Subject screening number.

The Investigator/s should complete and store the lists of evaluated Subjects. For each one the following information should be included: identity, screening number, date of visit.

The Investigator will also maintain a pre-screening log to record details of all Subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. This log will not include the identity of Subjects.

The study monitor (CRA) will contact and visit the investigational site at study initiation, throughout the study and after the study completion to perform the site closure visit. CRA will be allowed to verify the various study records: eCRF, ISF and source data (source data is any information in original records and certified copies of original records on clinical findings, observations or other activities in a study necessary for the reconstruction

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and evaluation of the study). Source data are contained in source documents – in fully respect of Subject's confidentiality – in order to fulfill both the Sponsor's responsibility in assuring the proper conduct of the study regarding protocol and GCP adherence and the completeness and accuracy of the data recorded on the eCRF.

The Investigator and/or study team members are expected to be available during the monitoring visits, to answer questions and to provide any missing information. The site might be audited by Sponsor personnel or inspected by regulatory national and international authorities during and after the study has been completed.

#### 4.12 DATA MANAGEMENT

The eCRFs are to be completed using a Sponsor-designated EDC system. The Site will receive training, as per ICH/GCP requirements, and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the Investigator or a designee.

At the end of the study, the Investigator will receive Subject data for the site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.


The Investigator must ensure that the clinical data required by the clinical investigation plan are carefully reported in the eCRF. The Investigator must also check that the data reported in the eCRF correspond to those in the official files. All data entered in the eCRF will have a Source Record (electronic or paper clinical files to be identified during selection visits). All medical terms, conditions, adverse events, drugs use indication and in general all free text comments must be reported in English. Drugs should be reported using the active ingredient in English. Data must be entered into eCRFs in English by the designated site personnel as soon as possible after a Subject visit, and monitors will have access to data recorded. These data will be reviewed versus source documents by study monitors for completeness and acceptability during monitoring visits. Any correction to the eCRFs' entries must be carried out by the Investigator or a designated member of staff. Corrections are recorded in an audit trail that records the old information, the new information, and identification of the person making the changes, date of correction made and reason for change. In the interests of completeness of data acquisition, the questions which are repeated in each section of the eCRFs should be answered in full, even if there are no changes from a previous examination. A reasonable explanation must be given by the Investigator for all missing data.

The Investigator or designees named in the Clinical staff list, will review the eCRF for accuracy and completeness. The Investigator must electronically sign and date the eCRF pages as indicated.

#### 4.13 INVESTIGATIONAL DEVICE ACCOUNTABILITY

Each site will be provided with MD inventory and accountability forms to maintain accurate written documentation of all devices transfer processes between the Sponsor, the site, the Investigator, and the patient enrolled. The MD inventory form will be used to document when and how many MDs are delivered to the study site. Site staff has to countersign the form to confirm date of receipt and amount received.

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The study product provided for this study will be used only as directed in this study protocol.

The Principal Investigator (or delegates) will indicate the date of the surgical procedure and fill the information in the Subject IP Accountability Form for each patient.

At the end of the clinical investigation and/or before the expiration date, any partially used/unused component must be returned to Sponsor for destruction.

Dispose of BCL System components must occur in accordance with applicable local, state, and federal laws and regulations.

#### 4.14 FINAL STUDY REPORT

Upon completion or termination of the study, a report shall be completed in accordance with the applicable regulations, even if the clinical investigation was terminated prematurely. The report must be submitted within 6 months of completion or termination of the trial. Where applicable, the clinical investigation report shall be made available to the Principal Investigator for review and comment. The Sponsor shall maintain records confirming that the clinical investigation report has been provided for review. In accordance with applicable requirements, the clinical investigation report shall be provided to the EC and regulatory authorities.

The Investigator's final report will include:


- Introduction: A brief description of the rationale and objectives of the trial.
- Methods: A description of the methods employed and any deviations from the investigational plan.
- Trial population: A statement of the number of Subjects evaluated, of the number of drop-outs and reasons for them, and description of the initial nature and severity of medical conditions for which the Subjects were evaluated.
- Results and discussions: A clinical assessment of the effect of the investigational treatment on the medical condition of the Subjects and a description of complications reported with an indication of their relationship to the investigational treatment.
- Conclusion: A summary statement of the Principal Investigator's opinion of the performance and safety of the investigational treatment in the Subjects enrolled at investigational site.

### 5. STUDY MONITORING

#### 5.1 GENERAL REQUIREMENTS

The Sponsor or its designees will conduct investigational site monitoring to ensure that the Investigator and his/her collaborators are in compliance with the investigational plan and the Investigator's Agreement. The monitors will verify source documentation against completed CRFs and resolve any discrepancies. Monitors and the Sponsor will evaluate circumstances where an investigator deviates from the investigational plan.

The Sponsor retains the right to remove either the investigator or the investigational site from the study. The Sponsor will fulfill its responsibilities in collecting and tracking data forms and instituting quality control measures for the data entry verification and trial compliance. The Sponsor will review significant new

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information including unanticipated adverse events and ensure that such information is provided to the Competent Authorities, investigators and to all reviewing Ethics Committees.

#### 5.1.1 Subject Termination

All Subjects are expected to continue in the "CS-BCL-EU2021" study except in the event of death or upon a Subject's early withdrawal from the clinical study. Although every Subject is informed of her right to withdraw at any time from the clinical study. All measures should be taken by the Investigator to encourage Subjects to return for required follow-up visits. If a large number of Subjects are lost to follow-up, attaining clinical study objectives could be jeopardized. The Investigator may prematurely discontinue or withdraw any Subject from the study if any of the study procedures are deemed potentially harmful to the Subject.

Once a Subject has been enrolled in the study, she may withdraw her consent to participate in the study at any time without prejudice. Participation in this clinical investigation is entirely voluntary. In as much as possible, every attempt should be made to conduct an exit/final visit (including physical exam, review of concomitant medications, adverse events, etc.). The reason for early discontinuation or withdrawal will be documented in the source documents and case report forms.

Subjects are terminated from the study at death. All terminations should be recorded on the End of Study CRF after monitoring.

#### 5.1.2 Lost to Follow-Up


A Subject will be considered lost to follow-up and terminated from the study when all of the following criteria have been met:

- Failure to complete two consecutive visits (without due cause); and
- Documentation of three unsuccessful attempts (on three different days over a period of approximately 1 month) by the Investigator or designee to contact a Subject; and
- A letter from the Investigator to Sponsor or designees requesting Subject termination from the clinical study; and
- Prior agreement from Sponsor to remove the Subject from the clinical study.

### 5.2 STUDY OVERSIGHT

Primary data collection based on source-documented hospital chart reviews will be performed by the Sponsor personnel or its designee monitor at each clinical site. eCRFs will be completed in an expedited manner. The site will be visited regularly to ensure that the study is conducted in full compliance with all applicable regulations and the investigational plan. A pre-study meeting will be held with the potential investigational site in order to inform the prospective investigator and staff concerning features of investigation plan, applicable regulations and requirements, and expectations of the study, including the number and time frame for subject enrollment, subject selection, informed consent, required clinical data and record keeping.

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The prospective investigational site will be evaluated to ensure that it has an adequate subject base and can provide sufficient staff and documentation support to conduct the study properly.

The Sponsor study monitor will maintain personal contacts with the investigator and staff throughout the study by telephone, mail, e-mail, and on-site visits. The monitor will compile and file an observation report at each visit. Monitoring is intended to ensure continued protocol compliance, adequate subject enrollment, and accurate data reporting.

Upon closure of the study at an investigational site, the study monitor will make a final onsite visit. The purpose of this visit is to collect all outstanding study documents, ensure that the investigator's files are accurate and complete, review record retention requirements with the investigator, make a final accounting of all study supplies shipped to the investigator, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements for the study are met. The observations and actions made at this visit will be documented as a final report for investigators and the Sponsor's acceptance.

### 5.3 DATA MANAGEMENT AND REVIEW

The Sponsor agrees to be responsible of the verification that the trial is conducted implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that the trials are conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, GLP, and the applicable federal, state and local laws, rules and regulations and guidelines relating to the conduct of the clinical trial.

The Investigator, or an individual designated by the Investigator, is responsible for recording all data from the trial on the eCRF's supplied by the Sponsor.


The Sponsor personnel or its designee will review completed eCRFs at regular intervals throughout the investigation. To this end, the investigator must permit inspection of the investigation files and subject CRFs by such representatives and/or responsible governmental agencies.

## 6. SPONSOR RESPONSIBILITIES

### 6.1 ROLE OF THE SPONSOR

As the initiator of this clinical study, the Sponsor has the overall responsibility for the conduct of the investigation. The Sponsor will have certain direct responsibilities and will delegate other responsibilities.

The general duties of the Sponsor (or its designee) consist in submitting the clinical investigation notification to National Competent Authorities, obtaining EC/IRB approvals, selecting qualified investigator, obtaining a signed Investigator's Agreement ensuring proper investigational site monitoring, and ensuring that informed consent is obtained. The Sponsor will prepare written progress reports and a final report, as required.

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The Sponsor or its designees will conduct investigational site monitoring to ensure that the investigator and the collaborators are in compliance with the investigational plan and the Investigator's Agreement. The monitors will verify source documentation against completed CRFs and resolve any discrepancies. Monitors and the Sponsor will evaluate circumstances where the Investigator deviates from the investigational plan. The Sponsor retains the right to remove either the Investigator or the investigational site from the study.

## 6.2 STUDY SUSPENSION OR TERMINATION

The Sponsor reserves the right to terminate this study and remove all study materials from the study site at any time. The study may be suspended or terminated for any of the following reasons:

- It becomes apparent that Subject enrollment is unsatisfactory with respect to quality or quantity.
- Data recording is inaccurate and/or incomplete.
- Violation or deviations from the signed protocol.
- The incidence and/or severity of adverse events in this or in other studies indicate a potential health hazard caused by the treatment under study.

Should a determination be made that the study should be suspended or terminated at investigation site then:

- Enrollment shall be suspended or terminated at investigation site.
- Currently enrolled subjects will be followed according to the protocol, which may be amended to accommodate study suspension or termination.
- The Sponsor (or its designee) shall promptly inform the investigators and Ethic Committee of the suspension or termination and the reasons for it.

Should the Sponsor decide to terminate the study, the investigator will complete the CRFs as far as possible. The completed CRFs and any study materials will then be collected by the Sponsor or its designee.


## 6.3 SPONSOR STUDY FILES

The Sponsor or designee will maintain copies of correspondence, data, adverse device effects and other records related to the investigational plan and to the signed Investigator's Agreements.


## 6.4 PUBLICATION POLICY

All clinical information obtained in this study will be considered confidential and used only for research purposes. The identity of individual subjects will be kept confidential in so far as the law and safe medical practice allow. It is planned that the results of this clinical investigation will be submitted for publication in scientific journals or presented at scientific congresses; Subject identities will not be disclosed.

The Sponsor will comply with all requirements for publication of study results.

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The Investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

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## 8. APPENDIX

### 8.1 APPENDIX 1: Positive Margin Rate (PMR)

The positive margin rate (PMR) is defined as the proportion of patients with positive margins after breast-conserving surgery (BCS).

According to the consensus guideline criteria (Moran et al. 2014; Morrow et al. 2016) a positive margin is defined as follows:

- Invasive breast cancer (IBC): margins for cases that contain only invasive cancer, or a mixture of invasive cancer and ductal carcinoma in situ (DCIS) are considered positive if invasive cancer or DCIS is present on the inked specimen edge.
- DCIS: margins for cases that contain only DCIS are considered positive if DCIS is present <2 mm from the inked edge. Cases that are mainly DCIS, but also have one or more foci of microinvasion (defined as cancer <1 mm in diameter) will be considered to be DCIS, as per consensus guidelines.

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### 8.2 APPENDIX 2: BREAST-Q

**Purpose.** The BREAST-Q can provide essential information about the impact and effectiveness of breast surgery from the patient's perspective.


**Description.** The BREAST-Q is a rigorously developed patient-reported outcome measure for use in cosmetic and reconstructive breast surgery and clinical practice. The BREAST-Q conceptual framework covers 2 domains: quality of life; and patient satisfaction. Independent modules for breast cancer (mastectomy, breast-conserving therapy, reconstruction), augmentation and reduction/mastopexy were developed. Each module is composed of multiple independently functioning scales. The variety of scales provides flexibility to choose the subset of scales best suited to measure the outcomes of interest in any given study or clinical situation.

**Score interpretation.** There is no overall or total BREAST-Q score, only scores for each independent scale. Scales are transformed into scores that range from 0-100. The scores are computed by adding the response items together and then converting the raw sum scale score to a score from 0-100. For all BREAST-Q scales, a higher score means greater satisfaction or better QoL (depending on the scale).

#### Link:

<https://qportfolio.org/breast-q/breast-cancer/>

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