Boston Scientific

The nCYT Study: A Powered Study to Evaluate the Sensitivity and Specificity of Cytological Evaluation of Fallopian Tube Samples Collected by the Cytuity™ in Determining the Presence of Malignancy

Protocol Number: CLIN 0507
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Synopsis of the Clinical Investigation

Study Title	The nCYT Study: A Powered Study to Evaluate the Sensitivity and Specificity of Cytological Evaluation of Fallopian Tube Samples Collected by the Cytuity™ in Determining the Presence of Malignancy
Protocol Number	CLIN 0507
Sponsor	Boston Scientific Corporation 1192 Cherry Avenue San Bruno, CA 94066 1-888-272-1001
Product Name	Cytuity™
Regulatory Status	The Cytuity™ has been cleared by the FDA for the following Indications for Use: "The Cytuity™ is a hysteroscope accessory, placed through the working channel of a hysteroscope to obtain samples from the fallopian tube for cytological evaluation."
Primary Objective	The objective of the study is to evaluate the sensitivity and specificity of cytological evaluation of samples collected by the Cytuity™ in determining the presence or absence of malignancy in the fallopian tubes.
Study Design	The study is a prospective, multi-center, non-randomized study. Study subjects will be recruited from a population of women who are already scheduled to undergo salpingo-oophorectomy or salpingectomy. The study protocol requires hysteroscopic sampling of the fallopian tube with the Cytuity™ device at the time of scheduled surgery. Cytology results from the cells collected using the Cytuity™ will be independently evaluated at a core lab and compared to the respective clinical site's histological evaluation of the excised tissue. The histology results will not be shared with the core lab to avoid bias. Additionally, cytology results will not be shared with the study's subjects or study investigator as no medical decisions will be made based on Cytuity™ results. Any baseline testing, surgical histology evaluations, and all other clinical care will be in accordance with each participating institution's standard

	of care for patients undergoing salpingo-oophorectomy or salpingectomy.
Risk Status	The Cytuity™ device will be used in subjects at the time of scheduled surgery. Because the tissue that the Cytuity™ device contacts will subsequently be removed and because the device has been cleared by the FDA for use in obtaining samples from the fallopian tube for cytological evaluation, this study is proposed as a Non-Significant Risk (NSR) study.
Investigational Sites	Up to 15 clinical sites may participate in this study
Number of Participants	The Cytuity™ procedure will be performed on a maximum of 150 subjects. Subjects will be recruited until Cytuity™ cytology results can be compared with the surgical histology in at least 32 subjects determined to have a malignant neoplasm or malignancy and 18 subjects determined by surgical histology of the excised tissues to be negative for malignancy. Statistical conversion from subjects to fallopian tubes yields a requirement of 56 tubes, or samples, positive for malignancy. This is because the left and right fallopian tubes are treated as partially independent from one another in regard to the histology results (for example, if there is malignancy in the right tube, that does not mean that there is malignancy on the left). Based on an assumed 20% prevalence rate of (subject-level) malignancy, a sample size of 140 subjects (280 tubes) in which both fallopian tubes are tested is statistically likely to produce the minimum 56 positive tubes required.
Study population	Subjects who are scheduled to undergo a salpingo-oophorectomy or salpingectomy because of a pelvic mass suspicious for malignancy.
Inclusion Criteria	Inclusion Criteria: 1. Subject is medically cleared for surgery 2. Subject is scheduled to undergo salpingo-oophorectomy or salpingectomy for a pelvic mass suspicious for malignancy 3. Subject must be 18 years of age 4. Subject must be able to provide informed consent

Exclusion Criteria	Exclusion criteria: 1. Contraindication to hysteroscopy 2. Acute pelvic inflammatory disease 3. Active or recent lower pelvic infection 4. Pregnancy 5. Delivery or termination of a pregnancy in the past 6 weeks 6. Known tubal obstruction 7. Tubal ligation 8. Invasive carcinoma of the cervix or endometrium 9. Intolerance of anesthesia
Study Duration	Recruitment of subjects is expected to take approximately 12 months. Subjects will be on study from the time of informed consent until study exit, which is 24 hours post- Cytuity™ use or post-operative discharge, whichever occurs first. See Table 2 below for study-related contacts.
Safety Measures	Subjects participating in the study are already scheduled to undergo salpingo-oophorectomy or salpingectomy with the attendant risks and adverse events (pain, nausea, etc.) of that surgery. All Cytuity™ device-related, Cytuity™ procedure-related, serious and unanticipated adverse events will be recorded and assessed for seriousness, severity, and relatedness to the study device and/or study procedure.
Primary Endpoint	The primary endpoints of the study are to evaluate the sensitivity and specificity of the cytological samples collected from the fallopian tube in determining the presence or absence of malignancy for fallopian tube involvement as compared to the surgical histology results. Fallopian tube involvement is defined as: 1. Malignant cells that originated in the fallopian tube. This is detected by the surgical histology results from the fallopian tube. 2. Malignant cells that have migrated to the fallopian tube. This can be detected by surgical histology results of the ovaries or fallopian tubes.
Secondary Endpoints	1. PPV (positive predictive value), NPV (negative predictive value), and Diagnostic Accuracy will be calculated for Cytuity™ as

	compared to surgical histology of the ovaries and fallopian tube for fallopian tube involvement. 2. Sensitivity, specificity, PPV, NPV, and accuracy will be calculated for Cytuity™ as compared to surgical histology of the fallopian tube. 3. Sensitivity, specificity, PPV, NPV, and accuracy will be calculated for Cytuity™ as compared to surgical histology of the ovaries. 4. Sensitivity, specificity, PPV, NPV, and accuracy will be calculated for Cytuity™ as compared to surgical histology for fallopian tube involvement for subject level analysis.
Statistical Methods for Primary Endpoint	The sensitivity of the Cytuity™ procedure is estimated to be 80%, while the specificity is estimated to be 90% for the primary endpoint of fallopian tube involvement. Since sensitivity is a function of diseased fallopian tubes only, while specificity is a function of non-diseased fallopian tubes, the statistical hypotheses for sensitivity and specificity are considered to be independent. Each hypothesis is framed as a 1-sided test with a type I error rate of 2.5%. For sensitivity, the following hypothesis will be tested: H_{Null}: Sensitivity ≤ 60% versus $H_{Alternative}$: Sensitivity > 60% For specificity, the following hypothesis will be tested: H_{Null}: Specificity ≤ 70% versus HAlternative: Specificity > 70%
Independent Core Labs	Pathology (surgical histology/pathology): Site specific redacted reports reviewed by independent study pathologist: Brooke Howitt, MD Pathologist Stanford University Medical Center Cytology Core Lab (slide preparation) Calpath Medical Associates Campbell, CA Pathologist #1 (cytology review): Sharmila Pramanik, MD Pathologist Santa Clara Valley Medical

	Pathologist #2 (cytology review) Eric Yang, MD Pathologist Stanford University Medical Center Pathologist #3 (cytology adjudication) Teresa Darragh, MD Pathologist University of California San Francisco

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Definitions

Adverse Event (AE): any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, related to the investigational medical device or study procedure.

Adverse Device Effect (ADE): adverse event related to the use of an investigational medical device.

Serious Adverse Event (SAE): an adverse event, per the FDA, is serious when the patient outcome is

death
life-threatening
disability or permanent damage
hospitalization* – initial or prolonged (>24 hours)
required (medical or surgical) intervention to prevent permanent impairment or damage
congenital anomaly / birth defect
other serious (important medical events)

*Note: Planned hospitalization for a pre-existing condition is not considered a serious adverse event.

Serious Adverse Device Effect (SADE): adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated adverse device effect (UADE): means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including supplementary plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects [21 CFR 812.3(s)]

Seriousness:

Mild Severity: means the subject is aware of signs or symptoms, but easily tolerates them.

Moderate Severity: means the subject has discomfort enough to cause interference with usual activity

Severe Severity: means the subject is incapacitated by an inability to work or do usual activity

Relatedness: relatedness to both the Cytuity™ device and Cytuity™ study procedure (including AEs related to the use of the hysteroscope) will be reported.

> **Not related:** means there is an adverse event for which sufficient information exists to indicate that there is no causal connection between the event and the investigational device or study procedure. The adverse event is due to and readily explained by the participant's underlying disease state or is due to concomitant medication or therapy not related to the use of the device or the procedure. In addition, the adverse event may not follow a reasonable temporal sequence following the treatment procedure.
>
> **Possibly related**: means there is a reasonable possibility that the adverse event may have been primarily caused by the investigational device and/or study procedure. The adverse event has a reasonable temporal relationship to the use of the device or the study procedure and follows a known or expected response pattern to the investigational device or study procedure, but alternative etiology is equally or more likely compared to the potential relationship to the use of device or the study procedure.
>
> **Definitely related:** is an adverse event that can only be attributed to the investigational device and/or study procedure.

Positive Predictive Value (PPV): the probability that subjects with positive screening test (positive cytology results) truly have the disease (when compared to surgical histology results)

Negative Predictive Value (NPV): the probability that subjects with a negative screening test (negative cytology results) truly do not have the disease (when compared to surgical histology results)

Accuracy (diagnostic accuracy): the degree to which the diagnostic result (cytology result) conforms to the correct diagnosis (based on surgical histology results).

Sensitivity: the ability of a diagnostic test (cytological evaluation of samples collected from the Cytuity™ device) to correctly identify those with the disease (true positive rate).

Specificity: the ability of the diagnostic test (cytological evaluation of samples collected from the Cytuity™ device) to correctly identify those without the disease (true negative rate).

Adequate Sample: a sample where background and artifact do not impact review of cellular detail and the sample contains more than five clusters or has less than five clusters but contains neoplastic or malignant cells.

1 Introduction

1.1 Current Treatment

Histological evaluation of surgically excised fallopian tube and ovarian tissue is considered the gold standard for determining the presence of malignancy. No accurate and/or reliable diagnostic test exists for ovarian or fallopian tube malignancy. For example, the most commonly used blood test for ovarian cancer today has a sensitivity of as low as 32% for diagnosing early stage ovarian cancer.[1,2,3,4,5,6,7,8,9,10] It should be noted that this gold standard, histology of excised tissue, requires invasive surgery and removal of the anatomy, and therefore is considered an aggressive and drastic, sometimes necessary option for accurate diagnosis.

1.2 Need for New Treatment

The benefits of developing a system/device that could atraumatically, and minimally invasively, collect cells from the fallopian tube that could be evaluated cytologically for the presence or absence of atypical or malignant features are expected to be significant as current tests lack both sensitivity and specificity. Cytologic evaluation of cells collected from the female genital tract has yielded clinically useful information since the 1920s[11]. Evaluation of cells for atypical or malignant features has been used effectively to identify individuals who may be at increased risk for malignancy.

Work was done to develop a minimally invasive method for cell collection from the fallopian tube, but until the MAKO 7 device (now called Cytuity™ device) was developed, no such method has reliably collected cells from this part of the anatomy. In one ten (10) patient study, a standard brush biopsy catheter could not be passed through the length of the fallopian tube in patients, neither hysteroscopically nor laparoscopically.[12] Access to the fallopian tube has been challenging due to its significant tortuosity and narrow inner diameter, as well as lack of tactile feedback provided by the consistency of the wall of the fallopian tubes.

1.3 Investigational Product

nVision Medical developed the MAKO 7 device to be used through the working channel of a hysteroscope for cell collection from the fallopian tube. nVision Medical was acquired by Boston Scientific Corporation in 2018 and the MAKO 7 is now called Cytuity™. The MAKO 7 and Cytuity devices are equivalent. The MAKO 7 / Cytuity™ device is FDA cleared as a hysteroscope accessory, placed through the working channel of a hysteroscope to obtain samples from the fallopian tube for cytological evaluation.

In a previous study, undertaken and submitted in support of FDA clearance, the MAKO 7/ Cytuity™ device was evaluated in forty (40) subjects (80 fallopian tubes) who were already scheduled to undergo a laparoscopic tubal ligation. Study endpoints included 1) ability of the device to navigate the fallopian tube, 2) ability of the device to collect a sample adequate for cytological evaluation, and 3) adverse events. Access was achieved in 71/71 (100%) of unblocked fallopian tubes and 71/80 (89%) of all tubes attempted. The nine (9) tubes that were not accessed were determined to have pre-existing tubal occlusion, as determined by methylene blue dye injection. The study pathologist determined that 70/71 (99%) of the samples were adequate for cytological evaluation. There were no adverse events reported.

A subsequent study was undertaken with the purpose of demonstrating the effectiveness of the MAKO 7 / Cytuity™ device in collecting samples from the fallopian tube for cytological evaluation that were adequate to enable determination and/or differentiation of normal versus atypical versus malignant cells. Furthermore, for information only, sensitivity and specificity for malignancy were assessed. The study was a prospective, multi-center, observational study of 50 subjects. The study subjects were already scheduled to undergo salpingo-oophorectomy for a pelvic mass suspicious for malignancy or for BRCA1 or BRCA2 mutations. The protocol required hysteroscopic sampling of cells from the fallopian tube with the MAKO 7 / Cytuity™ device. Fallopian tube cytology results were then compared to fallopian tube histology results generated from the evaluation of surgically excised fallopian tube specimens and examined by the study site pathology department. For further evaluation, fallopian tube cytology results were compared to histology results of the ovaries as well. The MAKO 7 / Cytuity™ device was able to obtain samples that were adequate to enable the determination and/or differentiation of normal versus atypical versus malignant cells with an overall percent agreement (concordance) between fallopian tube cytology and fallopian tube cytology of 95%. The MAKO 7 / Cytuity™ device also signaled a sensitivity and specificity of 100% for fallopian tube involvement.

This current study seeks to provide additional information on sensitivity and specificity in a larger patient population.

1.4 Legal Manufacturer

Boston Scientific Corporation
300 Boston Scientific Way
Marlborough, MA 01752, United States

1.5 Regulatory Classification

The Cytuity™ device is a class II device cleared by the FDA [K160510] with the following indication for use:

"The Cytuity™ is a hysteroscope accessory, placed through the working channel of a hysteroscope to obtain samples from the fallopian tube for cytological evaluation."

In this study, the Cytuity™ device will be used in subjects at the time of scheduled salpingo-oophorectomy or salpingectomy. Because the tissue that the Cytuity™ device contacts will be removed and because the device has been cleared by the FDA for use in obtaining samples from the fallopian tube for cytological evaluation, this study is proposed as a Non-Significant Risk (NSR) study.

1.6 Device Accountability

The sponsor and investigator are jointly responsible for the accountability of every unit of investigational product used for the clinical study.

An inventory of sterile investigational Cytuity™ devices will either be shipped or hand carried to the investigational site by the sponsor.

It is the responsibility of the clinical Investigator to ensure that all investigational products received at the site are inventoried and accounted for throughout the study. A device accountability log will be used to record device receipts, use, and disposition at the site. This log will be maintained in the site study file.

1.7 Intended Purpose of the Device in the Clinical Investigation

The objective of this study is to evaluate the sensitivity and specificity, estimated to be 80% and 90% respectively, of cytological evaluation of samples collected by the Cytuity™ device in determining the presence or absence of malignant cells that originated in the fallopian tube or malignant cells that have migrated to the fallopian tubes. The Cytuity™ device is currently cleared for cell collection from the fallopian tube. This study is not intended to provide data regarding the rate of successful cell collection.

1.8 Required Training and Experience Needed to Use the Device

As cleared by the FDA, the Cytuity™ device requires that the device is "…to be used only by physicians who are knowledgeable hysteroscopists."

Since this study requires access to an enriched patient population, i.e. patients who have malignancies, investigators may include gynecologic oncologists rather than the target user, gynecologists who are skilled at hysteroscopy. As a result, training not typically required of the target user will be provided for all investigators. Lower Cytuity™ device access rates and lower sample adequacy rates may be expected with this investigator population.

Prior to the start of the study, the investigator and clinical study staff will undergo training on the use of Cytuity™ device, the clinical study protocol, and study

procedures and requirements. Sponsor personnel (or designees) will conduct the training.

Clinical research staff will be supplied with the clinical protocol, device instructions for use, case report forms, and other supporting materials as needed.

Training of study personnel will be documented on the appropriate training record and maintained in the site study file and in the sponsor's trial master file.

1.9 Study Overview

The study is a prospective, multi-center, non-randomized study. Subjects will be recruited from a population of women who are already scheduled to undergo salpingo-oophorectomy or salpingectomy.

The procedure requires hysteroscopic sampling of the fallopian tube with the Cytuity™ device at the time of scheduled surgery. A skilled hysteroscopist or a gynecologist who has undergone the sponsor's training module is required to perform the procedure.

Directly before the scheduled surgery, fallopian tube cytology collection will be performed with the Cytuity™ device. Following placement of the hysteroscope, the fallopian tube ostium is located, the distal tip of the Cytuity™ device will be placed at the tubal ostium and the balloon will be deployed into the fallopian tube. Cells are captured on the surface of the balloon. The balloon will then be retracted into the device's sheath. The device is then withdrawn from the working channel of the hysteroscope and the distal end of the device containing the sheathed-balloon will be cut and immersed into a specimen container with a sufficient volume of cytopreservative. This process is repeated for the contralateral fallopian tube and the device is placed into a separate labeled specimen tube. The hysteroscope is removed before any laparoscopic insertion or surgery is performed.

The specimen containers holding the cut end of the device will be transferred to the central study core lab for slide preparation, which will be used for all sites. Cytology samples will be prepared and analyzed using the Pap stain method. The slide(s) are sent to study pathologist#1 for cytology case report form completion which will include classification of the cytology sample into the following categories: positive (malignant or neoplastic) or negative (benign or atypical). The case report form is reviewed by the sponsor.

The slides will then be sent to study pathologist #2 for review and classification of the cytology sample into the following categories: positive (malignant or neoplastic) or negative (benign or atypical). Upon completion the case report forms are reviewed by the sponsor and study slides are sent back to the sponsor.

The sponsor compares the cytology results between pathologist #1 and pathologist #2 for concordance. Concordant results are later compared to surgical pathology/histology. If there is discordance, the slides are held for adjudication with pathologist #3. Pathologist #3 meets with both other pathologists to review the slides and evaluates the sample. Pathologist #3 completes the case report form and makes the final determination through concordance with either pathologist #1 or pathologist #2.

Once the ovary(ies) and/or fallopian tube(s) have been surgically excised, they will be sent to the pathology department/center of the clinical site. They will then be analyzed according to standard of care (including micro-sectioning of the fallopian tube); no unique or experimental methods for evaluation should be used. The site's surgical pathology report is redacted and sent to an independent study pathologist to complete the histology/pathology case report form (CRF). When malignancy is present, the form will be marked positive. When benign, benign mass or cyst, or inflammatory changes are present, the form will be marked negative. The completed form is returned to the sponsor. The surgical pathology source documents remain at the clinical site.

Fallopian tube cytology results from two independent and concordant and/or adjudicated results will then be compared to surgical pathology/histology results independently generated from the surgically excised fallopian tube and ovarian tissue specimens.

Figure 1 below illustrates the study flowchart.

Note that any baseline testing, pathology (histology) evaluations, and all other clinical care will be in accordance with each participating institution's standard of care for patients undergoing salpingo-oophorectomy or salpingectomy.

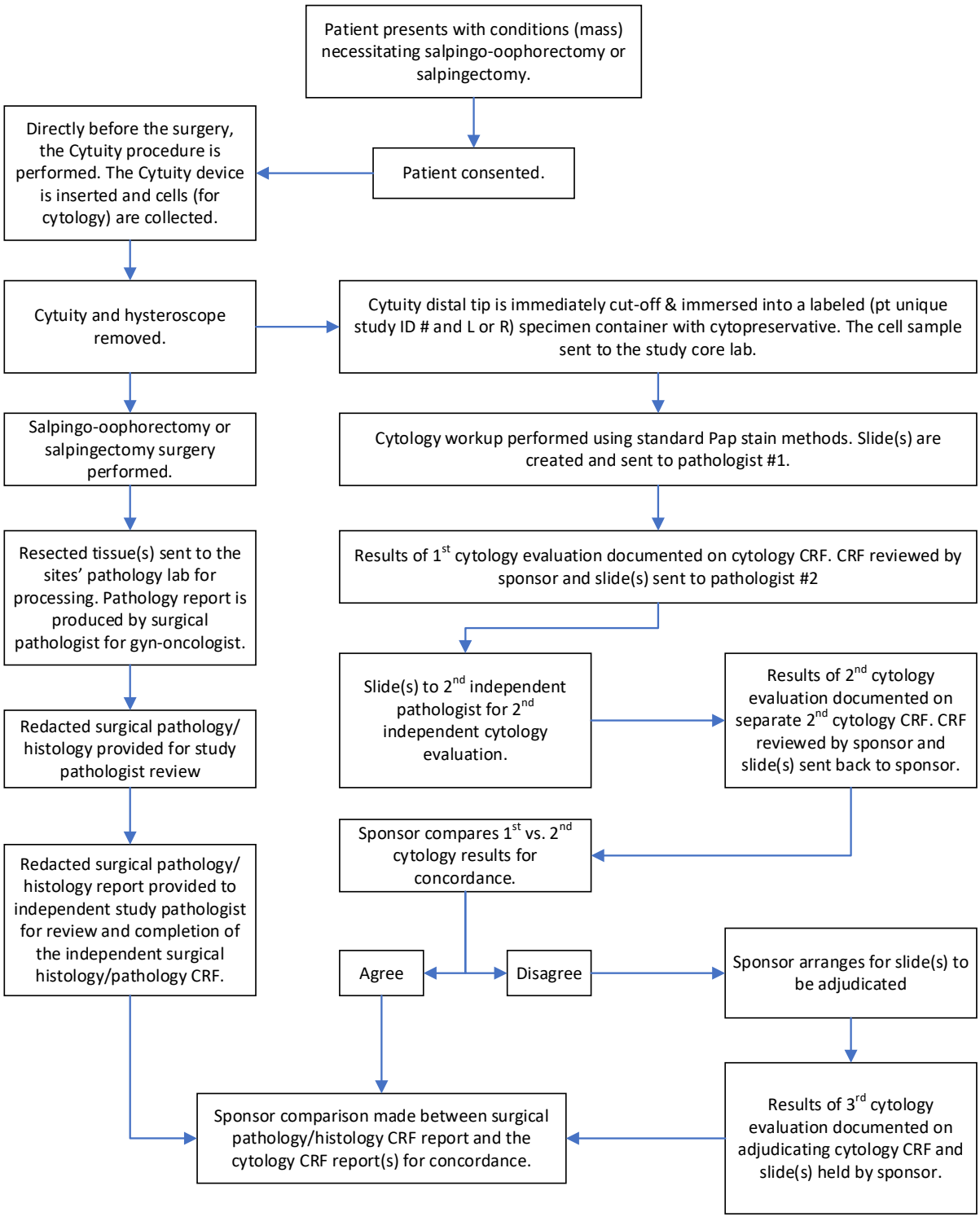


Figure 1. Study Flowchart

2 Justification for Clinical Investigation Design

Direct biopsy using the Cytuity™ device can collect cells from the fallopian tube for cytological evaluation in women, including those presenting with a pelvic mass suspicious for malignancy. A high sensitivity would allow gynecologists to better diagnose disease in its early stages, while a high specificity would send patients to surgery only if they have signs of disease.

Subjects participating in this study are already scheduled to undergo salpingo-oophorectomy or salpingectomy with the attendant risks of that surgery. The study device and procedure present minimal additional risk to subjects participating in this study, since the contacted anatomy will be removed from the subject immediately after study device use and because the device has received FDA clearance for collecting cells from the fallopian tube.

There is no risk for inaccurate diagnosis using the Cytuity™ device as cytology results will not be shared with the study's subjects or the investigator to prevent any medical decisions being based on Cytuity™ results. The subject's treatment following the Cytuity™ procedure will be the same standard of care that the subject would have received without participating in this study.

3 Risks and Benefits of the Investigational Device and Clinical Investigation

The sponsor undertook a risk management process to analyze the hazards associated with the device in accordance with the requirements of a quality management system and ISO 14971.[13] This process determined those events or attributes of the device that could pose a hazard to the patient or user, and the steps necessary to mitigate those hazards to an acceptable level. Risk reduction and control measures were implemented to reduce the residual risk as far as possible, and no remaining risk factors were found requiring additional action at this time. The anticipated clinical benefits and anticipated adverse events or device effects are detailed below.

3.1 Anticipated Clinical Benefits

While there are no direct benefits to the subject's participating in the study, participation will provide information about the study device that could benefit other women in the future.

3.2 Anticipated Adverse Events and Adverse Device Effects

Per the device instructions for use, there are risks associated with hysteroscopy and use of the Cytuity™ device.

Additionally, in this study, there are risks associated with general anesthesia as the patient is scheduled to undergo general anesthesia for their scheduled salpingo-oophorectomy and/or salpingectomy.

Risks related to anesthesia or hysteroscopy include:

- Nausea / vomiting
- Dizziness / light headedness

Risks related to hysteroscopy include:

- Cramping
- Bleeding/spotting
- Vaso-vaginal response
- Hypervolemia
- Infection
- Perforation of the uterus or fallopian tubes, with possible injury to bowel, bladder, or surrounding blood vessels.

Table 1. Potential Adverse Events related to the Cytuity™ device and Mitigation Strategy

Risk	Mitigation
Perforation of the fallopian tube is a risk because of its tortuosity and narrow dimensions.	a. No rigid portion of the device enters the fallopian tube. Instead, a very small balloon (less than 1 mm diameter) is everted through the tube. Because the balloon is self-navigating, the eversion of the balloon will minimize the physician's manual advancement of the device through the tube and therefore the risk of perforation is expected to be minimized. b. A salpingo-oophorectomy or salpingectomy will be performed directly after the Cytuity™ device procedure.
A foreign object will be introduced into the subject and therefore infection may occur.	c. A sterilized device will be supplied to the physician. d. The device instructions for use mandate sterile technique.
This study could prolong the time the subject is under general anesthesia by an estimated 5-7 minutes per Cytuity™ device use.	e. Prior to the study, the physician will be trained on the bench on how to use the Cytuity™ device accurately and in an efficient manner, therefore minimizing overall time of the procedure.

3.3 Risk Mitigation

Subjects participating in the study are already scheduled to undergo salpingo-oophorectomy or salpingectomy with the attendant risks of that surgery. Any events that occur as a result of the planned surgery will be medically managed by the subject's physician per the institution's standard of care. The study device and procedure present minimal additional risk to subjects participating in this study, since the contacted anatomy will usually be removed from the subject immediately after study device use and because the device is FDA cleared for cell collection from the fallopian tube. Standard risks associated with hysteroscopic instruments include perforation, infection and bleeding. It is not expected that the Cytuity™ device is associated with any increased risks as compared to commercially available hysteroscopic instruments. The Cytuity™ device procedure will increase the amount of time that the subject is under general anesthesia by an estimated 5-7 minutes per Cytuity™ device use. Additional Cytuity™ risks and mitigations are noted in Table 1 above. There is the potential that unknown risks exist.

This investigation will be conducted by investigators that are qualified by training and experience in the treatment of patients presenting for salpingo-oophorectomy or salpingectomy. Adequate measures including eligibility criteria limitations, subject screening and pre-visit assessment of their health condition have been incorporated into the clinical investigation to minimize such risks.

Investigators are also familiar in the use of hysteroscopes or have gone through the sponsor's training module.

3.4 Risk-to-Benefit Rationale

The sponsor believes that any potential risks presented by this investigation have been minimized and that the overall residual risk is deemed acceptable.

The study device and procedure present minimal additional risk to subjects participating in this study, since the contacted anatomy will be removed from the subject immediately after study device use.

4 Objective

The primary objective of the study is to evaluate the sensitivity and specificity, estimated to be 80% and 90% respectively, of cytological evaluation of samples collected by the Cytuity™ device in determining the presence or absence of malignant cells that originated in the fallopian tube or malignant cells that have migrated to the fallopian tubes. The results obtained from the cytological samples will be compared against the results

obtained from the gold standard. The gold standard is the surgical histology (pathology) assessment of the fallopian tubes, and in cases of malignant cell migration, the ovaries.

5 Design of the Clinical Investigation

5.1 General

This clinical investigation is a prospective, multi-center, non-randomized study. Subjects will be recruited from a population of women who are already scheduled to undergo salpingo-oophorectomy or salpingectomy. The study protocol requires hysteroscopic sampling of the fallopian tube with the Cytuity™ device immediately prior to the scheduled surgery.

Cytology results from the cells collected using the Cytuity™ device will be independently evaluated at two pathologists. Concordant and/or adjudicated cytology results are compared to the site's surgical histology results from the removed tissue(s).

Pathology results (histology) will not be shared with pathologists conducting cytology evaluations and cytology results will not be shared with the site or the pathologist evaluating histology evaluations to remove bias. Additionally, cytology results will not be shared with the study's subjects or investigator as no medical decisions will be made based on Cytuity™ results.

Any baseline testing, pathology (histology) evaluations, and all other clinical care will be in accordance with each participating institution's standard of care for patients undergoing salpingo-oophorectomy or salpingectomy.

5.2 Participants

The study population will include participants presenting with a pelvic mass suspicious for malignancy who are already scheduled to undergo a salpingo-oophorectomy or salpingectomy. Screening of these participants is done to determine if they meet inclusion and exclusion criteria.

5.2.1 Inclusion Criteria

A participant may be enrolled in this study if she meets all of the following criteria:

1. Subject is medically cleared for surgery
2. Subject is scheduled to undergo salpingo-oophorectomy or salpingectomy for a pelvic mass suspicious for malignancy
3. Subject must be 18 years of age
4. Subject must be able to provide informed consent

5.2.2 Exclusion Criteria

1. Contraindication to hysteroscopy
3. Acute pelvic inflammatory disease
4. Active or recent lower pelvic infection
5. Pregnancy
6. Delivery or termination of a pregnancy in the past 6 weeks
7. Known tubal obstruction
8. Tubal ligation
9. Invasive carcinoma of the cervix or endometrium
10. Intolerance of anesthesia

5.2.3 Screen Failures and Enrollment

Any individual participant that fails to meet inclusion and exclusion criteria is considered a screen failure.

Screen failures can occur prior to enrollment or after enrollment. Screen failures that occur prior to enrollment are logged but no other study data is collected or analyzed. A participant is considered enrolled in the clinical investigation after she has provided written informed consent.

When an enrolled subject fails to meet inclusion and exclusion criteria, no additional data beyond baseline and reason for screen failure need be collected.

5.2.4 Analysis Data Sets

An enrolled subject may voluntarily withdraw consent at any time during the study. Additionally, enrolled subjects may be withdrawn by the investigator (e.g. if the investigator determines hysteroscopy will not be attempted). The reason for withdrawal will be documented.

Once the subject is enrolled, the hysteroscope is placed and ostia identified, the subject is part of the intent to treat (ITT) population. Subjects may still be screen failures after hysteroscopic visualization of the ostia if they fail any other eligibility criteria such as discovery of tubal ligation. Screen failures are not part of the ITT data set but are part of the enrolled data set.

The modified intent to treat (mITT) population are those subjects with an adequate Cytuity™ cell sample. Primary and secondary endpoints will be evaluated using this mITT population.

5.2.5 Enrollment Duration

The enrollment period is expected to take approximately 12 months.

5.2.6 Total Expected Clinical Investigation Duration

Recruitment of this study is expected to take approximately 12 months followed by data analysis. Individual study participation is approximately 1 day after the study procedure.

5.3 Procedures

5.3.1 Consenting Visit or Contact

Patient charts (medical history, including pregnancy test for females of child bearing potential) will be previewed for study eligibility, but no study-specific information will be collected on study case report forms before informed consent.

It is typical to ensure that prior to performing the salpingo-oophorectomy or salpingectomy, the subject is tested for pregnancy (for females of childbearing potential). This test is therefore part of the standard of care.

If the subject meets all pre-procedure eligibility criteria and agrees to participate in the study, written informed consent will be obtained.

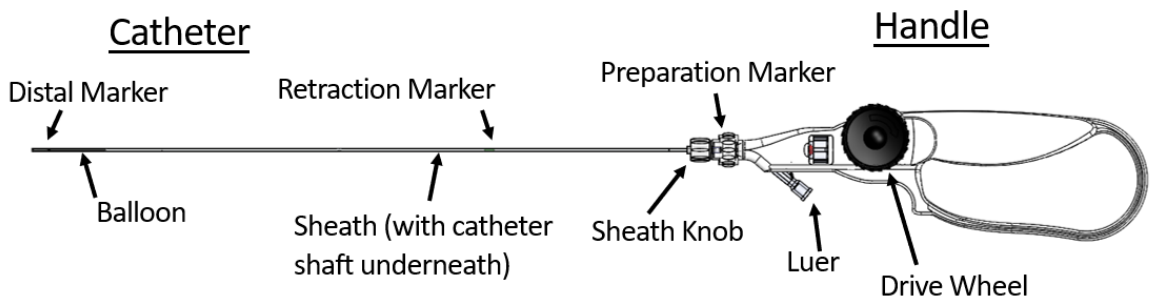
Medical history and demographics related to the study procedure are collected on case report forms following informed consent.

5.3.2 Study Treatment

Cytuity™ procedures for collection of cells from the fallopian tube will be performed immediately prior to the scheduled salpingo-oophorectomy (S-O) or salpingectomy.

As shown in Figure 2, the device is comprised of a catheter and a handle. The catheter includes a balloon, a shaft (which is made up of a stainless steel tube and a Nylon tube), a sheath, and a sheath knob. The handle includes a drive wheel and a Luer in the handle body. The Luer attaches to a commercially available inflation device via a stopcock supplied with Cytuity™.

Figure 2. Cytuity™ device



Outside the body, the Cytuity™ device is prepared by pressurizing the balloon and pre-extending the sheath and balloon 1.5cm.

The Cytuity™ device is pressurized using a commercially available inflation device that is attached to the device Luer. The sheath knob is then advanced approximately 1.5cm forward to the preparation mark. By rotating the drive wheel, the balloon is then extended forward until the tip of the balloon aligns with the tip of the extended sheath. The preparation is complete and the inflation device is then removed.

Just prior to the scheduled S-O or salpingectomy surgery, the physician inserts the hysteroscope into the subject and visualizes the tubal ostia. Upon successful visualization, the prepared Cytuity™ device is inserted into the working channel of the hysteroscope until the distal tip of the catheter is positioned immediately proximal to the ostium of a fallopian tube. The handle is advanced to cannulate the ostium with the pre-extended balloon. Then the balloon is further advanced into the fallopian tube by rotating the drive wheel.

Cells are collected from the fallopian tube on the surface of the balloon. Then the balloon is deflated by relieving pressure using the stopcock. The device is then retracted into the sheath and removed from the working channel of the hysteroscope and from the subject. Alternatively, the hysteroscope may remain in the subject for cell collection at the contralateral tubal ostium. A second Cytuity™ device is used for the second collection. Upon each Cytuity™ device removal from the subject, both balloon and sheath (distal tip) are to be simultaneously cut off and immersed into cytopreservative by stirring to agitate the cells. The vial is labeled with the unique subject's study ID#, and "L" for left or "R" for right tube.

Complete instructions are provided in the Cytuity™ device instruction for use (DFU) provided with each study device.

Following Cytuity™ use, the hysteroscope is removed. The surgical instrumentation can then be placed and the subject proceeds to the planned surgery.

A cytology specimen log will be completed to show transfer of the vials from the site either directly to the cytology core lab or to the sponsor as an interim provider of transport to the cytology core lab.

Samples may be stored at room temperature pending transfer if needed.

5.3.3 Prior to Study Exit

Subjects are exited 24 hours post- Cytuity™ use or at discharge, whichever occurs first. The only time the follow-up period is extended is if the subject has a Cytuity™ study or device-related adverse event. In these instances, the subject is followed until the investigator deems the adverse event is resolved or for 30 days, whichever comes first.

The following data is collected at the day of study exit:

- Any adverse events up to study exit
- The reason for study exit (e.g. completion of the study)

The subject has no additional visits or follow-up required. See Table 2.

Table 2. Schedule of Assessments

	Screening / Informed Consent	Cytuity™ Study Procedure/ Salpingo-oophorectomy or salpingectomy	Subject Study Exit	Lab Test Results (no subject involvement)
Window (days)	-21	0	+1*	NA
Medical History, including review of pregnancy status (for women of child bearing age)	X			
Demographics	X			
Inclusion / exclusion criteria determination	X			
Informed Consent	X			
Pregnancy Test**	X			
Cell Collection using Cytuity™ device		X		
Adverse Events		X	X	
Cytology and Surgical Histology Results				X

*Unless a Cytuity™ study or device related AE occurs, in which case the AE will be followed until resolution or for 30 days, whichever comes first.

**Pregnancy test must be within 21days of study procedure.

5.3.4 Post-Operative Pathology

Per site standard procedures, excised tissue will be sent to site-specific pathology department/facility. The histological evaluation will include standard of care only (including micro-sectioning of the fallopian tubes); no different, unique or experimental methods will be used.

Transfer of each subject's surgical pathology (histology) report diagnostic data is a study requirement. All protected health information will be redacted by the site and the report will be labeled with the subject's study identification number. The redacted histology report will be provided to the sponsor. The redacted report will be reviewed by an independent study pathologist who will complete the study histology case report form. The study pathologist reviewing histology may contact the site's surgical pathology lab for clarification of the redacted report if warranted. If clarification is required, all communications between the site pathology lab and the study pathologist reviewing histology must be attached to the redacted report and included in the study data.

The study pathologist will use the redacted site pathology report to document the histology results of fallopian tube malignancy, ovarian malignancy, and other malignancy on a study case report form.

5.3.5 Post-operative Cytology

Cytuity™ collected cytology samples will be delivered to the sponsor and then the core lab for slide preparation.

The core lab will be responsible for logging in received samples and processing the samples into slides. This requires a centrifugation step and the creation of a monolayer preparation on a microscope slide with the recovered fallopian tube cells. The slide will be stained to make the cells visible using the Pap stain method. The slide(s) are then transferred to Pathologist #1. Pathologist#1 will review and interpret the slides for evidence of malignancy.

Pathologist #1 will document the cytology results of the fallopian tube samples on a study case report form for sponsor review. The sponsor will then forward the slide(s) labeled with the patient study ID number to pathologist #2. The 2nd pathologist will review and interpret the slides for evidence of malignancy. Pathologist #2 will document the cytology results of the fallopian tube samples on a study case report form for sponsor review. The slide(s) are returned to the sponsor.

The sponsor will review the results between pathologist #1 and pathologist #2 for concordance. If the results are in agreement (concordant), the sponsor will compare the concordant cytology results with the surgical histology/pathology results. If the cytology results are not in agreement (discordant), the sponsor will arrange for pathologist #3 to adjudicate. The adjudicating pathologist will review and interpret the slide(s) for evidence of malignancy. He/she will likely agree with either pathologist #1 or #2, ultimately providing the final cytology result. The results will be recorded on a CRF. The adjudicating pathologist's interpretation is

final. The slide(s) and CRF are returned to the sponsor for final comparison to the independent pathology (histology) case report forms.

5.3.6 Activities Performed by Sponsor or Sponsor Representatives

The sponsor or designee will conduct all site investigator training, site staff training, core lab training, study pathologist training and site initiation visits.

One or more representatives of the sponsor may be present during the study procedure at the request of the investigator and under supervision of the investigator to assist with device preparation prior to subject use; to assist with collecting holding the cell collection vial after subject use; and secure sample transfer to the cytology core lab post subject use.

The sponsor may transfer cytology samples from the sites to the core cytology lab and then to and from pathologists reviewing cytology slides. The site's histology lab and study pathologist reviewing histology are blinded to the results of the cytology core lab and the pathologists reviewing cytological slides.

The sponsor or designee will monitor sites as detailed below in the section titled Monitoring Plan.

The sponsor will complete all data review, statistical analysis, and write the final study report.

Boston Scientific personnel will not do the following:

- Practice medicine.
- Provide medical diagnosis or treatment to subjects.
- Discuss a subject's condition or treatment with a subject.
- Independently collect critical study data (defined as primary or secondary endpoint data).
- Enter data in electronic data capture systems or on paper case report forms.

5.4 Monitoring Plan

Study site monitoring will be performed by qualified monitors who may be employees or consultants to the sponsor or a qualified CRO selected by the sponsor.

Each site will be visited regularly in an effort to ensure that the study is conducted in compliance with the study protocol and all applicable guidelines, laws and regulations.

To monitor, study visits may include, but are not limited to, the review of device supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents found in the subject's medical records. Monitoring will also include the assessment of the site's overall progress, including but not limited to the site's ability to keep accurate records and to report study related data to the study sponsor in a timely fashion.

The investigator agrees to participate in study visits conducted at a reasonable time, in a reasonable manner.

In addition to study related logs, plans, and IRB approved documents (protocol, informed consent, etc.), investigators must maintain information in the study subject's medical records to corroborate data collected on the CRFs. This ensures the validity of the study data collected and is used by the sponsor or designees to monitor the study.

Data / CRF corrections and/or ambiguous data points may be resolved in person during monitoring visits, via data clarification forms (DCFs) provided to the site, and/or data queries. Findings of non-compliance and/or deviations from the protocol shall be reviewed with the investigator(s) and disclosed in a written monitoring report. The sponsor shall then either secure compliance or may discontinue shipments of the device to the investigator until compliance is achieved and/or terminate the investigator's participation in the investigation.

6 Statistical Considerations

6.1 Hypothesis

As sensitivity is a function of diseased fallopian tubes only, while specificity is a function of non-diseased fallopian tubes, the statistical hypotheses for sensitivity and specificity are considered to be independent. Each hypothesis is framed as a 1-sided test with a type I error rate of 2.5%.

For sensitivity, the following hypothesis will be tested:

H_{Null}: Sensitivity ≤ 60% versus

$H_{Alternative}$: Sensitivity > 60%

For specificity, the following hypothesis will be tested:

H_{Null}: Specificity ≤ 70% versus

$H_{Alternative}$: Specificity > 70%

6.2 Primary Outcome

The primary endpoint of the study is to evaluate the sensitivity and specificity of the cytological samples collected from the fallopian tube in determining the presence or absence of malignancy for fallopian tube involvement as compared to the current gold standard, the surgical pathology (histology) results.

Fallopian tube involvement is defined as:

1. Malignant cells that originated in the fallopian tube. This is detected by the surgical histology results from the fallopian tube.
2. Malignant cells that have migrated to the fallopian tube. This can be detected by surgical histology results of the ovaries or fallopian tubes.

The site's pathology report will contain the surgical histology evaluation of the removed fallopian tube specimens. These results will be compared to corresponding results from cytologic evaluation of fallopian tube samples. Sensitivity and specificity will be calculated for the Cytuity™ device as compared to surgical histology of the ovaries and fallopian tube for fallopian tube involvement.

Note that in most cases where malignant cells have migrated into the fallopian tube from the ovary, fallopian tube histology can be used to confirm presence of malignancy in the fallopian tube as outlined in #2 above. However, due to washing required for specimen preparation, in some cases fallopian tube histology may be negative although malignant cells *may have been present*. That is, malignant cells may have been washed out. Therefore, when the histology of the tube is negative, but the histology of the same sided ovary is positive and the cytology results of the fallopian tube are positive, this result will be categorized as a true positive. This finding will be called 'favorable discordance' relative to cytology results.

The following formulas will be used to determine sensitivity and specificity:

$$sensitivity = \frac{number\ of\ true\ positives}{number\ of\ true\ positives + number\ of\ false\ negatives}$$

$$specificity = \frac{number\ of\ true\ negatives}{number\ of\ true\ negatives + number\ of\ false\ positives}$$

6.3 Secondary Outcomes

The secondary endpoints will include the following:

- Positive Predictive Value (PPV), Negative Predictive Value (NPV), and Diagnostic Accuracy will be calculated for Cytuity™ as compared to surgical histology of the ovaries and fallopian tube for fallopian tube involvement.
- Sensitivity, specificity, PPV, NPV, and accuracy will be calculated for Cytuity™ as compared to surgical histology of the fallopian tube.
- Sensitivity, specificity, PPV, NPV, and accuracy will be calculated for Cytuity™ as compared to surgical histology of the ovaries for epithelial malignancies.*
- Sensitivity, specificity, PPV, NPV, and accuracy will be calculated for Cytuity™ as compared to surgical histology for fallopian tube involvement for subject level analysis.

*Epithelial cancers, which consist of high and low-grade serous carcinomas, endometrioid, clear cell and mucinous subtypes make up approximately 95% of all ovarian cancers.

6.4 Sample Size Determination

The Cytuity™ procedure will be performed on a maximum of 150 subjects.

Subjects will be recruited until Cytuity™ cytology results can be compared with the surgical histology in at least 32 subjects determined to have a malignant neoplasm or malignancy and 18 subjects determined by surgical histology of the excised tissues to be negative for malignancy.

As this analysis will be conducted on tube level, the sample size was converted to look at the number of tubes that would be required. Previous data suggest that when 1 fallopian tube is positive for malignancy, the subject's other tube is positive about 75% of the time, making a total correlation of 80% is a reasonable assumption. The following formula was used for the statistical conversion:

Statistical conversion from subjects to fallopian tubes yields a requirement of 56 tubes, or samples, positive for malignancy. This is because the left and right fallopian tube are treated as partially independent from one another in regard to the histology results (for example, if there is malignancy in the right tube, that does not mean that there is malignancy on the left).

Based on an assumed 20% prevalence rate of (subject-level) malignancy, a sample size of 140 subjects (280 tubes) in which both fallopian tubes are tested is statistically likely to produce the minimum 56 positive tubes required.

6.5 Statistical Methods

This trial was designed with formal statistical hypotheses for both sensitivity and specificity. The sample size was determined based on a fallopian tube-level (each tube will be considered a data point), and assuming a high correlation of 75% between tubes in individual subjects. Previous data suggest that when 1 fallopian tube is positive for malignancy, the subject's other tube is positive about 75% of the time so making a total correlation of 75% is a reasonable assumption.

Since sensitivity is a function of diseased tubes only, while specificity is a function of non-diseased fallopian tubes, the statistical hypotheses for sensitivity and specificity are considered to be independent. Each hypothesis is framed as a 1-sided test with a type I error rate of 2.5%.

For sensitivity, the following hypothesis will be tested:

HNull: Sensitivity ≤ 60% versus
HAlternative: Sensitivity > 60%

For specificity, the following hypothesis will be tested:

HNull: Specificity ≤ 70% versus
HAlternative: Specificity > 70%

For the sample size calculation, the expected sensitivity of the Cytuity™ device is approximately 80% and the expected specificity is approximately 90%. Based on these parameters and requiring > 80% power for both hypotheses above, 32 subjects positive for malignancy and 18 subjects negative for malignancy are required.[14]

Since this is a prospective study in which it is anticipated that the number of subjects testing negative will far exceed subjects testing positive, the sample size calculation is driven by the requirements for the sensitivity hypothesis. Conversion from subjects to fallopian tubes yields a requirement of 56 tubes positive for cancer.[15] Based on an assumed 20% prevalence rate of (subject-level) malignancy, a sample size of 140 subjects (280 tubes) in which both fallopian tubes are tested is statistically likely to produce at least the 56 positive tubes required.

Because the primary analysis is based on fallopian tubes, the analysis must account for the subject-level correlation.[16] A Logistic random-effects model will be used to calculate the point estimates and 95% (2-sided) confidence intervals for sensitivity and specificity.[17,18] The adjustment proposed by Obuchowski will be performed for comparison.[13]

6.5.1 Treatment of missing, spurious data, drop-outs and withdrawals

Statistical treatment of missing, unused, invalid, or spurious data, drop outs, outliers, and withdrawals will be specified in the final report.

7 Data Management

7.1 Case Report Forms

This study will utilize case report forms (CRF). Each CRF page will be identified using the subject's unique study identification number followed by an "L" for left tube and "R" for right tube.

The investigator must review, sign, and date the CRFs as indicated on the forms; these responsibilities cannot be delegated to another person. It is the investigator's responsibility to comply with regulatory requirements including, but not limited to, the maintenance of accurate, complete and current records relating to the CRFs.

Query reports may be generated by the sponsor following data review or following monitoring visits. In general, data clarification forms (DCFs) and/or queries will be generated to make auditable additions or data corrections to the CRF.

7.2 Data Management

Data management may be handled by the sponsor or a clinical research organization (CRO) designee.

The details of data entry, data review, data cleaning and data querying may be described in a Data Management Plan (DMP). This plan may be updated throughout the investigation as amended data management requirements and investigation-specific data conventions are determined.

7.3 Data Retention

Because of the potential for errors or inaccuracies in transcribing data into CRFs, source documentation must be maintained in each subject's medical chart and/or electronic medical record. The CRFs and source documentation must be made available for inspection by the monitors, as designated by the sponsor, or regulatory inspectors. Subject files will be created at the beginning of the study, maintained throughout the study and retained for two years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer needed to support a marketing application to the FDA.

8 Protocol Amendments

Investigators may not modify this protocol without obtaining written concurrence of the sponsor, the IRB and when required, regulatory authorities.

9 Protocol Deviations

The investigator agrees to conduct the investigation in accordance with this protocol. An investigator may not plan to deviate from this protocol without first receiving approval in writing from the sponsor and IRB, except when necessary to eliminate apparent immediate hazards to a participant.

Deviations will be documented on CRFs. Investigators will also adhere to procedures for reporting investigation deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

Protocol deviations to the in/exclusion criteria and deviations that affect the primary endpoint are considered major protocol deviations.

9.1 Corrective and Preventive Actions

The sponsor or its representatives will evaluate protocol deviations during monitoring visits. Individual event corrections and/or corrective and preventive actions may be recommended at that time. In addition, deviations occurring across investigational sites will be reviewed by the sponsor on a periodic basis to determine if more global corrective and/or preventive actions may be required or a protocol change is warranted.

9.2 Investigator Disqualification Criteria

The sponsor reserves the right to terminate an investigator/investigational site for any of the following reasons:

- Failure to secure participant informed consent prior to enrollment.
- Failure to report serious adverse device effects within 24 hours of becoming aware.
- Repeated investigational plan deviations.
- Repeated failure to appropriately complete case report forms.
- Failure to enroll an adequate number of participants.
- Loss of or unaccounted investigational product.

10 Statements of Compliance

10.1 Investigator Responsibilities

The principal investigator will be responsible for fulfilling the clinical study requirements as specified in this clinical protocol. The study center must have the necessary resources to comply with the requirements. Investigators will be selected for participation in the clinical study based on their ability to fulfill all requirements outlined in the investigator agreement.

The investigator shall provide the subject ample time and opportunity to inquire about details of the trial and to decide whether to participate in the trial before informed consent is obtained and shall answer all questions about the trial to the satisfaction of the subject.

10.2 Institutional Review Board (IRB) Requirements

No study activities will begin without documented IRB approval of the clinical protocol, informed consent form, and any material to be provided to potential subjects. The IRB has the authority and responsibility to review and approve the study and its conduct in accordance with local regulations. The primary purpose of the IRB is to protect the rights and welfare of the subjects enrolled in the clinical study.

The sponsor intends to submit to a central IRB for study approval. For sites requiring review by a site-specific IRB, this information will be supplied to the investigators and the investigator is responsible for submitting those materials as needed to their site-specific IRB. The investigator will notify the sponsor in writing when approval from the IRB is granted. A letter of approval from the IRB is required, and a copy of this letter must be provided to sponsor. This approval should reference the name of the study and specific version of the clinical protocol and the informed consent document(s).

The sponsor will manage annual renewals if/when a central IRB is utilized. For site-specific IRBs, the investigator is responsible for annual renewals with the IRB or per the IRBs review schedule. The renewal letter based on continuing review by the IRB must also be provided to sponsor.

The investigator is responsible for reporting protocol deviations and any safety related findings to the IRB according to their local IRB requirements. If a subject receives an investigational device procedure without signing an informed consent, the investigator must notify the IRB in writing according to the timeframes designated by the IRB.

11 Informed Consent Process

Prior to the subject providing written informed consent, the investigator or his/her designee will inform all subjects regarding the investigational nature of the study and will discuss all study risks and answer all of the subject's questions.

The subject will be informed by the investigator that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation (withdraw) at any time without penalty or loss of benefits to which the subject is otherwise entitled. The subject will be informed by the investigator that his/her medical records (as it relates to this study) will be subject to review by the sponsor's representatives and public health authorities, including the U.S. Food and Drug Administration (FDA). Subject identifying information will not be released publicly and will be available only to the sponsor and regulatory authorities.

A signed, written informed consent must be obtained from the subject prior to study activities. The signed consent form will be provided to the subject and they will also be kept by the study investigator.

When pre-approved by the sponsor, a certified translation of the informed consent form to another (non-English) language will be acceptable.

12 Adverse Events

Adverse events will be recorded on CRFs by study personnel from the time the hysteroscope enters the subject until study exit (defined as 24 hours post Cytuity™ use or discharge, whichever occurs first). If a Cytuity™ study or device related AE has occurred during this period, it will be followed until resolved or until 30 days post the salpingo-oophorectomy or salpingectomy surgery.

12.1 Severity

The assessment of severity is a clinical determination of the intensity of an adverse event. The severity assessment for a clinical adverse event should be completed by the investigator. These will be categorized as mild, moderate, or severe per the definitions noted above in this protocol.

12.2 Relatedness

The potential relationship of the event to the investigational device or study procedure will be determined by the investigator. Relatedness will be categorized as not related, possibly related, or definitely related per the definitions noted above in this protocol.

12.3 Reporting Requirements

Normal post-operative incidents such as pain and nausea will not be recorded as adverse events. Only serious adverse events, unanticipated adverse device effects, investigational device and/or study related adverse events will be documented on case report forms.

12.4 Procedures for Reporting SAEs and UADEs

In case of a serious adverse event (SAE), and all unanticipated adverse device effects (UADEs), the investigator should notify the sponsor within 24 hours and the reviewing IRB per their reporting requirements. The sponsor will assist in reporting to the IRB to ensure consistency of reporting.

13 Suspension or Premature Termination of the Study

The sponsor is responsible for the ongoing safety evaluation of the investigational product and should promptly notify, in writing, all investigators and of governing IRBs of any findings that could adversely affect the safety of participants, the trial conduct, or alter an approval of the trial. Should the sponsor decide that there are safety concerns that require immediate amendment to the protocol, informed consent, device instructions for use, or conduct of the study, this will be communicated to all sites and the governing IRBs without delay. If updates to the protocol, informed consent or device instructions for use can resolve the problem, updates will be made and re-submitted for IRB approval.

In the event that system safety issues, poor trends, and/or an unreasonable risk to subjects emerges as a result of this clinical testing, the study will be terminated.

If at any point the sponsor obtains information that suggests there is an unreasonable risk to subjects, the sponsor, shall as soon as possible, terminate the clinical investigation or the portions of the investigation presenting that risk.

The sponsor will notify all investigators and all governing IRBs.

14 Revision History

Version	Date	Summary of Changes
01	06Mar2018	• Initial release.
02	11Apr2018	• Clarified language throughout • Removed exclusion criteria regarding the inability to hysteroscopically visualize fallopian tube ostia • Added 2nd cytopathology core lab and adjudication lab to review cytology cell samples, while keeping independent histopathology CRF completion of site pathology reports. • Added details related to collection of cytology samples and processing of cytology samples

03	22Oct2019	• Change sponsor name and contact info from nVision to Boston and product name from MAKO 7 to Cytuity. • Updated SAE and UADE definitions to match CRFs and FDA definitions. • Add pathologist names • Clarify the cytology slide review process to match the process used for all prior subjects and in use now. This includes flowchart updates to match. • Minor updates referencing CRFs and DCFs changed to reflect use of eCRFs and queries in EDC • Minor updates to reflect that while the MAKO 7 used a stopcock packaged separately, the stopcock for Cytuity™ is packaged with the device. • Clarified roles of Sponsor representatives who may be present during cases.

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