Statistical Analysis Plan

TRIAL FULL TITLE	STREAMLoc- Streamlined Localization using SCOUT® at Biopsy: An analysis of process improvement, cost savings and enhanced patient experience.
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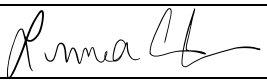
SIGNATURE/DATE	 1SEP2021

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1 Abbreviations and Definitions

AE	Adverse Event
ADE	Adverse Device Effect
BI-RADS	Breast Imaging, Reporting and Data System
CIP	Clinical Investigation Plan
CRF	Case Report Form
DCF	Data Clarification Form
EMR	Electronic Medical Records
ICF	Informed Consent Form
IP	Investigational Product
ISO	International Standards Organization
ITT	Intention-to-treat
PI	Principal Investigator
PP	Per protocol
REB	Research Ethics Board
SAP	Statistical Analysis Plan
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SDV	Source Data Verification

2 Introduction

2.1 Preface

SCOUT® has been identified as an alternative to other localization options, providing maximum flexibility in patient visit scheduling. In the COVID-19 era, it would follow that improved efficiencies, leading to a decrease in patient visits to the breast center, as well as reduced contact with the technicians prior to surgery, is the preferred treatment option for patient and clinician safety and reduced logistical burden. Taveh et al. showed that by deploying the SAVI SCOUT® at the time of tumor biopsy, the need for a second procedure to localize the tumor was eliminated, thus reducing the number of patient visits and potential COVID- 19 exposure. The authors demonstrated that wireless localization using SAVI SCOUT® was an effective and time-efficient alternative to wire localization, resulting in excellent physician and patient acceptance. Parkinson et al. found insertion of SCOUT at biopsy resulted in at least one (1) less patient visit to the breast center.

This Canadian registry is intended to assess the utility of SAVI SCOUT® in the Canadian public healthcare system where there are limited resources and a conservative approach to patient and clinician exposure to harm (i.e., radiation, COVID-19 exposure, patient emotional trauma). By assessing the utility of reflector insertion at the time of biopsy, this study will be able to measure the impact on patient visits to the breast center for invasive procedures between biopsy and surgery, and quantify this value to the public healthcare system. The efficacy and safety of this system will be further assessed, as well as the acceptance of clinicians and patients.

2.2 Scope of the analyses

These analyses will assess the utility, performance and safety of SCOUT® device and will be included in the clinical study report.

Utility will be assessed based on the primary endpoint: The number of patient visits to the breast center for invasive procedures from the time of biopsy to surgery.
Performance will be assessed based on device success, procedural success, clinician assessment and participant satisfaction scores.

Safety will be assessed based on the rate of device-related adverse events.

3 Study Objectives and Endpoints

3.1 Study Objectives

Primary Objective: To demonstrate the utility of the SCOUT® Surgical Guidance system to improve workflow and efficiency in Canadian centers treating breast cancer.

Secondary Objective: To further evaluate the safety and performance of the SCOUT® Surgical Guidance system in 500 consented BI-RADS 4C/5 patients according to the instructions for use.

3.2 Endpoints

Primary Endpoint: The number of patient visits to the breast center for invasive procedures from the time of biopsy to surgery.

Secondary Endpoint:

1. Device success: percent successful localization, detection and retrieval;
2. Device safety: rate of device-related adverse events;
3. Procedural success: absence of close margins (DCIS: <2mm), positive margins (tumor on ink) or requirement for re-excision.
4. Duration (days) from assessment to surgery and biopsy to surgery;
5. Radiologist assessment: ease of placement; ability to position reflector in desired location; scheduling flexibility; visibility on ultrasound/ mammography (immediate and late); artifact (Tomo/MRI if applicable).
6. Surgeon assessment: ease of detection; ease of device retrieval.
7. Participant satisfaction questionnaire: anxiety; convenience; pain; overall experience compared to expectation
8. Process improvement with implementation of same-day biopsy and SAVI SCOUT® placement.

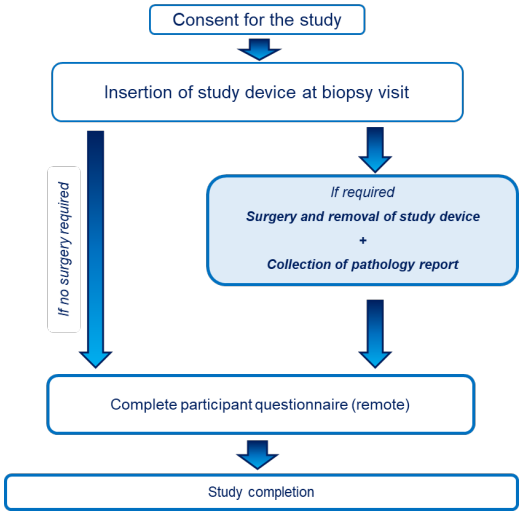
4 Study Methods

4.1 General Study Design and Plan

This is a single-arm, multicenter, non-randomized cohort study. This is a non-blinded study with no active control for this study. However, the primary endpoint will be compared to historical controls.

The registry is divided into three periods:

1. Inclusion Period: from registry eligibility screening until reflector insertion;
2. Device Period: from reflector insertion at biopsy to removal at surgery;
3. Outcomes Period: from completion of surgery to pathology report of outcomes.



4.2 Inclusion-Exclusion Criteria and General Study Population

This study will include five hundred (500) BI-RADS 4C/5 patients undergoing biopsy of a breast lesion at an investigative center.

The inclusion criteria are as follows:

1. Woman >18 years and < 80 years of age;
2. Classified as BI-RADS 4C or 5;
3. Lesion depth is < 6 cm from skin surface;
4. Non-palpable lesions;
5. Informed consent obtained.

The exclusion criteria are as follows:

1. Multicentric breast cancer;
2. Pregnant or lactating;
3. Known or suspected nickel-titanium allergy.

4.3 Randomization and Blinding

N/A

4.4 Study Assessments

	Consent*	Biopsy**	Surgery	Final Outcomes***
Patient Data				
Informed Consent	X			
Demographic information (age, height, weight, diagnosis)		X		
Neoadjuvant therapy (start and stop date)			X	
Device and Procedural Data				
Reflector insertion data (success, deployment within lesion or distance from lesion, depth of reflector, type of guidance used, number of reflectors used, type of lesion, reflector detection)		X		
Reflector detection (before incision or after incision)		X[i]	X	
Reflector retrieval (success, identification and retrieval duration)			X	
Operative time			X	
Adverse events (including device deficiencies)		X	X	

Scheduling Data				
Date of assessment		X		
Date of biopsy and insertion		X		
Date of surgery			X	
Satisfaction Assessments				
Radiologist assessment: ease of placement; ability to position reflector in desired location; scheduling flexibility; visibility on ultrasound/mammography; artifact (Tomo/MRI if applicable)				X[ii]
Surgeon assessment: ease of detection; ease of reflector removal				X[ii]
Participant satisfaction questionnaire			X[iii]	
Pathology Report data				
Margins (positive; close <2mm; negative >2mm)				X
Re-excision required (after surgery)				X
Excised tissue volume/weight & specimen size				X

[*]Performed prior to biopsy
[**]Reflector insertion performed at time of biopsy
[***]No additional participant visit; data recorded from pathology report
[i] If performed
[ii] Collected once per clinician at completion of registry
[iii] Window up to 2 weeks post-surgery (remote completion)

Identification of any number ranges for numeric endpoints along with their corresponding text descriptors.

- Continuous variables will be collected for: age, weight, height, operative time and adverse event rate, duration between events
- Categorical variables will be established for device success, procedural success, clinician assessment, participant satisfaction

5 Sample Size

No formal sample size calculation has been performed. Five hundred (500) participants will be included in this registry. This sample size has been selected to adequately support a multi-center experience reflective of the Canadian healthcare system and associated workflow.

Further, the Canadian Agency for Drugs and Technologies in Health (CADTH) assessed the evidence of

a competitive device and noted the requirement for a cohort size greater than 200 in order to draw conclusions of effectiveness.[i] It is estimated that this sample size will result in a robust Canadian data set.

6 General Analysis Considerations

6.1 Timing of Analyses

The final analysis will be performed after:

- All participants have completed the study and all assessment and outcome data is entered.
- Data monitoring is complete as per the monitoring plan and data clarification forms (DCF) have been resolved.
- The database has been locked.

6.2 Analysis Populations

A patient is considered enrolled in the registry as soon as they:

1. Have provided signed consent agreeing to be part of this registry; and
2. Undergo the insertion of the SCOUT® Reflector at the time of biopsy

Note- If a patient has given consent but the Reflector is not inserted at biopsy, the patient will not receive a participant number and will not be considered as enrolled in the registry. No patient data will be collected.

Participation in the registry will be considered complete after surgery, documentation of surgical outcomes and completion of the Participant Assessment Questionnaire. This will be documented on a study completion form. It is expected the duration of each participant will be approximately <7 months and will vary based on each participant's treatment plan.

6.2.1 Per Protocol Population

The per protocol (PP) population will include all consented participants in whom a SCOUT® Reflector has been inserted and who subsequently undergo breast surgery.

Endpoint analysis will be performed on the PP analysis set.

6.2.2 Intention-to-treat (ITT) Population

The ITT population includes all participants in whom the SCOUT® Reflector has been inserted. Any participants who have a reflector inserted and do not undergo surgery will be exited from the registry using a study completion form. The occurrence of this scenario is expected to be low ($\leq$ 10%). Reasons may include:

1. Benign concordant biopsy results.
2. Participant death prior to surgery due to metastases.
3. Lesion is metastatic from another location.
4. Participant declines surgery.

5. Participant is ineligible for surgery.

Descriptive data and adverse event analysis will be performed on the ITT analysis set. The PP and ITT endpoints will be calculated separately and compared. Differences between their results will be summarized and discussed.

6.2.3 Safety Population

Adverse events will be collected and analyzed for all events categorized as procedure or device-related for all enrolled participants between the point of inclusion to completion of surgery.

6.3 Covariates and Subgroups

Subset analysis will be performed for participants who have undergone neoadjuvant therapy (if applicable). Endpoints will be assessed separately and compared to the full cohort for safety, performance and utility.

6.4 Missing Data

In addition, the means and ranges of all variable distributions and outlying data or improbable combinations of variables will be examined before analysis is undertaken.

Endpoint analysis will be performed with and without using imputation of missing data (where applicable) to estimate the effect of missing data on the ITT and PP population. Differences between their results will be summarized and discussed.

6.5 Interim Analyses and Data Monitoring

No interim analysis is planned.

The data will be monitored according to the Monitoring Plan through central and remote monitoring strategies. Outlier data will be queried and remote access to electronic medical records (EMR) may be requested for source data verification (SDV).

Each clinical site will be monitored according to the study monitoring plan to ensure to verify that:

- The rights and well-being of the participants are protected
- The reported study data are accurate, complete and verifiable from source documents
- The conduct of the study is in compliance with the currently approved Clinical Investigation Plan (CIP)/ amendment(s), Good Clinical Practice (ISO 14155), and applicable requirements of the research ethics board (REB)
- There is adequate participant enrollment

6.5.1 Stopping Rules

N/A

6.5.2 Analysis Methods to Minimize Bias

Endpoint data between sites will be assessed and compared to ensure there is no site-specific bias.

7 Summary of Study Data

Descriptive statistics will be generated for all endpoints using a 1-sided 95% confidence interval. Participant data will be quantified. For quantitative parameters, descriptive statistics will be reported: number, mean, standard deviation (SD), minimum, median and maximum values.

For categorical variables, frequency and percentage will be reported. The primary endpoint will be compared to historical data using one-way analysis of variance.

7.1 Variable Assessment

Variable	**CRF and data point**
Inclusion	Inclusion CRF_Reflector Location
Per protocol completion	Surgery CRF_Type of surgery
Intention to treat completion	Study Completion CRF_Reason for completion
Device insertion success	Inclusion CRF_Deployment within lesion
Device retrieval success	Surgery CRF_Reflector retrieval success
Procedural success	Outcomes CRF_Margin assessment
Efficiency endpoint	Additional visit CRF_Number of visits
Device Safety	Adverse Event CRF_Device Related

7.2 Derived variables

Variable	**Definition**	**Unit**
Duration (assessment to surgery) (DA_S)	Difference between assessment date and surgery date	Number of days
Duration (biopsy to assessment) (DB_S)	Difference between biopsy date and surgery date	Number of days
Implementation of same day biopsy	Percent of cases with DB_S=0 (start of site participation to study end)	Percent
Operative time	Difference between stop and stop times	Minutes

7.3 Protocol Deviations

MINOR DEVIATION: a violation that does not impact the patient's rights, safety of welfare, compromise the integrity of study data and/or affect subject's willingness to participate in the study.

Examples:

- Missing original signed and dated consent form (only a copy is available)
- Missing pages of consent form
- Failure to follow study procedure (that does not affect patient safety)
- Failure to perform a laboratory test

MAJOR DEVIATION: a violation that may impact the patient's rights, safety or welfare, affect the integrity of study data and/or affect subject's willingness to

participate in the study.
Examples:

- Failure to obtain informed consent
- Enrollment of a patient not meeting all eligibility criteria
- Failure to report a serious adverse event

Deviations that impact the primary endpoint calculation will be identified and associated participant data will be assessed separately as well as with the cohort to identify the impact to the final calculation. An example of this would be if the participant was intentional booked for a "back-up wire" prior to surgery due to lack of physician confidence or poor planning.

7.4 Demographic and Baseline Variables

Variable	Type of data/ unit
Age	Continuous/ Yrs
Height	Continuous/ Meters
Weight	Continuous/ Kg
Diagnosis	Categorical
BiRads classification	Categorical

7.5 Procedure Variables

Variable	Type of data/ unit
Lesion type	Categorical
Guidance type	Categorical
Lesion location	Categorical
Morphology classification	Categorical
Lesion size	Continuous/ mm
Lesion depth	Continuous/ cm
Reflector detection	Nominal
Deployment within lesion	Categorical
Distance from lesion	Continuous/ mm
Type of surgery	Categorical
Retrieval success	Nominal

7.6 Treatment Variables

Variable	Type of data/ unit
Neoadjuvant therapy	Nominal
Duration of neoadjuvant therapy	Calculation (start- stop date)/ days
Number of visits for invasive procedures	Continuous

8 Utility Analyses

Number of visits for invasive procedures will be reported as: number, mean, standard deviation (SD), minimum, median and maximum values.

The primary endpoint will be compared to historical data using one-way analysis of variance.

9 Performance Analyses

Device and procedure success will be calculated as a percentage of the total number of cases, as well as the total number of reflectors used in the study.

10 Safety Analyses

- All reported adverse events will be categorized and described.
- Frequency and/ or percentage will be reported
- Adverse device effects (ADE) rates will be calculated separated
- ADEs will be sub-classified as appropriate
- Each participant will only be counted once and any repetitions will be ignored; the denominator will be the total population size
- Serious Adverse Events: A table of all anticipated and unanticipated serious adverse events, grouped by organ system, with number and frequency of such events in each arm/group of the clinical study. (See Adverse Events definition below).
- Other (Not Including Serious) Adverse Events: A table of anticipated and unanticipated events (not included in the serious adverse event table) that exceed a frequency threshold (for example, 5 %) within any arm of the clinical study, grouped by organ system, with number and frequency of such events in each arm/group of the clinical study.

11 Satisfaction Analyses

Clinician and participant satisfaction assessment data will be categorized and reported as frequency data.

12 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data.

13 Summary of Changes to the Protocol and/or SAP

n/a

14 References

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