Protocol Title: Role of Contrast Enhanced Spectral Mammography to Predict Upgrade Rates of Biopsy Proven Atypical Ductal Hyperplasia

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TITLE: Role of Contrast Enhanced Spectral Mammography to predict upgrade rates of biopsy proven atypical ductal hyperplasia

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Study Exempt from IND Requirements per 21 CFR 312.2(b).

SCHEMA

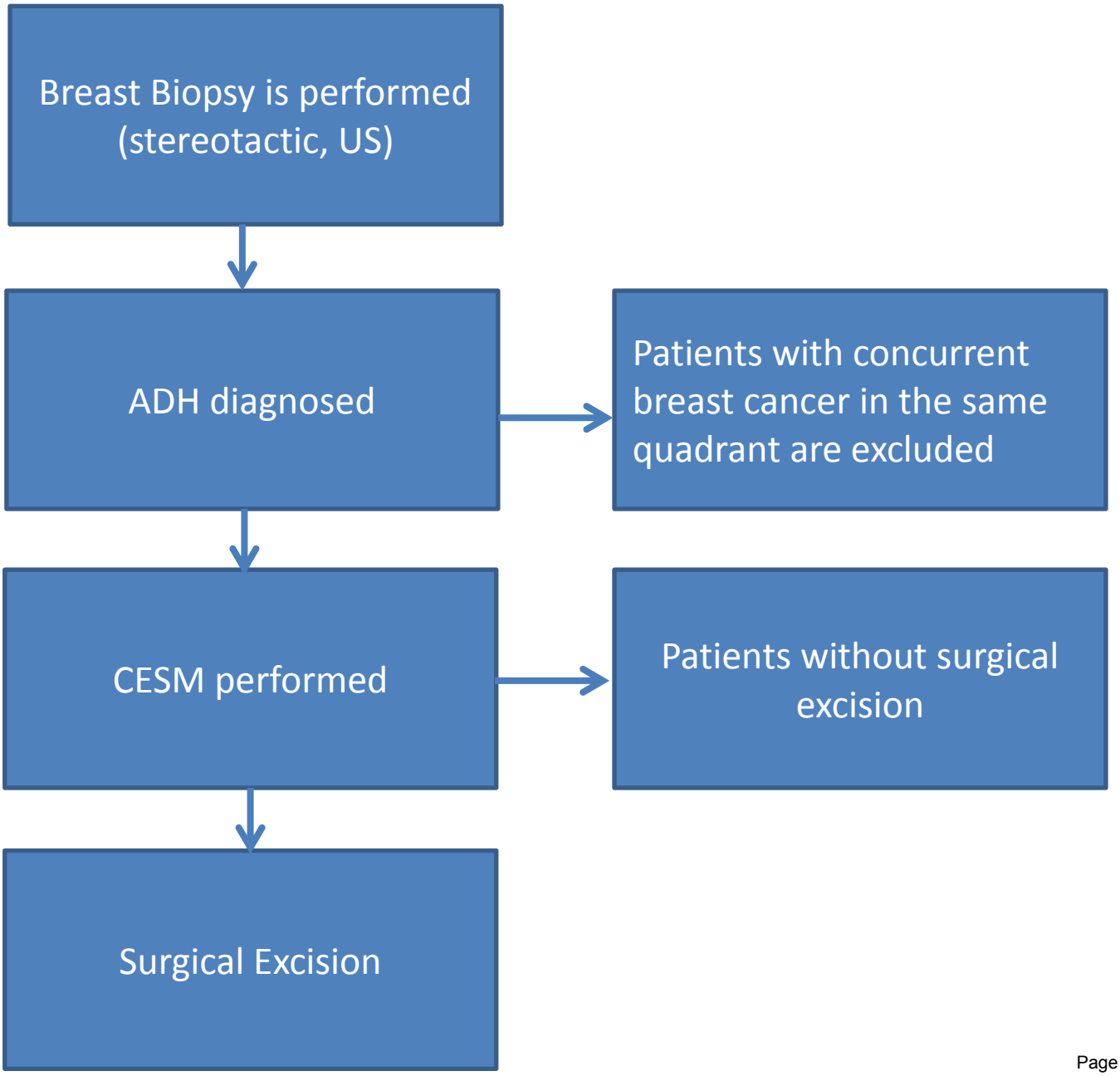

TABLE OF CONTENTS

1. OBJECTIVES

Our study objective is to determine whether contrast enhanced spectral mammography (CESM) can predict which cases of atypical ductal hyperplasia (ADH) diagnosed at core needle biopsy will upgrade to breast malignancy at the time of surgical excision.

Hypothesis: CESM can reliably predict which cases of ADH will upgrade to malignancy at the time of surgical excision.

1.1 Study Design

This is a prospective clinical pilot study evaluating whether CESM can predict upgrade rates to malignancy at the time of surgical excision. All study participants with a diagnosis of ADH on core needle biopsy, who will be getting subsequent surgical excision, will have a CESM prior to surgical excision. CESM outcomes will be compared with the surgical outcomes to determine whether CESM can predict upgrade to malignancy.

Study Population: Women $\geq$ 30 years of age with a diagnosis of ADH identified by ultrasound and stereotactic core biopsy who will be getting subsequent surgical excision will be included in this study.

Recruitment and Enrollment: No formal publicity of the research study will be performed. Subjects will be approached for study participation by a research coordinator after their diagnosis of ADH and completed diagnostic work-up for this diagnosis. Interested subjects will then be enrolled in the study.

Image acquisition: CESM will be performed according to BIDMC clinical protocols for image acquisition. Omnipaque 350 (the standard CT contrast agent) will be used at a dose of 1.5 mL of contrast per kilogram of body weight at an injection rate of 3 mL/second to a maximum in dose of 150 ml. The patient's weight will be confirmed with measurement on a scale by the technologists, as is done in clinical practice, and documented on both clinical forms and case report forms.

Image interpretation: Two radiologists will independently interpret the CESM exam. Radiologists will have access to all the pertinent prior history and routine imaging. Each radiologist will document their interpretation of the biopsy site and up to 2 additional findings per exam using the Breast Imaging-Reporting and Data System (BI-RADS). The radiologist will also provide a BI-RADS code for the overall exam. If there is a discrepancy in interpretation for any finding, then a third radiologist will be the tie-breaker. The description of the site of atypia will be excluded from the clinical report and will be entered into a research note to be included in the online medical record. This will ensure that the surgeon will not be biased by the CESM interpretation of the area of atypia. In addition, all individual and final interpretations will be documented in the case report forms. Incidental findings identified on CESM (defined by >2cm away and distinct from the biopsied mass) will be managed according to standard of care.

Pathology: Two pathologists will review the percutaneous biopsy specimen and the excisional biopsy specimen and provide independent interpretations regarding the presence/absence of

ADH, DCIS, and invasive cancer. If there is disagreement, a third pathology will be the tie-breaker. Final pathology will be recorded on the case report form as well as the online medical record.

Surgical Management: The presumed initial surgical treatment plan will be recorded based on the imaging findings at the time of diagnostic imaging. The final surgical treatment will also be recorded.

1.2 Primary Objectives

To determine whether CESM can predict upgrade rates of biopsy proven ADH at surgical excision

1.3 Secondary Objectives

To evaluate how CESM impacts surgical management of patients diagnosed with ADH

2. BACKGROUND

2.1 Study Disease(s)

Atypical ductal hyperplasia (ADH) is a common pathology result after percutaneous breast biopsy. Although not malignant itself, ADH is viewed as a precursor lesion to breast cancer. The literature reports highly variable upgrade rates of ADH to breast cancer (1-4). As a result, the standard of care is to perform surgical excision on all patients with this diagnosis at biopsy to identify potential cancer.

2.2 Rationale

Preliminary attempts to identify those cases of ADH that will upgrade to cancer using breast MRI has been performed and has shown promise (5-9). CESM is an imaging tool that uses a dual energy technique after contrast administration to identify breast cancer. The exam provides two sets of images for interpretation. One set has the appearance of conventional mammographic images and the other highlights areas of contrast uptake, similar to breast MRI. As a result, a CESM provides information on both morphology/density and vascularity, without the need for breast MRI. This is beneficial as CESM is a lower cost, faster, more universally accessible exam than MRI given that it is an add-on unit to conventional mammography equipment.

Our objective is to perform a preliminary study to determine whether we can predict upgrade of atypia to malignancy using CESM. The results of this study will drive a larger study on the role of CESM in this setting.

3. PARTICIPANT SELECTION

Given that this study involves an FDA approved imaging test that is used in clinical care with a well-established risk profile, and does not involve a therapeutic agent or investigational device, informed consent will be performed by any member of the study team, including the study

coordinator.

3.1 Eligibility Criteria

3.1.1 Women
3.1.2 Age, Minimum 30 years. CESM is an imaging exam that uses radiation and is not typically employed in women younger than age 30 due to potentially negative biologic effects on glandular breast tissue.
3.1.3 Participants who had a percutaneous breast biopsy (to include stereotactic, tomosynthesis, or ultrasound guided) that revealed ADH
3.1.4 Participants will be undergoing surgical excision to remove the ADH.
3.1.5 Participants must have normal organ and marrow function as defined by a GFR ≥60 mL/min/1.73 m^2 to be performed per clinical protocol.

CLINICAL PROCOTOL USED AS REFERENCE FOR THIS STUDY:
(i) Patients ≥65 years without underlying renal insufficiency get GFR tested within 6 months of the exam.

(ii) Patients < 65 years without underlying renal insufficiency do not require an GFR calculation)

(iii) Patients ≥65 years with known underlying renal insufficiency get GFR tested within 1 month of the exam.

(iv) Patients < 65 years with known renal insufficiency get GFR tested within 1 month of the exam.

3.1.6 Because of the potential teratogenic effects of radiation, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, until the CESM is performed. Should a woman become pregnant or suspect she is pregnant, she should inform the study team prior to getting the CESM.
3.1.7 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Participants with a core biopsy diagnosis of atypia with associated malignancy (in the same quadrant) will be excluded.
3.2.2 Participant had a breast MRI that was performed after the diagnosis of ADH but before surgical excision
3.2.3 Participants who have a known allergy to contrast media.
3.2.4 Participants who have a known severe allergic response to one or more allergens, as defined by anaphylaxis.
3.2.5 Participants with persistent asthma as defined by the National Heart, Lung, and Blood Institute.
3.2.6 Participants with renal insufficiency or failure, as determined by a point of care renal function blood test.
3.2.7 Participants who are breastfeeding are excluded because there is an unknown but potential risk for adverse events in nursing infants secondary to contrast administration in the mother.
3.2.8 Participants with the following underlying medical conditions: multiple myeloma, myasthenia gravis, dysproteinemias, severe cardiac disease, aortic stenosis, primary pulmonary hypertension, cardiac arrythmia, or severe cardiomyopathy. These underlying medical conditions may make the participant more likely to develop a contrast reaction. This is based on the ACR contrast manual version 10.3 and hospital policy.
3.2.9 Participants with thyroid carcinoma or thyroid disease for whom systemic radioactive iodine therapy is part of planned diagnostic work-up or treatment within 2 months following the contrast mammogram study.
3.2.10 Participants with a concurrent active illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, thyroid storm.
3.2.11 Pregnant women are excluded from this study because CESM uses radiation with the potential for teratogenic or abortifacient effects. This will be defined by a urine pregnancy test prior to the CESM study.

3.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5. TREATMENT AND/OR IMAGING PLAN

The CESM exam will be performed according to clinical protocol. Omnipaque 350 (the standard CT contrast agent) will be administered at a dose of 1.5 mL of contrast per kilogram of body weight at an injection rate of 3 mL/second, according to clinical protocol. Images will be acquired within approximately 2-12 minutes of contrast injection. A low energy and high energy image will be acquired of each breast in two projections for a total of four images per breast. The voltage will be based on breast tissue thickness and will conform to the Mammography Quality Standards Act guidelines for quality control. The total radiation dose of CESM has been shown to be approximately 20-80% greater than the dose of a standard mammogram (11,12). Please see 1.1 above for the detailed study design.

A clinical report will be generated and entered into the online medical record. The description of the site of atypia will be excluded from the clinical report and will be entered into a research note to be included in the online medical record. This will ensure that the surgeon will not be biased by the CESM interpretation of the area of atypia.

All incidental areas identified on the CESM study (>2cm away and distinct from the biopsied mass) will be managed according to standard of care.

5.1 Pre-Treatment Criteria

5.1.1 GFR ≥60 per the clinical protocol. If a GFR is not available, then a point of care renal function test will be performed and reviewed on the day of the exam before the patient receives the CESM.

5.1.2 Negative urine pregnancy test. If the patient is of child-bearing potential, then this will be performed and reviewed on the day of the CESM before the patient receives the exam.

5.2 Duration of Follow Up

Participants will be followed until they have surgical excision for their ADH. No additional follow-up will subsequently be performed unless clinically indicated.

The de-identified imaging data may be used for future undefined research. This has been included in the informed consent document.

5.3 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- If surgical excision is not performed within 2 years of the study.
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. Given that the contrast mammogram will be acquired according to standard of care technique without alterations in duration, contrast agent, or contrast type and given that the AE profile for this imaging exam is well established, we will not be capturing AEs for the purposes of analysis. We intend to only capture AEs for those patients who initiate phone calls to our department. Should a patient contact the research team, the PI or co-investigator will evaluate and decide the best management, to include referring patient to the primary care physician for further management or sending patient to the emergency department.

The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

6.1 Expected Toxicities

6.1.1 Adverse Event List(s) for contrast mammogram

Risk of toxicity is related to the contrast agent that is administered during the imaging exam. Risks include allergic, allergic-like, or physiologic type of reaction to the contrast agent. There is also the risk for contrast induced nephropathy.

Risk of toxicity is also related to the risk of biologic harm from radiation administered during the exam. However, this risk is non-measurable during the course of this study.

6.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

6.3 Expedited Adverse Event Reporting

6.3.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

6.3.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

6.4 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

6.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

7. IMAGING AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

8. STUDY CALENDAR

	Visit 1[a]
	Screening & exam
Informed Consent	X
Medical History	X
Urine pregnancy Test	X[b]
Blood Test	X[b]
Contrast Mammogram	X

[a] If abnormal findings are detected on the contrast mammogram, there is the potential that additional standard of care tests and procedures will need to be performed. These may occur on the same day of the contrast mammogram or at a later date.
[b] Blood and urine samples will be taken if standard of care samples are not available.

9. MEASUREMENT OF EFFECT

9.1.1 Methods for Evaluation of Disease on Conventional mammography, ultrasound

Two radiologists will retrospectively and independently review the pre-biopsy mammogram and ultrasound that had been performed for clinical purposes. They will each provide a BI-RADS code of the biopsied area based on the combined assessment of the relevant pre-biopsy imaging. If there is a discrepancy in interpretation, then a third radiologist will be the tie-breaker.

9.1.2 Methods for Evaluation of Disease on CESM

Two radiologists will prospectively review the CESM, and will use a third as tie-breaker. The CESM will be evaluated for the biopsy site and up to two additional findings in either breast. The biopsy site will be evaluated for abnormal findings that would suggest malignant involvement such as abnormal enhancement around the biopsy site, abnormal calcifications or masses. The result of the consensus will be documented in the clinical

report.

All measurements should be taken and recorded in metric notation using a digital measurement tool. A BI-RADS code will be assigned to each finding. This code provides a probability of malignancy score as well as a management recommendation.

9.1.3 Methods for Evaluation of Disease on Pathology

Each biopsy and surgical excision specimen will be reviewed by two pathologists independently to determine the presence of malignancy. If there is a discrepancy, then a third pathologist will be the tie-breaker.

9.2 Other Response Parameters

9.2.1 Methods for Evaluation of Impact on Surgical Management
The treatment plan that would be recommended based on imaging at the time of ADH diagnosis will be documented on a CRF form. This will be compared with the final treatment plan that is created after the CESM study is performed. Included in this evaluation will be a description of additional procedures initiated by the CESM exam. This will include the number of false positive and true positive additional biopsies, additional surgical procedures, and additional department visits.

10. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

10.1 Data Reporting

10.1.1 Method

Patients will be registered in the Oncore system. Study patient data will be captured in an institutional RedCap system designed and maintained by the study team.

10.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths

while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

11. STATISTICAL CONSIDERATIONS

This is a pilot study in which patients with a diagnosis of ADH on percutaneous biopsy will have a CESM prior to surgical excision to determine whether CESM can predict upgrade of atypia to malignancy.

Based on the literature of breast MRI, which we assume to have similar performance to CESM, we would need 130-150 patients to show that the false negative rate is less than 3% with 95% confidence to allow CESM to be used for this indication in clinical practice. Given the limitations of recruiting that number of patients, and the absence of any data on this topic for CESM, a decision was made to do a pilot study to first determine whether CESM can distinguish between benign and malignant pathology.

Therefore:
Null hypothesis: the proportion of patients with positive CESM findings is the same in the malignant and benign groups;

The alternative hypothesis is that the proportion of patients with positive CESM findings is different in the malignant and benign groups (two-tailed hypothesis).

11.1 Study Design/Endpoints

The primary outcome will be whether the biopsy site on CESM is coded as benign or malignant and how that correlates with the pathologic diagnosis of the surgically excised specimen, as benign or malignant.

The biopsy site and up to 2 additional findings will be coded according to the Breast Imaging-Reporting and Data System (BI-RADS), ranging from 1-5. An overall code for each exam will then be generated that corresponds to the most suspicious finding in the study. BI-RADS codes 1, 2, and 3 associated with the corresponding categories of negative, benign findings, and probably benign findings will be classified as negative (benign). BI-RADS codes 4 and 5 associated with the corresponding categories of suspicious and highly suspicious for malignancy will be classified as positive (malignant).

Negative truth is defined by a benign diagnosis by the final outcome of pathologic review. Positive truth is defined by a malignant diagnosis (ductal carcinoma in situ and invasive caner) by the final outcome of pathologic review.

The secondary outcome will be to understand the impact of CESM for ADH evaluation on surgical management. The pre-CESM and post-CESM final surgical management plans will be compared descriptively.

11.2 Sample Size, Accrual Rate and Study Duration

For the primary outcome:
The expected group sizes for 0.05 significance level and 0.9 power, assuming sensitivity of 0.9 and specificity of 0.8 (based on aggregate data from multiple studies in the literature, references 6-10), and 0.2 incidence rate (20% of cases becoming malignant in the sample based on data from our clinical practice), suggest 6 patients in the malignant group, 5.5 of whom are expected to have positive CESM findings, and 24 patients in the benign group, 5 of whom are expected to have positive CESM findings.

Given that we identify 60 number of atypia per year and expect 30% enrollment, we expect recruitment to be approximately 1.5 years.

Although we will be calculating CESM's performance characteristics (including sensitivity, specificity, positive predictive value, negative predictive value, and false negative rate), we will not be using these performance characteristics as primary objectives in our study as the number of participants involved is too small to draw significant conclusions.

For the secondary outcome: This is exploratory and descriptive statistics will be used to evaluate the impact of CESM on surgical management of ADH.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	5	+		=	
Not Hispanic or Latino	25	+		=	
Ethnic Category: Total of all subjects	30 (A1)	+	(B1)	=	(C1)
Racial Category					
American Indian or Alaskan Native	0	+		=	
Asian	5	+		=	
Black or African American	12	+		=	
Native Hawaiian or other Pacific Islander	0	+		=	
White	13	+		=	
Racial Category: Total of all subjects	(A2)	+	(B2)	=	(C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

11.3 Interim Monitoring Plan

There are no plans to conduct interim monitoring unless requested by the DSMC (see section 11.2).

11.4 Analysis of Primary Endpoints

See sections 11.1 and 11.2

11.5 Analysis of Secondary Endpoints

See sections 11.1 and 11.2

12. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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