DILON TECHNOLOGIES

MARGINPROBE®

(MarginProbe System – Model SA0590020)

User Manual

User Manual P/N: PB0590220

Caution: Federal law restricts this device to sale by or on the order of a physician

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PATENTS

This product is protected by the following US Patents: 7,899,515; 8,147,423; 8,319,502; 9,750,425. Chinese Patents: ZL200680019026.4; ZL200980124258.X; ZL200780051197.X. EU patents: EP1890596; EP2129281; EP2304456; EP2118801.

TRADEMARKS

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This User Manual refers to: MarginProbe® System - Model SA0590020

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1. BEFORE YOU START

Warning

- Read this manual to become familiar with all operating procedures and clinical requirements before attempting to operate the system.
- The MARGINPROBE® system may be serviced only by Dilon Medical Technologies qualified personnel.

Conventions Used in this Manual

The following conventions in the form of notes, cautions and warnings are used in this manual:

Note

The content of this ***Note*** offers general information that is important to keep in mind.

Caution

A ***Caution*** alerts the user to the possibility of a potentially hazardous situation which, if not avoided, may result in minor or moderate injury to the user or damage to the equipment.

Warning

A ***Warning*** alerts the user to the possibility of injury, death, or serious adverse reactions associated with the use or misuse of the system.

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2. SAFETY AND REGULATORY ISSUES

This chapter describes the safety issues regarding the use and maintenance of the MARGINPROBE® system, with special emphasis on electrical safety.

The system is designed for safe and reliable use, when used in accordance with proper operation procedures. The user and all other personnel operating the system should be familiar with the safety information provided in this chapter. Dilon Medical Technologies assumes no liability whatsoever for any damage or injury as a result of an application of a product which is not in strict accordance with the instructions provided with the product.

Warning

- Read this chapter to be familiar with all of its safety requirements and operating procedures prior to operating the system.
- The MARGINPROBE® probe is designed for use only with the MARGINPROBE® console.
- High voltage is present inside the console.
- Always be aware of the possible dangers and take proper safeguards as described in this guide.
- For complete contact information please refer to page A of this manual.

Intended Use

The MARGINPROBE® System is an adjunctive diagnostic tool for identification of cancerous tissue at the margins (≤ 1mm) of the main ex-vivo lumpectomy specimen following primary excision and is indicated for intraoperative use, in conjunction with standard methods (such as intraoperative imaging and palpation) in patients undergoing breast lumpectomy surgery for previously diagnosed breast cancer.

Device Users

The users are medical professionals. The probe will be applied to the tissue by a surgeon.

Warnings, Precautions, and Contraindications

Contraindications

The MARGINPROBE® System should not be used:

- To replace standard tissue histopathology assessment
- On *ex-vivo* lumpectomy specimens that have been exposed to saline, ultrasound gel or local anesthetic solutions.
- On *in-vivo* tissue (i.e. it should not be used within the lumpectomy cavity)
- On tissues other than breast tissue (i.e. it should not be used on Sentinel Lymph Nodes)
- Closer than 1.5 mm to a fine needle localization guidewire

Warnings

- The MARGINPROBE® should be used on tissue specimens within 20 minutes of excision.
- The MARGINPROBE® should not be used in patients who undergo full cavity excision following removal of the main lumpectomy specimen during the initial lumpectomy procedure.
- The MARGINPROBE® has not been studied in patients with:
  - Multicentric disease (histologically diagnosed cancer in two different quadrants of the breast), unless resected in a single specimen
  - Bilateral disease (diagnosed cancer in both breasts)
  - Neoadjuvant systemic therapy
  - Previous radiation in the operated breast
  - Prior surgery at the same site in breast
  - Implants in the operated breast
  - Pregnancy
  - Lactation
  - Cryo-assisted localization

Precautions

- The main *ex-vivo* lumpectomy specimen is defined as the initially excised lumpectomy specimen, without any of the lumpectomy cavity shavings that may have been subsequently taken during the procedure. The device has not been studied for use on tissue shavings excised from the lumpectomy cavity.
- The MARGINPROBE® system should be used in addition to standard intraoperative methods of assessing margin status.
- Moving the probe before suction release may potentially damage and affect tissue histopathology
- The MARGINPROBE® Probe should only be used with the MARGINPROBE® Console.
- The MARGINPROBE® Probe is designed for single patient, single-use only and must be properly discarded after use.

- The MARGINPROBE® Probe is supplied sterile. If the sterile pack is torn or has been opened, do not use the probe.
- Do not use a MARGINPROBE® Probe that has passed its expiration date

Potential Adverse Effects of the Device on Health

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Extension of procedure time
- Errors in device reading
- Unnecessary removal of healthy tissue with a potential negative impact on cosmetic results or cosmetic appearance.
- Infection
- Local tissue damage
- Bleeding

For the specific adverse events that occurred in the clinical studies, please see the next section (Clinical Data) below.

Clinical Data

MarginProbe Post Approval Study:

The MarginProbe Post Approval Study was conducted to confirm the study results observed in the pivotal IDE clinical trial of MarginProbe. The study was mandated as part of the PMA approval and the PAS protocol was approved under PMA P110014 S001. A subsequent amendment was approved under PMA P110014 S010 to allow for remote follow up. The results of this Post Approval Study demonstrated consistency with the Pivotal Study results and confirms product performance in a study that is consistent with the "real world" usage.
A summary of the clinical study is presented below.

Summary of the Post-Approval Study Methods

A. Study Objective

The study objective was to enhance the body of clinical evidence beyond the pivotal IDE study. Specifically, the PAS was designed to determine the MarginProbe System's diagnostic accuracy at the Margin Level and impact on Positive Margin[1] presence originating from the Main ex-vivo lumpectomy specimen after the initial lumpectomy surgery.

B. Study Design

This was a prospective, multicenter, randomized, double arm, controlled study of adjunctive use of the MarginProbe System (SOC + Device) vs. Standard of Care, including additional inspection (SOC + Additional Inspection).

The surgeon performed a lumpectomy to obtain the main specimen, which potentially contained the diagnosed lesion. All main specimens were suture oriented, so as to uniquely define the aspects of the specimen relative to the body (lateral, medial, superior, inferior, deep, anterior). The orienting suture was placed in the center of the margin as indicated by the surgeon. The surgeon visually inspected and palpated the tissue and margins were resected if deemed necessary.

Randomization took place immediately after the main specimen was excised, oriented, center marked, palpated, and palpation-based margins resected, if necessary. In the Device arm, MarginProbe was used on the six margins of the specimen. According to device readings, margins were resected, as necessary. Intra-operative imaging was performed following device use.

Pathological assessment was standardized and identical for both study arms. Pathologists were blinded to the randomization assignment when they evaluated each

[1] A positive margin is defined in this study as a margin microscopically measured and reported in the histology report to have cancer within 1 mm or less of the inked surface.

sample. Subjects were followed until the end of the lumpectomy procedure. Data were collected up until six (±1) months after the lumpectomy.

In the event that re-excision (lumpectomy/mastectomy) was required during the data collection period, the data collection period was reinitiated according to the above outline. Data were collected on any additional ipsilateral surgical procedures, including axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB). The study flow chart is presented in Figure 2-1below.

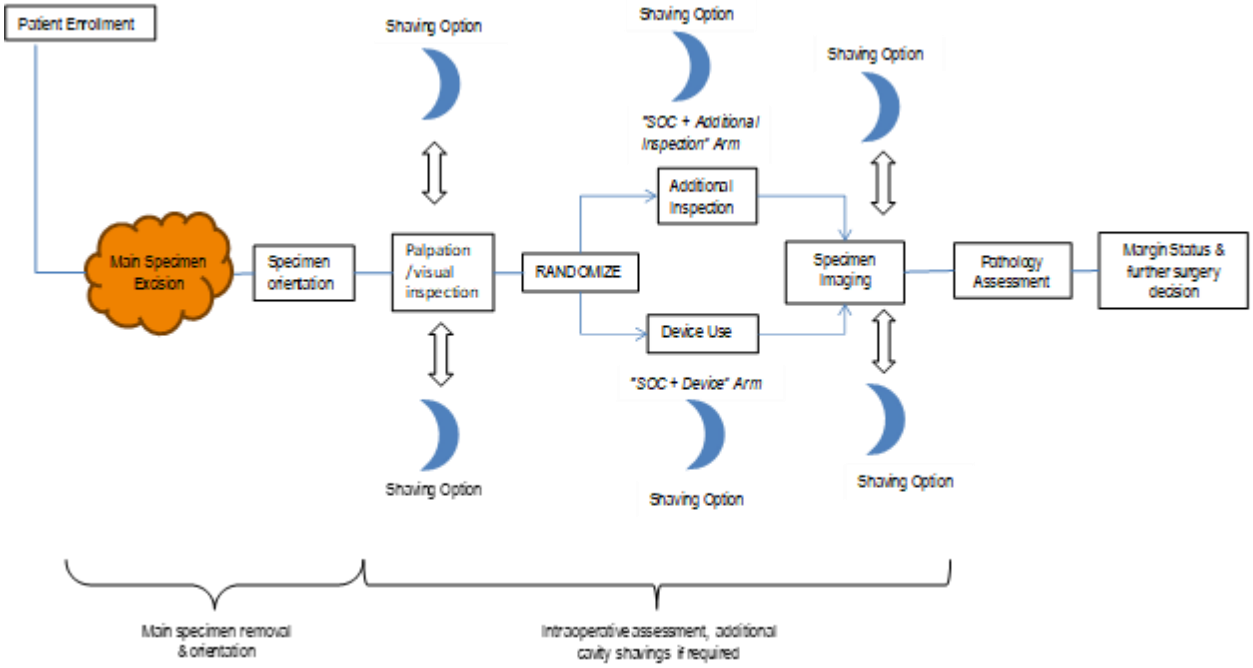


Figure 2-1: PAS Study Design

C. Study Population

The study was a multi-center study randomizing 440 subjects (recruited 438), 220 in each arm (recruited 214 subjects in the SOC + Device arm and 224 subjects SOC + Additional Inspection arm). The study was designed to include a maximum of 20 centers within the United States (U.S.), with at least half of them being new centers that did not enroll subjects in the pivotal IDE study. A total of eleven centers were utilized in the study and a summary of each center with their enrollment is provided in section F.

1. Eligibility Criteria

Enrollment in the Post Approval Study was limited to patients who met the following inclusion criteria:

1) Women histologically diagnosed with carcinoma of the breast.
2) Women with non-palpable malignant lesions, requiring image guided localization.

3) Undergoing lumpectomy (partial mastectomy) procedure.
4) Age 18 years or more.
5) Signed ICF.

Patients were not permitted to enroll in the Post Approval Study if they met any of the following exclusion criteria:

1) Multi-centric disease (histologically diagnosed cancer in two different quadrants of the breast).
2) Bilateral disease (diagnosed cancer in both breasts).
3) Neo-adjuvant systemic therapy.
4) Previous radiation in the operated breast.
5) Prior surgery in the same site in the breast.
6) Woman histologically diagnosed by an open biopsy procedure.
7) Implants in the operated breast.
8) Pregnancy.
9) Lactation.
10) Participating in any other investigational study for either drug or device which could influence collection of valid data under this study.
11) Subjects for whom complete cavity shaving is planned (sites where this is the routine practice of the investigator will also be excluded from participation in the study).

2. Disposition of Patients:

Table 2-1 presents the disposition for the 470 subjects screened for participation in the study. Of the 470 subjects screened, 25 did not meet inclusion/exclusion criteria. Of the 445 subjects who met inclusion/exclusion criteria, 7 declined participation: 2 subjects chose to have surgery at a different facility, 2 withdrew consent, 1 declined due to logistical issues, 1 due to COVID-19 medical center restrictions prohibiting clinical study enrollment and 1 due to study suspension by IRB. The balance of enrolled subjects was 438 which is in line with the target sample size.

Table 2-1: Subject Disposition

	N [%]
Subjects screened	470 (100.0%)
Subjects that did not meet the inclusion/ exclusion criteria	25 (5.32%)
Subjects that met the inclusion/ exclusion criteria	445 (94.68%)
Subjects for whom participation declined	7 (01.49%)
Total subjects enrolled	438 (93.19%)

3. Demographic and Other Baseline Characteristics

presents demographic data by treatment group. The study population was women with a mean age of 63. There were no apparent differences in demographic characteristics between treatment groups. The study population reflects the United States breast cancer population in age at diagnosis, as well as incidence by race and ethnicity.[27] In fact, as opposed to many clinical studies wherein the minority population is underrepresented, this clinical study included a higher percentage of minority women with African Americans comprising nearly 18% of the study population.

Table 2-2: Demographic Data by Treatment Group

Parameter	Treatment Group		All	Difference in proportions (Device + SOC – SOC + Additional Inspection), 95% CI
	Device + SOC	SOC + Additional Inspection		
N (%)	214 (48.86%)	224 (51.14%)	438 (100.0%)	
Age (yrs) Mean (S.D.)	62.17 (10.79)	63.29 (10.71)	62.74 (10.75)	-1.13 (-3.15, 0.89)
Female n (%)	214 (100.00%)	224 (100.00%)	438 (100.00%)	
African American	34 (15.89%)	44 (19.64%)	78 (17.81%)	-3.75% (-10.90% - 3.39%)
American Indian or Alaska native	0 (00.00%)	1 (00.45%)	1 (00.23%)	-0.44% (-1.31% 0.43%)
Asian	8 (03.74%)	6 (02.68%)	14 (03.20%)	1.06% (2.24% 4.37%)
Other, Mixed	1 (00.47%)	1 (00.45%)	2 (00.46%)	0.02% (-1.24% 1.28%)
White	142(66.36%)	148 (66.07%)	290 (66.21%)	0.28% (-8.58% 9.14%)
White-Hispanic	20 (09.35%)	14 (06.25%)	34 (07.76%)	3.09% (-1.93% 8.12%)
Not known	09 (04.21%)	10 (04.46%)	19 (04.34%)	-0.26% (-5.2% 4.76%)

Table 2-3 presents baseline characteristics by treatment group. There were no apparent differences in baseline characteristics between treatment groups. The study population reflects the average BMI of 29.6 for women in the United States.[28] The BRACA categorization for the women in the study was largely unknown at the time of enrollment which is consistent with clinical practice. This was also largely unknown in the PMA pivotal clinical study as well as BRACA testing is commonly not performed until after lobectomy is performed.

Table 2-3: BMI, BRCA and Bra Cap Size

Parameter	Treatment Group		All	Difference in proportions (Device + SOC – SOC + Additional Inspection), 95% CI
	Device + SOC	SOC + Additional Inspection		
BMI - mean (std)	29.68 (7.13)	29.39 (6.48)	29.53 (6.80)	-0.29 (-1.56, 0.99)
BRCA				
Yes	3 (01.40%)	2 (00.89%)	5 (01.14%)	0.51% (-1.49%, 2.51%)
No	49 (22.90%)	37 (16.52%)	86 (19.63%)	6.38% (-1.06%, 13.82%)
Not Known	162 (75.70%)	185 (82.59%)	347 (79.22%)	-6.89% (-14.48%, 0.71%)
Total	214 (100.00%)	224 (100.00%)	438 (100.00%)	
Bra Cup Size n (%) Subjects				
A	6 (02.80%)	4 (01.79%)	10 (02.28%)	1.02% (-1.79%, 3.83%)
B	35 (16.36%)	30 (13.39%)	65 (14.84%)	2.96% (-3.70%, 9.63%)
C	51 (23.83%)	54 (24.11%)	105 (23.97%)	-0.28% (-8.27%, 7.72%)
D	28 (13.08%)	36 (16.07%)	64 (14.61%)	-2.99% (-9.59%, 3.61%)
DD	16 (07.48%)	19 (08.48%)	35 (07.99%)	-1.01% (-6.08%, 4.07%)
DDD	2 (00.93%)	6 (02.68%)	8 (01.83%)	-1.74% (-4.22%, 0.73%)
E	1 (00.47%)	1 (00.45%)	2 (00.46%)	0.02% (-1.24%, 1.28%)
F	1 (00.47%)	0 (00.00%)	1 (00.23%)	0.47% (-0.45%, 1.38%)
G	0 (00.00%)	2 (00.89%)	2 (00.46%)	-0.89% (-2.12%, 0.34%)
Not known	74 (34.58%)	72 (32.14%)	146 (33.33%)	2.44% (-6.40%, 11.27%)
Total	214 (100.00%)	224 (100.00%)	438 (100.00%)	

Table 2-4 presents pre-operative diagnosis by treatment group. Table 2-4 presents the number of subjects with a diagnosis, with specific categories combined. For subjects with IDC + ILC, the Mixed Invasive category was used, and for subjects with invasive and non-invasive diagnoses, the Mixed category was used. The Device and Control groups were similar with respect to diagnosis. The study population is largely consistent with the PMA

pivotal study demographics albeit not exactly the same and is consistent with expectations in clinical practice in the US.

Table 2-4: Frequency Distribution of Subject Diagnosis (Combined Categories)

Subject Diagnosis	Treatment Group		All	Difference in proportions (Device + SOC – SOC + Additional Inspection), 95% CI
	Device + SOC	SOC + Additional Inspection		
Invasive Ductal Carcinoma	95 (44.39%)	99 (44.20%)	194 (44.29%)	0.20% (-9.11%, 9.50%)
Invasive Lobular Carcinoma	12 (05.61%)	17 (07.59%)	29 (06.62%)	-1.98% (-6.62%, 2.66%)
Ductal Carcinoma in Situ	47 (21.96%)	49 (21.88%)	96 (21.92%)	0.09% (-7.66%, 7.84%)
Tubular Carcinoma	1 (00.47%)	0 (00.00%)	1 (00.23%)	0.47% (-0.45%, 1.38%)
Mucinous Carcinoma	3 (1.40%)	0 (00.00%)	3 (00.68%)	1.40% (-0.17%, 2.98%)
Medullary Carcinoma	0 (00.00%)	0 (00.00%)	0 (00.00%)	0.00% (0.00%, 0.00%)
Papillary Carcinoma	2 (00.93%)	1 (00.45%)	3 (00.68%)	0.49% (-1.07%, 2.05%)
Other	7 (03.27%)	9 (04.02%)	16 (03.65%)	-0.75% (-4.25%, 2.76%)
Mixed [b]	45 (21.03%)	45 (20.09%)	90 (20.55%)	0.94% (-6.63%, 8.51%)
Mixed Invasive [a]	2 (00.93%)	4 (01.79%)	6 (01.37%)	-0.85% (-3.01%, 1.31%)
Total	214 (100.00%)	224 (100.00%)	438 (100.00%)	

[a] Mixed invasive=Invasive Ductual Carcinoma+Invasive Lobular Carcinoma.
[b] Mixed=more than 1 diagnosis and not only invasive carcinoma.

4. <u>Surgical Procedure</u>

Table 2-5 presents the number and percent of subjects with a palpable tumor excised during lumpectomy. While all subjects had non-palpable lesions at screening (inclusion criteria), the lesion may or may not have been palpable in the specimen after removal. There were no apparent differences between treatment groups with respect to palpable tumors during excision.

Table 2-5: Frequency Distribution of Palpable Tumor during Lumpectomy by Treatment Group

Was the Tumor Palpable in The Excised Specimen	Treatment Group		All
	Device + SOC	SOC + Additional Inspection	
No	117 (54.67%)	110 (49.11%)	227 (51.83%)

Yes	97 (45.33%)	114 (50.89%)	211 (48.17%)
Total	214 (100.00%)	224 (100.00%)	438 (100.00%)

5. Pathology

Main specimen

Table 2-6 presents the volume of the main specimen. There were no apparent differences between treatment groups with respect to weight and volume of the main specimen.

Table 2-6: Descriptive Statistics of Specimen Volume by Treatment Group

Specimen Parameter	Treatment Group		All
	Device + SOC	SOC + Additional Inspection	
Mean (Std) Volume (cm^3)	50.19 (78.35)	46.58 (55.68)	48.34 (67.63)

Table 2-7 presents tumor type (as assessed by post-operative histopathology) by treatment group.
In Table 2-7, tumor type is presented as recorded in the CRF, and each subject could have more than one tumor type.

Table 2-7: Frequency Distribution for Tumor Type by Treatment Group

Subject Diagnosis	Treatment Group		All
	Device + SOC	SOC + Additional Inspection	
Invasive Ductal Carcinoma	141 (42.73%)	147 (41.76%)	288 (42.23%)
Invasive Lobular Carcinoma	18 (05.45%)	25 (07.10%)	43 (06.30%)
Ductal Carcinoma in Situ	143 (43.33%)	151 (42.90%)	294 (43.11%)
Tubular Carcinoma	4 (01.21%)	2 (00.57%)	6 (00.88%)
Mucinous Carcinoma	6 (01.82%)	7 (01.99%)	13 (01.91%)
Medullary Carcinoma	1 (00.30%)	0 (00.00%)	1 (00.15%)
Papillary Carcinoma	0 (00.00%)	2 (00.57%)	2 (00.29%)
No tumor found	10 (03.03%)	12 (03.41%)	22 (03.23%)
Other	7 (02.12%)	6 (01.70%)	13 (01.91%)
Total	330 (100.00%)	352 (100.00%)	682 (100.00%)

6. Resected Margins

Table 2-8 presents average volume of resected margins by treatment group during the lumpectomy. It appears that there is a trend toward a slightly higher volume in the Device group however, this difference is not statistically significant.

Table 2-8: Descriptive Statistics of Resected Margins Volume per Subject by Treatment Group

Specimen Parameter	Treatment Group		All
	Device + SOC	SOC + Additional Inspection	

	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Volume (cm^3)	214	16.17 (19.83)	224	9.03 (15.66)	438	12.52 (18.16)

Note: The overall number of shavings is 660 for the SOC + Device arm and 361 for the SOC + additional inspection arm.

7. Specimen Management

Table 2-9 presents margin width in the operated breast after lumpectomy and re-excision procedures. The dimension of the excised sample is consistent between Device and Control groups.

Table 2-9: Margin Width in the Operated Breast after Lumpectomy and Re-Excision Procedures

	Device + SOC			SOC + Additional Inspection		
	Lumpectomy	Re-excision Procedure		Lumpectomy	Re-excision Procedure	
	N (%)			N (%)		
	1	2	3	1	2	3
>1 mm	163 (76.17%)	23 (67.65%)	1 (100.00%)	142 (63.39%)	22 (78.57%)	2 (100.00%)
<1 mm	51 (23.83%)	11 (32.35%)	0 (00.00%)	82 (36.61%)	6 (21.43%)	0 (00.00%)
All	214 (100.00%)	34 (100.00%)	1 (100.00%)	224 (100.00%)	28 (100.00%)	2 (100.00%)

D. Data Source

1. Data Sets analyzed:

All 438 women were included in the Safety analysis set.

The Efficacy Analysis was performed using data from all subjects that were randomized to either Device or Control, had valid histology data and had valid MarginProbe data (when assigned the Device Group). This analysis data set was termed All Valid Subjects, AVS. The AVS analysis set is consistent with the Safety data set and includes all 438 randomized subjects (214 Device and 224 Control). This was the data set utilized to analyze the Secondary Endpoint II.

For the Primary Endpoint, the analysis data set was based upon the Device performance and therefore included all Positive Specimen Subjects (PSS). A total of 214 subjects were included in this analysis data set. Further, the Secondary Endpoint (I) required an evaluation of Negative Specimen Subjects (NSS) and included 224 subjects in total. There were no subjects excluded from the Efficacy Analyses.

Table 2-10:Data Sets Analyzed - Number of Patients

		Treatment Group	

Analysis Set	Subjects Included	Device + SOC N (%)	SOC + Additional Inspection N (%)	All N (%)
Safety Set	All subjects for whom surgical procedure was initiated	214 (100.00%)	224 (100.00%)	438 (100.00%)
Effectiveness Sets				
AVS (SE II[a])	All randomized subjects	214 (100.00%)	224 (100.00%)	438 (100.0%[b])
PSS (PE[a])	Positive Specimen	89 (41.59%)	125 (55.80%)	214 (48.86%)
NSS (SE I[a])	Negative Specimen	122 (57.01%)	102 (45.54%)	224 (51.14%)

[a] Corresponding name of analysis set from the Main SAP.
[b] Represents the percent of all subjects included in effectiveness analyses.

E. Key Study Endpoints

1. <u>Co-primary effectiveness endpoints:</u>

1) Sensitivity at the Margin Level
2) Specificity at the Margin Level
3) Incomplete Surgical Resection (ISR[2]) - Positive Margin on the Main ex-vivo lumpectomy specimen after the initial lumpectomy surgery that was not addressed by taking a shaving(s) corresponding to the positive margin(s).

[2] ISR is a focused assessment of what is within the control of the MarginProbe device and that is to cause additional cavity shavings. The pathology of the shavings is outside of the scope of this endpoint.

2. Secondary effectiveness endpoints:

1) Proportion of subjects with Positive Margin presence on the Outermost Shaving after the initial lumpectomy surgery (PMO[3])
2) Cosmesis evaluation:
   - Objective evaluation by an evaluator blinded to arm assignment.
   - Subject's self-reported evaluation.
3) Repeat lumpectomy rate - Proportion of subjects who underwent a repeat lumpectomy procedure.
4) Repeat lumpectomy and mastectomy rate - Proportion of subjects who underwent a repeat lumpectomy procedure or a mastectomy.
5) Diagnostic Accuracy at the Subject Level (ignoring location) - Proportion of subjects from whom shavings were taken.

3. Safety Endpoint:

The safety endpoints in this study were Adverse Events (AE's) and Serious Adverse Events (SAE's).

F. Total number of Enrolled Study Sites and Subjects, Follow-up Rate

A total of eleven (11) centers were utilized in the study and a summary of each center with their enrollment and follow up rate are provided in Table 2-11below.

Table 2-11: Number and Percentage of Subjects' Randomization to Each Center, and Overall, by Treatment Group

Site #	Site Name	Treatment Group			Follow-up Rate	
		Device + SOC	SOC + Additional Inspection	All	VISIT 2 All	*VISIT 3 All
		N (%)	N (%)	N (%)	N (%)	N (%)
1	Pinnacle	18 (45.00%)	22 (55.00%)	40 (100.0%)	40 (100.0%)	39 (97.50%)
2	Summit	09 (47.37%)	10 (52.63%)	19 (100.0%)	19 (100.0%)	16 (84.21%)
3	Moffitt	38 (50.00%)	38 (50.00%)	76 (100.0%)	76 (100.0%)	41 (53.95%)
4	Johns Hopkins	40 (50.00%)	40 (50.00%)	80 (100.0%)	80 (100.0%)	35 (43.75%)
5	Rush	25 (49.02%)	26 (50.98%)	51 (100.0%)	51 (100.0%)	48 (94.12%)
6	New Mexico	17 (48.57%)	18 (51.43%)	35 (100.0%)	35 (100.0%)	33 (94.29%)
7	Northshore	20 (50.00%)	20 (50.00%)	40 (100.0%)	40 (100.0%)	39 (97.50%)
8	Montefiore	21 (46.67%)	24 (53.33%)	45 (100.00%)	45 (100.00%)	40 (88.89%)
9	Baptist	19 (47.50%)	21 (52.50%)	40 (100.0%)	40 (100.0%)	39 (97.50%)

[3] PMO is a clinically relevant endpoint that considers the pathology of the shavings.

11	Sibley	06 (60.00%)	04 (40.00%)	10 (100.0%)	10 (100.0%)	6 (60.00%)
12	Suburban	01 (50.00%)	01 (50.00%)	02 (100.0%)	02 (100.0%)	2 (100.00%)
	Total	**214 (48.86%)**	**224 (51.14%)**	**438 (100.0%)**	**438 (100.0%)**	**338 (77.17%)**

***Relevant to Secondary Cosmesis Endpoints only.**

G. Study visits and length of follow-up

1. Visit 1: Screening Visit

Eligibility was determined during the screening visit. Eligible subjects signed an informed consent form and a HIPPA release as part of the enrollment process.

2. Visit 2: Procedure Visit

Main Specimen

The main specimen (the initially excised lumpectomy specimen which potentially contained the diagnosed lesion) was excised using the surgeon's routine surgical technique. The main specimen was suture oriented, to uniquely define the aspects of the specimen relative to the body (lateral, medial, superior, inferior, deep, anterior). The orienting sutures were placed in the center of the margin, as identified by the surgeon. The surgeon visually inspected, palpated the tissue and related resection of margins was performed based on their assessment, if deemed necessary.

Randomization

Randomization took place immediately after the main specimen had been excised, oriented, center marked, palpated, and additional palpation-based resections performed. Specimen imaging (by ultrasound or radiography) was performed after randomization and device use (Device + SOC arm) or additional inspection (SOC + AI arm) was done.

Use of MarginProbe

For subjects in the device arm (Device + SOC), the MarginProbe was applied to the main specimen, at multiple locations on all specimen margins. The specimen surface was considered to have 6 margins: Medial, Lateral, Inferior, Superior, Anterior and Deep: each margin with its center marked by the surgeon. The device was applied to all 6 margins sequentially. The surface area of every margin of the main specimen was sampled, around and relative to the center marking. Additionally, the MarginProbe was applied to any areas not sampled that were suspicious by palpation and/or visual inspection. Device output was displayed to the user in real-time. Any device positive margin with one or more positive device readings was resected from the lumpectomy cavity. Positive margins not resected required a documented reason for the absence of resection. All excised tissues were submitted for routine permanent histopathology.

Blinding/Masking

For subjects in the Device + SOC (MarginProbe) arm, the device was used by the surgeon, while for subjects in the DOC+ Additional Inspection (Control) arm the device was not used. Consequently, participating surgeons were not able to be masked to the treatment. To reduce any potential surgical bias, each subject was randomized after

the main specimen was excised and additional palpation-based resections were performed. In this way the surgeon was not aware of the outcome until after specimen excision; whether or not s/he would have MarginProbe as an adjunct for positive margin detection.

Pathology

Pathological assessment was identical for both study arms. Pathologists were blinded to subject (specimen) allocation. Surgeons coordinated with pathologists to ensure that orientation conventions were agreed upon and that pathologists' interpretation of margin boundaries (medial, lateral, inferior, superior, anterior, and deep) were consistent with the surgeons. Margin depth, d, was to be noted in increments of 0.5 mm up to 2 mm, and in increments of 1 mm in the range 2-10 mm. Dimensions were to be noted for all specimens (main ex-vivo lumpectomy specimen and shavings). For the purpose of defining endpoints, a positive margin was defined as a margin microscopically measured and reported in the histopathology report to have cancer within 1 mm or less of the inked surface.

3. Visit 3: Follow- Up Visit

Subjects were followed until the end of surgical treatment.

Data were collected regarding all ipsilateral breast surgical procedures and their respective permanent histopathology data. Data were to be collected up until the earlier of the following events:

- Six (± one) months after the surgery date
- Conversion of the subject to mastectomy
- Latest ipsilateral repeat lumpectomy procedure

In the event that a re-excision (lumpectomy or mastectomy) procedure was performed during the data collection period, the data collection period was repeated according to the above outline. Data were collected on any repeated ipsilateral procedure, including ALND and SLNB. The end of data collection marked the study completion for each individual subject.

Summary of the Post-Approval Study Results

H. Final safety findings (key endpoints)

A total of sixteen (16) Serious Adverse Events were reported in the Post Approval Study (see Table 2-12 below):

Table 2-12: Serious Adverse Events by Severity and Treatment Group According to Patients

Severity	Treatment Group		
	Device+SOC N=214	**SOC+ Additional Inspection N=224**	**Total N=438**
Mild	2 (0.93%)	0 (0.00%)	2 (0.46%)
Moderate	1 (0.47%)	6 (2.68%)	7 (1.60%)

Severe	3 (1.40%)	4 (1.79%)	7 (1.60%)
Total	6 (2.80%)	10 (4.46%)	16 (3.65%)

A total of 190 AEs (not including SAEs) were reported in study, 98 (51.6%) within the Device+SOC group and 92 (48.4%) within the SOC+ Additional Inspection group. For 90 subjects AEs were reported, 48 (53.3%) subjects within the Device+SOC group and 42 (46.7%). From the 98 AEs within the Device+SOC group, 97 were classified as unrelated to the device and 1 was classified as possible related to the device. 2 deaths occurred during this study:1 death, at the Device+SOC group and 1 death at the SOC+ Additional Inspection group. The death at the Device+SOC group was classified as unrelated elated to the device. **Use of the MarginProbe device was safe and was not associated with increased risk over Control.**

I. Final effectiveness findings (key endpoints)

1. Co-primary effectiveness endpoints:

Success was demonstrated for all 3 co-primary endpoints, therefore meeting study objectives. The results confirm the ability of the device to assist in positive margin detection, reducing the presence of positive margins at the end of the lumpectomy by 45.45%.

- Sensitivity at Margin Level is 70.2%.
- Specificity at Margin Level is 48.7% for best case and 47.6% for worst case.

The Sensitivity and Specificity at Margin Level co-primary endpoints were met at 70.2% and between 47.6% (worst case) and 48.7% (best case) respectively. These results, comparable to the 73.8% sensitivity and 45.1% specificity reported in the MarginProbe Pivotal trial, confirm the device's consistent, predictable, and reliable ability to detect microscopic residual disease at the surface of the lumpectomy specimen.

- Incomplete Surgical Resection (ISR) rate (Device+SOC=17.29%, SOC+Additional Inspection=31.70%, P=0.00056).

The device showed superiority over control in detection and immediate resection of all positive margins on the main specimen, thereby mitigating the primary risk of lumpectomy: Incomplete Surgical Resection (ISR) of cancer from the breast. ISR was significantly lower in the device arm compared to the control arm which was standard of care with additional inspection (17.29% vs. 31.7%, P=0.00056). These results again confirm and validate findings from the MarginProbe Pivotal Trial, which reported ISR as 15.4% and 38.3% for device and control respectively. (P<0.0001)

2. Secondary effectiveness endpoints:

Table 2-13 below presents the Secondary endpoints. The PMO endpoint met the established success criteria. The other secondary endpoints were all trending in the

positive direction however, they did not achieve statistical significance primarily due to missing data or limited data size.

Table 2-13: Secondary Endpoints

Endpoint	Description	Data set	Results	Conclusion
Positive Margin Presence on the Outermost Shaving after the Initial Lumpectomy Surgery (PMO)	1 = At least one positive margin on final pathology after first lumpectomy 0 = No positive margins on final pathology after first lumpectomy	All subjects	SOC + Device: With PMO/Without PMO(Rate) 51/163(23.83%) SOC + Additional inspection: With PMO/Without PMO(Rate) 83/141(37.05%)	PMO rate is statistically significantly improved in the SOC + Device arm
Cosmesis blinded evaluation	1 = Objective cosmesis evaluation is Excellent/Good 0 = Objective cosmesis evaluation is Fair/Poor The SOC+Device rate is compared to the SOC+Additional Inspection, using 10% non-inferiority margin.	Only subjects with cosmesis evaluation All subjects, best case scenario for the SOC+Device arm. Subjects with missing evaluation, counted as success. Subjects with missing evaluation, counted as failure. All subjects, worst case scenario for the SOC+Device arm.	SOC + Device: Excellent/Good vs. Fair/Poor (Rate) 85/78(52.15%) 136/78(63.55%) 136/78(63.55%) 85/129 (39.72%) 85/129 (39.72%) SOC + Additional inspection: Excellent/Good vs. Fair/Poor (Rate) 96/68(58.54%) 96/128(42.86%) 156/68(69.64%) 96/128 (42.86%) 156/68(69.64%)	Cases 1,3,4,5 The cosmesis blinded evaluation rate is not statistically significantly non-inferior in the SOC+Device arm. Case 2 The cosmesis blinded evaluation rate is statistically significantly non-inferior in the SOC+Device arm.
Repeat lumpectomy rate	1 = At least one Repeat Lumpectomy procedure	All subjects, excluding subjects with a	SOC + Device: With repeat lumpectomy/Withou	Repeat lumpectomy rate is not statistically

Endpoint	Description	Data set	Results	Conclusion
	0 = No Repeat Lumpectomy procedure	mastectomy second surgery	t repeat lumpectomy (Rate) 17/193(8.10%) SOC + Additional inspection: With repeat lumpectomy/Without repeat lumpectomy (Rate) 24/192(11.11%)	significantly improved in the SOC + Device arm
Repeat lumpectomy or mastectomy rate	1= At least one Repeat Lumpectomy or Mastectomy procedure 0 = No Repeat Lumpectomy or Mastectomy procedure	All subjects, excluding 3 subjects with negative margins referred to a mastectomy reoperation.	SOC + Device: With repeat lumpectomy or mastectomy /Without repeat lumpectomy or mastectomy (Rate) 17/193(8.96%) SOC + Additional inspection: With repeat lumpectomy or mastectomy /Without repeat lumpectomy or mastectomy (Rate) 24/192(13.90%)	Repeat lumpectomy or mastectomy rate is not statistically significantly improved in the SOC + Device arm
Diagnostic accuracy at the subject level: Sensitivity at the subject level	Subjects are scored dichotomously: 1 (TP) = If at least one margin was shaved 0 (FN) = If no margins were shaved	Subjects with at least one histologically positive margin (margin£1 [mm]) on the main ex-vivo lumpectomy specimen.	SOC + Device: True positives/False negatives (Rate) 52/37(58.4%) SOC + Additional inspection: True positives/False negatives (Rate) 51/71(41.8%)	The Sensitivity at the subject level is statistically significantly improved in the SOC + Device arm
Diagnostic accuracy at the subject level: Specificity at the subject level	Subjects are scored dichotomously: 1 (TN) = If no margins were shaved	All subjects with no histologically positive margins (margin>1 [mm]) on the	SOC + Device: True negatives/False positives (Rate) 8/117(6.4%) SOC + Additional inspection:	The Specificity at the subject level is statistically significantly non-inferior in the

Endpoint	Description	Data set	Results	Conclusion
	0 (FP) = If at least one margin was shaved The SOC+Device rate is compared to the SOC+Additional Inspection, using 52% non-inferiority margin.	main ex-vivo lumpectomy specimen	True negatives/False positives (Rate) 39/63(38.23%)	SOC+Device arm.
Cosmesis self-reported evaluation	1 = Objective cosmesis evaluation is No difference/Slight difference 0 = Objective cosmesis evaluation is Moderate difference/Large difference the SOC+Device rate is compared to the SOC+Additional Inspection rate, using 10% non-inferiority margin. The self-evaluation score is the average over 8 characteristics: Breast size Breast texture	All subjects with at least one self-evaluated characteristic and in addition have completed the 6-month follow-up visit (in window)	SOC + Device: No difference/Slight difference vs. Moderate difference/Large difference (Rate) 113/16(87.60%) SOC + Additional inspection: No difference/Slight difference vs. Moderate difference/Large difference (Rate) 133/11(92.40%)	The cosmesis self-reported evaluation rate in the SOC+Device arm is statistically significantly non-inferior to the SOC+Additional Inspection arm.

Endpoint	Description	Data set	Results	Conclusion
	Nipple appearance Breast shape Breast elevation Scar tissue Fit to bra Fit to clothing			

J. Study Strengths and Weaknesses

Table 2-14 summarizes the strengths and weaknesses of the of the Post Approval Study

Table 2-14: Strengths and weaknesses of the Post Approval Study

Strengths	Weaknesses
The actual incremental contribution of the MarginProbe device to a higher number of cavity shavings can be determined because the reason for taking a cavity shaving - i.e. SOC (clinical suspicion, or imaging) versus a positive MarginProbe reading - was documented.	The study design allows for an additional option to perform cavity shavings in the SOC+Device arm versus the SOC arm. The additional option in the SOC+Device arm may be responsible for an decrease in ISR in the SOC+Device arm.
ISR, primary endpoint - reflects a specimen assessment which does not give any credit to intraoperative re-excision when only some of the positive margins on the main specimen are detected. This shows the actual potential of the technology to assist in real usage and not only in controlled environment.	ISR does not penalize false positive MarginProbe readings in the positive main specimen cohort. False positive MarginProbe readings in the positive main specimen cohort cause the resection of healthy tissue.
	ISR does not consider false positive MarginProbe readings in the negative main specimen cohort. False positive MarginProbe readings in the negative main specimen cohort cause the resection of healthy tissue.
	Questionable clinical relevance in the time of "no tumor on ink" for IDC. This is addressed by the secondary endpoint of re-excision rate.

MarginProbe Pivotal Study:

A clinical pivotal study was performed to establish a reasonable assurance of safety and effectiveness of the MarginProbe System. The MarginProbe System is an adjunctive diagnostic tool for identification of cancerous tissue at the margins (≤ 1mm) of the *ex-vivo* lumpectomy specimen following primary excision and is indicated for intraoperative use, in conjunction with standard methods (such as intraoperative imaging and palpation) in patients undergoing breast lumpectomy surgery for previously diagnosed breast cancer in the US. The pivotal study was performed under IDE # G070182. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between September 2008 and March 2010.

The MarginProbe System pivotal study was a prospective, multicenter, randomized (1:1), controlled, double-arm study. Breast cancer patients were randomized to either receive standard of care (SOC) lumpectomy or Standard of Care lumpectomy with adjunctive MarginProbe device use (SOC + Device).
Key Aspects of the protocol are as follows:

1. Patient Study Inclusion and Exclusion Criteria

Enrollment in the pivotal study was limited to patients who met the following inclusion criteria:

- Women histologically diagnosed with carcinoma of the breast
- Women with non-palpable malignant lesions, requiring image guided localization.
- Undergoing lumpectomy (partial mastectomy) procedure.
- Age 18 years or more
- Signed informed consent form

Patients were not permitted to enroll in the pivotal study if they met any of the following exclusion criteria:

- Multicentric disease (histologically diagnosed cancer in two different quadrants of the breast)
- Bilateral disease (diagnosed cancer in both breasts)
- Neoadjuvant systemic therapy
- Previous radiation in the operated breast
- Prior surgical procedure in the same breast
- Implants in the operated breast
- Pregnancy
- Lactation

2. Patient Treatment

Patients were first enrolled and taken to the operating room for resection of the main lumpectomy specimen. The main lumpectomy specimen and lumpectomy cavity palpation and related re-excisions were performed before patient randomization. For all main specimens, the center of each of the 6 margins was suture marked. Patient were then randomized to either the SOC or SOC+Device arm intraoperatively, immediately after the main lumpectomy specimen was excised, oriented, center marked, palpated, and additional palpation based re-excision performed.

For patients randomized to the SOC+Device arm the surgeon:

- Applied the MarginProbe device to each of the 6 faces of the excised main lumpectomy specimen—sampling 5 – 8 points (and up to 12 points for larger specimens). The points sampled were at both evenly spaced and suspicious sites.
- Was required to react to Device feedback. A single positive reading on any margin classified that margin as positive and required the surgeon to remove additional tissue from that margin.
- Documented the reasons why additional margins were not re-exicised despite a positive MarginProbe device reading. For the purposes of CSR primary endpoint calculations, lumpectomy cavity shavings that were not possible due to physical limitations (proximity to the skin or pectoralis fascia) the margin was considered “addressed”.
- Was instructed not to use the MarginProbe device on shavings from the lumpectomy cavity shavings (even if a shaving was taken prior to randomization)
- Was instructed not to use the MarginProbe device within the *in-vivo* lumpectomy cavity.
- Was instructed not the use the MarginProbe device on *ex-vivo* lumpectomy tissue that had been exposed to saline or ultrasound gel. It was however acceptable to use the MarginProbe device on *ex-vivo* lumpectomy tissue exposed to sterile water.
- Was instructed not to use the MarginProbe device in the 1.5 mm region of tissue surrounding a fine needle localization guidewire.

For both SOC and SOC+Device arm patients, lumpectomy specimens were imaged by ultrasound or radiography after randomization and device use. Additional lumpectomy cavity re-excisions were taken as deemed appropriate based on specimen imaging results. Figure 2-1 provides a diagrammatic representation of the study design.

Note that the study design allows for an additional option to perform lumpectomy cavity shavings in the SOC+Device arm (option for shaving at 3 time points) versus the SOC arm (option for shaving at 2 time points).

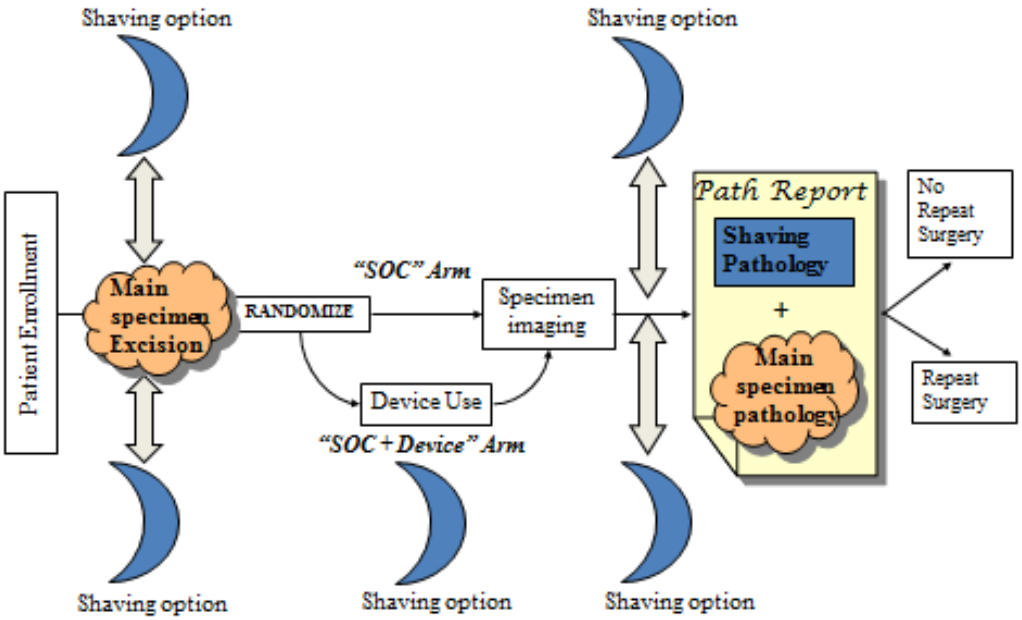


Figure 2-2: Pivotal Study Design

The MarginProbe device was not used during lumpectomy reoperations.

The study consisted of two phases – a training phase and a randomization phase. Each surgeon had to complete the training phase before being able to randomize patients. Surgeons who had attended 2 or more device procedures (training or randomized) were certified in device use.

3. Pathology Protocol

Pathological assessment was standardized and identical for both study arms. Pathologists were blinded to randomization.

A positive margin was to be defined in this study as a margin microscopically measured and reported in the histopathology report to have cancer within 1 mm or less of the inked surface.

Each investigational site performed the histopathology assessment using a Standard Operating Procedure. Re-cut slides from the first 4 patients at each investigational site (Training, SOC, or SOC+Device) were to be sent to a core-lab and were to be used to review the accuracy and reporting capabilities of the investigational site pathology.

Dimensions (L, W, D) of all excised tissues were recorded. Tissue volume was determined by use of the ellipsoid formula:

$V = (4/3)*\pi*L*W*D$

4. Duration of Patient Follow-up

Patients were followed until the end of the lumpectomy procedure. Data were collected regarding all ipsilateral breast surgical procedures and their respective permanent histopathology data. Data were to be collected up until the earlier of the following events: conversion to mastectomy, initiation of chemotherapy or two months after the surgery date.

5. Study Endpoints

The prespecified study endpoints are as follows:

Safety evaluation consisted of assessment of all adverse events and serious adverse events, which were summarized using descriptive statistics.

The primary effectiveness endpoint (CSR) is measured as all pathologically positive margins on the main specimen being intraoperatively re-excised or "addressed". A re-excised or "addressed" margin does not mean that the final true outermost margin is pathologically negative for cancer.

- A positive margin is defined as a margin microscopically measured and reported in the histology report to have cancer within 1 mm or less of the inked margin.
- The main specimen is defined as the lumpectomy specimen removed prior to patient randomization. The main lumpectomy specimen does not include additional shavings even if the cavity shaving was performed prior to patient randomization.

- If a margin has been indicated as positive by the device and documented to not have been re-excised as required by protocol, due to resection already undermining the skin or reaching the pectoralis fascia, this margin will be counted as "detected" and "addressed" for the purpose of CSR endpoint calculation although it was not "re-excised".

An illustration of how CSR is determined is provided in Figure 2-3.

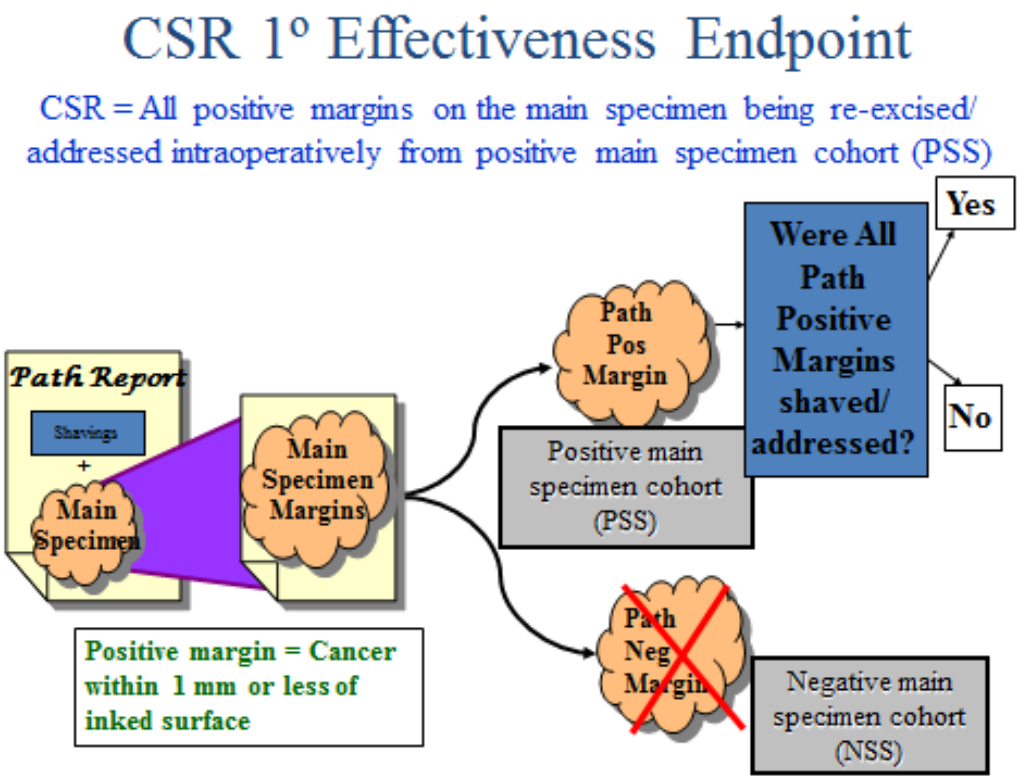


Figure 2-3: Illustration of CSR Primary Endpoint

Figure 2-4 below illustrates how the CSR assessment includes both clinically relevant scenario which is the conversion of a specimen which has a pathologically positive for cancer margin to a specimen with negative for cancer margins and the clinically irrelevant scenario in which the additional shaving resulted in the true outermost margin of the specimen remaining pathologically positive for cancer.

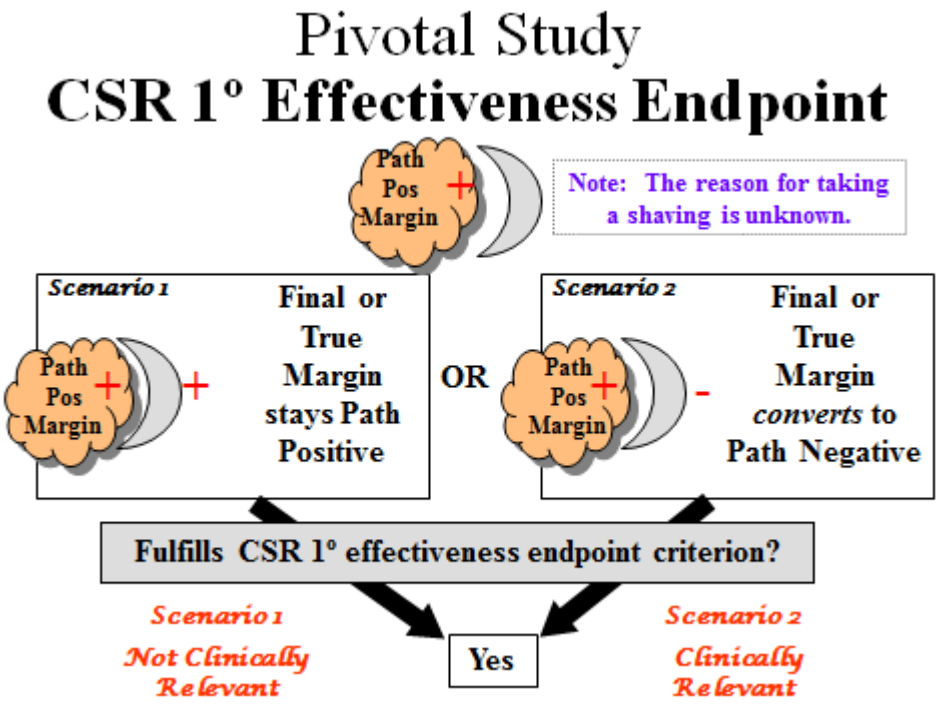


Figure 2-4: CSR and Clinical Relevance

While CSR is a focused assessment that is limited to what is within the control of the MarginProbe device, there are limitations to the CSR primary effectiveness endpoint. Some of these limitations are present because the reason and timing for taking additional shavings of the lumpectomy cavity were not documented—that is, whether a shaving was taken because of clinical suspicion, imaging, other assessment, versus a positive MarginProbe device reading and whether the shaving was taken before randomization or after specimen imaging. While the device readings for each margin and the margins shaved were documented, the timing of each shaving and the reason prompting the shaving was not collected.

Table 2-15: Strengths and limitations of the primary effectiveness endpoint, CSR summarizes the strengths and limitations of the CSR primary effectiveness endpoint for the pivotal study.

Table 2-15: Strengths and limitations of the primary effectiveness endpoint, CSR

Strengths	Limitations
A focused assessment limited to what is within the control of the MarginProbe device i.e. causing additional cavity shavings.	The study design allows for an additional option to perform cavity shavings in the SOC+Device arm versus the SOC arm. The additional option in the SOC+Device arm may be responsible for an increase in CSR in the SOC+Device arm.
A by specimen assessment which does not give partial credit to intraoperative re-exision of some positive margins on the main specimen but not all positive margins on the main specimen.	The incremental contribution of the MarginProbe device to a higher CSR cannot be determined because the reason for taking a cavity shaving - i.e. SOC (clinical suspicion, or imaging) versus a positive MarginProbe reading - was not documented.
	Questionable clinical relevance. CSR considers whether a shaving was taken or not taken at positive margins on a lumpectomy specimen. CSR does not consider whether the shaving taken converted the initially positive for cancer margin to a negative for cancer final margin.
	CSR does not penalize false positive MarginProbe readings in the positive main specimen cohort. False positive MarginProbe readings in the positive main specimen cohort cause the resection of healthy tissue.
	CSR does not consider false positive MarginProbe readings in the negative main specimen cohort. False positive MarginProbe readings in the negative main specimen cohort cause the resection of healthy tissue.

Secondary effectiveness endpoints are summarized in Table 2-16: Secondary Effectiveness Endpointsbelow.

Table 2-16: Secondary Effectiveness Endpoints

Endpoint	Definition
Incomplete Surgical Re-excision	Proportion of patients with at least 1 positive margin not resected/addressed. Differs from primary effectiveness endpoint, CSR, since Yes/No definitions are opposite. Differs from the CSR endpoint since it is calculated from the AVS dataset rather than the PSS dataset.
Full Detection	Rate of patients with all positive margins on main specimen detected by device
Re-excision Procedure Rate	Rate of repeated ipsilateral breast surgical procedures (including mastectomies)
Positive Margin Presence	Rate of patients with at least 1 positive margin remaining after lumpectomy
TTV excised in the primary lumpectomy procedure (cm^3)	Average volume of total amount of tissue excised in lumpectomy

6. Pre-Specified Analysis Plan

For the primary efficacy analysis, a sample size of 116 valid primary effectiveness patients per arm was determined to provide at least 90% power to demonstrate superiority of SOC+Device over SOC.

The analysis populations are defined in Table 2-17: Analysis Populations.

Table 2-17: Analysis Populations

Analysis Population	Definition
All Valid Subjects (AVS)	The AVS subjects included all randomized patients with valid histology data (and valid MarginProbe System data in Device arm)

Positive Specimen Subjects (PSS)	The PSS subject is a subset of the AVS Analysis Set of subjects with at least 1 histologically positive main specimen margin at depth ≤1 mm
Negative Specimen Subjects (NSS)	The NSS subject is a subset of the AVS Analysis Set of subjects with no histologically positive main specimen margin at depth ≤1 mm.

Safety was assessed using the AVS population. The primary effective endpoint was based on PSS population, and the secondary effectiveness endpoints were based on AVS, PSS or NSS populations as shown in Table 2-18: The Primary Effectiveness Endpoints Population and Table 2-19: The Secondary Effectiveness Populations.

Table 2-18: The Primary Effectiveness Endpoints Population

Endpoint	Analysis Population	Scoring
CSR	PSS analysis set	Complete Surgical Re-excision (CSR) was scored dichotomously as follows: No: At least one positive margin on the main specimen not re-excised/addressed intraoperatively. Yes: All positive margins on the main specimen re-excised/addressed intraoperatively

Table 2-19: The Secondary Effectiveness Populations

Endpoint	Analysis Population	Scoring
Incomplete Surgical Re-excision	AVS analysis set. The groups were compared using 2-sided Fisher's Exact Test.	Incomplete Surgical Re-excision ("re-excision is used to mean "resection) was scored dichotomously: Yes: If at least 1 positive margin with d ≤ 1 mm on the main specimen was not resected/addressed intraoperatively. No: Otherwise This endpoint differed from the primary effectiveness endpoint, Complete Surgical Resection, since the Yes/No definitions were opposite.
Full Detection	PSS analysis set	Scored dichotomously for SOC+Device arm patients only:

Endpoint	Analysis Population	Scoring
	A 2-sided exact binomial 95% CI for the proportion of "Yes".	Yes: If all positive margins on the main specimen with d ≤ 1 mm were detected by the device (in Device arm) No: Otherwise
Re-excision Procedure Rate	AVS analysis set Compared the groups using a Poisson regression model.	Number of repeated ipsilateral breast surgical procedures (including mastectomies) for each patient. This endpoint was counted as an integer per patient; the count was increased by 1 with each subsequent surgery.
Positive Margin Presence	AVS analysis set Compared the groups using a Poisson regression model.	Scored dichotomously. Yes: If there was at least 1 positive margin with d ≤ 1 mm after the first lumpectomy No: Otherwise
TTV excised in the primary lumpectomy procedure (cm^3)	NSS analysis set Compared the groups using a 2-sided Wilcoxon Rank-Sum Test.	Total amount of tissue excised during lumpectomy for each patient.

The margin-level and patient level (ignoring location) sensitivity and specificity are reported for diagnostic performance of the MarginProbe device. These were not pre-specified in terms of an acceptable minimal sensitivity and specificity. The results here are based on the observed performance in the clinical pivotal study.

B. Subject Accountability

A total of 664 patients who were eligible for study enrollment underwent surgery and were allocated to either the roll-in group or randomization (enrollment allocation). Sixty-eight women were operated on in the roll-in phase and 596 were randomized equally to the Control (SOC arm) and Device treatment (Device +SOC arm) groups. All 664 women completed the study. Subject accountability is displayed below inTable 2-20: Patient Accountability, Pivotal Study.

Table 2-20: Patient Accountability, Pivotal Study

Disposition	Total n (%)
Eligible for Participation	721
Did Not Enter Study	57 (7.9)

Failed eligibility	25 (3.5)
Withdrew consent	6 (0.8)
Other	26 (3.5)
Eligible for Allocation	664 (92.1)
Allocated to Enrollment	664 (100)
Roll-in	68 (10.2)
Randomized to Treatment	596 (89.8)
Device	298 (44.9)
Control	298 (44.9)
Completed Study	664 (100)
Did Not Complete	0 (0)

All 664 women were included in the Safety analysis set. The AVS analysis set includes 596 randomized (298 Device and 298 Control) patients and differs from safety analysis set in 64 roll-in women, as shown inTable 2-21: Data Sets Analyzed: Number of Patients.

Table 2-21: Data Sets Analyzed: Number of Patients

Analysis Set	Patients Included	Treatment Group			Total n (%)
		Device n (%)	Control n (%)	Roll-In n (%)	
Safety Set	All patients for whom surgical procedure was initiated	298 (100.0)	298 (100.0)	68 (100.0)	664 (100.0)
Effectiveness Sets					
AVS	All Randomized Patients	298 (100.0)	298 (100.0)	NA	596 (100.0)
PSS	Positive Specimen Patients	163 (54.7)	147 (49.3)	NA	310 (52.0)
NSS	Negative Specimen Patients	135 (45.3)	151 (50.7)	NA	286 (48.0)

All randomized patients completed the study protocol. There was no loss to follow-up in the study. There was no missing data related to the CSR endpoint; 38/1788 (2%) of margins were not measured by the device.

C. Demographics and Baseline Characteristics

Demographic characteristics were similar for the Device and Control groups. Overall, the groups appeared to be comparable, as shown in Table 2-22 and Table 2-23.

Table 2-22: Demographics by Treatment Group

		Treatment Group	
Parameter	**Roll-In N=68**	**Device N=298**	**Control N=298**
Ethnic Origin n (%)			
White[a]	59 (86.8)	250 (83.9)	260 (87.2)
African-American or Black	5 (7.4)	22 (7.4)	17 (5.7)
Asian	2 (2.9)	12 (4.0)	10 (3.4)
Native Hawaiian or Other Pacific Islander	0 (0)	3 (1.0)	1 (0.3)
Other	2 (2.9)	11 (3.7)	10 (3.4)

[a] Includes Hispanics.

Table 2-23: Baseline Characteristics by Treatment Group

		Treatment Group	
Parameter	**Roll-In N=68**	**Device N=298**	**Control N=298**
Age (yrs) Mean (SD)	63.6 (11.1)	60.3 (11.4)	60.2 (11.1)
BMI (mean)	28.0	27.9	28.6
Bra Cup Size n (%)			
AA	0 (0.0)	2 (0.7)	4 (1.3)
A	6 (8.8)	16 (5.4)	16 (5.4)
B	21 (30.9)	101 (33.9)	73 (24.5)
C	24 (35.3)	99 (33.2)	93 (31.2)
D	12 (17.6)	62 (20.8)	92 (30.9)
E	1 (1.5)	2 (0.7)	5 (1.7)
F	1 (1.5)	1 (0.3)	1 (0.3)
>F	1 (1.5)	1 (0.3)	2 (0.7)
Unknown	2 (2.9)	14 (4.7)	12 (4.0)

Table 2-24 presents the number of patients with a diagnosis, requiring that certain categories be combined. For patients with invasive types of carcinoma the mixed invasive category was used, and for patients with more than 1 diagnosis who did not have more than one type of invasive carcinoma, the mixed category was used. The treatment groups appear to be similar with respect to diagnosis.

Table 2-24: Patient Diagnosis by Treatment Group (Per-diagnosis Analysis)

Patient Diagnosis	**Treatment Group**			**All**
	Device	**Control**	**Roll-In Phase**	
	N (%) Patients	**N (%) Patients**	**N (%) Patients**	**N (%)**
Invasive Ductal	24 (8.1)	22 (7.4)	7 (10.3)	53 (8.0)
Invasive Lobular	26 (8.7)	13 (4.4)	2 (2.9)	41 (6.2)

Mixed Invasive[a]	8 (2.7)	5 (1.7)	1 (1.5)	14 (2.1)
Ductal Carcinoma in Situ	83 (27.9)	78 (26.2)	19 (27.9)	180 (27.1)
Tubular Carcinoma	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Mucinous Carcinoma	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.3)
Mixed[b]	155 (52.0)	179 (60.1)	39 (57.4)	373 (56.2)
Total	298 (100.0)	298 (100.0)	68 (100.0)	664 (100.0)

a Mixed invasive=Invasive Ductal Carcinoma+Invasive Lobular Carcinoma.
b Mixed=more than 1 diagnosis and not only invasive carcinoma.

Tumor stage results are presented in Table 2-25below. The majority of patients were diagnosed with stage II breast cancer and below.

Table 2-25: Tumor Stage

Treatment Group	0		I		II		III		IV		Unknow		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Device	81	27.2	155	52.0	51	17.1	4	1.3	1	0.3	6	2.0	298	100.0
Control	84	28.2	161	54.0	44	14.8	6	2.0	0	0	3	1.0	298	100.0
Roll-In Phase	21	30.9	34	50.0	12	17.6	1	1.5	0	0	0	0	68	100.0
All	186	28.0	350	52.7	107	16.1	11	1.7	1	0.2	9	1.4	664	100.0

Receptor status is presented in Table 2-26. There were 84 subjects in device and control arms, and 19 in the roll-in subjects, for which HER2 status was not preformed.

Table 2-26: Receptor Status

Receptor Status	Roll-In N=68	Device N=298	Control N=298
ER+	60/68 (88.2)	251 (84.2)	258(86.6)
PR+	52/68 (76.4)	223 (74.8)	217 (72.8)
HER2+	3/49 (6%)	20/214 (9%)	33/214 (15%)
HER2-	42/49 (85%)	175/214 (82%)	163/214 (76%)

D. Surgical Procedure

The mean duration of anesthesia time (hours: minutes) was 2:03 for the Device group, 1:52 for the Control group and 2:11 for the Roll-in group. This time includes surgical procedures, resections, completion of the protocol procedures, and device use. The mean duration of device use was 5 minutes for the Device group and 6 minutes for the Roll-in group.

Table 2-27presents the number and percent of patients with a palpable tumor excised during lumpectomy. While all patients had non-palpable lesions at screening (inclusion criteria), the lesion may or may not have been palpable in the *ex-vivo* lumpectomy specimen. There were no apparent differences between treatment groups with respect to palpable tumors during excision.

Table 2-27: Frequency Distribution of Palpable Tumor during Lumpectomy by Treatment Group

Was The Tumor Palpable in The Excised Specimen?	Treatment Group			All
	Device	Control	Roll-In Phase	
	N (%) Patients	N (%) Patients	N (%) Patients	N (%) Patients
No	196 (65.8)	188 (63.1)	43 (63.2)	427 (64.3)
Yes	102 (34.2)	110 (36.9)	25 (36.8)	237 (35.7)
Total	298 (100.0)	298 (100.0)	68 (100.0)	664 (100.0)

Source: Statistical Table M-38 in Appendix 10.2.2.

Various intraoperative evaluations were used at surgeon discretion in both the SOC and SOC+Device arms and included radiological exam, ultrasound, ultrasonic guidance, touch cytology, gross assessment, and frozen section.

The reason for performing a lumpectomy cavity shaving—that is, whether a shaving was prompted by gross visualization/palpation, positive MarginProbe device readings, imaging, touch prep cytology or frozen section analysis--was not documented.

The methods of excision used during lumpectomy included the following: electrocautery, sharp excision, and scissors.

Table 2-28 describes number of patients undergoing SLNB with dye or radioisotope or both.

Table 2-28: Number of Patients undergoing SLNB with Dye or Radioisotope or Both

	Roll-In N=68	**Device N=298**	**Control N=298**
SLNB performed	59 (72%)	223 (75%)	225 (75)

Pathology

Table 2-29presents weight and volume of the main specimen. There were no apparent differences between treatment groups with respect to weight and volume of the main specimen. The mean size (diameter) of the main specimen was 4.85 cm for the Device group, 4.89 cm for the Control group, and 4.7 cm for the Roll-in group.

Table 2-29: Descriptive Statistics of Specimen Weight and Volume by Treatment Group

Specimen Parameter	Treatment Group						All	
	Device		Control		Roll-In Phase			
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Weight (g)	294	51.4 (42.2)	290	55.8 (49.8)	67	48.6 (69.4)	651	53.0 (49.0)
Volume (cm^3)	296	59.7 (51.4)	298	61.3 (52.5)	68	54.6 (67.5)	662	59.9 (53.7)

Source: Statistical Table M-46 in Appendix 10.2.2.

Overall mean tumor size was similar for the groups (MarginProbe=1.7 cm^3, Control=1.6 cm^3).
The tumor type (as assessed by post-operative histopathology) by treatment group are presented in Table 2-30. The treatment groups appear to be similar with respect to tumor type. The number of positive margins on the main specimen, by treatment group, also appears to be similar.

Table 2-30: Frequency Distribution for Tumor Type by Treatment Group

Tumor Type	Treatment Group			All
	Device	Control	Roll-In Phase	
	N Specimens (%)	N Specimens (%)	N Specimens (%)	N Specimens (%)
Invasive ductal	158 (53.0)	179 (60.1)	40 (58.8)	377 (56.8)
Invasive lobular carcinoma	46 (15.4)	26 (8.7)	9 (13.2)	81 (12.2)
Ductal carcinoma in-situ	207 (69.5)	229 (76.8)	46 (67.6)	482 (72.6)
Tubular Carcinoma	5 (1.7)	6 (2.0)	2 (2.9)	13 (2.0)
Mucinous Carcinoma	10 (3.4)	3 (1.0)	2 (2.9)	15 (2.3)
Medullary Carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Papillary Carcinoma	0 (0.0)	2 (0.7)	1 (1.5)	3 (0.5)
Non malignant (NM)	19 (6.4)	19 (6.4)	5 (7.4)	43 (6.5)
Other	5 (1.7)	7 (2.3)	0 (0.0)	12 (1.8)
Total Patients	298 (100.0)	298 (100.0)	68 (100.0)	664 (100.0)

The average weight and volume of resected margins by treatment group during the lumpectomy is presented in
Table 2-31. The treatment groups appear to be similar with respect to weight and volume of resected margins.

Table 2-31: Descriptive Statistics of Resected Margins Weight and Volume by Treatment Group

Specimen Parameter	Treatment Group						All	
	Device		Control		Roll-In Phase			
	n [a]	Mean (SD)	n [a]	Mean (SD)	n [a]	Mean (SD)	n [a]	Mean (SD)
Weight (g)	1000	6.6 (6.8)	329	7.5 (6.7)	219	6.0 (5.2)	1548	6.7 (6.6)
Volume (cm^3)	1044	7.9 (10.7)	344	9.1 (10.1)	252	7.4 (8.2)	1640	8.1 (10.2)

[a] Difference between weight and volume in number of margins is due to missing data.
Source: Statistical Table M-54 in Appendix 10.2.2.

E. Study Results

1. Safety Results

14 adverse events (AEs) were reported, all being categorized as serious adverse events (SAEs) per study protocol definition. One SAE was possibly related to the study device, a wound infection requiring hospitalization and treatment with antibiotics.

Table 2-32: Frequency of Serious (All) Adverse Events by System Organ Class, Preferred Term, and Treatment Group

System Organ Class/Preferred Term		Treatment Group							
		Device N=298		Control N=298		Roll-In Phase N=68		Any N=664	
		N SAEs	N (%) Patients	N SAEs	N (%) Patients	N SAEs	N (%) Patients	N SAEs	N (%) Patients
Any	Any	6	6 (2)	5	5 (2)	3	3 (4)	14	14 (2)
Infections and infestations	Any	2	2 (1)	1	1 (0)	2	2 (3)	5	5 (1)
	Acute tonsillitis	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)
	Breast abscess	0	0 (0)	1	1 (0)	0	0 (0)	1	1 (0)
	Cellulitis	0	0 (0)	0	0 (0)	1	1 (1)	1	1 (0)
	Postoperative wound infection	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)
	Urinary tract infection	0	0 (0)	0	0 (0)	1	1 (1)	1	1 (0)
Injury, poisoning and procedural complications	Any	2	2 (1)	3	3 (1)	0	0 (0)	5	5 (1)
	Fractured sacrum	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)
	Post procedural haemorrhage	0	0 (0)	2	2 (1)	0	0 (0)	2	2 (0)

System Organ Class/Preferred Term		Treatment Group							
		Device N=298		Control N=298		Roll-In Phase N=68		Any N=664	
		N SAEs	N (%) Patients	N SAEs	N (%) Patients	N SAEs	N (%) Patients	N SAEs	N (%) Patients
	Procedural dizziness	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)
	Procedural pain	0	0 (0)	1	1 (0)	0	0 (0)	1	1 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Any	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)
	Uterine leiomyoma	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)
Reproductive system and breast disorders	Any	0	0 (0)	1	1 (0)	0	0 (0)	1	1 (0)
	Breast haematoma	0	0 (0)	1	1 (0)	0	0 (0)	1	1 (0)
Vascular disorders	Any	1	1 (0)	0	0 (0)	1	1 (1)	2	2 (0)
	Hypertension	0	0 (0)	0	0 (0)	1	1 (1)	1	1 (0)
	Hypertensive crisis	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)

Adverse events associated with device malfunction or incorrect device readings causing incorrect surgeon action is both a safety and an effectiveness issue. Incorrect surgeon action is therefore further discussed in the Effectiveness Results section below. While an approximately 5 minute prolongation of the operative procedure associated with device use, this prolongation cannot be associated with specific patient adverse events. In addition, while damage to the tissue exposed to the MarginProbe device is a potential problem, an assessment for tissue damage was not considered to be feasible in the pivotal study. From the available data this issue has not been reported.

2. Effectiveness Results

Primary Effectiveness Endpoint: There were a total of 163 patients in the SOC+Device arm and a total of 147 patients in the SOC arm who were in the PSS dataset (i.e. with at least one positive margin by histology on the main specimen). The CSR primary effectiveness endpoint results are provided in Table 2-33.

The device failed to give a reading on 38 (2%) margins out of 1788 margins measured from 298 subjects. This did not impact the primary endpoint.

Table 2-33: The CSR Primary Effectiveness Endpoint Results

Primary Endpoint	Dataset	SOC + Device	SOC	Difference (95% CI)	
CSR	PSS	71.8% (117/163)	22.4% (33/147)	49.3% (39.0%,58.7%)	p < 0.0001

Table 2-34: - Secondary Effectiveness Endpoint Results

Secondary Endpoints	Dataset	SOC + Device	SOC	p-value or CI
Incomplete Surgical Re-excision	AVS	15.4% (46/298)	38.3% (114/298)	p < 0.0001*
Full Detection	PSS	62.6% (102/163)	NA	95% CI: 54.7% – 70%*
Re-excision Procedure Rate	AVS	20.8% (82/298)	25.8% (94/298)	p = 0.3177*
Positive Margin Presence	AVS	30.9% (92/298)	41.6% (124/298)	p = 0.0082*
TTV excised in the primary lumpectomy procedure (cm^3)	NSS	92.7 cm^3	69.9 cm^3	p = 0.0031*

* Unadjusted analysis

Of the endpoints listed, the clinically relevant endpoint of re-excision procedure rate showed a 5 percentage point reduction in the SOC+Device arm versus SOC arm.

The reoperation procedure rate is further described in Table 2-35. Note that fewer patients in the SOC+Device arm required a second operation (71 patients in the SOC+Device arm versus 85 patients in the SOC arm). Recall that the MarginProbe device was only used during the initial lumpectomy operation and not during reoperations. More patients in the SOC+Device arm versus the SOC were converted to mastectomy. There are numerous reasons

for conversion to mastectomy and therefore this finding cannot be directly attributable to device use.

Table 2-35: Reoperation Procedure Rate

	Lumpectomy	Additional Resections			Total	p-Value
Procedure #	**1**	**2**	**3**	**4**		
SOC+Device	298	62	7	2	71 (23.8%)	0.3177
SOC	298	77	7	1	85 (28.5%)	

Conversion to mastectomy in device arm = 18/298 p = 0.46
Conversion to mastectomy in control arm = 13/298

The following additional analyses, Table 2-36 and Table 2-37, provide information regarding diagnostic performance of the device per margin and per patient (ignoring location).

Table 2-36: Diagnostic Performance (per-margin)

	Sensitivity(%) (95% CI)‡	Specificity(%) (95% CI) ‡	PPV†(%) (95% CI) ‡	NPV†(%) (95% CI) ‡
SOC+Device	73.8 (68.1,79.4)	45.1 (41.8,48.3)	21.6(20.1,23.1)	89.4(87.2,91.4)
SOC	33.9 (27.5,40.5)	83.4 (81.1,85.7)	29.5(25.1,34.3)	86.0(84.8,87.2)
(SOC+Device) -SOC	39.9(31.4,48.1)	-38.3(-42.4, -34.5)	-7.9(-12.8, -3.4)	3.4 (1.0,5.7)
Device only††	75.2(69.3,80.5)	46.4 (42.6,49.9)	22.3 (20.7,23.8)	90.1 (88.0,92.1)
SOC	33.9 (27.5,40.5)	83.4 (81.1,85.7)	29.5(25.1,34.3)	86.0(84.8,87.2)
Device-SOC	41.3(33.0,49.5)	-37.0(-41.4, -33.0)	-7.2(-12.1,-2.6)	4.1(1.8,6.4)

†PPV and NPV calculated using Bayes theorem on sensitivity and specificity, assuming a common prevalence across the two study arms of 17.0%. ‡95% Bootstrap percentile intervals.

†† There were 38 margins with a missing device reading. (6 pathology positive margins and 32 pathology negative margins)

Table 2-37: Diagnostic Performance per patient ignoring location

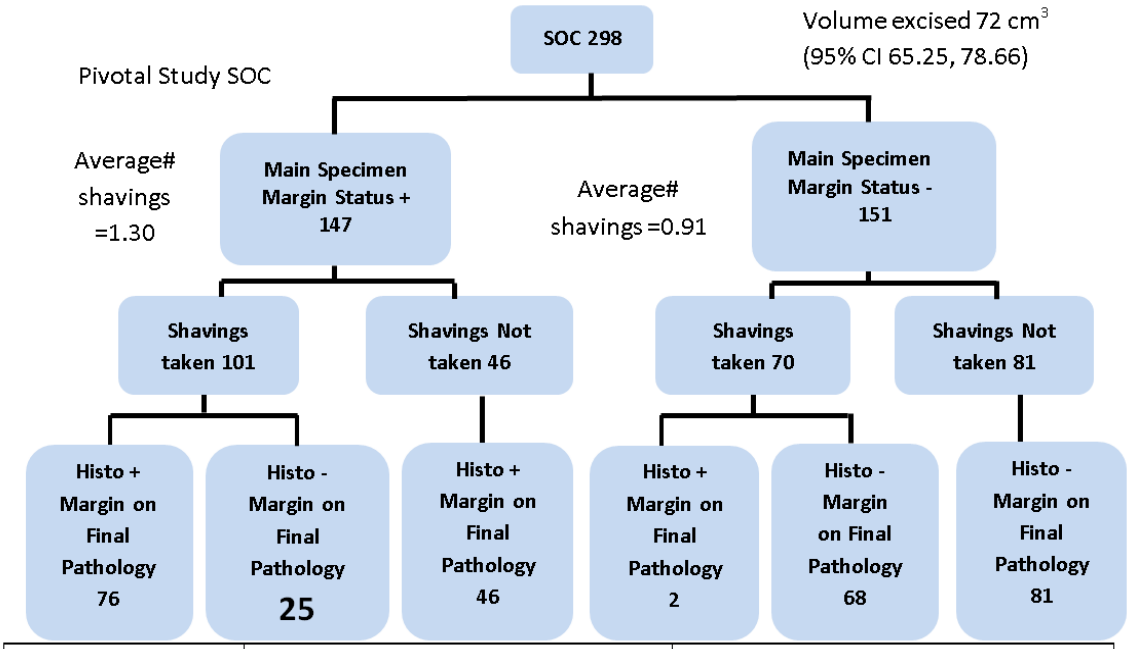
	Sensitivity(%) 95% CI	Specificity (%) 95% CI	PPV†(%) 95%CI	NPV†(%) 95% CI
SOC+Device	98.8(95.6,99.9)	5.9(2.6,11.3)	53.2(52.1,54.4)	81.9(49.0,95.4)
SOC	68.7(60.1,76.1)	53.6(45.4,61.8)	61.6(56.7,66.3)	61.3(54.4,67.7)
(SOC+Device) -SOC	30.1(22.6,38.2)	-47.7(-56.6, -38.3)	-8.4(-13.6, -3.5)‡	20.6(-9.2,42.0)‡
Device only	96.3(92.2,98.6)	8.9(4.7,15.0)	53.4(51.9,54.9)	68.9(46.2,85.2)
SOC	68.7(60.1,76.1)	53.6(45.4,61.8)	61.6(56.7,66.3)	61.3(54.4,67.7)
Device-SOC	27.6%(19.6,36.0)	-44.7% (-54.0, -34.9)	-8.2 (-13.5,-3.1)‡	7.6(-16.6,27.9)‡

†PPV and NPV calculated using Bayes theorem assuming a common prevalence across the two study arms of 52%.
‡95% Bootstrap percentile intervals.

The Figures 2-3 and 2-4 provide a more comprehensive assessment of what occurred in each arm of pivotal study.

As shown in Figure 2-5, 298 SOC patients were enrolled. An average of 72 cm3 of tissue was excised during the initial lumpectomy. There were 147 patients with cancer positive main specimens and 151 cancer negative main specimens. Of the 147 cancer positive main specimens, 25 or 17% were converted to cancer negative final margins with cavity shavings.

In the SOC arm, shavings were not taken in 46+81 or 127/298 subjects.

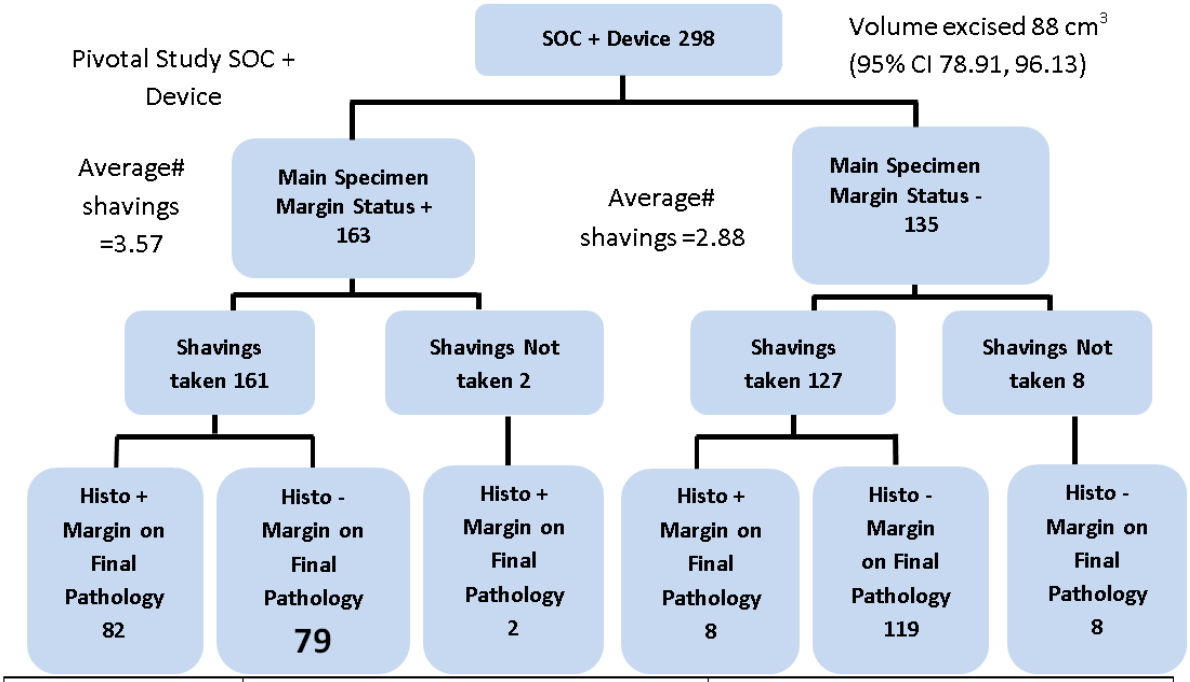


Main Specimen	+		-	
Final Margin	-	+	+	-
Totals	17% (25/147)	83% (122/147)	1.3% (2/151)	98.7% (149/151)

Figure 2-5: Pivotal Study Patient Flow Chart - SOC Arm

As demonstrated in Figure 2-6 298 patients were enrolled in the SOC+Device arm. An average of 88 cm3 of tissue was excised during the initial lumpectomy. There were 163 patients with cancer positive main specimens and 135 cancer negative main specimens. Of the 163 cancer positive main specimens, 79 or 49% were converted to cancer negative final margins with cavity shavings.

In the SOC+Device arm, shavings were not taken in 2+8 or 10/298 subjects.



Main Specimen	+		-	
Final Margin	-	+	+	-
Totals	**48.5%** (79/163)	51.5% (84/163)	5.9% (8/135)	94.1% (127/135)

Figure 2-6: Pivotal Study Patient Flow Chart - SOC+Device Arm

Summary of Supplemental Clinical Information

A. Pivotal Study Additional Analyses

While not powered to detect differences across subpopulations, there was a trend for outside of US patient populations to experience greater clinically relevant benefit than for the US population of patients enrolled as shown in Table 2-38: Pivotal Study Results across Subpopulations.

Table 2-38: Pivotal Study Results across Subpopulations

		US Patients n = 566		**Israel Patients n = 98**	
Endpoint		SOC + Device	SOC	SOC + Device	SOC
1º	CSR	69.7%	22.4%	85.7%	22.7%
2º	Incomplete Surgical Re-excision	17.3%	38.8%	6.1%	35.4%
2º	Full Detection*	59.9%	N/A	81%	N/A
2º	Re-excision Procedure Rate	34.5%	48%	4.8%	22.7%
2º	Positive Margin Presence	53.5%	82.4%	38.1%	86.4%
2º	Total Tissue Volume Excised (cm^3)	92.4	82.6	97.6	95.9
Diagnostic Device Performance		SOC + Device	SOC	SOC + Device	SOC
Sensitivity (%) 95% CI†		73.4 (66.8,79.6)		87.8 (76.8,98.8)	
Specificity (%) 95% CI†		44.7% (40.8,48.8)		53.9% (46.0,62.0)	

*Full detection is for Device (not SOC+Device arm)
†95% Bootstrap percentile intervals.

B. Product Development Clinical Studies

Product development clinical studies were conducted at various stages of the product development process, as summarized inTable 2-39. None of these studies were pre-approved by FDA.

Table 2-39: Summary of Developmental Clinical Studies

Study Number	Study Name	# Subjects	Product Description	Primary Objective	Principal Results
III	"Point-by-point" study in pathology - phase II 3/2006 – 6/2007	N=76	MarginProbe System Probe & MarginProbe System Type 1.0 system console	Obtain database set and assess performance – phase II	Device use has no permanent effect on tissue (macroscopic or microscopic) Device performance per-point on bread-loafed lumpectomy specimens: sensitivity 100% and specificity 87% on homogeneous samples, sensitivity 70% and specificity 70% on full dataset
V	Intraoperative blinded study - phase II 6/2006 – 5/2008	N=175	MarginProbe System Probe & MarginProbe System Type 1.0 system console	Assess intraoperative performance on the resection surface of lumpectomy specimens and evaluate adjunctive device contribution to SOC	Even with a limited point sampling by the device, per-patient detection rate is superior with Device+SOC (73%) as compared to SOC alone (46%)

Study Number	Study Name	# Subjects	Product Description	Primary Objective	Principal Results
MAST	Pilot Study 11/2006 – 11/2007	N=300	MarginProbe System Probe & MarginProbe System Type 1.0 system console	Assessment of device detection performance and clinical utility in a randomized, controlled (patient is blinded), intended use fashion. Assess cosmetic outcome associated with device use compared to SOC.	- Device is safe for intraoperative use - Re-excision rate is reduced by 56% (p=0.0027) - Positive margin identification guiding intraoperative resection is superior in Device+SOC arm (60%) compared to SOC (41%) - Cosmesis is not affected by device use - Excised tissue volume is not affected by device - Performance is the same for both palpable and non-palpable lesions

The product development study results were used to develop the MarginProbe System algorithm in the manner described in Figure 2-7: Algorithm Development Process.

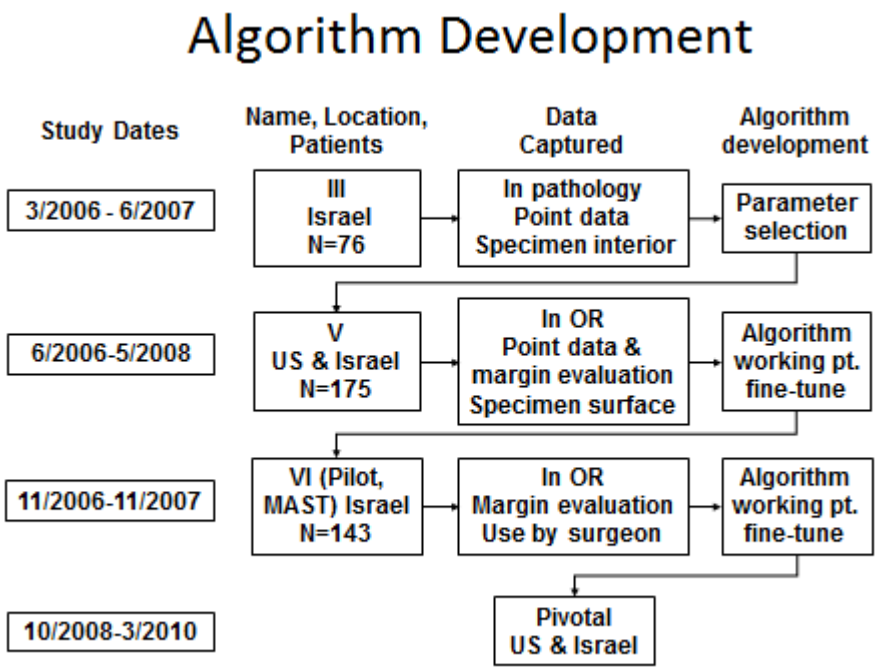


Figure 2-7: Algorithm Development Process

1. Study III

Study III was conducted to create the classification database of actual tissue measurements using the MarginProbe paired with their histology at point level. For each point measured with the device the pathology was taken at that same point. Device measurements were performed at the interior of the lumpectomy specimen (following its sectioning at the pathology lab).

The specimens used for this study were taken from women with palpable tumors who had undergone lumpectomy or mastectomy. The study was performed in Israel at 4 study sites. The patient demographics and cancer specifics of the specimens used to create the classification dataset are summarized in Table 2-40. Table 2-41 illustrates the classification data set that was derived in Study III.

Table 2-40: Study III - Patient Demographics and Cancer Specifics

Sites	4 (Israel)	
N	77 patients and 81 specimens (4 patients bilateral disease)	
Mean Age (range)	62.64 years (36 - 85)	
Mean Tumor Size (range)	1.65 cm (0.1 – 3.5)	
Fine Needle Localization	33 specimens	
Sentinel Node Biopsy (Both Blue Dye & Radioisotope)	43 specimens	
Cancer Pathology	Infiltrating Ductal (IDC)	46
	DCIS	8
	Mixed	8
	Infiltrating Lobular (ILC)	6
	Other	3
	Not stated	4
Grade	I	3
	II	34
	III	20
HER2 positive	18	
Estrogen Positive	60	
Progesterone Positive	46	

Table 2-41: Study III - Classification Data Set

Number of tissue measurement data points	869
- Excluded data points	116
Valid data points	753
- Normal	588 (78%)
- Malignant	165 (22%)

The ROC curves of the device performance in Study III are shown Figure 2-8. This figure includes three datasets: (1) tissues containing at least 75% of a single tissue type; (2) all tissues containing at least 50% of a single tissue type; and (3) the full dataset collected in the experiment, containing cancers of all sizes (down to 0.15-mm-diameter features).

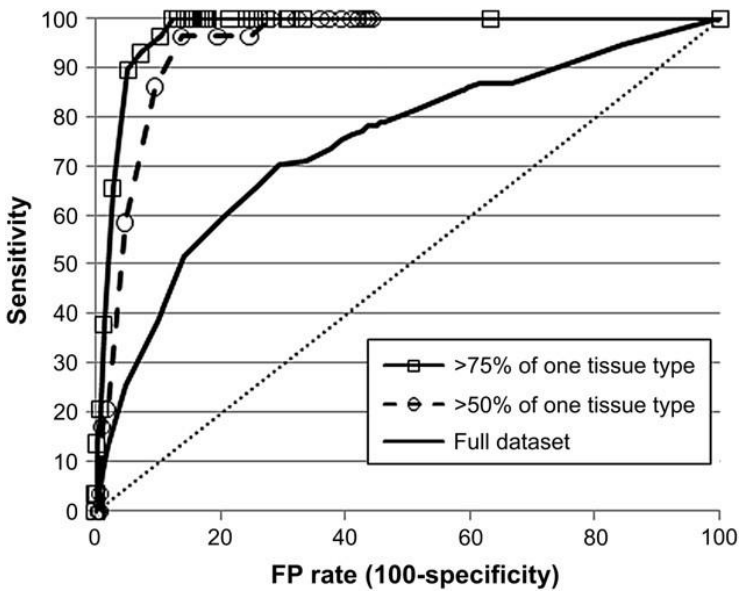


Figure 2-8: Study III - ROC curves of 3 different datasets

When the composition of the tissue being measured by the probe (i.e. directly underneath the 7 mm footprint of the probe) was more homogeneous, there was greater sensitivity and specificity in MarginProbe readings as shown in Table 2-42.

Table 2-42: Study III - Sensitivity and Specificity in MarginProbe Readings

Percentage single tissue type within probe's 7 mm diameter footprint	Specimen description	Device Performance
> 75% singe tissue type	22 cancerous, from 15 patients 425 nonmalignant	Sensitivity 1.00 (95% CI: 0.85–1) Specificity 0.87 (95% CI: 0.83–0.90)
≥ 50% single tissue type	29 cancerous, from 18 patients, and 567 nonmalignant	Sensitivity 1.00 (95% CI: 0.88–1) Specificity 0.72 (95% CI: 0.68–0.76).
Full dataset containing cancers of all sizes (down to 0.15-mm-diameter features)	165 cancerous sites from 50 patients, and 588 nonmalignant sites	Sensitivity 0.70 (95% CI: 0.63–0.77), Specificity 0.70 (95% CI: 0.67–0.74)

The performance for different histopathology types are also summarized in Table 2-43. [The two most common groups, invasive ductal carcinoma (IDC) and ductal carcinoma in situ (DCIS), have sensitivities of 0.68 (95% CI: 57–77) and 0.63 (95% CI:45–79), respectively]

Table 2-43: Study III - Device Sensitivity for Different Histopathology Subgroups

Cancer histopathology	Number of samples	Detected	Detection rate (95% CI)
Infiltrating Ductal Carcinoma (IDC)	87	59	0.68 95% CI:57– 77
Ductal Carcinoma in-situ (DCIS)	35	22	0.63 95% CI:45–79
Infiltrating Lobular Carcinoma (ILC)	7	5	0.71
IDC+ DCIS	25	21	0.84
ILC+ DCIS	3	3	1.00
Other	8	6	0.75
Full dataset	165	116	0.70

2. Study V

Study V was a blinded study with MarginProbe System Type 1.0 device to assess performance of the device on the cut surface tissue of lumpectomy specimens, as compared to histology.

Surgeons were blinded to the device outputs and could not act on device outputs. The device measurements (maximum of 20) were taken intraoperatively on the surface of fresh intact lumpectomy specimens. The orientation of each measurement site was noted. For each marked site, the corresponding 7 mm wide tissue specimen was processed *en-face* and microscopically evaluated as positive or negative for malignancy.

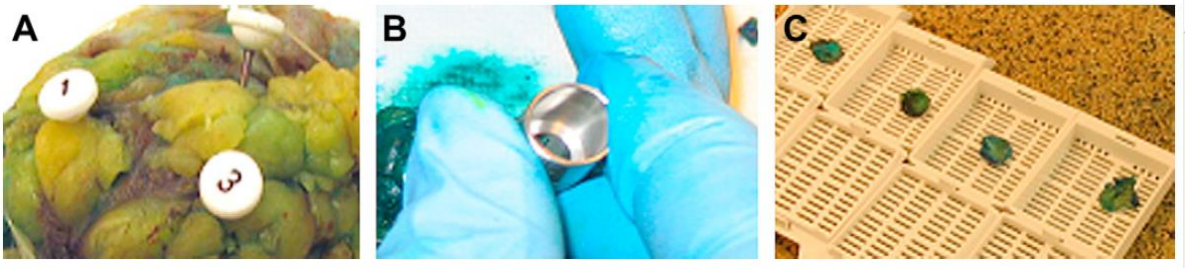
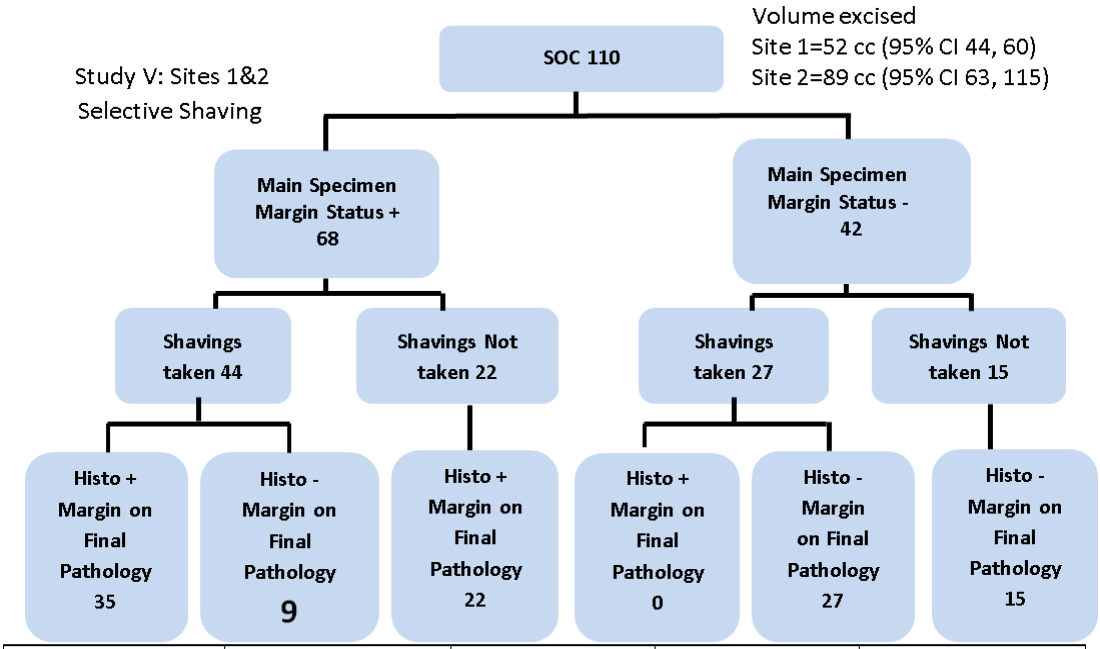


Figure 2-9: Study V - Sampling Process

A total of 175 subjects were enrolled in 3 sites during this study. Surgeons at 2 institutions included in this study (site 1: US site, n=101 patients; site 2: OUS site, n=9 patients) excised additional margins only where deemed necessary ("selective" re-excision). Practice at the third institution (US site, n=65 patients, 66 specimens) was to routinely re-excise all margins from the cavity ("total" re-excision).

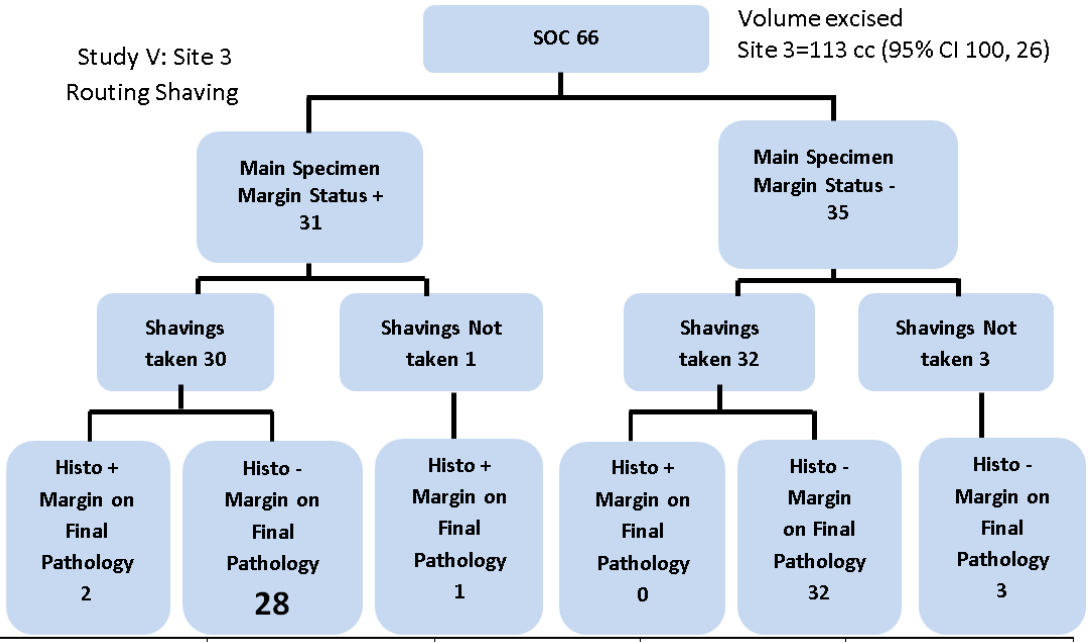
While results from Study V served to further inform the MarginProbe product development, Study V also serves to provide a comparison of differences in standard of care selective versus empiric total cavity shaving. Patients who receive empiric, routine re-excision of all margins have greater conversion of initial positive lumpectomy margins to final negative margins. The observed effect is illustrated below in Figure 2-10 and Figure 2-11 comparing the final pathologies from patients treated at study sites 1 and 2 (selective re-excision) versus study site 3 (total re-excision).

There is also literature (see references list below) suggesting that the standard, empiric practice of complete/partial lumpectomy cavity shavings in the same operative setting as the initial lumpectomy can reduce the incidence of incomplete cancer resection and produces greater volumes of tissue resection.



Main Specimen	+	+	-	-
Final Margin	-	+	+	-
Totals	9/68	57/68	0/42	42/42

Figure 2-10: Study V - Final Pathologies from Patients Treated at Study Sites 1 and 2 (Selective Re-excision)



Main Specimen	+	+	-	-
Final Margin	-	+	+	-
Totals	28/31	3/31	0/35	35/35

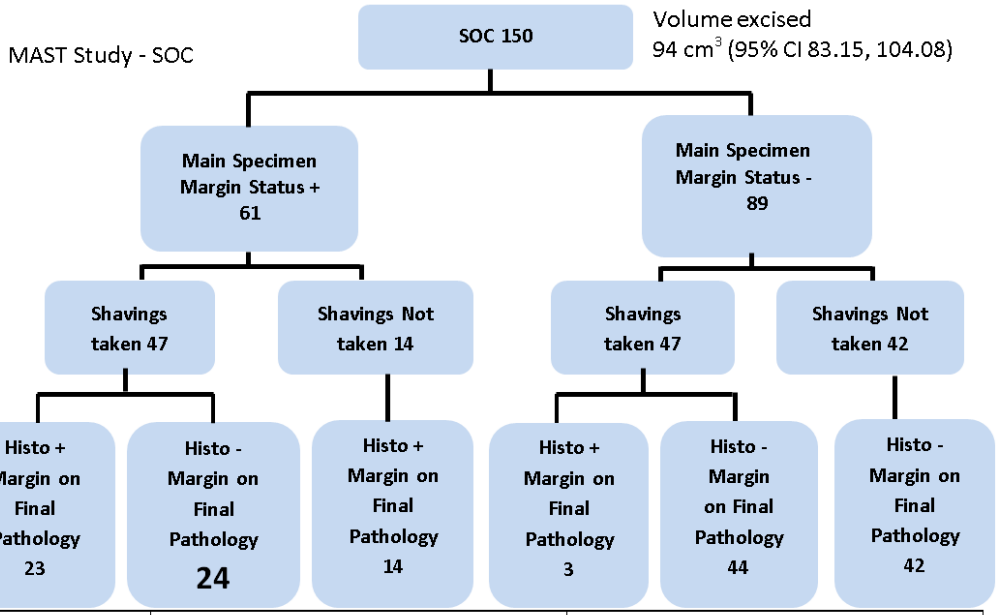
Figure 2-11: Study V - Final Pathologies from Patients Treated at Study Site 3 (Total Re-excision)

3. MAST Study

This MAST pilot study was performed in Israel. It was a prospective, randomized, controlled study designed to compared SOC lumpectomy with to SOC+Device lumpectomy. Three hundred subjects at 11 sites were enrolled (n=149 device arm; n=151 control arm).

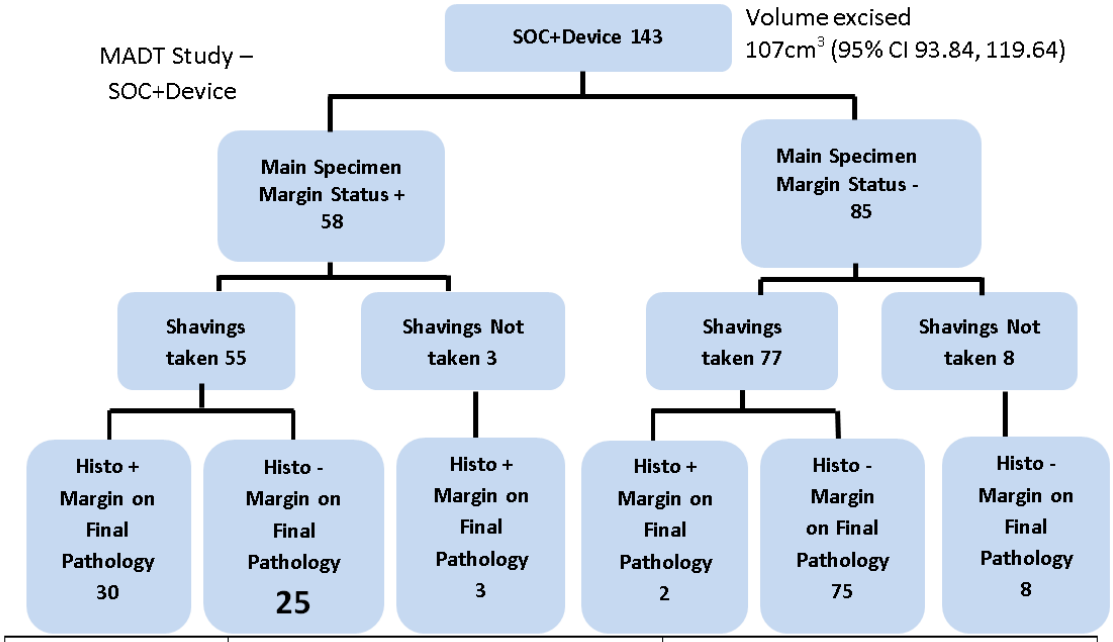
The MAST study design was similar to the Pivotal study however there were some differences. The MAST study involved a different MarginProbe device algorithm, different device use instructions (i.e. surgeons used the device at their discretion with respect to extent of device use and tissue targeted and were not required to act on positive MarginProbe device readings), an assessment of post-lumpectomy breast symmetry using a 4 point scale, and intra-operative pathology as part of SOC--being used in approximately 20% of the cases.

The difference in protocols across studies may be reflected in the results of the SOC arm in the MAST Study compared to the pivotal IDE investigation. The results are provided in Figure 2-12 and Figure 2-13 below.



Main Specimen	+		-	
Final Margin	-	+	+	-
Totals	39.3% (24/61)	60.7% (37/61)	3.4% (3/89)	69.6% (86/89)

Figure 2-12: MAST Study - Final Pathologies - SOC Arm



Main Specimen	+		-	
Final Margin	-	+	+	-
Totals	43.1% (25/58)	56.9% (33/58)	2.4% (2/85)	97.6% (83/85)

Figure 2-13: MAST Study - Final Pathologies - SOC+Device Arm

Electrical and Mechanical Safety Precautions

- **There are no user-serviceable parts inside the system**.
- Make sure that all personnel are familiar with the system's controls and know how to shut down the system instantly in case of an emergency.
- Keep all covers and panels of the system closed. Removing the covers creates a safety hazard.
- Any handling of the system other than intraoperative use should be performed when the system is shut down and disconnected from its electrical power source.
- The console is portable and weighs approximately 16 Kg (35 lbs). Carefully lift, carry and lay down the console only by using two handles either on the top or the bottom of the console (Figure 4-2).
- The system is grounded through the grounding conductor in the power supply cable. This protective grounding is essential for safe operation.
- Portable and mobile communications equipment and OR electrical equipment can affect medical electrical devices. Interference may occur in the vicinity of the equipment.
- Do not use any accessories or cables other than those specified and provided. Use of such accessories or cables may result in damage to the system. Connecting any third-party equipment to the system is strictly forbidden without written approval from Dilon Medical Technologies.

Warning

- To avoid risk of electric shock, this equipment must only be connected to a grounded supply main.

Compliance with International Regulatory Standards

The MARGINPROBE® system complies with the requirements of the following:

- **IEC 60601-1:2005/ Amd1:2012** - Medical Electrical Equipment- Part 1: General Requirements for basic Safety and essential performance.
- **IEC 60601-1-2: 2014, EN 60601-1-2: 2015** - Medical Electrical Equipment, Part 1-2: General Requirements for Safety. Collateral Standard: Electromagnetic Compatibility, Requirements And Tests
- **IEC 60601-1-6:2010/AMD1:2013** - Medical Electrical Equipment – Part 1-6: General Requirements for Basic Safety and Essential Performance – Collateral Standard: Usability
- **ISO 10993-1:2018** - Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing

- **ISO 11135:2014/AMD 1:2018** - Sterilization of Health Care Products. Ethylene Oxide Requirements for Development, Validation and Routine Control of a Sterilization Process for Medical Devices

Device Regulatory Labels

The following labels are affixed to the system and accessories:

Probe Identification Label

The probe identification label, located on the sealed pack, includes the following information:

- Name and part number of the probe
- Name and address of the manufacturer
- Serial number, lot number, date of manufacture & date of expiration
- Cautionary symbol: Single-use only
- Cautionary symbol: Consult operating instructions
- Cautionary symbol: Do not use if package is damaged
- Indicator that the probe has been sterilized by ethylene oxide

Console Identification Label

The console identification label, located on the console's back panel, includes the following information:

- Name and address of the manufacturer
- Name and model number and part number of the console
- Date of manufacture and Serial number of the console
- Electrical rating and fuse type definition
- Cautionary symbol: Refer to instruction manual/booklet Applied part is ‘Type BF’

Electrical Hazard Label

This label warns against dangerous electrical voltages within the console.

EtO Exposure Indicator

This indicator, found on the blister packaging of the probe, is a chemically-sensitive indicator that turns green when exposed to ethylene oxide and indicates that the contents of the pack are sterile.

Warning

If the indicator on the probe's sealed pack is any color other than green, or if the indicator is missing, do not use the probe!

The following labels are the accompanying documents for the Probe and for the System:

Probe Instruction for Use (IFU)

The MARGINPROBE® Sterile Disposable Probe Instruction for Use is provided with the probe package.

User Manual

The MARGINPROBE® User Manual is provided with the console package.

3. CONSOLE UNPACKING AND STORAGE

1. Unpack the console.
2. Check the console for external damage.
3. Check that the power cord matches the electrical wall socket in the facility.

Note

Any damage to the packaging or to the system found prior to opening the package should be reported to Dilon Medical Technologies and to the insurance carrier.

If the power cord is damaged or if the power cord's plug does not match the wall socket of your facility contact your Dilon Medical Technologies Service representative.

Equipment List

The MARGINPROBE® console shipment package contains the following:

Equipment Item	*P/N #*	*Quantity*
MARGINPROBE® Console	SA0590020	1
USER Manual – English (this document)	PB0590220	1

Storage Conditions at User Site

Caution

Do not store the MARGINPROBE® system or the sterile probes where they may be exposed to heat, direct sunlight, water or any other liquids.

MARGINPROBE® Console

Environmental Parameter	*Storage Condition at User Site*
Temperature	+10°C to +40°C (+50°F to +104°F)
Humidity	20% to 85% RH

MARGINPROBE® Probe

- Use before the expiry date indicated on the label.
- Store at room temperature below 40°C / 104°F, in a dry place, protected from light.

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4. SYSTEM DESCRIPTION

Introduction

The MARGINPROBE® system consists of a console and a sterile, disposable probe (Figure 4-1). The MARGINPROBE® console consists of internal electrical components, a pneumatic system and a graphic user interface module. The user interface module incorporates a color display, audio components and operation buttons.

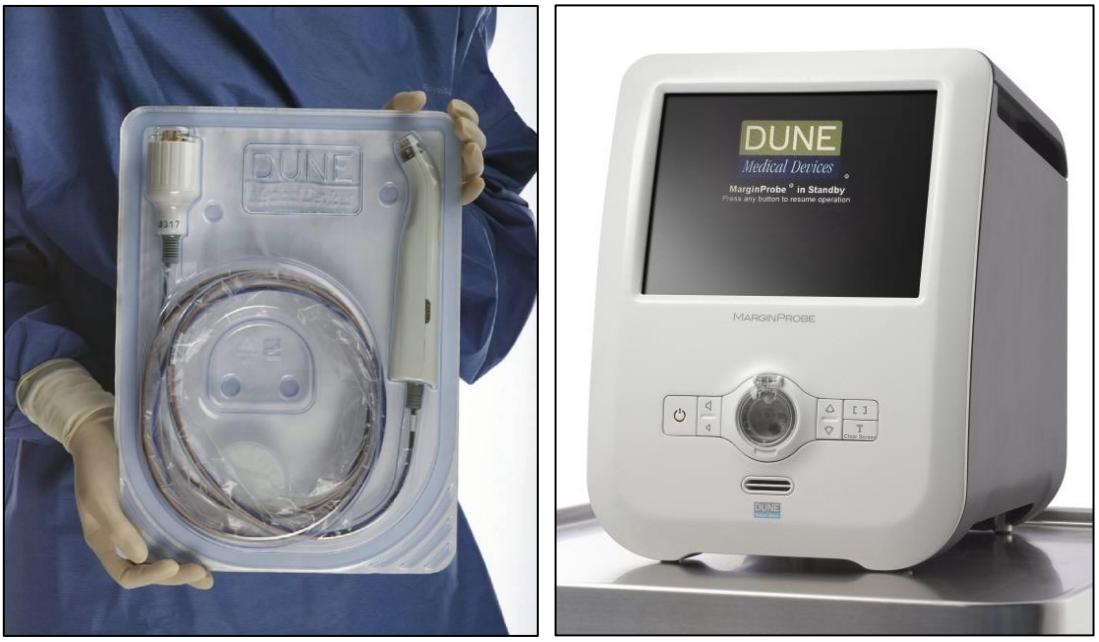

Figure 4-1: MarginProbe System

Console

The console (Figure 4-2) incorporates modules for signal generation and collection, electric and pneumatic control, data processing and display. The console includes a connector for attaching the probe cable.

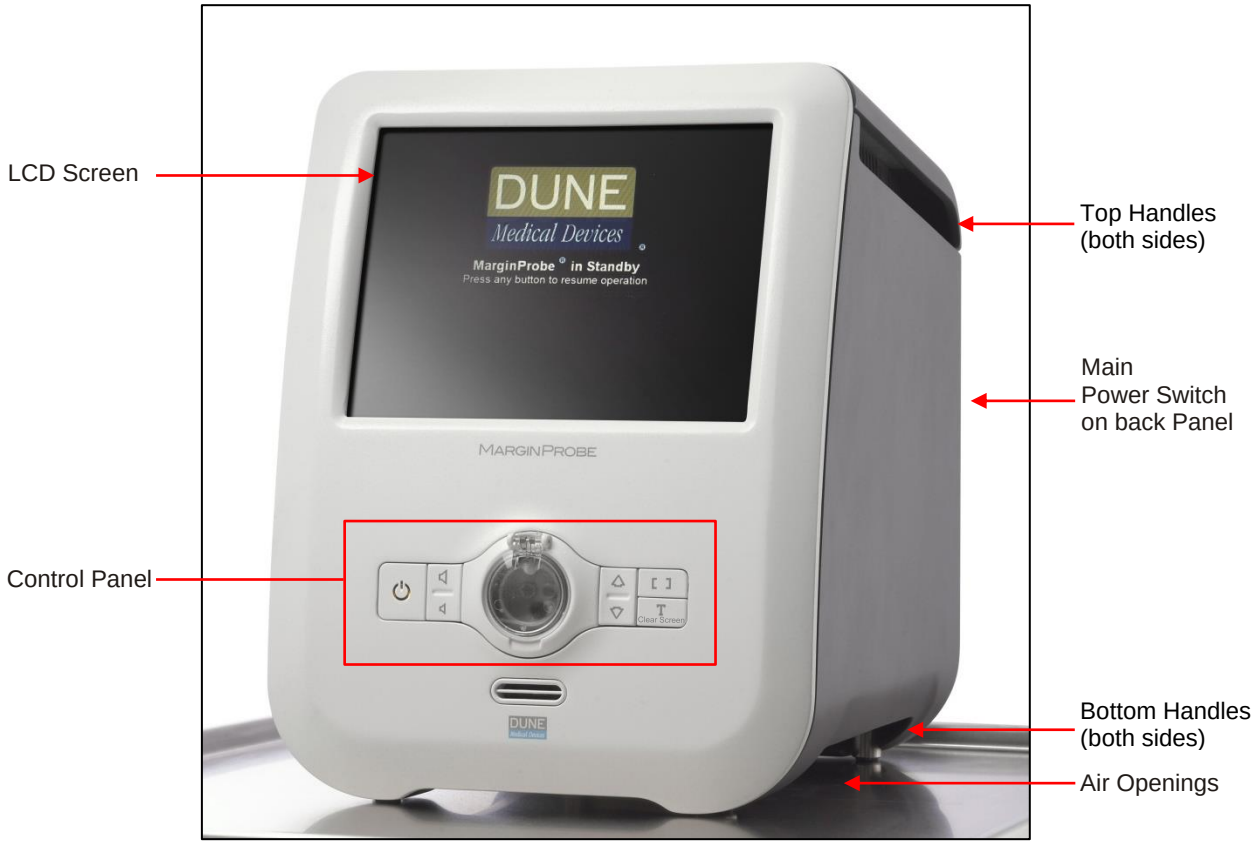

Figure 4-2: System Description: Console

Control Panel

The control panel on the front of the console incorporates all system controls as noted in Figure 4-3. These controls will be described in detail in the Operating Instructions chapter (Section 5).

Several of the functions performed from this panel may also be performed from the probe; these will be explained in the Operating Instructions chapter.

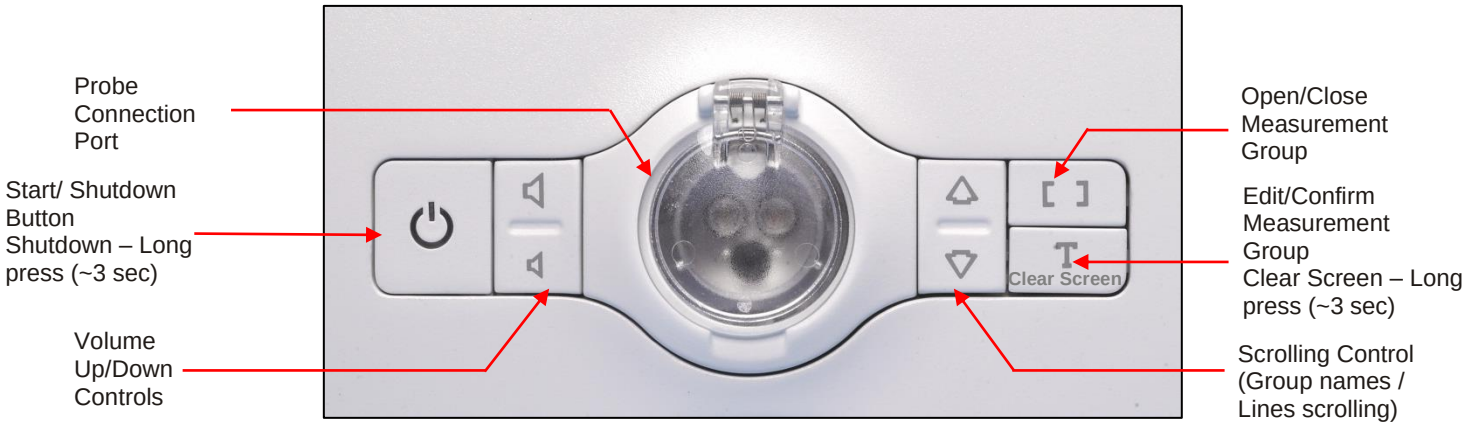

Figure 4-3: System Description: Control Panel

Summary of control panel buttons

A full description of control panel buttons can be found in the Operating Instruction chapter (Section 6).

User Interface

The graphical user interface (Figure 4-4) consists of an LCD screen and displays the system's status at any given point and the results of the measurements.

The user interface will be described in detail in the Operating Instructions chapter (Section 6).

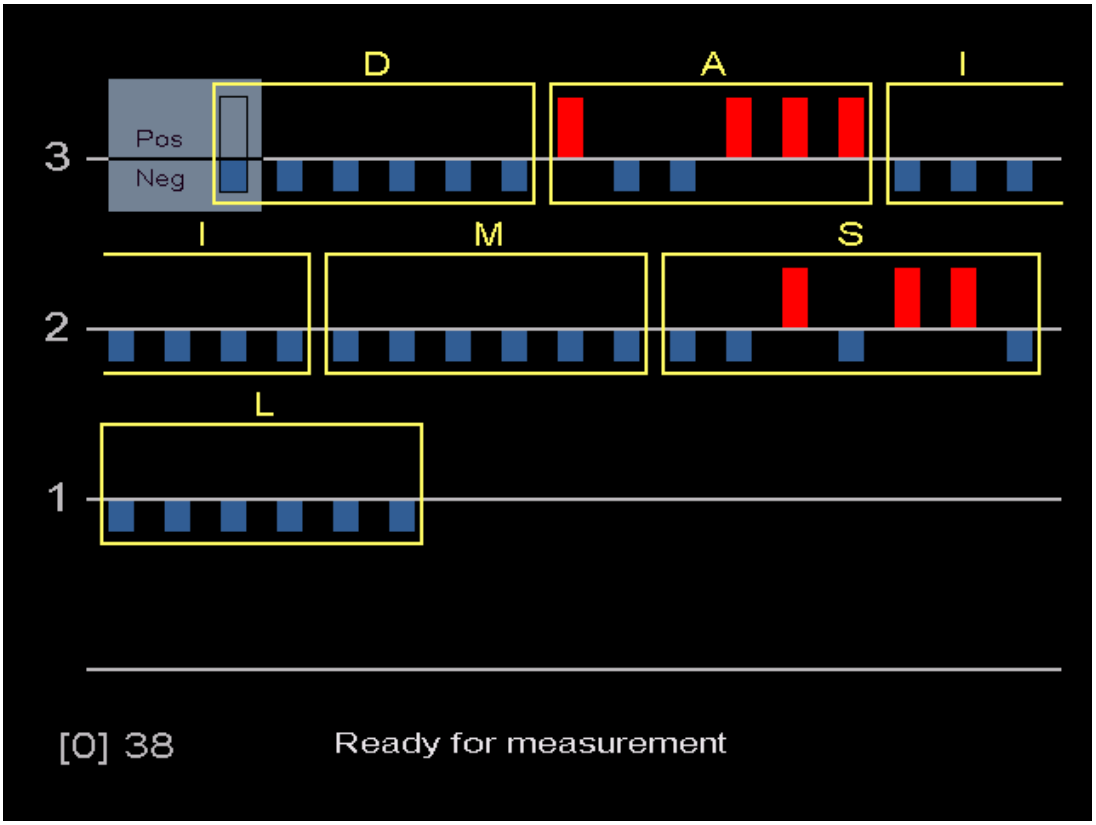

Figure 4-4: Graphic User Interface

Probe Components

The probe is a hand-held, sterile, disposable unit (Figure 4-5) with a 3-year shelf life. It includes the sensor/FFS module, attachment mechanism, calibration module, control button, LED indicators and biological air filter. It is connected to the console with a built-in connector that combines electrical and vacuum connections. The energy is electromagnetic at the RF range. It is confined to the vicinity of the probe tip. The energy level per measurement is less than 0.2 mJ with a power lower than 0.3 mW. The max field voltage is 1V p-p.

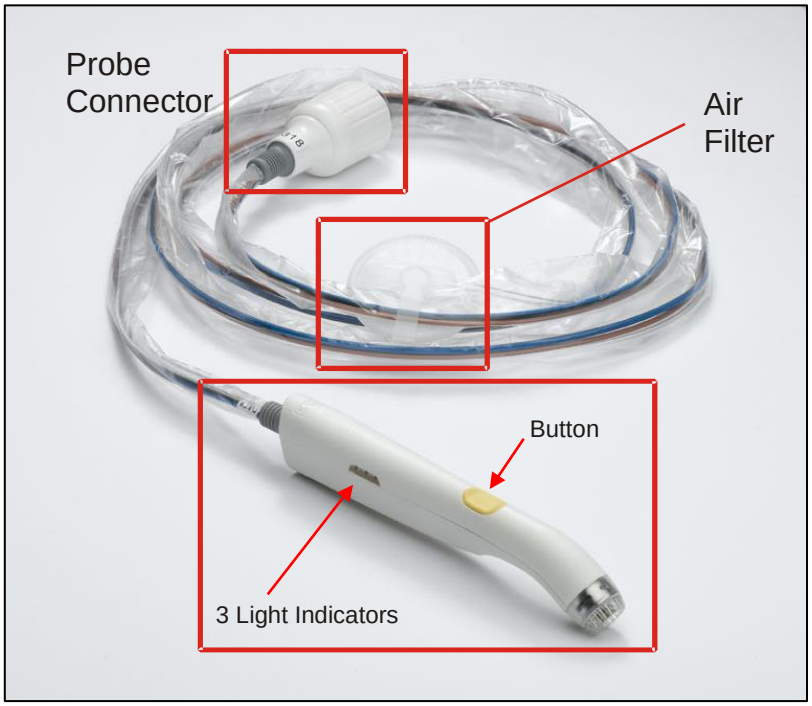

Figure 4-5: System Description: Probe Assembly

Coupling and Measurement

The tip of the probe incorporates the tissue-sensor attachment mechanism and the sensor that measures the tissue.

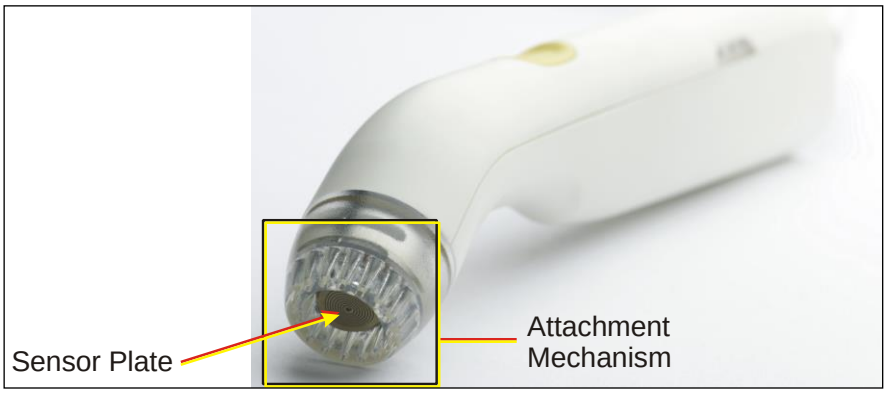

Figure 4-6: Probe Tip

Probe Control Button

The system can be operated during a procedure by pressing the probe control button (Figure 4-7):

- **Double-Click:** opening and closing measurement groups.
- **Single-Click:** scrolling between measurement groups name.
- **Long Click:** editing and confirming measurement groups name.

For additional information refer to the Operating Instructions chapter (Section 6, Grouping Measurements According to Margins).

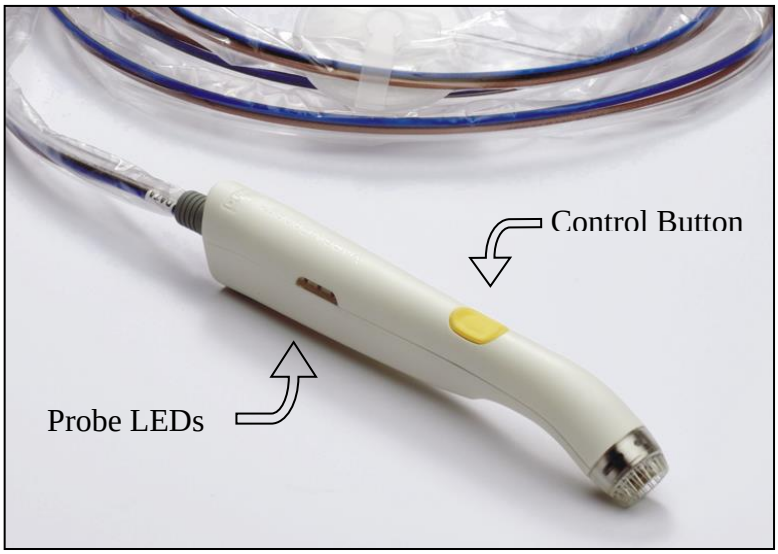

Figure 4-7: Control Button and Probe LEDs

Probe Light Indicators

The probe features three light indicators (Figure 4-5 and Figure 4-7), each one signifying a different result of a point measurement; during calibration and in standby mode, all lights will be on. Refer to the Operating Instructions chapter for complete details (Section 6).

Probe Connector

The probe connector (Figure 4-8) couples the probe to the MARGINPROBE® console. The body of the connector and the connection port are notched to each other with a dimple on the inner rim of the port and a depression for the dimple in the rim of the connector, so that the connector may only be inserted in the correct orientation.

A half-turn to the right secures the connector in place.

Figure 4-8: Probe Connector

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5. CONSOLE PREPARATION FOR USE

Facility Requirements

Ensure that the site meets the requirements described in the following section:

Space Requirements

Space with adequate ventilation and free airflow should be allocated. The working area for the system should be prepared according to the system dimensions presented in Figure 5-1.

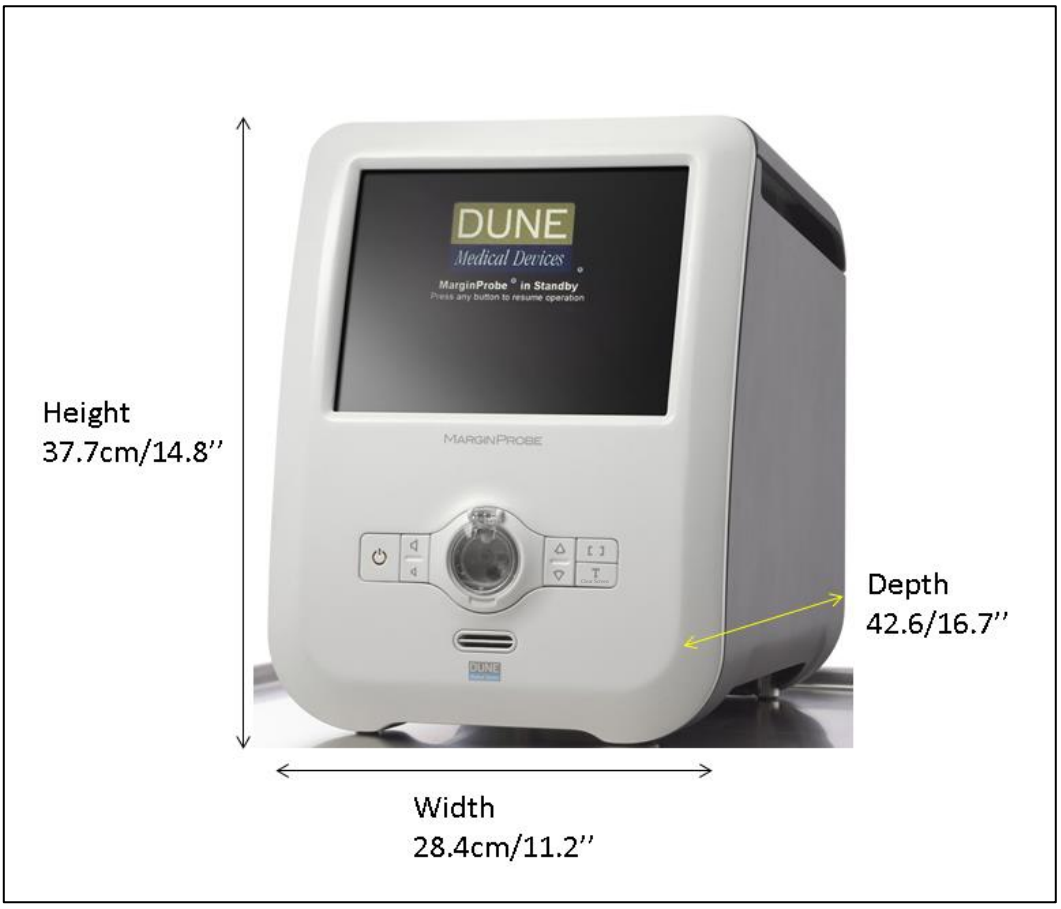

Figure 5-1: System Dimensions

Caution

Do not cover the console and its air openings when switched on.

Ensure that air openings at the bottom of the Console are not blocked.

Electrical Requirements

The system will require a separate line supply for the following (appropriate to local requirements):

- 100-240V~, 50-60 Hz, single phase
- 150VA Max power

The electrical requirements are printed on the console identification label (located on the console's back panel).

> ***Warning***
>
> To ensure safe operation, the system must be connected to a properly grounded electrical wall socket.

Equipotential Ground connection

The Console is provided with an Equipotential Ground Connection on its back panel.

> ***Warning***
>
> Use only a proper equipotential ground cable (section 10) to connect Console to O.R equipotential ground connection port.

Operational Environmental Requirements – MARGINPROBE®

Environmental Parameter	Operational Range
Temperature	15°C to 30°C / 59°F to 86°F
Humidity	30% to 80% at temperature < 29°C / 84°F
Altitude	0 to 2000m (0 to 6560 feet)

6. OPERATING INSTRUCTIONS

Introduction

The probe was designed to measure breast tissue. Before performing a measurement on the specimen, make sure that the specimen is wiped free of excess fluid. Do not apply saline or ultrasound gel to the tissue before measurements are taken. If necessary, clean the surface of the tissue with sterile water.

An individual measurement is automatically performed by applying the probe tip perpendicular to the tissue and ensuring stable contact for the suction holes in the perimeter. Once in contact with tissue, the tip is automatically attached by slight suction and a measurement is taken.

Warning

- Do not apply saline or ultrasound gel to the tissue before performing a measurement.
- Take measurements within 20 minutes after specimen excision.

Console Placement

The system is designed for use in a surgical environment. Console preparation is carried out by performing the following:

1. Console should be kept in the environmental conditions referred as "Storage conditions at user site" (page 3-1) for at least 3 hours before use.
2. Check the console for external damage.
3. Place the console on a stable plane such as a table or an OR cart. The console should not be placed directly on the floor.
4. When placing on a cart, the console can be secured to the cart by using a strap.

Caution

- Do not use the console if it is wet or if water drops are seen on any of its covers.
- Don't place the console directly on the floor or on a surface where liquids or liquids containers are likely to be found in its close surrounding.

Note

Assure the console is placed such that its screen is clearly visible by the operator.

Connecting the Console

1. Release the power cord from its holder.
2. Verify that the power cord plug matches the electrical wall socket, connect it and ensure that it is firmly connected to the wall socket.

Note

Do not attempt to connect the console to the electrical wall socket if the power cord is damaged or if the power cord's plug does not match the wall socket.

3. Turn on the main power switch on the back panel (Figure 6-1):

Figure 6-1: Electrical Connection (Picture for illustration only)

4. Check that the power light indicator is orange, indicating that the console is connected to the power supply and is ready for use.

Preparing the System for Operation

Caution

- Check the integrity of the screen at the start of every day's scheduled procedures. Do not use the system if the screen is damaged.
- When placing on a cart, the console can be secured to the cart by using a strap.

Prepare two probe packages to be available for each procedure: one for immediate use and the other ready in case probe replacement is required (section 9). Do not open the probe package before the MARGINPROBE® console has completed its initialization as described below.

Press the start/shutdown button on the control panel; the power light indicator will turn green and the system will initialize its software while exhibiting a splash screen with the logo and an initialization progress bar. Typical initialization time is up to 2 minutes.

When initialization is complete – and if a probe is not connected to the console – a **"Connect Probe"** message will pop up on the screen (Figure 6-2):

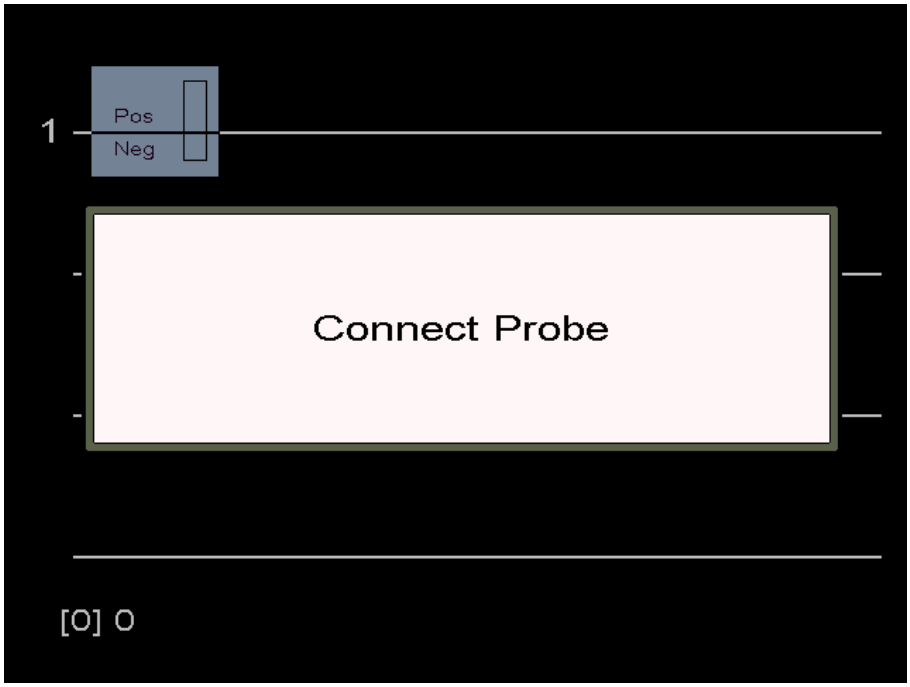

Figure 6-2: Connect Probe Popup Window

The first screen that appears after initialization reflects the way the console was shut down in the previous session. In case of a normal shutdown, a clean

screen (without measurements) will appear. If the system was not shut down properly, the screen will display all of the measurements from the previous session. You can always toggle between the new screen and that of the previous session by pressing the **T** button on the control panel until screen changes (long press).

If no action was taken for ten minutes, the system will switch to **Standby** mode in which a screen saver will appear stating **"MarginProbe® in Standby Mode"** (Figure 6-3). Refer to the Standby Mode chapter for complete details (Section 1).

Note

- Any popup displayed on the screen can be removed for ten seconds by pressing the ▲ or ▼ buttons on the console control panel or by a single click on the probe button.
- Resuming operation from **Standby** mode is done by pressing any of the buttons on the console control panel or by a single click on the probe button.

Figure 6-3: Standby Mode Message

Connecting the Probe outside the Sterile Field

The console is placed outside the sterile field while the probe is used inside the sterile field. The length of the probe cable is 2.7 meters (8 feet 10 inches) to enable proper maintenance of the sterile field around the patient.

1. **Circulating Nurse:** open the probe's cardboard box and remove the plastic blister from the box.
2. **Circulating Nurse:** open the plastic blister containing the sterile probe outside the sterile field.
3. **Scrub Nurse:** remove the sterile probe from the blister, and hand the connector to the circulating nurse out of the sterile field.
4. **Circulating Nurse:**
   - Align the recess in the connector with the feature in the console (Figure 6-4).
   - Position the probe connector with its axes aligned to that of the connection port (Figure 6-5).
   - Insert the probe and turn the probe connector one half a turn to the right (clockwise), until it is secured in place (Figure 6-6).

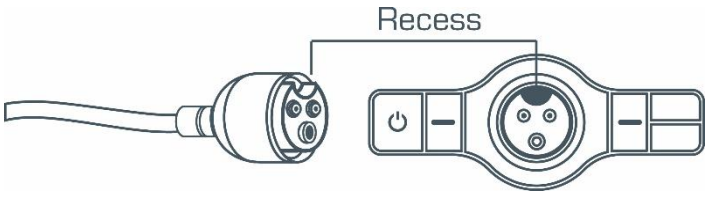

Figure 6-4:Aligning the recess in the connector with the feature in the console

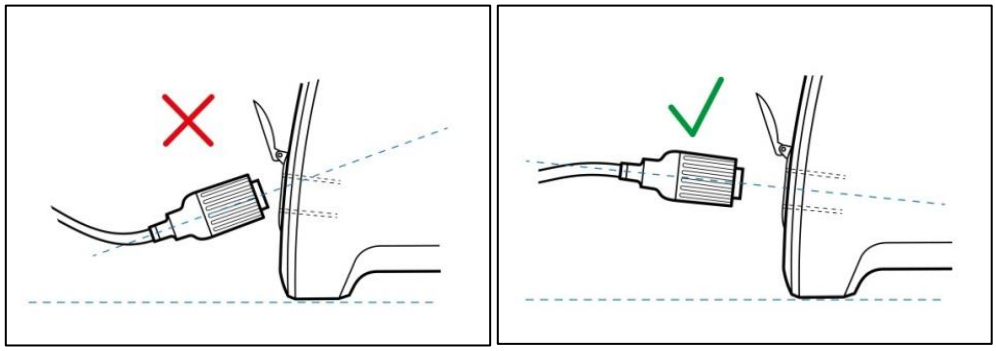

Figure 6-5: Probe Connection to Console: Correct Position

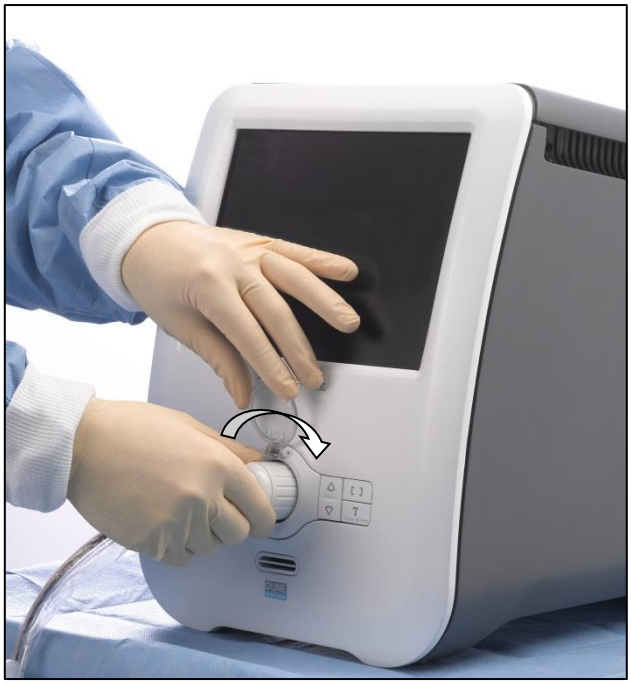

Figure 6-6: Seccuring the probe in Place

Note

The connector and the port are both notched to prevent incorrect insertion.

Caution

- Although the console's connector is covered, visually check it to ensure that there are no foreign objects in the connector every time before connecting a new probe.
- Do not use a new probe if its package is damaged. If the package was dropped, visually inspect the probe and do not use if damaged.

Operating the System

The system senses that a probe has been connected and automatically proceeds to the calibration process, during which a **"Calibrating…"** message and progress bar appear on the screen (Figure 6-7).

The calibration process takes approximately 10 seconds, during which all the probe's light indicators are illuminated. In the event of a calibration failure a second calibration will occur. In case that the second calibration fails a popup message will appear on the screen asking to press the probe's button while holding the probe in the air. A third calibration failure will require replacement of the probe.

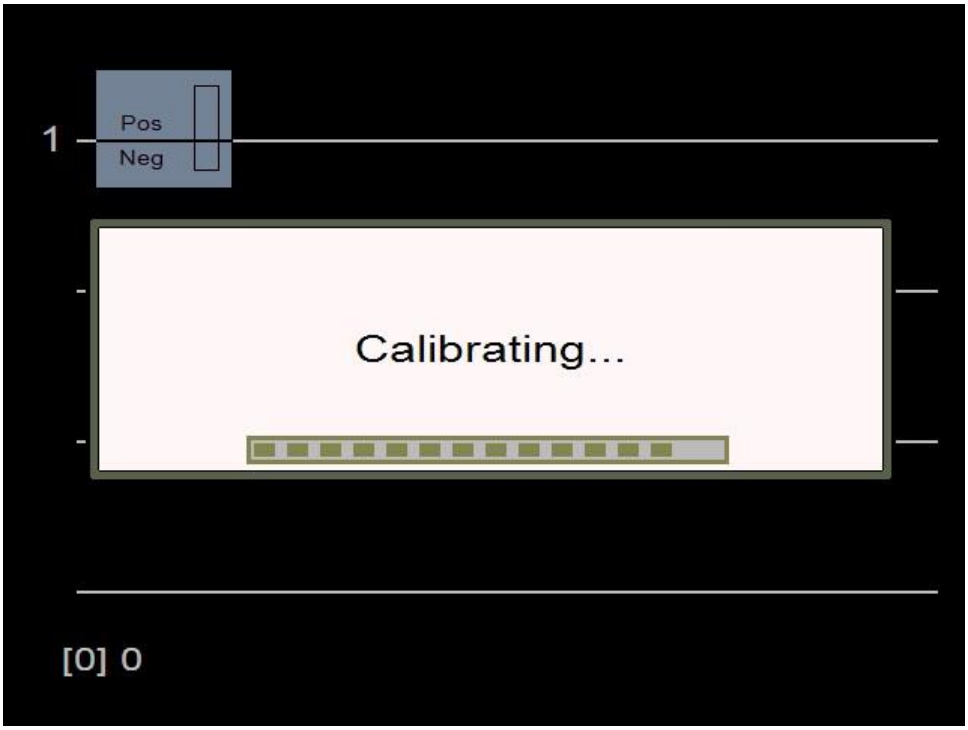

Figure 6-7: Calibrating Message

If the system is restoring the operation of a probe in use, the same calibrating message will appear on the screen.

While measuring a specimen, additional calibration of the probe may be required and automatically triggered. When this occurs, the calibrating message will appear and all the light indicators on the probe will turn on.

Resuming operation after **Standby** mode will also trigger a calibration.

Note

During Calibration process hold the probe in the air until calibration is completed.

Probe Identification

After the calibration process, the probe type is determined by its ID microchip.

The system will be ready to measure the specimen immediately after calibration (Figure 6-8):

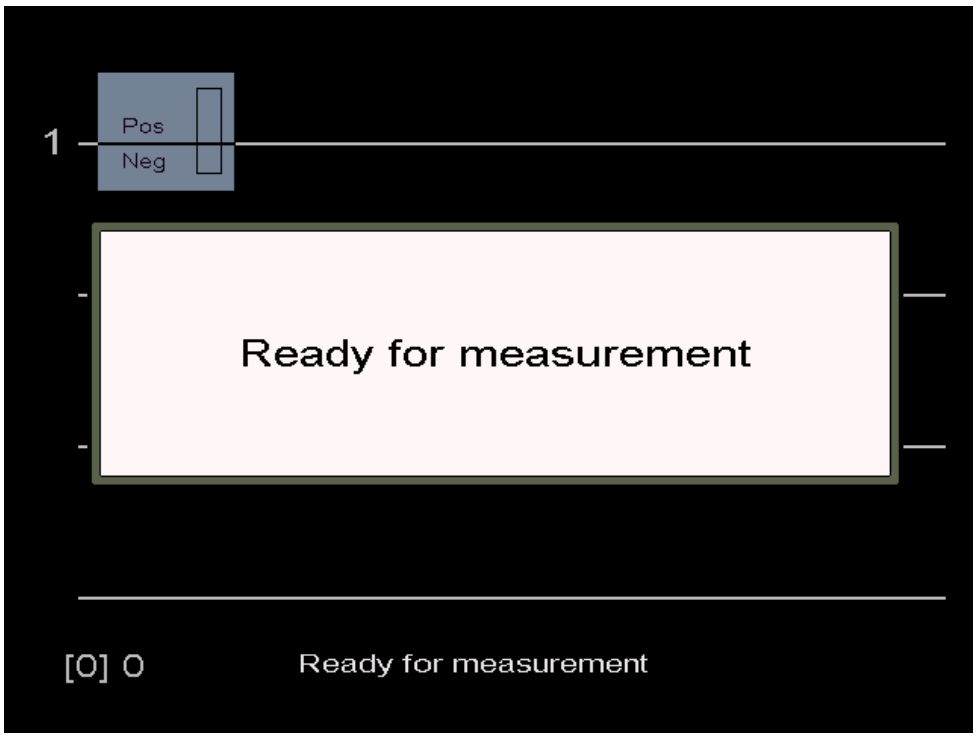

Figure 6-8: New Probe Screen

A probe may be re-connected when restoring an ongoing procedure (e.g. if the system was turned off and had to be restarted in the middle of an operation, such as in the event of a power failure, etc.).

Note

Note

- When connecting a probe to the console, the system identifies the probe, and if the probe was used for a prior procedure an error message is displayed on the screen declaring the probe has exceeded its usage limit.
- Please refer to Table 9-1: “Error messages troubleshooting guide” for a complete description of the messages displayed by the console.

T Clear Screen

The first displayed screen depends on how the system was shut down in the previous session. If the system was not shut down properly, the first screen will show the results of the previous session. In all other cases the first screen will be blank. To reach the desired screen to begin measuring press the **T** button until

the screen changes (long press). This will toggle between a clear screen and the screen showing the results of the previous session.

Note

Note

- Ensure no previous records are displayed on the screen at the beginning of new procedure.
- By this point during surgery, the surgeon has already removed and blotted the surgical specimen, marked it for orientation, and established the borders and faces of the specimen: **Lateral, Superior**, **Medial**, **Inferior**, **Anterior**, and **Posterior (Deep)**

Grouping Measurements According to Margins

Point measurements per margin are grouped together within brackets which facilitates ease of review/analysis. The brackets may be opened and closed using the control button on the probe or the buttons on the control panel:

- Double-clicking on the probe control button or pressing the [ ] button on the control panel opens a measurement group (frame). A pop up window will appear on the screen with the margin name in red (Figure *6-9*).

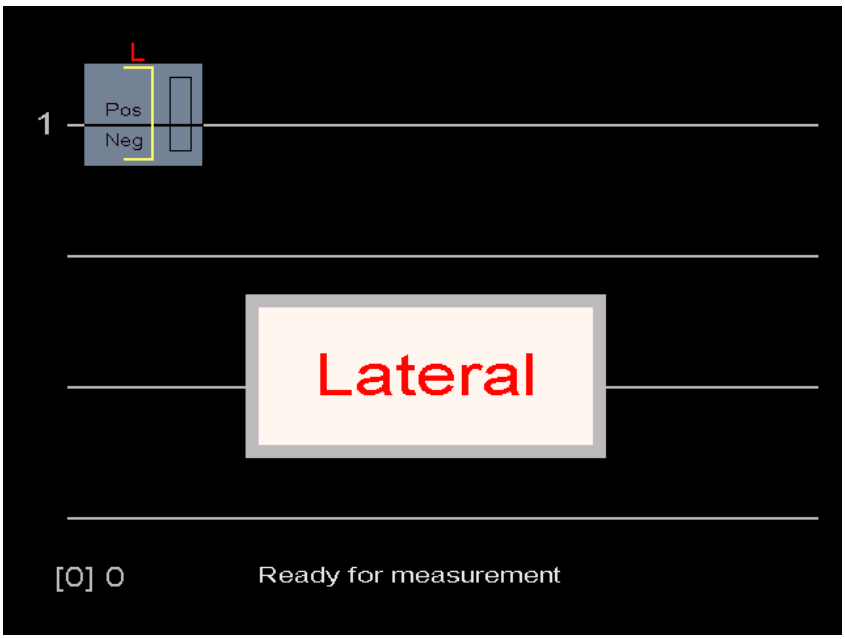

Figure 6-9: Choosing the Margin to be Measured

Single-click the control button to change the margin name and continue to single-click until desired margin label is reached. A bracket with a **red** letter above it, indicating the

margin name will also appear on the screen. The letters correspond to the margins as follows:

- **L = Lateral**
- **M = Medial**
- **A = Anterior**
- **S = Superior**
- **I = Inferior**
- **D = Posterior (Deep)**

The margin names may also be changed by pressing the ▲ or ▼ buttons on the control panel and scrolling to the desired margin label.

After choosing a margin name, press and hold the probe control button to confirm the setting. The letter above the bracket will turn **yellow** (Figure 6-10) and measurements may be performed. Margin confirmation may also be done from the console control panel by pressing the **T** button.

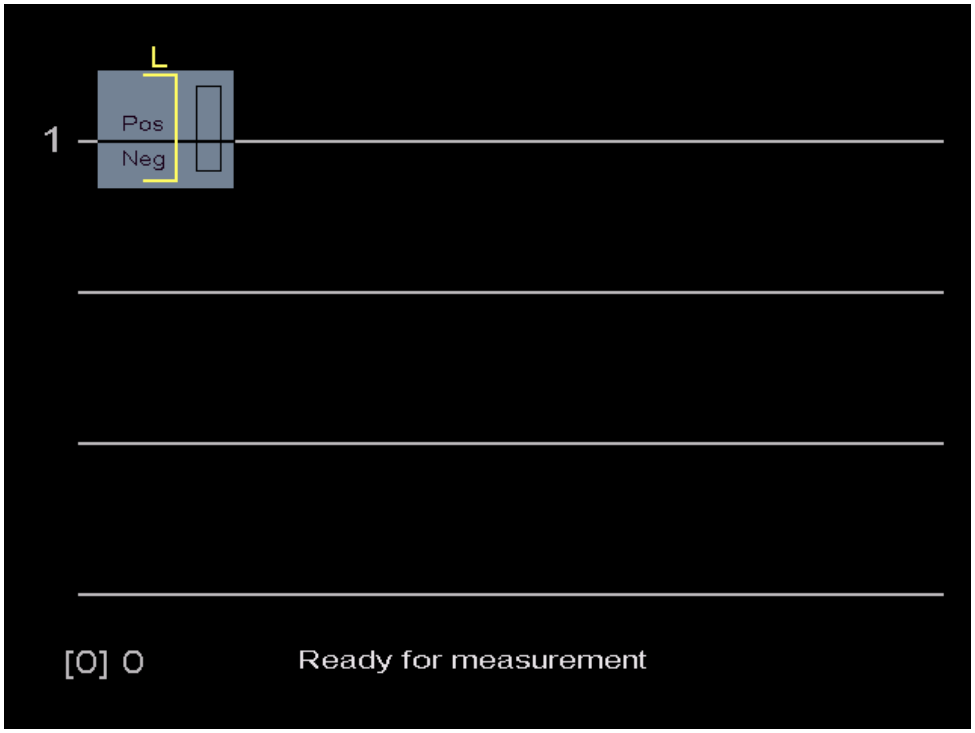

Figure 6-10: Confirmed Chosen Margin

At this point measurement can be taken for the selected measurement group.

After completion of measurements on the selected margin, double-clicking again on the probe button after approving the group (or pressing the **[ ]** button on the control panel) closes the measurement group (frame).

Note

- Confirmation of margin label will take place automatically when measuring starts, even if the control button was not pressed.
- To cancel measurement grouping in labeled brackets (before obtaining any measurements), first press and hold the button to approve the name, and then double-click to cancel the brackets.

Grouping Measurements by Numbers: groups may also be named by numbers instead of letters (e.g. for measuring points on the specimen outside of the margin grouping framework). To open a numbered group, scroll to the numbers by pressing the probe control button or the ▲ or ▼ buttons on the control panel.

Every time a group of measurements is closed, the next numbered group created will be labeled by the next number.

Changing Measurement Group (Frame): can only be done before closing the brackets. Changing the label is done by pressing and holding the probe control button (to enable editing), and scrolling by clicking to the desired label (or by using the buttons on console control panels: **T** button to enable editing and the ▲ or ▼ buttons for scrolling to the desired label). This can be done even if measurements were taken. After the brackets have been closed, changing the label is no longer possible.

Measurements can also be taken without grouping them by brackets.

Note

In order to standardize device output and establish a routine protocol, it is recommended to take measurements according to labeled specimen margins.

Performing Measurements

Each individual measurement produces a binary positive/negative display on the screen, as well as an audio indication.

The volume of the audio indication may be adjusted by pressing the up/down volume button on the control panel. When pressing the up/down volume button a beep will be heard. The volume of the beep corresponds to the volume of the audio indication.

When the system is ready for measurement, a partial vacuum is activated to aid in the initial coupling of the probe to the tissue surface. Place the tip of the probe in contact with the tissue point to be measured, and ensure that the entire tip is in contact with the tissue (Figure 6-11). A measurement is automatically initiated when tissue-to-sensor coupling is achieved.

It is recommended to perform 5 to 8 measurements per margin (up to 12 measurements on a large specimen). In each measurement an area of 7 mm in diameter is sampled to the depth of at least 1 mm.

Note

The specimen in Figure 6-11 is an artificial model for illustration purposes.

Figure 6-11: Probe Tip Application to the Specimen

At the end of the measurement the vacuum is released and the probe can easily be removed from the tissue. The table below summarizes possible system measurement outputs:

Table 6-1: Possible System Measurement Outputs (Figure 6-12):

Measured Indication	*Probe Color Indication*	*Audio Indication*	*Screen Color Indication*
Positive (malignant tissue detected)	**Red** 	Single Beep	Red bar above line-RED
Negative (no malignant tissue detected)	**Blue** 	Double Beep	Blue bar below line-BLUE
Failed Measurement	**Yellow** 	Error Tone	Empty Bar

Lift the probe after each system tone sounds. If the probe is left on the tissue after the tone, an additional measurement will be taken automatically.

Caution

- Lift the probe only after the tone sounds in order to prevent tearing of the tissue.
- Attach the probe tip only to tissue and avoid direct contact with other materials or surgical tools.

Attempt to evenly sample each margin surface area. In addition, suspected areas may be sampled as deemed necessary.

In case of failed measurements indicated by a blank bar, repeat the measurement.

As mentioned above, the probe is designed for single use, can only be connected to one console and can obtain a limited number of measurements. There is a time as well as total number of measurements limitations for using the probe once it has been connected to the console. When 30 or fewer measurements remain, a counter will appear on the screen (next to the "ready for measurement" text line) indicating the number of measurements left.

Note

If eight consecutive failed measurements are obtained, a message instructing the user to replace the probe will appear on the screen.

Caution

If the probe tip is not lifted from the tissue after a measurement, the system will continue to measure the same point repeatedly.

- Check the probe tip after measuring each margin;

  ⇒ If tissue remnants are found, measure the margin again after wiping the probe tip.

- If measurements are taken by the probe without being coupled to tissue or if the sensor plate is found to be jammed a message instructing the user to replace the probe will appear on the screen.
- The probe is for single use only and must be disposed after each case.

Interpreting Measurement Results

The device provides audible and visual indications regarding the assessment of tissue at each point measured.

Visual indication is by a colored bar on the screen that indicates a positive (red) or negative (blue) result. Point and margin data accumulate on the screen.

Using the probe control button, groups of points can be marked and oriented. **A margin with one or more positive points is indicated as a "device-positive margin" and should be shaved from the cavity**. Device output is adjunctive to other information available intra-operatively to guide the procedure.

The visual results are shown on the screen (Figure 6-12).

- A red bar indicates a positive point while the blue bar indicates a negative point.
- The yellow frame defines a group of measurements and the letter or number above the frame represents the group's label.
- The counter on the bottom-left side of the screen indicates the number of measurements that were taken within the current group (bracketed number) and the total number of measurements taken from beginning of the session.

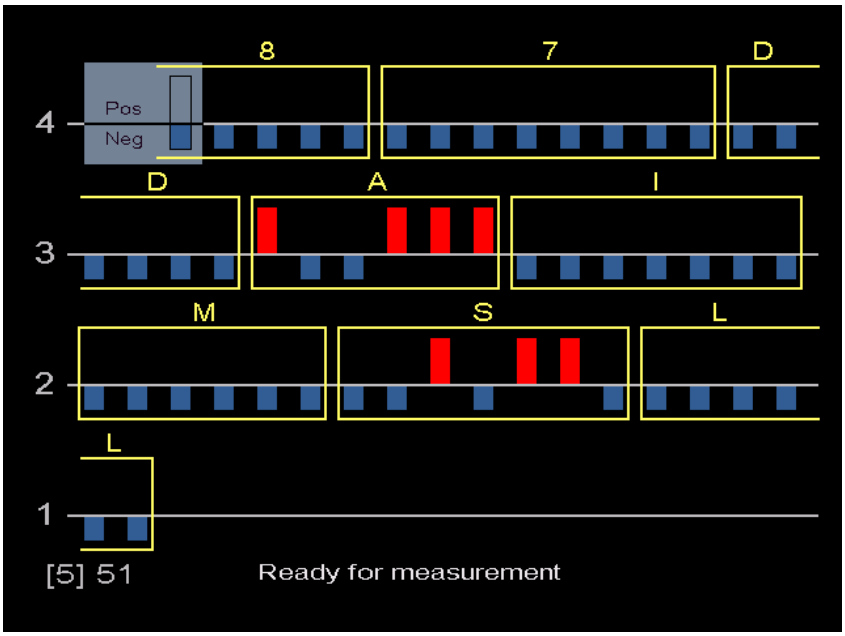

Figure 6-12: Measurement Results

Screen Scrolling

Data points accumulate on the screen from left to right and top to bottom.
When the measurements fill the screen, the rows will scroll downwards and data will continue to accumulate in the same manner.

Up to four rows will be displayed on the screen at any given time. Once the screen is full with measurements, the screen scrolling symbol will appear in the bottom-right corner of the screen. To view hidden rows, scroll up or down by pressing the ▲ or ▼ buttons on the control panel (Figure 6-13).

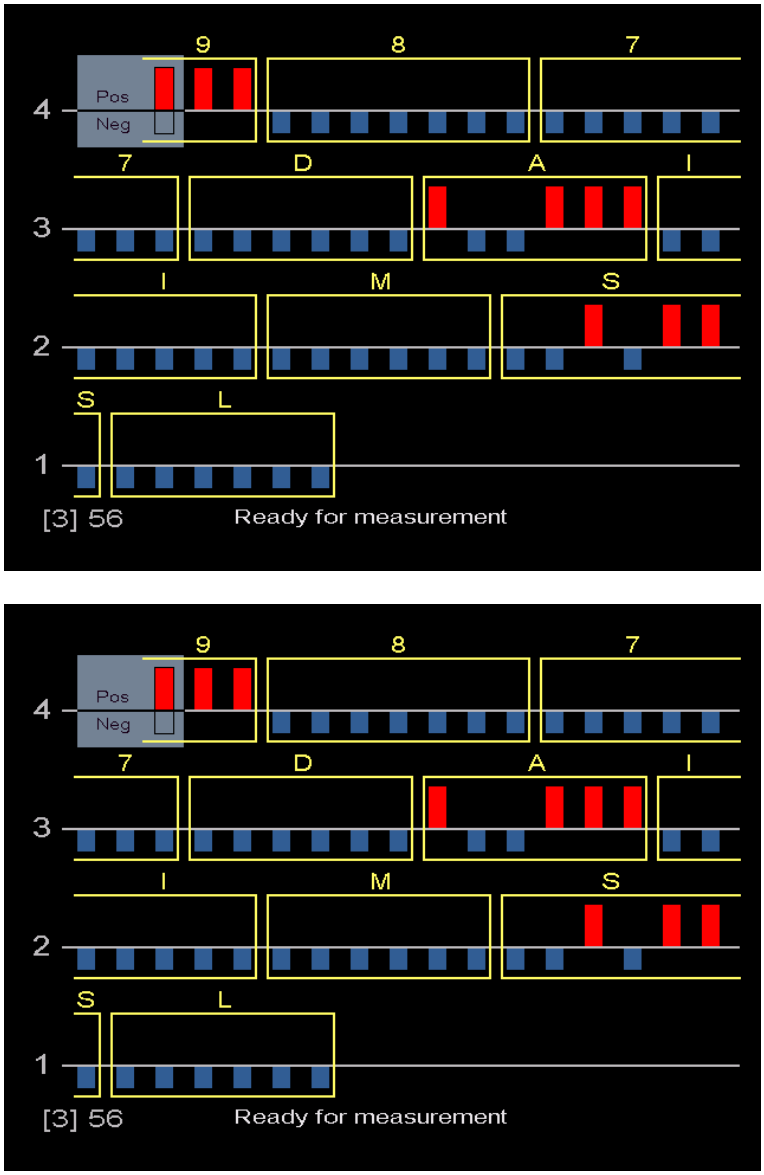

Figure 6-13: Screen Scrolling

Probe Usage Limitations

The MARGINPROBE® probe is a highly sensitive instrument, designed to detect extremely small differences in tissue characteristics. In order to provide results as intended, it is critical that the sensor be used in the manner validated during clinical development. The performance of the device depends on carefully controlled manufacturing, sterilization, and calibration procedures. The probe is designed and manufactured for single use. The performance of the device cannot be guaranteed if not used in accordance with the instructions provided.

Clearing the Screen and Removing Popup Messages

The screen can be cleared at any point. Press the **T** button until screen changes (long press).

Any pop-up displayed on the screen can be removed for ten seconds by pressing the ▲ or ▼ buttons on the control panel or by single-clicking the probe control button.

Note

To return back to the previous screen press again the T button until screen change (long press)

Standby Mode

After ten minutes of inactivity, the system will go into **Standby mode** and display a screensaver message: **"MarginProbe® in Standby. Press any button to resume operation"** (Figure 6-3). Pressing any button on the console front control panel or the probe button will clear the Standby screensaver message and set the system back to operational (Ready) mode. During standby mode, the pneumatic vacuum module is shut down.

When a probe is connected, a calibration process will automatically take place when resuming operation after **Standby mode**.

System Shutdown

To shut down the MARGINPROBE® system:

1. Press the start/shutdown button on the control panel (long press); the system will start the shutdown process and a pop-up message will appear stating: "**System preparing for shutdown. Press start-up button to cancel" (**Figure 6-14**)**.

2. Wait until the system power down and the power light indicator will turn orange.

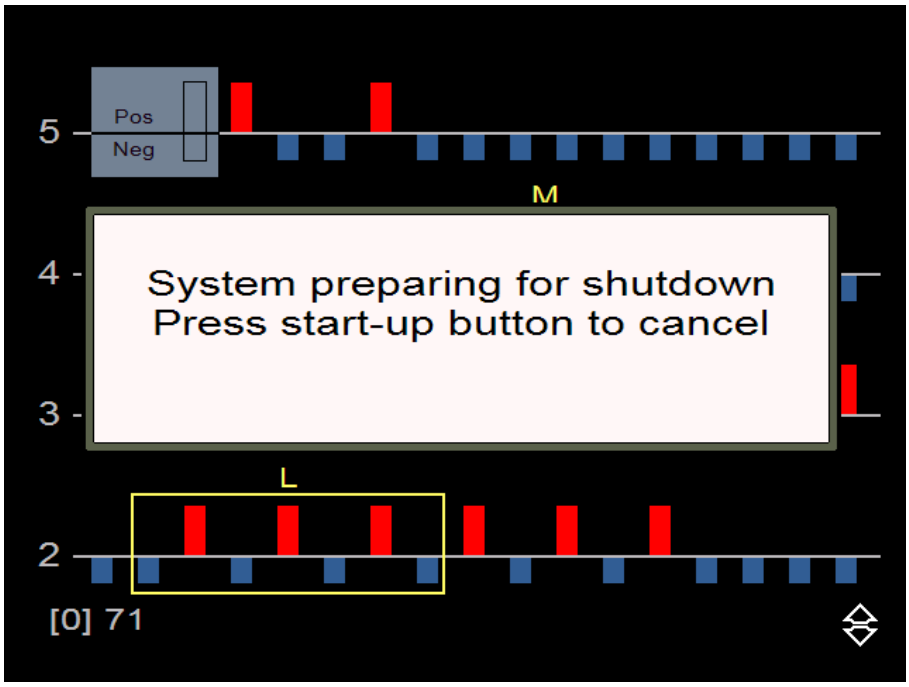

Figure 6-14: Shutdown Message

Note

- Apply long press on the start/shutdown button to initiate the shutdown process.
- In order to cancel the shutdown process after it has been initiated, press the start/shutdown button again (short press).

3. Turn off the main power switch on the back panel after shutdown process is complete (Figure 6-1).

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7. MAINTENANCE

Introduction

The MARGINPROBE® system is designed to operate reliably without any need for maintenance. However, the outer surfaces of the console should be kept clean and free of dust.

Exterior Cleaning

The outer surface of the system may be wiped clean with common disinfectants by using a moist cloth only. Avoid use of liquids that may penetrate the console.

Warning

Console cleaning should be performed only when the console is shut down and disconnected from the main power source. Cleaning with the console is turned on may be hazardous to the operator and/or destructive to the system.

Opening the Console: The operator should not open the covers, panels or the fuse housing of the console.
Only Dilon Medical Technologies technical personnel are authorized to open the console.

Warning

- The MARGINPROBE® console generates hazardous voltages within the main console.
- The system may be serviced only by Dilon Medical Technologies authorized technical personnel.
- No modification of this equipment is allowed.
- Fuse housing should not be opened by the user.

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8. SERVICE

1. The console can be serviced only by Dilon Medical Technologies authorized technical personnel.

2. Backup battery (keeps the right time and date) replacement is required every 7 years, by Dilon Medical Technologies authorized personnel.

Note

Improper use or maintenance of this system may invalidate the service warranty agreement.

Service Information

When communicating with Dilon Medical Technologies representatives regarding the system, always include the system model and serial number indicated on the console identification label located on the console's back panel.

Warning

Unauthorized servicing or modification of this system may expose the operator or patient to potential high voltage and radiofrequency hazards.

Questions or problems should be referred to your Dilon Medical Technologies representative, or to the Service Center. Please refer to Contact information for equipment manufacturer and technical services (Page A).

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9. TROUBLESHOOTING

Introduction

The MARGINPROBE® system is equipped with self-testing software routines that continuously monitor the systems operation. If a system malfunction is detected, an error message will appear on the screen.

The following troubleshooting guides do not attempt to list all possible system failures. Any fault not listed should be referred to Dilon Medical Technologies Service personnel.

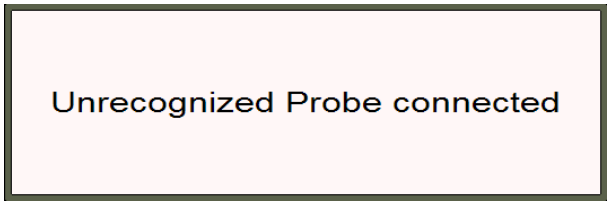
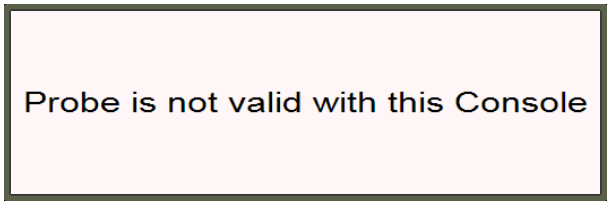
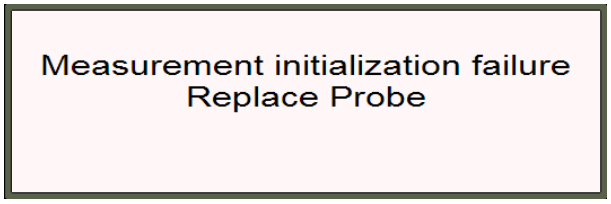
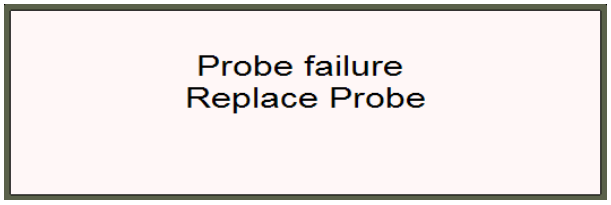
Warning

Do not attempt to open or disassemble the console covers.

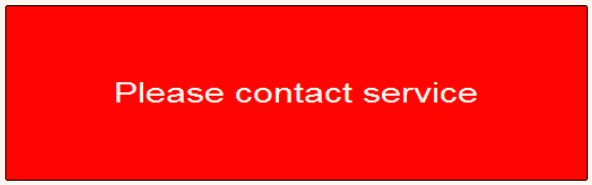
Troubleshooting Guides

Table 9-1 provides a list of error messages that may appear on the screen, their possible causes and corrective actions to be performed. If the corrective actions listed in the table do not solve the problem, contact your Dilon Medical Technologies Service representative.

Table 9-1: Error Message Troubleshooting Guide

Error Message Screen Pop-Up	*Error Message Text*	*Probable Cause*	*Corrective Action*
	**Unrecognized Probe connected**	A general problem was found in the probe.	Replace the probe and contact Dilon Medical Technologies Service
	**Probe has expired**	The probe expiration date has passed.	Replace the probe
	**Probe is not valid with this Console**	Probe was connected to a different Console in the past	Replace the probe
	**Measurement initialization failure** **Replace Probe**	The system detected an error in the probe calibration or measurement process.	Replace the probe and contact Dilon Medical Technologies Service
	**Probe failure** **Replace Probe**	The probe data was corrupted.	Replace the probe and contact Dilon Medical Technologies Service

Error Message Screen Pop-Up	*Error Message Text*	*Probable Cause*	*Corrective Action*
Probe has exceeded usage limit #1	**Probe has exceeded usage limit #1**	The probe has reached its usage limit *[The indicated Error # is for technical service use only]*	Probe can no longer be used for reliable measurements. Replace the probe.
Probe has exceeded usage limit #2	**Probe has exceeded usage limit #2**	The probe has reached its usage limit *[The indicated Error # is for technical service use only]*	Probe can no longer be used for reliable measurements. Replace the probe.
Probe has exceeded usage limit #3	**Probe has exceeded usage limit #3**	The probe has reached its usage limit *[The indicated Error # is for technical service use only]*	Probe can no longer be used for reliable measurements. Replace the probe.
Probe has exceeded capacity limit	**Probe has exceeded capacity limit**	The probe has reached its usage limit	Probe can no longer be used for reliable measurements. Replace the probe.
System reached max. number of measurements Clear screen	**System Reached Max. Number of Measurements Clear Screen**	The screen has displayed its maximal number of measurements.	Clear the screen (long press on the T button until screen changes).

Error Message Screen Pop-Up	*Error Message Text*	*Probable Cause*	*Corrective Action*
	**Please contact service at end of procedure**	The system has detected an internal error. a problem in one of the following: - cooling system - time of day - language set-up.	Continue normal operation and notify Dilon Medical Technologies Service at the end of the procedure. Note: - Language may have been reset to English. - This message is followed by Error number message for service purposes only. - A service symbol will appear on screen until service.
	**Shut system down and restart**	The system has detected an internal error.	Shutdown and restart the system. Resume normal operation. If problem persists, contact Dilon Medical Technologies Service.
	**Please Contact Service**	The system has detected a fatal internal error.	Shut down the system and re-start. Resume normal operation. If error message persists, contact Dilon Medical Technologies Service.
	**Fan failure** **System will shut down shortly** **Please contact service**	The system has detected a fatal failure in the heat dissipation fans.	Shut down the system and re-start. Resume normal operation. If error message persists, contact Dilon Medical Technologies Service.

Error Message Screen Pop-Up	*Error Message Text*	*Probable Cause*	*Corrective Action*
	**Temperature failure** **System will shut down shortly** **Please contact service**	System's internal temperature has risen above allowed temperature.	Wait for system to shut down. Allow the system at least additional two minutes to cool down, and then re-start the system. If problem persists, contact Dilon Medical Technologies Service.

Table 9-2 lists some possible symptoms of system malfunctions for which no messages are displayed. If the corrective actions listed in the table do not solve the problem, contact your Dilon Medical Technologies Service representative.

Table 9-2: System Malfunction Troubleshooting Guide

Symptom	*Probable Cause*	*Corrective Action*
Un-requested and/or repetitive measurements when probe is not coupled to tissue.	Vacuum system openings at tip of probe are blocked.	1. Try to clear any visible tissue remnants that block the openings at the tip of the probe. 2. If problem persists, replace probe and contact Dilon Medical Technologies.
Measurement failure *Note:* *If eight consecutive failed measurements are obtained, a message instructing the user to replace the probe will appear on the screen*.	Usage Error 1. Probe is lifted from tissue before beep is heard. 2. Inadequate coupling of probe to tissue. 3. Coupling obstacle: wires, clips or sutures present on specimen surface at point of measurement.	1. Leave probe coupled to tissue until beep is heard. 2. Ensure adequate coupling with proper suction by firmly holding probe tip perpendicular to tissue surface. 3. Assure that the probe tip is not placed over wires, clips or sutures. 4. When “Replace Probe” appears try to re-connect the same probe and resume operation. 5. If the “Replace Probe” message persists, replace the probe. 6. If problem persists, contact Dilon Medical Technologies.
	Probe Failure	1. Follow screen instruction and replace the probe if required. 2. If problem persists, contact Dilon Medical Technologies.
Calibration failure	Probe sensor plate may be covered or obstructed.	1. Hold the probe in the air and make sure the sensor is not covered. Click the probe control button to restart calibration 2. Follow screen instruction and replace the probe if required.
The initialization process does not start when turning on the	Electronic malfunction	1. Restart the system.

Symptom	*Probable Cause*	*Corrective Action*
console (a progress bar does not appear on the screen)		2. If problem persists, contact Dilon Medical Technologies.
Initialization process takes longer than usual (progress bar is shown)	Internal modules are initializing	1. Wait 5 minutes to complete initialization. 2. If problem persists, restart the system. 3. If problem persists after restarting the system contact Dilon Medical Technologies.
Measurement is not triggered upon coupling of probe to tissue	Vacuum airway is disconnected or damaged	1. Disconnect and reconnect the probe. 2. If problem persists, restart the system 3. If problem persists after restarting the system, replace the probe. 4. If problem persists after replacing the probe contact Dilon Medical Technologies.
System is not ready for measurement after connecting the probe Connect Probe message persists after probe connection	• Improper probe connection • Probe malfunction. • System malfunction.	1. Disconnect and reconnect the probe. 2. If problem persists, restart the system 3. If problem persists after restarting the system, replace the probe. 4. If problem persists after replacing the probe contact Dilon Medical Technologies.
No sound is heard upon completion of measurement *Note: lack of sound does not indicate system malfunction and the system may be used without the audible indication. Screen and light indications are accurate even in the absence of the audible indication.*	• System is muted • System speaker malfunction	1. Press volume up button on control panel. *(pressing the volume up/down button should produce an audible beep)*. 2. Continue normal operation using screen and LED indications. 3. Restart system at the end of the procedure and check the sound by pressing the up/down volume button. 4. If problem persists, contact Dilon Medical Technologies.

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10. SYSTEM SPECIFICATIONS

System Performance

- Effective measurement area: Ø 7.0 mm
- Detection depth: < 1 mm
- Tissue type: Detection of in-situ and invasive ductal and lobular breast carcinoma
- System warm-up time: < 2 minutes
- Measurement time (from tissue attachment to results display): ≤3 seconds

Transport and Storage Environmental Requirements

- Temperature: -25°C to +55°C (-13°F to +131°F)
- Relative humidity: 20% to 85%
- Atmospheric pressure: 570 to 1050 hPA

Operational Environmental Requirements

- Temperature: 15°C to 30°C (59°F to 86°F)
- Relative humidity: 30% to 80%
- Altitude: ≤ 2000 m (6560 ft.)
- Atmospheric pressure: 732 to 1014 hPA

Physical Specifications

- Console dimensions [WxDxH]: 29 x 43 x 38 cm
  11.4 x 16.9 x 15.3 inches
- Console weight: ~ 16 Kg / 35 Lbs.
- Water Protection Level IPX0
- Probe dimensions [LxW]: 196 x 23 mm x 34mm
  7.8 x 0.9 x 1.3 inches
- Probe box dimensions [WxDxH]: 34 x 25 x 4.3 cm
  13.4 x 9.9 x 1.7 inches

Electrical Specifications

- Power supply range: 100-240V~, 50-60Hz, single phase
- Supply power: 80VA Typical, 150VA Max.
- Power Cord: Europe/ Israel: 230V, 10A
  U.S.: Hospital Grade, 115V, 10A
- Max RF power emitted to probe: 1 dbm (1mW) , 50-500 MHz
- Equipotential Ground Connection
  Connecting leads cross section: 1.5mm^2 / 14AWG or larger
  Connector: Touchproof, DIN 42-802 compliant (6mm diam.)

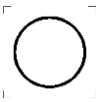
11. SYMBOLS

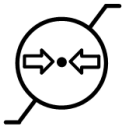
Graphical Symbols on Screen

Symbol	*Legend*
	Screen scrolling *For information refer to the Operating Instruction chapter (Screen Scrolling)*
	Please contact service at end of procedure *Refer to the Troubleshooting chapter (9)*
	System audio indication (sound) is muted *To resume sound refer to the Troubleshooting chapter (9)*

Graphical Symbols on Labels

Symbol	*Legend*
	Manufacturer
	Date of Manufacture
	CSA Mark
	Do not reuse
	Caution, Risk of danger or Attention

Symbol	*Legend*
	Use by (expiration date)
	Do not use if package is damaged
	Caution: risk of electric shock or Attention
	Sterilized Using Ethylene Oxide (Probe)
	Type BF applied part
	“ON” (power)
	“OFF” (power)
	Refer to instruction manual/booklet
	Equipotentiality (Equipotential Ground Connection)
	Alternating current
	Temperature limit

Symbol	*Legend*
	Humidity limitation
	Atmospheric pressure limitation
	Keep away from rain
	Fragile, handle with care
	Keep away from sunlight
	This side up
	Do not stack
	Single sterile barrier system with protective packaging outside
	Medical device