NYU Langone Health

Official Title:	SpotCheck: Comparison of Enhanced Telemedicine Versus In-person Evaluation for the Diagnosis of Skin Cancer
NCT Number:	NCT04411810
Study Number:	19-01242
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	• September 13, 2022

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

SPOTCHECK: COMPARISON OF ENHANCED TELEMEDICINE VERSUS IN-PERSON EVALUATION FOR THE DIAGNOSIS OF SKIN CANCER: A PILOT, PROOF-OF-CONCEPT STUDY

Principal Investigator:	*David Polsky, MD, PhD* *Dermatology* *522 First Avenue, SML-404* *New York, NY 10016* *David.polsky@nyulmc.org* *212-263-9087*
Additional Investigators:	*Tracey Liebman, MD, FAAD* *Dermatology* *240 38th Street, Eleventh Floor* *New York, NY 10016* *Tracey.liebman@nyumc.org* *212-263-5015* *Jennifer Stein, MD* *Dermatology* *240 38th Street, Eleventh Floor* *New York, NY 10016* *Jennifer.Stein@nyumc.org* *212-263-5889* *Yongzhao Shao, PhD* *Population Health* *650 First Avenue, Fifth Floor* *New York, NY 10016* *Yongzhao.Shao@nyulangone.org* *212-263-0324*
NYULMC Study Number:	s19-01242
Supporting Grants:	*Melanoma Research Alliance, Zlinkoff Fund for Medical Research*
IND/IDE Number:	*Approved investigational device*
Study Product Provider:	*Scibase (Nevisense provider)*

Initial version: October 10, 2019
Amended: March 6, 2020
Amended: August 10, 2020
Amended: September 28, 2020
Amended: December 29, 2020
Amended: May 05, 2021
Amended: June 24, 2021
Amended: November 1, 2021

Amended April 13, 2022

Amended: May 16, 2022

Amended: August 17, 2022

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Table of Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DCSU	Department of Dermatology Clinical Trials Unit
EIS	Electrical Impedance Spectroscopy (EIS)
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MOP	Manual of Procedures
NYU	New York University
NYULMC	New York University Langone Medical Center
NIH	National Institutes of Health
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

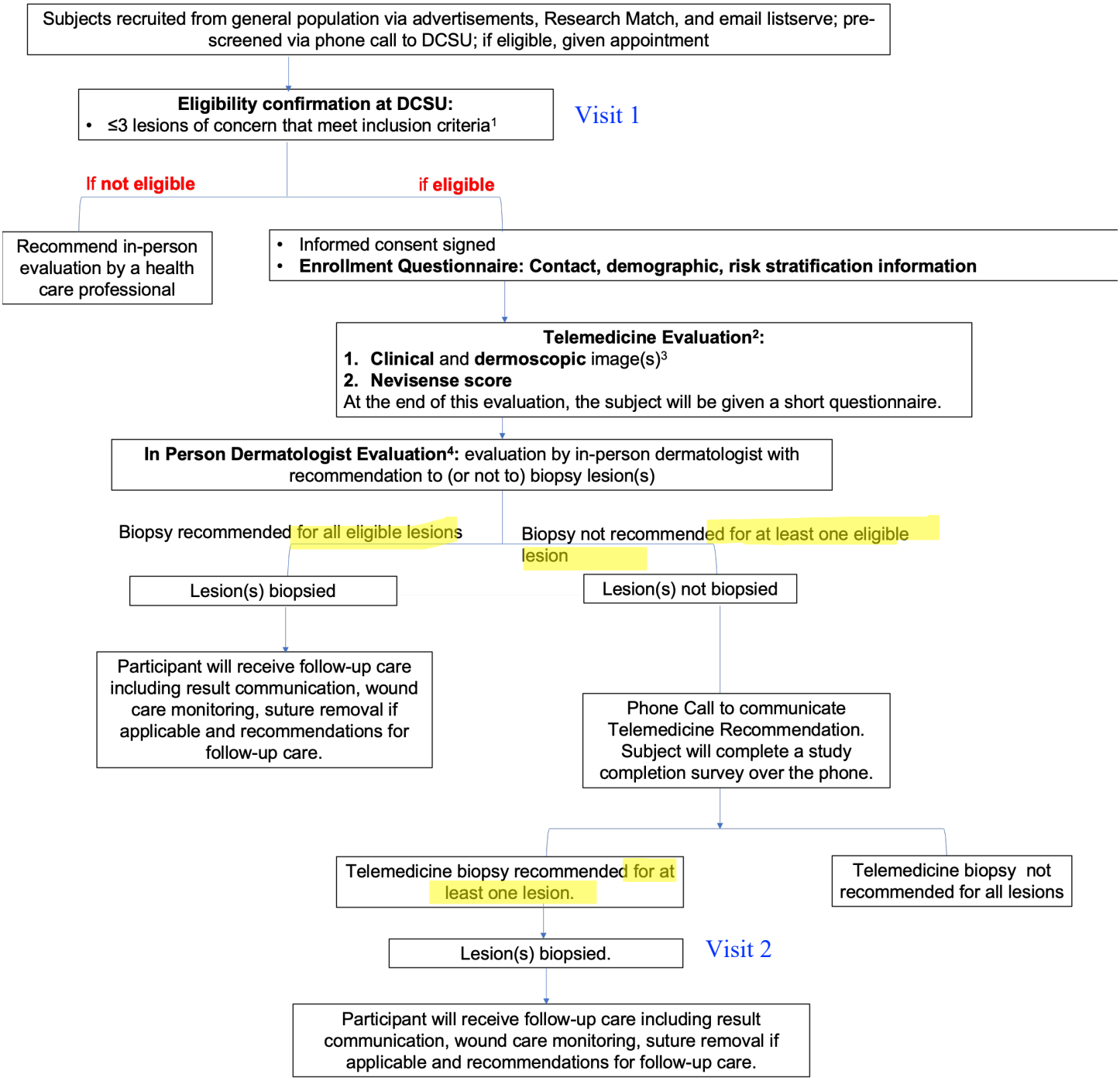
Protocol Summary

Title	SpotCheck: Comparison of enhanced telemedicine versus in-person evaluation for the diagnosis of skin cancer
Brief Summary	The aim of this pilot is to test a novel, telemedicine-based skin cancer diagnostic platform (SpotCheck) that has the potential to improve access to needed dermatologic care for those living in medically underserved areas. In this study we will recruit participants with 1-3 skin lesions concerning for skin cancer. Each concerning lesion will be evaluated by an enhanced telemedicine method using clinical images, a dermoscopic image, and a measurement by Nevisense, a low-cost skin cancer diagnostic device currently FDA-cleared for use in dermatologists' offices. Each subject will also be evaluated in-person by a clinical dermatologist with dermoscopy so the accuracy of the telemedicine diagnosis can be compared to the current gold standard. This pilot project will assess both diagnostic congruence and patient-centered outcomes regarding this service, which will provide preliminary data for larger follow up studies, including those in medically underserved areas.
Phase	Pilot Proof of Concept Study
Objectives	Aim 1: Determine the agreement between in-person and teledermatologist evaluations of concerning skin lesions identified by participants in a walk-in clinic setting Aim 2: Determine the degree to which the enhanced telemedicine method addresses patient needs and preferences (i.e. patient-centered outcomes)
Methodology	Prospective single arm study of a diagnostic intervention against the gold standard dermatological care, singly blinded to diagnosticians.
Endpoint	Primary endpoint: Congruency between biopsy recommendation of enhanced telemedicine evaluation and in-person dermatology evaluation Secondary endpoints: 1) Specificity, sensitivity, false-positive rate, false-negative rate, positive predictive value, and negative predictive value of enhanced telemedicine evaluation and in-person evaluation to diagnose skin cancer; 2)Participant satisfaction of intervention in addressing patient centered outcomes
Study Duration	Study is estimated to be open for 24 months or longer to be sufficiently powered
Participant Duration	Estimated duration is one to four weeks subject to participant's findings
Duration of IP administration	Clinical and dermoscopic image acquisition for teledermatologist evaluation will take <2 minutes per lesions, and Nevisense data acquisition will take <2 minutes per lesion
Population	At least 18 years of age Females and Males
Study Sites	NYU School of Medicine The Ronald O. Perelman Department of Dermatology Ambulatory Care Center Dermatology Clinical Trials Unit 240 East 38th Street, 12th Floor, New York, NY 10016
Number of participants	650 enrolled participants
Description of Study Agent/Procedure	Telemedicine evaluation using combined dermoscopic imaging with Dermlite Cam (3Gen) and/or Barco Demetra and electrical impedance spectroscopy using Nevisense 3.0
Reference Therapy	In-person dermatologist evaluation

This material is the property of the NYU School of Medicine and Langone Medical Center. Do not disclose or use except as authorized in writing by the study sponsor

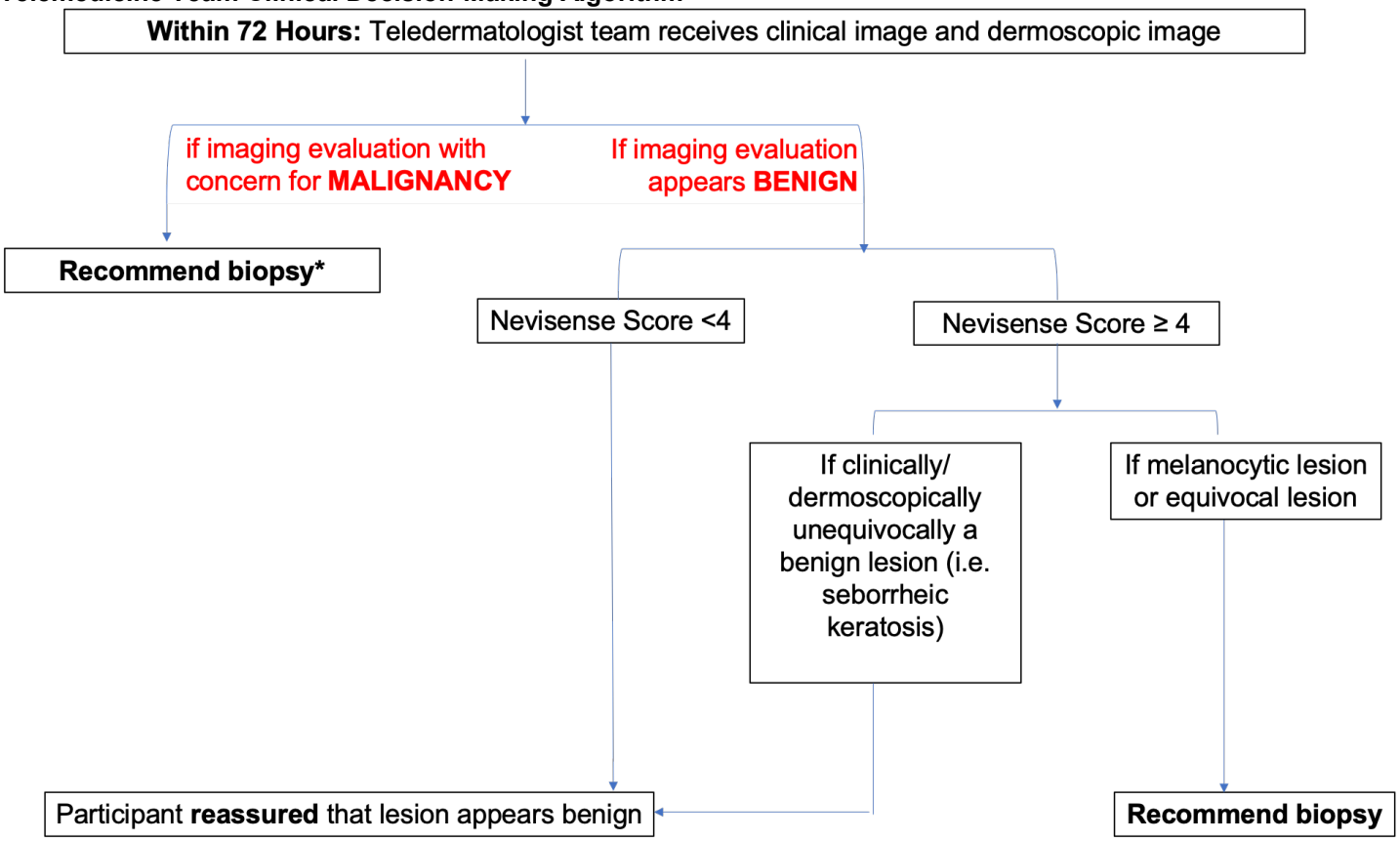
Key Procedures	Clinical and dermoscopic imaging of skin lesions, Nevisense measurement of skin lesion electrical impedance. Possible skin biopsy for lesion(s) identified as concerning for malignancy
Statistical Analysis	Percent agreement of biopsy recommendation in diagnostic intervention compared to control. For biopsied lesions, sensitivity and specificity of in-person dermatologist and teledermatologist evaluation for skin cancer diagnosis will also be determined. Success by patient centered outcomes will be analyzed by questionnaires using Likert scales.

Schematic of Study Design



1. Lesions must not be in a hair-bearing area on the scalp, in the mouth, on the lips, genitalia, nails, around/on the eyes, inside ear.
2. All lesions of all subjects will be evaluated by teledermatologist team. If at least one of three possible lesions was not recommended for biopsy by the in-person dermatologist, this subject will receive a telemedicine consensus recommendation report to (or not to) biopsy within 3 business days of participant evaluation. If all eligible lesions were recommended for biopsy by the in-person dermatologist, this subject will not receive the telemedicine evaluation report.
3. The following lesions will have clinical and dermoscopic image taken, but will not have a Nevisense score: Lesions on an acral site, lesions with recurrence after biopsy/excision, lesions in a scar, lesions with foreign material (e.g. tattoo, splinter, etc), lesions in an area of active sunburn, lesions on a stalk, lesions with crust. Bleeding or ulcerated lesions are will only have a clinical image taken (no dermoscopic or Nevisense score).
4. Current gold standard evaluation for skin lesion of concern. For subjects with more than 1 lesion evaluated, they may have 1 or more recommended for biopsy by the in-person dermatologist (or equally 1 or more recommended for no biopsy by the in-person dermatologist).

Telemedicine Team Clinical Decision-Making Algorithm



*Teledermoscopist will be given Nevisense data to assess impact of Nevisense score on decision to biopsy, however, if imaging concerning for malignancy, biopsy will always be recommended given that this device is being used in an investigational setting.

1 Key Roles

Dr. Yongshao Shao (biostatistician) will not be engaged in the research (i.e. will not be interacting with subjects nor have access to identifiable subject information).

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Recognition and diagnosis of early stage melanomas is associated with ≥98% 10-year survival for tumors <0.8mm in thickness. In contrast, more advanced stages have 10-year survivals ranging between 94% - 75% for localized disease, and much lower rates for regional and distant metastatic disease[1]. Nearly all patients diagnosed with early stage disease are cured surgically. Besides exhibiting reduced mortality, these patients experience less complicated and less costly care, and will not be exposed to the potential toxicities of the new systemic therapies for advanced disease[2].

Associations between access to healthcare and cancer health outcomes are well established. In melanoma, several studies reveal that populations with lower socioeconomic levels, decreased physician supply, and increased distance to a diagnosing provider are diagnosed with more advanced stage disease than populations with better access[3]. There is a need to reduce the barriers to access for diagnostic services when patients have a skin lesion of concern, especially in areas of decreased physician supply. In areas with ample physician supply, however, many benign growths are unnecessarily removed out of concern for melanoma because most providers do not use modern technologies to augment their diagnostic skills. Dermoscopy, which is a non-invasive, 10x magnification technique to visualize skin structures and colors not visible to the naked eye, improves diagnostic accuracy and thus decreases ratios of benign-to-malignant biopsy excisions[4].

Over the last several years, store-and-forward telemedicine technology has advanced, enabling expert diagnostic services to be provided to areas of low physician supply by providing images to providers working remotely. A recent Cochrane Review of store-and-forward teledermoscopy studies noted that these technologies are likely to appropriately triage lesions for in-person assessment by a health care provider[5].

The long-term goal of this project is to reduce poor melanoma outcomes among underserved communities by delivering state-of-the-art diagnostic expertise to these neighborhoods via telemedicine. In the proposed pilot study, we plan to model a walk-in clinic, like the CVS Minute Clinic, in the NYU Dermatology Clinical Studies Unit (DCSU). We will test the effectiveness of an enhanced teledermatology service to accurately evaluate up to 3 self-identified skin lesions of concern per member of the general public. In addition to obtaining clinical and dermoscopic images of the skin lesions, we will enhance the evaluation with a Nevisense device. Nevisense, which uses a small hand-held probe and electrical impedance spectroscopy (EIS), received FDA clearance (PMA) in 2017 “for use on cutaneous lesions with one or more clinical or historical characteristics of melanoma, when a dermatologist chooses to obtain additional information when considering biopsy”[7]. The validation study showed a sensitivity of 97% and specificity of 34% for the diagnosis of melanoma. The negative predictive value, important for a screening tool, was 98%[8]. Importantly, the lesions in this study were preselected by dermatologists. It is known that Nevisense can deliver false positive results for common benign skin lesions that are likely to be encountered frequently in a walk-in clinic setting. These lesions are easily diagnosed using teledermoscopy, so we will investigate whether the combined dermoscopic and Nevisense evaluation will have a higher sensitivity and specificity than either technique alone, and will be comparable to, or potentially more accurate than, an in-person evaluation by a clinical dermatologist. A similar service is available in Norway through ScreenCancer (www.screencancer.com). The Norwegian pharmacies use a dermatologist review of computer-enhanced dermoscopy images without Nevisense. Between 2010-2014, they conducted 25,836 scans in 109 pharmacies, recommended biopsies of 8% of lesions, and diagnosed 154 melanomas. In 2014, they diagnosed 4% of all Norwegian melanoma cases[9]. These results demonstrate the potential of our SpotCheck platform to improve the outcomes of melanoma patients, especially those with fair skin residing in medically underserved communities.

The overall goal of this research is to develop a platform that can increase patient access to expert skin cancer diagnostic services via telemedicine. This is especially important for medically underserved areas where melanoma outcomes are worse than in areas with greater access to in-person evaluations. If successful, the widespread availability of such services would be combined with public education efforts to encourage individuals with changing skin lesions to seek evaluation. With decreased travel times to high quality diagnostic services, such efforts may decrease the diagnosis of more advanced melanomas (with a concomitant increase in the diagnosis of earlier stage tumors), and potentially decrease melanoma mortality.

2.2 Name and Description of the Investigational Agent

The investigational agent is the combined use of clinical images, dermoscopic imaging with Dermlite Cam (3Gen) and/or the Barco Demetra and electrical impedance spectroscopy using Nevisense 3.0 (Scibase) for the purpose of a telemedicine evaluation.

Clinical images for the purpose of teledermatology will be captured with a study specific camera or through the use of Epic Haiku which is an application that can be downloaded onto NYU approved electronic mobile devices to capture clinical images. The images are directly imported into the patient's medical record, without being stored on the device itself. The clinical images stored in EPIC EMR patient medical record will include a research note detailing the location of each lesion and 3 photos of each lesion at various distances, approximately 6 inches, 12 inches, and 18 inches from the lesion. Dermlite Cam is a digital camera that captures images of the skin under cross-polarized and non-polarized light and is 510(k) exempt.

The Barco Demetra is a non-invasive skin imaging system, which acquires multispectral and white light dermoscopic images and clinical photographs of the skin which can then be stored, retrieved, displayed, and reviewed by trained medical practitioners. The Barco Demetra received 510(k) Premarket approval (510(K) Number: K192829). The 510(k) Premarket Approval can be found in Supplement V. The 510(k) Summary can be found in Supplement W. This device is intended to be used in a normal working environment of medical practitioners examining skin conditions. The Demetra system involves a hardware imaging device and a stand-alone software application. The hardware device is a portable, battery-powered medical device for acquiring and visualizing images of the skin and uploads all images to cloud storage. The software application is cloud software with an associated web application, and this software can be used to visualize images and related data and can generate consultation reports. For the purposes of teledermatology, dermoscopic and clinical photographs (at approximately 6 inches, 12 inches, and 18 inches) will be taken using the Barco Demetra.

Nevisense 3.0 measures electrical impedance of skin lesions and provides an output called the electrical impedence spectroscopy (EIS) score. Electrical impedance is a measure of a material's overall resistance to the flow of alternating electric currents of various frequencies. The principle is that electrical impedance is different in normal versus abnormal tissue. An earlier version, Nevisense 2.0 received premarket approval (PMA) status from the FDA (PMA Number: P150046). The Summary of Safety and Effectiveness of this device is attached in Supplement A. The Administration and Service Instructions is listed as Supplement B. The pivotal study was conducted under IDE #G090108. This device is indicated for use on cutaneous lesions with characteristics of melanoma when a dermatologist chooses to obtain additional information when considering biopsy. However, Nevisense 2.0 will not be used in this research study. Rather, Nevisense 3.0 will be used. Nevisense 3.0 has an updated software that no longer requires a reference non-lesion skin area measurement and has higher specificity as compared to Nevisense 2.0. There is no change in the hardware. Nevisense 3.0 received t FDA approval in April 2020. We will be using Nevisense 3.0 due to the added advantage of saving time and its enhanced diagnostic performance. Any risk of the unapproved Nevisense 3.0 device will be mitigated by the fact that other diagnostic tools will be used on every lesion of concern (clinical images and dermoscopic images) and the fact that each concerning lesion will be assessed by an in-person dermatologist, the current gold standard for diagnostic evaluation. Any data collected as part of this study will not be used in support of this PMA supplement or amendment.

2.2.1 Clinical Data to Date

The largest prospective study, which formed the basis of the FDA PMA, showed that among lesions pre-screened by a dermatologist, EIS has the ability to distinguish between benign lesions and melanoma with a sensitivity of 97% and a specificity of 34%[8]. The same study also showed that as compared to dermoscopic examination alone, EIS showed superior sensitivity but not specificity[8]. Prior studies also demonstrate the EIS technology to have a lower false negative rate when compared to the 'gold standard' of skin cancer screening using visual inspection plus dermoscopy.[10] A more recent study showed that Nevisense can be a useful tool to help guide decision-making for clinically atypical nevi with low/intermediate-level concern for early stage melanoma that would otherwise qualify for three-month sequential dermoscopic imaging/monitoring. This technique is typically employed in patients with multiple atypical nevi. The combined use of Nevisense and dermoscopic monitoring for changes over a 3-month period for these lesions demonstrated a sensitivity of 100% and specificity of 69%.[11] The high sensitivity and reasonable specificity make it an ideal tool to augment screening examinations. Notably all studies with Nevisense have required lesions to be pre-screened as suspicious for melanoma by dermatologists. Of note, although the study was designed to measure the performance of Nevisense in diagnosing melanoma, it correctly identified 100% of 55 non-melanoma skin cancers (e.g. basal cell carcinoma, etc.).

2.3 Rationale

Detection of melanoma at its earliest stages is associated with high surgical cure rates, without the need for additional, potentially toxic and expensive systemic therapies. Rural and other medically underserved communities have higher rates of melanoma mortality that is associated with reduced access to dermatologic diagnostic services. We aim to study the effectiveness of an augmented telemedicine diagnostic platform for melanoma and other skin cancers that can potentially be deployed in pharmacies and urgent care centers that would be more available in rural communities than dermatologist offices.

The study will evaluate participant-selected lesions of adults in the New York City metropolitan area to simulate the walk-in clinic or pharmacy community setting. The control is an in-person evaluation by a community dermatologist, the current gold

standard. We aim to assess the sensitivity and specificity of the platform compared to the in-person dermatological examination in the diagnosis of melanoma and other skin cancers. Since the Nevisense evaluation is one component of the platform, and the current FDA approval is for it to be used in dermatologist offices to aid in biopsy decisions, we will also examine the degree to which teledermatologists can use the clinical and dermoscopy images to evaluate whether each study lesion would have been appropriate for the Nevisense evaluation had they seen the patient in-person. Finally, we will examine whether the combined teledermoscopy/clinical images plus Nevisense will have greater sensitivity and specificity to diagnose melanoma and other skin cancers than either approach alone.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

All subjects will have Nevisense EIS measurements for each skin lesion included in the study. Nevisense 3.0 is a non-significant risk device. It is ***not*** intended as an implant and **does *not*** present a potential for serious risk to the health, safety, or welfare of a subject. Is ***not*** purported or represented to be for a use in supporting or sustaining human life and does ***not*** present a potential for serious risk to the health, safety, or welfare of a subject, is ***not*** for a use of substantial importance in curing, mitigating, or treating disease and **does *not*** present a potential for serious risk to the health, safety, or welfare of a subject.

In data presented to the FDA, 1.5% of study participants experienced an adverse event. Most of these events (33/36) were mild in severity. Three events that qualified as moderate or severe were deemed to be unrelated to the device. Mild events that may or may not have been related to the device included bleeding during measurement, itching at the measurement site, pain, soreness, bruising, slight tingling, or headache. Nevisense safety information is outlined in its instructions for use and can be found in detail in Supplement C.

We estimate that approximately 10% of subjects will undergo skin biopsy. This is the gold standard diagnostic test for skin lesions deemed suspicious for cancer. Immediate physical risk is involved for participants undergoing skin biopsy, which includes bleeding, irritation, bruising, allergic reaction to topic antibiotic or adhesive, possible infection, need for repeat biopsy if the initial biopsy is non-diagnostic, and/or wound dehiscence. Long-term physical risk includes scarring at the site of biopsy. Immediate psychological risk may include mood changes that are anxious or depressive in nature from the possibility of a lesion suspicious of melanoma. Immediate economic risk may include parking and transportation fees to allow for the clinical visits, and obtaining treatment of possible skin cancer(s) that may be identified during this study. We do not anticipate long-term physiological, social, legal, economic or other risks as a result of the participation in the study. The value of early detection of melanoma and its attendant increased survival supersedes the minor risks anticipated in the study. Alternative to skin biopsy is observation for change, which would only be appropriate in a medical office, and not a pharmacy setting. Observation runs the risk of tumor growth, diagnosis of melanoma at a later stage, and worse prognosis.

2.4.2 Known Potential Benefits

Study subjects will have up to three lesions of concern screened by a dermatologist for skin cancer at no cost. We anticipate participation in the study to offer immediate and long-term psychological benefit for subjects who have benign lesions and who receive reassurance. We estimate ~90% of subjects will have lesions not requiring biopsy and will receive such reassurance. Of the remaining subjects, it is likely that 8% will undergo a biopsy and receive a benign diagnosis, which will also be reassuring.

For subjects who are found to have malignant diagnoses (~2%), we anticipate substantial long-term physical, psychological, and economic benefit from this free screening service. These subjects would benefit from earlier detection of a malignancy that otherwise may have gone un-diagnosed. Inevitably the potential for early detection of melanoma or other skin cancers is associated with less costly treatment and less complicated care, decreased morbidity and mortality and overall improved outcomes.

3 Objectives and Purpose

3.1 Primary Objective

The primary objective of the study is to assess the concordance in biopsy recommendations between the in-person dermatologist evaluation and the enhanced telemedicine evaluation of participant-identified skin lesions concerning for skin cancer in a walk-in clinic setting.

3.2 Secondary Objectives

1. To compare the diagnostic accuracy of the enhanced telemedicine method, and its separate individual components (Nevisense, teledermoscopy), to the in-person dermatologist with respect to the diagnosis of skin cancer (confirmed histopathologically).

i. At the conclusion of the study, and as an additional control, the in-person dermatologist will review the enhanced telemedicine data to compare her in-person diagnoses with diagnoses she would have provided had she been functioning as the teledermatologist.

2. To assess patient satisfaction and preferences (patient-centered outcomes) regarding the teledermatologist evaluation for skin lesions suspicious for skin cancer
3. To determine the proportion of participant-selected skin lesions for which the Nevisense measurement would be considered appropriate by the in-person and teledermatologists.
4. To create a database of dermoscopic images and Nevisense scores of the benign and malignant skin lesions encountered in the walk-in clinic setting.

4 Study Design and Endpoints

4.1 Description of Study Design

4.2 This is a prospective pilot study of a store-and-forward telemedicine diagnostic assessment of participant-selected skin lesions concerning for skin cancer, controlled against an in-person dermatologist assessment (gold standard evaluation). The study will be a single arm design with each participant undergoing telemedicine data acquisition (i.e. clinical and dermoscopic imaging and Nevisense measurement), immediately followed by the in-person dermatologist assessment. The in-person dermatologist will be blinded to the Nevisense score at the time of the visit. Using the telemedicine data, the teledermatology team will render a biopsy/no-biopsy recommendation within 3 business days of the participant evaluation. They will be blinded to the results of the in-person dermatologist's diagnostic evaluation. Study Endpoints

4.2.1 Primary Study Endpoints

The primary endpoint is the agreement in the biopsy/no biopsy recommendations between the teledermatology team using the telemedicine data and the in-person dermatologist. We will report a biopsy sensitivity and specificity based on the in-person evaluation as the gold-standard. The primary objective of the study is to describe the discrepancy between the telemedicine diagnostic evaluations and the in-person dermatologist evaluation for the assessment of participant-identified skin lesions concerning for skin cancer.

4.2.2 Secondary Study Endpoints

Secondary endpoints include:

1. The performance metrics of the telemedicine system in diagnosing skin cancer. We will calculate the sensitivity, specificity, positive and negative predictive values of the telemedicine system and the in-person dermatologist. We will also separately calculate those metrics for the individual components of the telemedicine system, namely, the teledermoscopy imaging and the Nevisense measurement.
2. The satisfaction of the participants with the telemedicine evaluation. This endpoint, based on questionnaire responses, will contribute to achieving the secondary objective of determining the degree to which the telemedicine system would satisfy patient needs and preferences.
3. The proportion of lesions for which the Nevisense evaluation would be considered appropriate and helpful in arriving at the final biopsy recommendation. This endpoint will help achieve the secondary objective of determining the usefulness of Nevisense in the evaluation of participant-selected lesions concerning for skin cancer.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Be 18 years of age or older
2. Have 1-3 lesions for evaluation
3. Fluent in English language

Please note that the study will employ 2 diagnostic modalities: 1) clinical images (via photos of varying distances for each lesion uploaded to Epic EMR) and dermoscopic imaging via dermoscopic photos captured with the DermLite Cam and/or the Barco Demetra ; and 2) EIS as determined by the Nevisense device. We anticipate that subjects will present with skin lesions that do not meet the inclusion criteria for Nevisense (described in Section 6.1.4) but are suitable for clinical and dermoscopic imaging. For example, the original investigational studies with Nevisense 2.0 did not include large numbers of individuals from ages 18-30 or Fitzpatrick skin types 5-6, and thus safety and effectiveness has not been well established in these groups. While the FDA PMA has cautioned the use of Nevisense for diagnostic purposes in these patients, there is no contraindication to use in these populations. Any potential risk from using this device in these populations will be

mitigated by the fact that other diagnostic tools will be used on every lesion of concern (clinical images and dermoscopic images) and the fact that each concerning lesion will be assessed by an in-person dermatologist, the current gold standard for diagnostic evaluation.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Lesions of the hair-bearing scalp, in the mouth, on the lips, genitalia, nails, on/around the eyes, inside the ear, which contain foreign matter
- Lesions that were previously biopsied
- Pregnant women, children, fetuses, neonates and prisoners are not included in the study
- Nevisense device exclusion **(photos will be taken and dermatologist exam will be conducted but no Nevisense device measurements will be attempted):**
    a. primary skin lesions with a diameter greater than 20 mm;
    b. lesions where the skin is ulcerated or bleeding lesions;
    c. lesions that contain a scar or fibrosis consistent with previous trauma;
    d. lesions located in areas of psoriasis, eczema, acute sunburn or similar skin conditions;

5.3 Vulnerable Subjects

Pregnant women, children, fetuses, neonates and prisoners are not included in the study. The elderly are included in the study as they are at particular risk for melanoma and the devices used in the evaluation do not pose significant risks, and the risks of skin biopsy (should they be recommended) are minimal.

5.4 Strategies for Recruitment and Retention

Recruitment of study participants will be from advertisements in local newspapers (e.g., the New York Post, Daily News) and with social media virtual publications on Facebook and Instagram. The advertisement includes general information about the clinical trial and eligibility criteria, the Dermatology Clinical Studies Unit phone number, and a QR code that interested participants will be able to scan using their mobile devices. The QR code will link to the clinicaltrials.med.nyu.edu page that states more detailed information about the investigative approach and the study team as well as an online form to contact the study team. We will also work with the Perlmutter Cancer Center to advertise the study to individuals on their lists. Please find the advertisements intended for publication as Supplement D and E. Additionally, participants will be recruited via the Research Match online platform, of which NYU is a participating institution. If needed, we will also use the Epic electronic health records to recruit patients from NYULMC. Participants meeting eligibility criteria after a pre-screening phone call (Section 7.3.1) will be directed to schedule an appointment with the DCSU for enrollment. The DCSU hosts a wide variety of dermatology studies and does not hold any particular stigma for participants. Our enrollment target is 500 subjects at a rate of 5 subjects per week. We anticipate pre-screening 650 participants to reach our enrollment goal.

At the DCSU, study participants: 1)will be informed of the details of the study and given time to review the IRB approved Informed Consent form; 2) given the opportunity to ask questions; and 3) will be enrolled after signing an informed consent form (ICF) in a private encounter. After the participant consenting process, lesion eligibility will be confirmed by the study team, and participants will provide the study team with contact information, demographic information, past medical history of skin cancer, family history of skin cancer, natural hair color, eye color, likelihood of burning with unprotected sun exposure, likelihood of tanning with unprotected sun exposure, tanning bed exposure, moderate to severe sunburn exposure, history of atypical or dysplastic nevi, estimate of number of moles on body, estimate of number of freckles on face, and identification of up to three lesions (location, onset, quality, and prior treatment) by completing the Enrollment Questionnaire (Supplement K). Study personnel will have access to these data in order to contact participants for follow up communications including the telemedicine report, biopsy results, wound healing check, scheduling, and administering the study completion questionnaire. Study personnel will also have access to telemedicine data on each participant including clinical images, dermoscopic images, and Nevisense scores. Information about participants will be recorded either on source documents or directly into REDCap depending on what is more convenient for the study team and on whether there are temporary technological barriers to direct REDCap documentation. Any source documents will be kept in the patient's study binder and file cabinets at DCSU. The data will later be entered into the REDCap database case report forms. Only study personnel will have access to the source documents and the REDCAP forms. Study participants will be assigned a participant study ID number.

In total, the study requires participant involvement for about 1-4 weeks, depending on whether a biopsy is recommended and the participant's availability. Retention measures include calling participants 3 separate times to ensure a return visit for biopsy (if recommended), to communicate teledermatology and/or biopsy results and check wound healing, and/or to

conduct the study completion questionnaire. In the event of three failed attempts to reach the participant regarding biopsy results, the participant will be sent a certified letter communicating the biopsy results and need for follow-up medical care (if needed) (Supplement F). In the event that we are unable to make contact with the subject to communicate the teledermatology recommendation, we will send a certified letter with the recommendation printed (Supplement G).). In the event that the teledermatology team recommends a biopsy and a participant cannot be contacted to schedule the biopsy or does not show up for a scheduled biopsy appointment, we will send a certified letter instructing them to contact us (Supplement H). At any point during the participant's involvement in the study, they can reach the DCSU by telephone to contact study personnel with concerns regarding wound healing, results interpretation, etc. Medical issues will be referred to one of the physician site investigators (e.g. dermatology resident or attending medical monitor). For emergencies, participants may contact Dr. Shirin Bajaj with information provided in the emergency card. (Supplement H)

5.5 Duration of Study Participation

From screening to the end of the study completion questionnaire, participation may last between 1-4 weeks depending on whether a biopsy is performed.

5.6 Total Number of Participants and Sites

Recruitment will end when 500 participants are eligible for study participation. The only site is the NYU School of Medicine.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants may withdraw voluntarily from the study at any time upon request. An investigator may terminate participation in the study if:

- Any sudden clinical adverse event (AE), laboratory error, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

5.7.2 Handling of Participant Withdrawals or Termination

Participants can withdraw voluntarily at any time during the study. If a participant withdraws prior to receiving a recommendation to have their lesion(s) biopsied, the biopsy will not take place. However, in the interest of participant safety, we will attempt to contact the participant on 3 separate occasions and, if needed, send a certified letter to deliver the biopsy recommendation (Supplement G). If a participant withdraws after biopsy is conducted but before the pathology results are available, all efforts to contact the participant with results and check on wound healing will continue. In the unlikely event that a participant presents with a clinically obvious melanoma (for which a biopsy would be recommended) and chooses to withdraw prior to completing the evaluation and/or undergoing a biopsy, we will still recommend a biopsy to this participant and will facilitate an appointment in our clinic if participant is amenable.

In the event of a significant number of withdrawals or terminations and enrollment has already closed, enrollment will re-open to capture 500 participants.

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Insufficient compliance to protocol requirements
- Technological malfunction
- Insufficient data quality
- Unanticipated loss of human resources such as study staff or clinical dermatologists.

Study may resume once concerns about protocol compliance, technology function, data quality, and/or resources are addressed and satisfy the IRB.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

The Procedural Intervention is the telemedicine evaluation; the Control is the in-person dermatologist evaluation. The Procedural Intervention includes 3 components:

1) Clinical images (from 6 inches, 12 inches, and 24 inches from the lesion) captured and uploaded to the subject's EPIC EMR medical chart as a research note or captured by the Barco Demetra and uploaded to its associated software
2) Close up clinical and dermoscopic imaging of the lesion(s) of concern with a dermoscopy camera (DermLite Cam, 3Gen, San Juan Capistrano, CA or Barco Demetra, Barco NV, Kortrijk, BE)
3) An electrical impedance spectroscopy measurement of said lesions using the Nevisense 3.0 device (Scibase, Sundbyberg Sweden)
4) Store-and-forward telemedicine evaluation of the imaging and Nevisense measurements by a team of 3 dermatologists.

The goal is to determine whether the lesion(s) of concern to the participant is a benign skin growth, or a possible skin cancer in need of a biopsy to definitively establish the diagnosis. The Nevisense 2.0 device is FDA cleared for use in dermatologists' offices. The Nevisense 2.0 device will not be used in this study. Rather, the updated, not yet approved Nevisense 3.0 device will be used. The 3.0 version consists of a software update and provides a simpler a workflow that no longer requires a reference measurement from the subject's normal skin, thus saving time. The 3.0 device has no change in the hardware.. Verbal FDA clearance occurred in January 2020 and formal FDA clearance is expected in April 2020. Regardless of approval, the proposed use of Nevisense 3.0 in a telemedicine setting for this study represents an off-label use of the device.

It measures electrical impedance of the lesion with single-use electrodes (i.e. changed between each participant). The device has a hardware probe that takes the measurement in <10 seconds and a software component that displays the data on the control unit screen.

Risks related to the device may be expected in <1.0% of cases. Most common to least common side effects include bleeding during measurement, pain, soreness, bruising, slight tingling at measurement site, headache, or itching at the measurement site. There may be unknown side effects. The DermLite Cam and Barco Demetra imaging devices pose non-significant risks to the participant. Capturing clinical and dermoscopic images with this device will take <1 minute per lesion.

6.1.1 Acquisition

DermLite Cam will be purchased from 3Gen. The Nevisense 3.0 will be provided by SciBase. The disposable electrodes will be purchased from SciBase. The commitment letter from SciBase is found as Supplement I.

The Barco Demetra device has been approved by NYU MCIT for research use (see included email from Patrocinio Domingo, Lead IT Controls and Regulatory Compliance Analyst).

6.1.2 Formulation, Appearance, Packaging, and Labeling

The Nevisense device is commercially available in the US. The Nevisense appears a control unit with a probe. The disposable electrodes are marked both on the package box and in each individual electrode packaging. The package insert is found as Supplement B. The product is available on the commercial market for human use in the form planned in this trial.

The DermLite Cam device appears as a single piece camera with a charging cable and USB computer cable. As part of the camera unit, an extensor arm exists to allow for the capture of standardized clinical images. The package insert is found as Supplement J.

The Barco Demetra digital dermatoscope appears as a two-piece device consisting of the Demetra Scope Head and Rechargeable grip/battery back with a battery charging station. The device also comes with a non-contact cone and user guide. The package insert is found as Supplement X.

6.1.3 Product Storage and Stability

There is no particular storage needs for stability for either the Nevisense device or DermLite Cam. Both will remain locked in the DCSU when not in active use, accessible only to study personnel.

6.1.4 Device Specific Considerations

Nevisense 3.0 will be used with the latest software upgrade as a one-time exposure of <8 seconds per lesion. Disposable electrodes that contact the participant are 5mm x 5mm in size.

According to the FDA PMA, current indications for Nevisense use are the following:

- primary skin lesions with a diameter between 2 mm and 20 mm;
- lesions that are accessible by the Nevisense probe;

- lesions where the skin is intact (i.e., non-ulcerated or non-bleeding lesions);
- lesions that do not contain a scar or fibrosis consistent with previous trauma;
- lesions not located in areas of psoriasis, eczema, acute sunburn or similar skin conditions;
- lesions not in hair-covered areas;
- lesions which do not contain foreign matter;
- lesions not on special anatomic sites (i.e., not for use on acral skin, genitalia, eyes, mucosal areas).

We will follow these indications except for prohibiting areas of psoriasis or eczema as the study personal taking the Nevisense measurements in this study will most often not be a physician and will not have the dermatological expertise to diagnose these conditions or similar conditions. Any potential risk from using this device in such skin conditions will be mitigated by the fact that other diagnostic tools will be used on every lesion of concern (clinical images and dermoscopic images) and the fact that each concerning lesion will be assessed by an in-person dermatologist, the current gold standard for diagnostic evaluation.

Additionally, lesions with crust, on a stalk, recurrent after biopsy or excision will not be included for Nevisense measurement as these lesion types were excluded from the pivotal studies for FDA PMA. . Crust (the medical term for a scab) is defined as dried serum or blood, typically overlying skin ulceration, or resulting from the rupture of vesicles or pustules.[12]

The DermLite Cam will be used to acquire 3 images of <5 seconds per lesion (one clinical, one polarized dermoscopic, and one non-polarized dermoscopic). Images will be stored in a dedicated computer folder in the Dermatology Department server share using software (MoleCam, MoleMap, NZ) already in use by the telemedicine team in the NYU Department of Dermatology Pigmented Lesion Clinic. The telemedicine dermatology team will review the images using this dedicated software.

In addition to the DermLite Cam images, a study specific camera or EPIC HAIKU will be used to acquire 3 clinical images of <5 seconds per lesion (from 6 inches away, 12 inches away, and 18 inches away). Images will be stored in the patient's medical record in Epic, to which the teledermatology team has access. Clinical images taken through Epic Haiku or the study specific camera will not be stored elsewhere. Images taken with the study specific camera will be deleted from the camera once images are uploaded to EPIC.

The Barco Demetra device will be used to acquire 3 images of <5 seconds per lesion (one clinical, one polarized dermoscopic, and one non-polarized dermoscopic) as well as 3 additional clinical images of <5 seconds per lesion (from 6 inches away, 12 inches away, and 18 inches away). Images will be stored in the authenticated and data-encrypted Demetra Cloud accessible via the web by the telemedicine team in the NYU Department of Dermatology Pigmented Lesion Clinic. The telemedicine dermatology team will review the images using this dedicated cloud software. Clinical and dermoscopic images taken by the Barco Demetra device will not be stored elsewhere.

Lesions with bleeding or ulceration will only have a clinical image taken and not have a dermoscopic image taken.

The telemedicine dermatology team will consist of Dr. David Polsky, Dr. Tracey Liebman, and Dr. Jennifer Stein, who are all pigmented lesion experts. They will be listed as co-investigators. They will submit independent, blinded to each other, diagnoses for each lesion on REDCap. If at least one teledermatologist believes the lesion to be a malignant diagnosis, the lesion will be recommended for biopsy. If the participant has not already had the lesion biopsied by the in-person recommendation, the participant will be told this concern for malignancy and telemedicine recommendation for biopsy.

6.2 Study Agent Accountability Procedures

The two devices and photos will be used by study personnel. Nevisense measurements will be taken by all study team members that have completed the Nevisense training, as per page 4 of the device Instructions For Use (Supplement C). Most often, the individual obtaining Nevisense measurements will be non-physician study team members to simulate the eventual use in a pharmacy setting. Data acquired from the devices will be transferred to the participant source documents at the time of their visit. The results of the control evaluation will also be recorded at the time of the visit. At the end of each day, the data will be entered into the REDCap database case report forms and verified by a second study staff member. The devices will stay in a locked office in the DCSU when not in use. The images will be stored on an NYU server, behind institutional firewall, and backed up according to standard institutional schedules, minimizing the possibility of data loss.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

- Assessment of eligibility (number of lesions, location of lesions)
- Informed Consent
- Enrollment questionnaire (Supplement K)
- Nevisense EIS measurement
- Imaging of the lesion(s) of concern using the DermLite Cam and stored on MoleCam software and MoleCam drive behind NYU MCIT firewall OR using the Barco Demetra and stored on its associated cloud server
- Imaging of the lesion(s) of concern uploaded to EPIC EMR research note using study specific camera or EPIC HAIKU
- Numbering of skin lesions using Devon Skin Marker to verify same lesion evaluated across all assessments
- Administration of part 1 of study completion questionnaire (Supplement L)
- Skin lesion examination by in-person dermatologist
- Phone call to communicate telemedicine recommendation within 3 business days (phone script as Supplement M & N)
- Skin biopsy, if recommended by either the in-person dermatologist or the telemedicine evaluation
    - A skin biopsy is a small procedure that removes a sample of skin from the surface of the body. The method utilized will be either a shave or punch technique. The maximum size of a punch biopsy will be 6mm and these wounds are generally closed with absorbable sutures and do not require a return visit for suture removal A skin biopsy takes <15 minutes including preparation time, administration of intradermal anesthesia using lidocaine 1% with epinephrine 1:100,000, removal of the skin sample, achievement of hemostasis, dressing the wound, and providing instructions for home care. Samples will be placed in formalin for routine processing.
- Administration of final study completion questionnaire (Supplement L).

7.1.2 Standard of Care Study Procedures

- Histopathological diagnosis of biopsied skin lesions
- Phone calls to discuss skin biopsy results and check on wound healing
- If necessary, suture removal visit is scheduled (if nylon sutures were placed during skin biopsy) and/or wound check visit.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

- Routine dermatopathology examination of skin biopsy specimens

7.2.2 Specimen Preparation, Handling, and Storage

Skin biopsy specimens will be transferred on the day of removal to the NYU Dermatopathology Laboratory for processing and diagnosis, which is estimated to take 1-2 weeks. Biopsy samples will be labeled with participant identifying information including name and MRN.

7.3 Study Schedule

As described below, the study schedule includes a variable number of visits that depend upon the outcome of the initial evaluation. Briefly, 3 outcomes are possible:

1) The lesion(s) is diagnosed as not suspicious for skin cancer by both the in-person dermatologist and telemedicine team, and no biopsy is recommended
2) The lesion(s) is diagnosed as not suspicious for skin cancer by the in-person dermatologist, but suspicious for skin cancer by the telemedicine team, and a biopsy is recommended when the telemedicine team results are communicated to the participant
3) The lesion(s) is diagnosed suspicious for skin cancer by the in-person dermatologist, and a biopsy is performed at the initial visit, or scheduled to be performed at a follow up visit. In this scenario, the recommendation of the telemedicine team will not be communicated to the participant since we do not yet know if a ‘no biopsy’ recommendation by the telemedicine team is a safe alternative to a ‘biopsy’ recommendation by the in-person dermatologist.

Based on the outcomes described above, the participant will have either 1 visit and 1 phone call (initial evaluation and follow-up phone call), or an additional visit for telemedicine recommended biopsy and an additional phone call with biopsy results.

7.3.1 Pre-Screening

Pre-Screening Visit (no time frame prior to enrollment)

- Participant reads general requirements for eligibility and calls to schedule an appointment at the DCSU if study requirements are met
- During the scheduling phone call, study staff determine if the prospective participant meets eligibility criteria (Supplement O & P)
- During the phone call, eligible participants have the option to view and discuss the consent form electronically. If they opt to do so, participants will be sent a consent form through RedCap, which they can view during the phone call and sign at any time prior to Visit 1. After signing the electronic consent form, participants also have the option to fill out the enrollment questionnaire electronically.

7.3.2 Enrollment/Baseline

Enrollment/Initial Visit (Visit 1, Day 1)

- Participant and lesion eligibility confirmed by study personnel
    - This is the formal study screening prior to official enrollment (i.e. signing informed consent)
- Participant given Key Information Sheet with an overview of the study (Supplement Q)
- Conduct informed consent procedure and obtain signed ICF, if not conducted electronically prior to visit
- Assign subject ID for participant
- Obtain demographic information, medical history, medication history as part of enrollment questionnaire (Supplement K). If not conducted electronically prior to visit
- Acquire clinical images, dermoscopic image, and Nevisense data for each lesion
    - Nevisense procedure: the lesion is cleansed with an alcohol wipe and the electrical impedance measurement is conducted using a spring-loaded probe and disposable electrode measuring 5mm x 5mm. The measurement takes <1 minute and the electrical impedance score (EIS) will be recorded. Larger lesions may require a second measurement at another location within the lesion.
    - Record any adverse events from the procedure
    - Neither participants nor the in-person dermatologist will be aware of the score.
- Study team will number the skin lesions using Devon Skin Marker to verify same lesion evaluated across all assessments including the in person dermatologist
- Fill out questionnaire assessing telemedicine evaluation experience so far (Supplement L)
- In-person dermatologist examination of lesion(s) using naked eye and dermoscopy
- If a biopsy is recommended by the in-person dermatologist, participant will be offered a skin biopsy procedure or offered a second appointment within 1-2 weeks for the biopsy procedure
    - If a biopsy is performed, the participant is given at-home instructions for wound care (Supplement R) and the expected wait time for the biopsy results
    - Alternatively, the participant can choose to have the procedure done at another facility. The signed ICF includes permission for the study team to obtain those medical records
    - Follow-up care to the skin biopsy will proceed per standard clinical practice and includes result communication, wound care monitoring, suture removal if applicable and recommendations for follow-up care.
- If a biopsy is not recommended by the in-person dermatologist, the participant is given the expected wait time for telemedicine recommendation phone call.

7.3.3 Intermediate Visits

Phone Call: For Participants without a Skin Biopsy recommendation by the in-person dermatologist for at least 1 lesion (Day 4+/-2)

- Communicate telemedicine recommendation (Supplement M & N)
    - If a skin biopsy is recommended, schedule participant for another in-person visit at the DCSU for skin biopsy procedure.
    - Alternatively, the participant can choose to have the procedure done at another facility. The signed ICF includes permission for the study team to obtain those medical records
    - If a skin biopsy is not recommended, thank the subject for their participation
- Administer the study completion questionnaire (Supplement L)

Visit 2: For Participants in whom a skin biopsy was recommended by the telemedicine team (Day 7+/-2)

- Perform skin biopsy
- If a biopsy is performed, the participant is given at-home instructions for wound care (Supplement R) and the expected wait time for the biopsy results

- Follow-up care to the skin biopsy will proceed the same as standard clinical practice with Visits 4 and 5

Phone Call For Participants with Skin Biopsy after Teledermatologist recommendation (Day 17+/-3)

- Record adverse events as reported by participant
- Communicate biopsy pathological report results and medical advice for next steps if needed or reassurance (Supplement S)
- Ask about symptoms and signs of wound healing progression

Optional Visit 3: Wound Check for biopsy site performed on Visit 2 (Day 21+/-3)

- Check site of biopsy for healing and any AEs
- Communicate medical advice for next steps if necessary.

7.3.4 Study Completion

Once all lesions have been evaluated, all biopsy results have been communicated, and all wounds are healing well, participants will be given a study completion questionnaire (Supplement L) regarding his/her overall experience in the study. At this point, participation in the study is complete.

7.3.5 Withdrawal/Early Termination Visit

Participants may withdraw at any time by contacting the DCSU staff via phone call or in-person. For participants who did not undergo a skin biopsy, no follow-up care is needed. Participants who underwent a skin biopsy will be offered a final visit to communicate biopsy results, and for a wound check or suture removal if needed. They will also receive a referral to the NYU Skin & Cancer clinic for follow up care if needed. Any adverse events will also be recorded.

7.3.6 Unscheduled Visit

Participants may call and report a concern or adverse event at any time during the study duration. The most likely reason for an unscheduled visit would be related to poor wound healing. The DCSU staff will handle the questions and refer to one of the study physicians as needed. The participant may be asked to come to the DCSU in for an in-person evaluation and management. The most likely management outcome if wound infection is suspected would be providing antibiotic ointment to the participant. Unscheduled visits will be recorded in a separate field in the participant's case record form.

8 Assessment of Safety

8.1 Specification of Safety Parameters

- Safety parameters are not included in primary or secondary endpoints
- Safety parameters to be recorded include participant adverse reactions to the imaging with the Nevisense device, as well as any adverse events recorded during intermediate, unscheduled or final study visits as reported by participants
- Any new onset symptoms, signs, illness or experience during the participant duration of the study will be recorded, quality of new onset signs, symptoms, illness or experience will be recorded

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity

- a congenital anomaly or birth defect
- an important medical event

that is caused by, or associated with, the study agent, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application). Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or ICF, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

This definition could include an unanticipated adverse device effect on health or safety 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 a supplementary plan or application).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- ***Related*** *– The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.*
- ***Not Related*** *– There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.*

8.2.3 Expectedness

Principal Investigator Dr. David Polsky will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures. The expected AE's for the Nevisense device have been described in FDA clearance documents. There are no expected AE's for the clinical and dermoscopic imaging.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate visit note. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

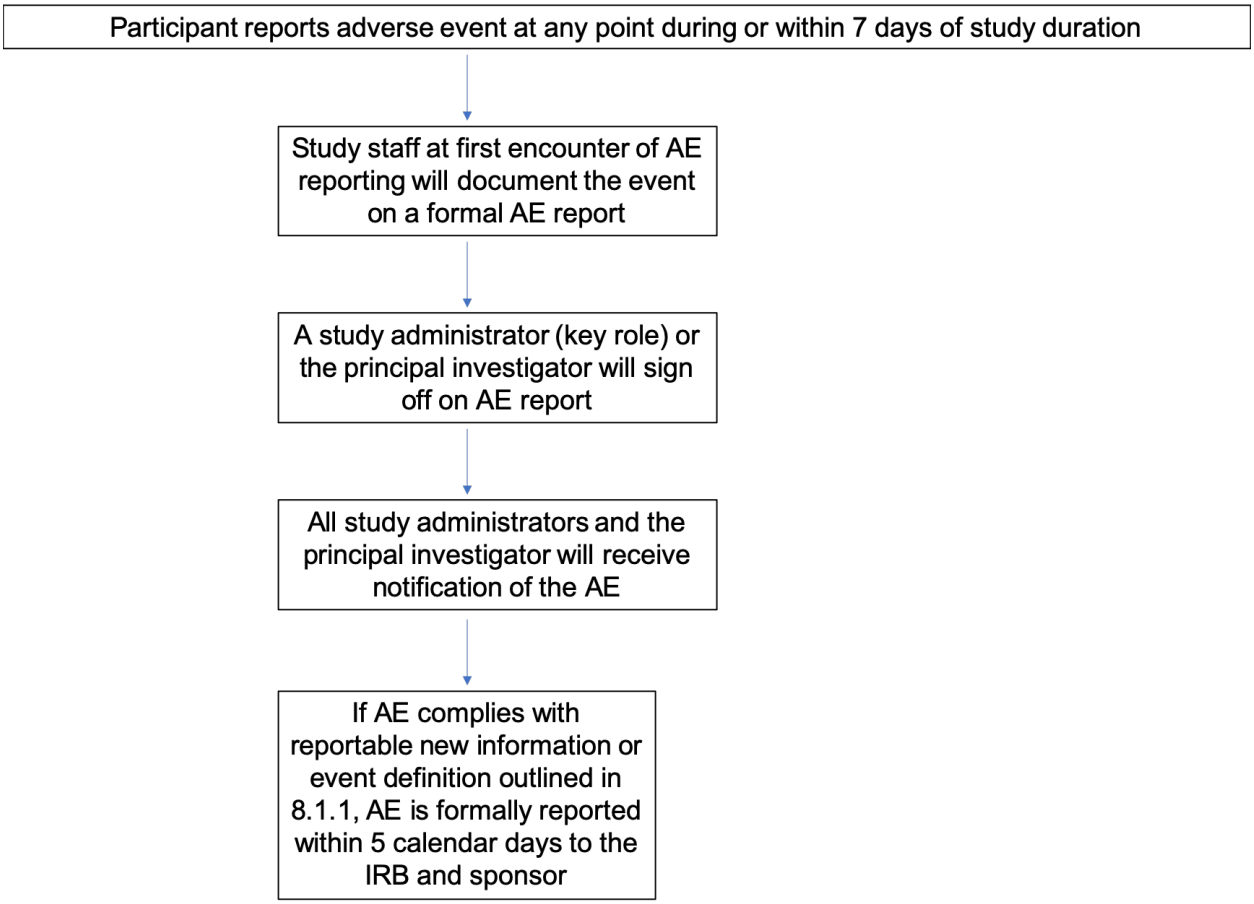
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

AEs will be documented in the visit note including an event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. AEs occurring with 7 days from end of participant study duration. The study staff that are responsible for completing AE reports are study administrators that first hear the participant report the event. The study staff that are responsible for signing off on AE reports include the principal investigator and/or study administrators recorded in key roles in the investigational protocol. All study administrators in key roles and the principal investigator will receive notification of all AEs. AEs are reportable to the IRB within 5 calendar days if the event or new information is consistent with the following:

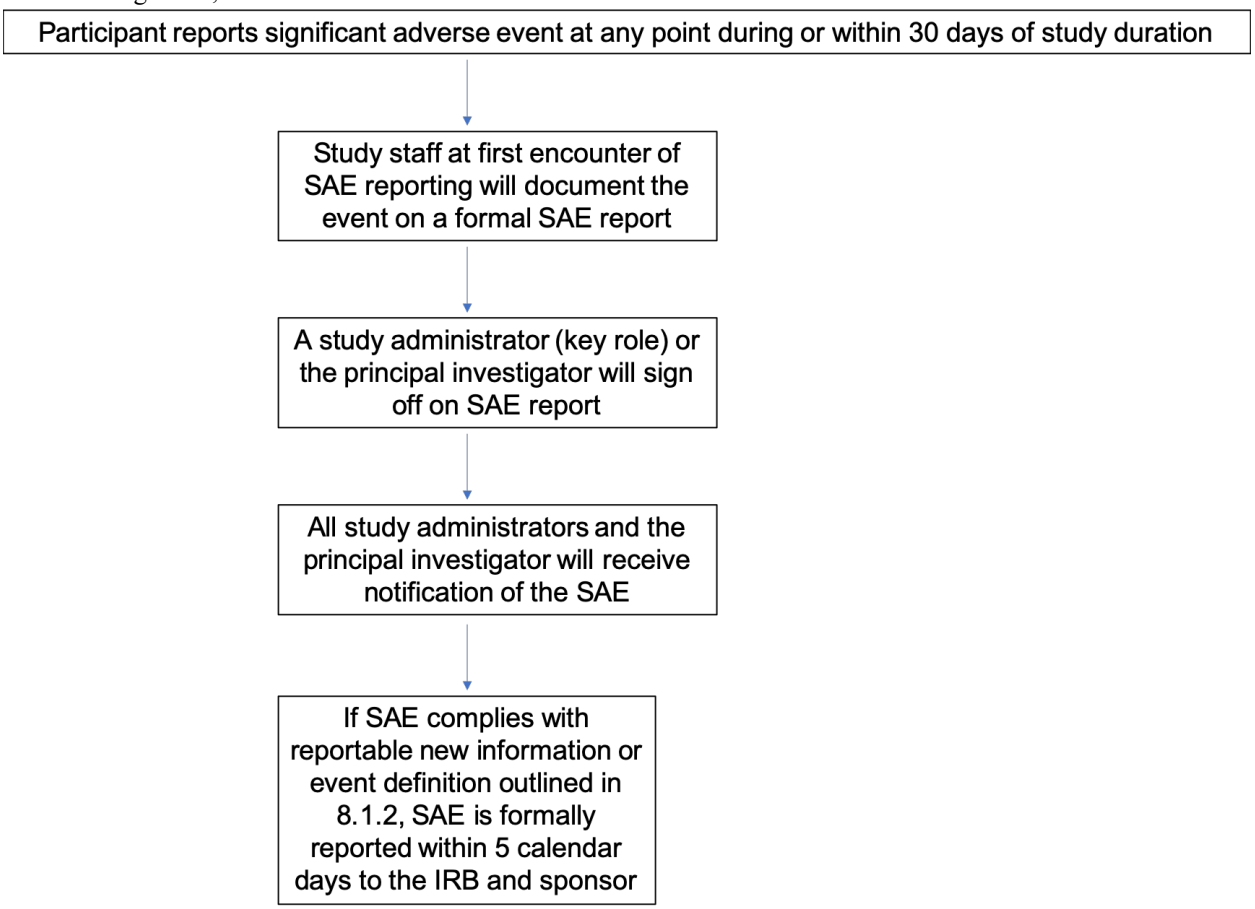
- new information indicating a change to the risks or potential benefits of the research, in terms of severity or frequency (such as analysis indicating more severe or frequent side effect or an FDA labeling change or withdrawal from market)
- protocol deviation or violation, only if one or more of the following criteria is met:
  1. it was intended to eliminate apparent immediate hazard to a research participant
  2. it was harmful (caused harm to participants or others or placed them at increased risk of harm)
  3. it represented possibly serious or continued noncompliance
- a complaint unresolved by the research team or that indicates increased or unexpected risks
- incarceration of a participant, when the principal investigator believes it is in the best interest of the participant to remain in the study
- an unanticipated adverse device effect
- new information about the 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



8.4.2 Serious Adverse Event Reporting

SAEs will be documented in the visit note including an event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. SAEs occurring with 30 days from end of participant study duration. The study staff that are responsible for completing SAE reports are study administrators that first hear the participant report the event. The study staff that are responsible for signing off on SAE reports include the principal investigator and/or study administrators recorded in key roles in the investigational protocol. All study administrators in key roles and the principal investigator will receive notification of all SAEs. SAEs are reportable to the IRB within 5 calendar days if the event or new information is consistent with the following:

- new information indicating a change to the risks or potential benefits of the research, in terms of severity or frequency (such as analysis indicating more severe or frequent side effect or an FDA labeling change or withdrawal from market)
- protocol deviation or violation, only if one or more of the following criteria is met:
  1. it was intended to eliminate apparent immediate hazard to a research participant
  2. it was harmful (caused harm to participants or others or placed them at increased risk of harm)
  3. it represented possibly serious or continued noncompliance
- a complaint unresolved by the research team or that indicates increased or unexpected risks
- incarceration of a participant, when the principal investigator believes it is in the best interest of the participant to remain in the study
- an unanticipated adverse device effect
- new information about the 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



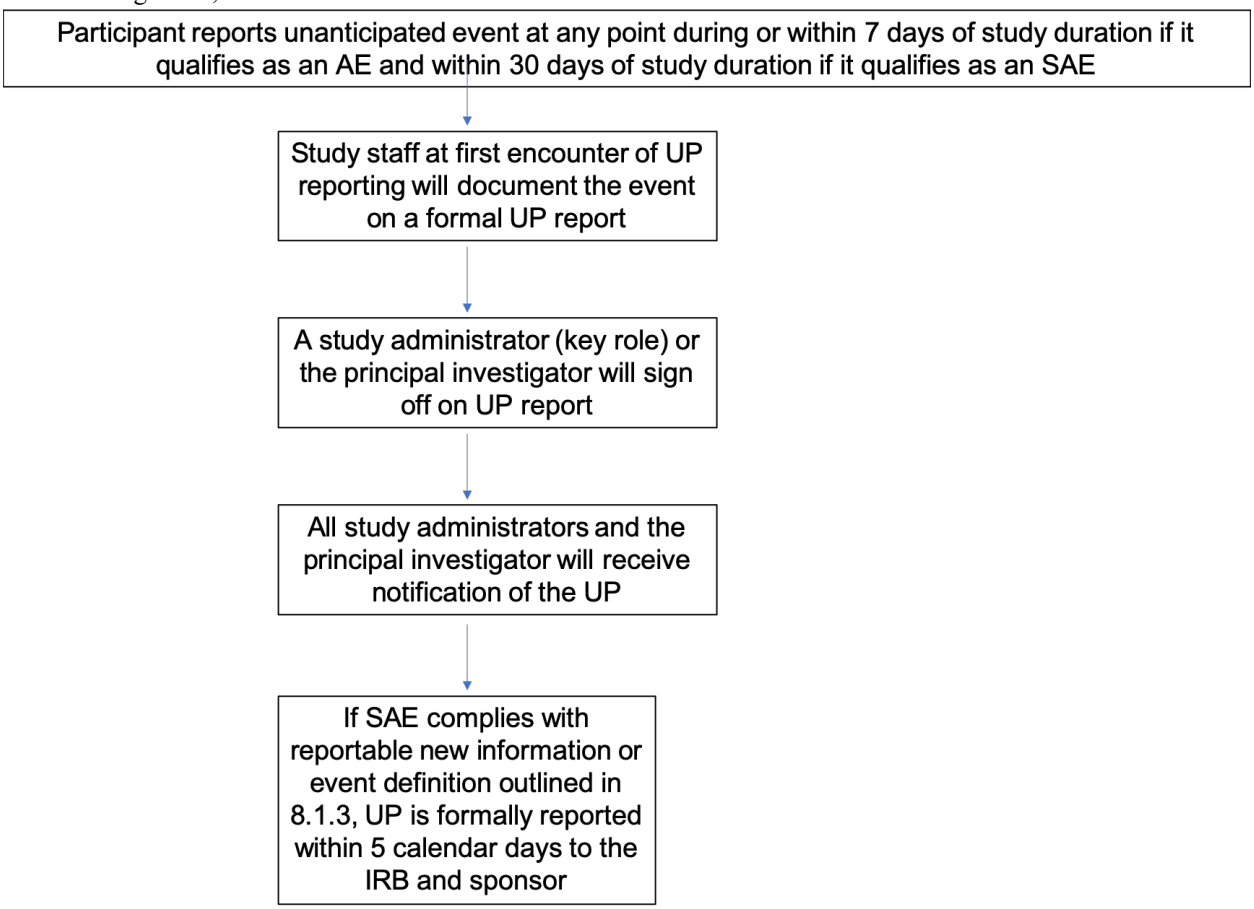
8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the criteria for UPs indicated in section 8.1.3 require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs will be reported to the IRB within 5 calendar days of the investigator becoming aware of the event.



8.5 Study Halting Rules

The study will be halted when three grade 3 AEs determined to be "related" are reported to the IRB.

8.6 Safety Oversight

Safety oversight will be under the direction of an appointed Medical Monitor (MM), a medical expert that advises the study investigators and monitors participant safety. The role of the Medical Monitor is to 1) Review all AEs on a regular basis throughout the trial; 2) Be available to advise the investigators on trial-related medical questions or problems, and 3) Evaluate cumulative participant safety data and make recommendations regarding the safe continuation of the study. The Medical Monitor is Dr. Shirin Bajaj. Dr. Shirin Bajaj is a Clinical Instructor in the Ronald O. Perelman Department of Dermatology.,. She is actively conducting clinical research on the use of lasers in dermatology,. She is well-qualified to serve as the Medical Monitor for this study.

9 Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Site Investigators, , Adriana Lopez, Duy Tran, Efe Kakpovbia and Vignesh Ramachandran will conduct the monitoring activities and report to the medical monitor Dr. Shirin Bajaj. These doctors are PGY-3 and PGY-4 dermatology residents, and are not members of the telemedicine team.
- Dr. Polsky (study PI) is a member of the telemedicine team and needs to remain blinded to the data until the study conclusion, so he cannot conduct the clinical monitoring. The monitoring team will report their monthly findings to Dr. Polsky while maintaining blinding of specific participant identifiable details.
- The monitoring will consist of monthly reviews of all the CRFs and the image database to ensure that all records are complete (i.e. no missing data). They will review the frequency and nature of any adverse events and participant withdrawals from the study. They will also review the screening and enrollment data to insure that eligible participants are not being incorrectly excluded from the study, and that ineligible participants are being appropriately excluded.

10 Statistical Considerations

10.1 Statistical Hypotheses

Primary endpoint:
We will not perform hypothesis testing in this pilot study; we will use descriptive statistics and summarize preliminary evidence from this pilot study.

Secondary endpoints
We will not perform hypothesis testing in this pilot study.

10.2 Analysis Datasets

All eligible lesions evaluated by both the teledermatologists and the in-person dermatologist.

10.3 Description of Statistical Methods

10.3.1 General Approach

The general approach will be to determine the agreement between in-person recommendation and the telemedicine (tele) recommendation. For this reason the data will be categorical in nature and the specific measures to be assessed are described below. We will also examine the performance characteristics of the tele approach (e.g. sensitivity, specificity, etc.) using the in-person dermatologist biopsy decision as the 'gold standard'(primary endpoint). However, it is possible that with respect to the pathology results (secondary endpoint), the tele approach may have a higher sensitivity and specificity to diagnose skin cancer than the in-person dermatologist. For this reason, we will also examine the performance of the tele and in-person biopsy decisions against the pathology results as the 'gold standard'.

10.3.2 Analysis of the Primary Efficacy Endpoint(s)

To determine the agreement between in-person recommendation and the telemedicine (tele) recommendation we can calculate the number of discordant benign vs. malignant diagnoses; specifically, the number of subjects that were recommended a biopsy from the in-person dermatologist but were recommended no biopsy from the teledermatology team, and the number of subjects that were recommended no biopsy from the in-person dermatologist but biopsy by the teledermatologist team. We can calculate the Kappa coefficient as a measure of the degree of concordance or agreement with confidence intervals. We can also calculate "sensitivity" and "specificity" of the tele method assuming in-person diagnosis as the gold standard. Similarly, we can separately evaluate the agreement between in-person and: 1) dermoscopy alone; and 2) Nevisense (EIS score $\geq$4) without dermoscopy. We will also estimate the improvement (if any) of using both methods compared to one method. We expect the Kappa coefficient to be close to one, and high "sensitivity" and "specificity" (close to 1) for the SpotCheck method assuming in-person diagnosis as the gold standard.

10.3.3 Analysis of the Secondary Endpoint(s)

Secondary endpoint (1) will be a descriptive analysis of Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value, using the histopathology results as the gold standard. We will assess potential difference or advantages in terms of: a) enhanced telemedicine diagnostic system; b) telemedicine Nevisense alone; c) telemedicine clinical + dermoscopy alone; and d) in-person dermatologist diagnosis. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value will be reported with an upper and lower confidence interval. Lesions with missing data will not be included in the relevant analyses (see Study Design schematic footnote 3). Participants lost to follow-up for reporting his/her biopsy results will be included in the analysis as the data required for analysis has been collected.

As another secondary endpoint, we will be evaluating the enhanced telemedicine service's impact on patient centered outcomes. Descriptive statistics for this secondary endpoint (2) (patient questionnaires, Supplement L will be presented as percentages. Study completion questionnaires may be qualitatively analyzed for themes and quantified by thematic representation across participants. Participant agreement of thematic categories will be calculated as percentages as a summary measure. Factors for stratification may include participants with a biopsy procedure and those without biopsy procedure as well as diagnosis of malignancy or benign lesion within those with biopsy. Participants with missing study completion questionnaire results due to inadequate duration of phone call will not be included.

As a final secondary endpoint (3), we will estimate the number of lesions that may benefit from the additional information of the Nevisense score to the clinical and dermoscopic exam. This estimation will be provided by the in-person dermatologist, and separately by each of the three teledermatologists (Supplement T & U). The estimates will be expressed as percentages. Any lesion with missing data in the in-person dermatologist and teledermatologist plan will not be included in analysis. Participants lost to follow-up will still be included in analysis of this endpoint as required data for this endpoint determination has been captured in the first visit.

10.3.4 Safety Analyses

Safety events will be coded in a medical dictionary for similar presentations of symptoms, signs, illness, or experience. Each AE will be counted once for a given participant and will be presented with severity, frequency, and relationship to the diagnostic method. The outcome and duration of each AE will also be presented. AE will be ascertained as those that are reported to the study team at the relevant visit. All AEs leading to premature termination or withdrawal from study and all SAEs will be presented in a table.

10.3.5 Adherence and Retention Analyses

Adherence is not applicable. Participation is defined as all subjects that enroll into the study. Study retention is defined as participants that complete all visits through the last visit (study completion questionnaire) out of the number of subjects enrolled. Participants lost to follow up include all those that were unable to be contacted for biopsy scheduling, wound check, or study completion questionnaire administration.

10.3.6 Baseline Descriptive Statistics

Baseline characteristics used for baseline descriptive statistics include demographic information, past medical history of skin cancer, family history of skin cancer, natural hair color, eye color, tanning bed exposure, moderate to severe sunburn exposure, history of atypical or dysplastic nevi, estimate of number of moles on body, and estimate of number of freckles on face. Inferential statistics will not be used.

10.3.7 Planned Interim Analysis

Not applicable

10.3.7.1 Safety Review

Not applicable

10.3.7.2 Efficacy Review

Not applicable

10.3.8 Additional Sub-Group Analyses

Primary endpoint and secondary endpoints will be analyzed by age, sex, and race/ethnicity.

10.3.9 Multiple Comparison/Multiplicity

Not applicable

10.3.10 Tabulation of Individual Response Data

Not applicable

10.3.11 Exploratory Analyses

Exploratory analysis may be conducted using the continuous Nevisense score or categorical unequivocally benign lesion designation (using clinical and dermoscopic image alone) as factors of stratification before re-evaluation of primary endpoint again.

10.4 Sample Size

Number of subjects to recruit and screen is estimated to be 650 or fewer. Number of participants eligible is estimated to be 500 or fewer. Based on the previously mentioned Norwegian study, we anticipate a biopsy recommendation rate of 10% between the telemedicine and in-person evaluations. With each participant presenting with 1-3 lesions, an estimate of 1000 evaluated lesions (2 per participant on average) is possible. Assuming a biopsy recommendation 10% from this historical data, there will be likely 50 - 100 biopsies recommended and 450 - 900 lesions not recommended for biopsy.[9]

We anticipate 2% of the sample will be lost to follow up based on historical data. Missing data is estimated at 4% based on those lost to follow up and technical error based on historical data.[11] We anticipate 1% of participants to withdraw based on historical data.[12] Participants who have formally withdrawn from the study will not be included in primary or secondary endpoint analysis, nor will they be included in the analysis datasets.

10.5 Measures to Minimize Bias

10.5.1 Enrollment/Randomization/Masking Procedures

10.5.2 Subjects will be self-enrolled into the study by viewing an advertisement and making an appointment for enrollment at the DCSU. Enrollment procedures include eligibility verification and informed consent confirmation with signature. The in-person dermatologist (control arm) and telemedicine team (intervention arm) will each be blinded to the other's management recommendation. The in-person dermatologist will be blinded to the Nevisense score. Additionally, the teledermatologist team of 3 physicians will be masked to each other's management plan. If one teledermatologist is absent (due to vacation, illness etc.) and cannot make their recommendations, a minimum of 2 teledermatologists is satisfactory to make a consensus. If any teledermatologist recommends biopsy, the team recommendation will be biopsy. Periodic reviews of teledermatology diagnoses by the teledermatology team will be held in order to improve quality control during the study. Evaluation of Success of Blinding

Not applicable

10.5.3 Breaking the Study Blind/Participant Code

Breaking the study blind for all participants may occur in the event of an SAE. Both intentional and unintentional breaking of the blind will be reported to the principal investigator.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. For this study source documents will include case record forms (CRFs), clinical and dermoscopic images, patient questionnaires, in-person and teledermatologist data collection forms, and pathology reports. All data collected using paper documentation will be transferred to an electronic CRF maintained in REDCap. Paper copies for auditing purposes will be kept in a locked file cabinet in a locked office in the Dermatology Department. Images will be maintained on a NYULH computer server in a Department of Dermatology dedicated folder or in Epic.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

12 Quality Assurance and Quality Control

QA procedures include a study staff member at the DCSU verifying the exact lesion(s) of concern with the participant after the participant completes the enrollment questionnaire. DCSU study staff will double check the enrollment questionnaire for all missing information and ensure answers are filled out before the participant proceeds to the next step. All acquired images will be assessed for quality prior to acceptance and progression to Nevisense data acquisition. Study personnel will double check the Nevisense score prior to recording into the patient CRF.

QC procedures will be implemented beginning with the data entry system and an initial data QC check that will be run on the database once it is generated. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access of source data/documents, and reports for the purpose of inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.2.1 Telephone Pre-Screen:

This study will have 2 consent processes: The first is the research team will speak with interested participants over the telephone and ask for verbal consent before asking some eligibility criteria-related questions.

Advertisements will list, and interested participants will be given the DCSU phone number to reach if they are interested in participating in the study. A phone pre-screen process with potential interested subjects will take place by phone when the participant calls the DCSU. The research team will ask for verbal consent prior to asking the pre-screen questions to determine if a potential participant is eligible to enroll in the study. The questions are in regards to the eligibility criteria which consist of age, pregnancy status, lesion location and history of prior biopsy of the lesion. If the individual is eligible for the study then they will be scheduled for a screening visit. If they are not eligible or decide not to participate, any information collected will be immediately destroyed. Informed Consent Process

13.2.2 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study procedures and risks are given to the participant and written documentation of informed consent is required prior to starting the intervention.

13.2.3 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. In a private room at the DCSU, the investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document on the day of the consent discussion prior to any procedures being done specifically for the study. Alternatively, the participant may view and sign the consent form remotely through an electronic informed consent (e-consent) process prior to taking part in any study procedures. For the e-consent process, the discussion of consent will be conducted via phone after the telephone pre-screen. The participant will then receive a RedCap link to review and sign the electronic consent form. The RedCap consent document will include the same information contained within the paper informed consent document. In signing the consent form, subjects agree to comprehension of the nature of the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented. A sample informed consent form is provided in the appendix of the protocol.

Capacity will be assessed if a subject is able to reiterate the risks and benefits of the study, articulate their decision and the rationale for his or her decision. Persons with diminished capacity are allowed to participate in the study as it is of minimal risk and offers the direct benefit of free cancer screening. Decisionally impaired adults will be asked to verbally state their decision and rationale to ensure comprehension during assent.

13.3 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

Any clinical images captured using Epic Haiku or the study specific camera and include identifiable features (faces, full body images, tattoos, etc) will be stored directly in the patient's medical record as research note. The teledermatology team will have access to the patient's chart via an NYU EPIC MRN. Clinical images will not be stored on the device itself or any other platform. Identifiable images of participants will not be captured or stored in the DermLite Cam due to the standardized, constrained distance for clinical images required by this device.

Any clinical images captured using the Demetra that include identifiable features (faces, full body images, tattoos, etc) will be securely stored in the Demetra Cloud. The teledermatology team will have access to the patient's record via secure login access using username and password. Images are also stored on the Demetra device, which requires a user specific four-digit PIN code for operation.

The study monitor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

13.3.1 Research Use of Stored Human Samples, Specimens, or Data

There will not be storage of biological samples.

- Intended Use: Clinical and dermoscopic images, and Nevisense data may be used to study benign dermatological diagnoses and melanoma. No genetic testing will be performed.
- Storage: Access to the data (stored online) will be limited by password protection.
- Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- Tracking: not applicable.
- Disposition at the completion of the study: data described above will be maintained indefinitely. Study participants who request destruction of their data will be notified of compliance with such request and all supporting details will be maintained for tracking.

13.4 Future Use of Stored Specimens

Biological samples will not be obtained from the pathology laboratory and will not be used for future studies. Deidentified clinical and dermoscopic images may be used for future studies. Within the Informed Consent form, there is an optional

yes/no checkbox and place for an initial signature to provide this permission. These images could be used for research into the diagnosis of skin cancer and other conditions for which individuals with skin lesions are at increased risk, and to improve early detection. Any future studies with these images will be managed by the NYU IRB, just as this study is. One purpose of future studies would be to augment the strength of artificial intelligence diagnostics with a higher volume of images, particularly of the benign lesion category which currently is limited.

During the conduct of the study, an individual participant can choose to withdraw consent to have images stored for future research.

When the study is completed, access to study data and/or images will be provided through the DCSU.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL. Time for submission of CRFs are within 48 hours of the visit. Paper source documents will be housed centrally at the DCSU.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from paper source documents should be consistent with the paper source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, prior or concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by NYULMC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Study staff at the DCSU will collect data as well as review data, trial materials, and reports. The study team will conduct interpretation of data, plans for analysis, review of tables and listings, and plans for reporting at locations within the NYU Department of Dermatology (e.g. office of the PI, conference rooms, etc.). After the study is completed, the de-identified, archived data will be stored in a dedicated folder in the NYU Department of Dermatology server allocation under the supervision of David Polsky (PI), for use by other researchers once relevant approvals are in place.

14.2 Study Records Retention

Study documents will be retained for a minimum of 3 years after close-out or 5 years after final reporting/publication. However, images and associated meta-data will be retained indefinitely for potential use in future studies.

14.3 ClinicalSafety Monitoring:

Shirin Bajaj, MD is responsible for overall clinical safety monitoring. As noted in Section 8.6, Dr. Bajaj is a Clinical Instructor in the Ronald O. Perelman Department of Dermatology. She is well qualified to serve as the Medical Monitor for this study. Clinical safety monitoring will consist of reviewing monthly summarized data of all the REDCAP CRFs, put together by the study's research coordinator or research associate. Research coordinator/associate will include a MoleCam software report AND/OR Demetra software report with images and locations for each lesion, and research coordinator/associate will confirm that all records have no missing data The clinical safety monitoring report will also include frequency and nature of any adverse events, participant withdrawals, screen failures, number of enrolled participants, diagnoses, protocol deviations and the benign/malignant ratio. The literature suggests the typical benign: malignant ratio is about 29:1.[13-16] The definition of non-inferior in the clinical trial setting is most often defined as within 50% unidirectionally from the endpoint of the control.[17] In this case, a growth by 50% in this ratio becomes 44:1. Study stopping criteria will be when the teledermatology team reaches a benign: malignant ratio of 44:1, which will be a signal of unacceptably high added risk to the patient due to unnecessary skin biopsy procedure. If the Clinical Safety Monitor identifies a melanoma that was missed by the teledermatology team, and identified by the in person dermatologist, the Monitor will notify the PI and they will review the case. The clinical safety monitor will ensure all unanticipated problems involving risks to subjects or others are appropriately handled; interim safety reviews are performed; and the procedures for transmitting the results to the IRB are followed.

14.4 Data Integrity Monitoring:

The data safety team, comprised of the study coordinator and study associate will review all source documents and REDCAP database for accuracy and completeness. They will also review the screening and enrollment data to ensure that eligible participants are not being incorrectly excluded from the study, and that ineligible participants are being appropriately excluded. The data safety team will run monthly reports and confirm on the monthly review reports to the clinical safety monitor that all data in the REDCAP database and the CRFs are complete and accurate.

A monthly report will be prepared indicating the numbers of adverse events, subject complaints, numbers of subjects enrolled, numbers of screen failures, recommendations for continuing the study, and any protocol deviations.

14.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents. Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.6 Publication and Data Sharing Policy

All who occupy key roles for the study are eligible for authorship in study publications. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

15 Study Finances

15.1 Funding Source

The study will be financed through foundation grants and philanthropic funds available to the study PI. To date, the Melanoma Research Alliance and the Sergei S. Zlinkoff Fund for Medical Education have provided partial funding the study, and other foundation grant applications have been submitted.

15.2 Costs to the Participant

There is no cost to subjects for any study procedures including the in-person dermatologist, teledermatology evaluation or possible skin biopsy (if performed at our DCSU). If subjects are found to have a skin cancer, treatment of the skin cancer will not be covered by the study and any further cost for treatment will be incurred by the subject and their insurance

15.3 Participant Reimbursements or Payments

Participants will be compensated $25 for participating in the first visit of the study. If the participant qualifies for additional visits, he or she will be paid up to an additional $50 ($25 for each recommended return visit). Compensation will be provided in the form of a check that will be mailed to the mailing address provided to us. If the participant chooses to leave or withdraw from the study for any reason before finishing the entire study (including if he or she does not follow through with recommendations to biopsy a concerning skin spot(s) identified during the study and/or does not share with us results from skin biopsy(s) performed by outside providers of concerning skin spot(s) identified during the study), he or she will not receive the compensation to which they were entitled based on the above scheme for prorated payments.

16 Study Administration

16.1 Study Leadership

Not applicable

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the device manufacturer, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

All NYULMC investigators will follow the applicable conflict of interest policies.

18 References

1. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, Lazar AJ, Faries MB, Kirkwood JM, McArthur GA, Haydu LE, Eggermont AMM, Flaherty KT, Balch CM, Thompson JF, for members of the American Joint Committee on Cancer Melanoma Expert P, the International Melanoma D, Discovery P. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(6):472-92. doi: 10.3322/caac.21409. PubMed PMID: 29028110.
2. Buja A, Sartor G, Scioni M, Vecchiato A, Bolzan M, Rebba V, Sileni VC, Palozzo AC, Montesco M, Del Fiore P, Baldo V, Rossi CR. Estimation of Direct Melanoma-related Costs by Disease Stage and by Phase of Diagnosis and Treatment According to Clinical Guidelines. Acta Derm Venereol. 2018;98(2):218-24. Epub 2017/11/08. doi: 10.2340/00015555-2830. PubMed PMID: 29110018.
3. Harvey, Valerie M., et al. "Social determinants of racial and ethnic disparities in cutaneous melanoma outcomes." *Cancer Control* 21.4 (2014): 343-349.
4. Carli, P., et al. "Improvement of malignant/benign ratio in excised melanocytic lesions in the 'dermoscopy era': a retrospective study 1997–2001." *British Journal of Dermatology* 150.4 (2004): 687-692.
5. Chuchu, Naomi, et al. "Teledermatology for diagnosing skin cancer in adults." *Cochrane Database of Systematic Reviews*12 (2018).
6. Terushkin, Vitaly, et al. "Analysis of the benign to malignant ratio of lesions biopsied by a general dermatologist before and after the adoption of dermoscopy." *Archives of dermatology*146.3 (2010): 343-344.
7. Nevisense Premarket Approval (PMA): U.S. Food and Drug Administration; 2017. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?ID=320650.
8. Malvehy J, Hauschild A, Curiel-Lewandrowski C, Mohr P, Hofmann-Wellenhof R, Motley R, Berking C, Grossman D, Paoli J, Loquai C, Olah J, Reinhold U, Wenger H, Dirschka T, Davis S, Henderson C, Rabinovitz H, Welzel J, Schadendorf D, Birgersson U. Clinical performance of the Nevisense system in cutaneous melanoma detection: an international, multicentre, prospective and blinded clinical trial on efficacy and safety. Br J Dermatol. 2014;171(5):1099-107. Epub 2014/05/21. doi: 10.1111/bjd.13121. PubMed PMID: 24841846; PMCID: Pmc4257502.
9. Kjome RLS, Wright DJ, Bjaaen AB, Garstad KW, Valeur M. Dermatological cancer screening: Evaluation of a new community pharmacy service. Res Social Adm Pharm. 2017;13(6):1214-7. Epub 2016/12/15. doi: 10.1016/j.sapharm.2016.12.001. PubMed PMID: 27964893.
10. Svoboda, Ryan M., Abigail I. Franco, and Darrell S. Rigel. "Electrical Impedance Spectroscopy Versus Clinical Inspection Approaches: Melanoma Efficacy Detection Comparison." *SKIN The Journal of Cutaneous Medicine* 2.3 (2018): 162-167.
11. Rocha, L., et al. "Analysis of an electrical impedance spectroscopy system in short-term digital dermoscopy imaging of melanocytic lesions." *British Journal of Dermatology* 177.5 (2017): 1432-1438.
12. Marks JG, Miller JJ. 9 - Scaling Papules, Plaques, and Patches. In: Marks JG, Miller JJ, eds. *Lookingbill and Marks' Principles of Dermatology (Sixth Edition).* London: Content Repository Only!; 2019:113-134.

13. Bowns, Ian R., et al. "Telemedicine in dermatology: a randomised controlled trial." *Health Technology Assessment (Winchester, England)* 10.43 (2006): iii-iv.
14. Carli P, De Giorgi V, Crocetti E, et al. Improvement of malignant/benign ratio in excised melanocytic lesions in the 'dermoscopy era': a retrospective study 1997-2001. Br J Dermatol 2004;150:687-92.
15. Argenziano G, Cerroni L, Zalaudek I, et al. Accuracy in melanoma detection: a 10-year multicenter survey. J Am Acad Dermatol 2012;67:54-9.
16. English DR, Del Mar C, Burton RC. Factors influencing the number needed to excise: excision rates of pigmented lesions by general practitioners. Med J Aust 2004;180:16-9.
17. Hansen C, Wilkinson D, Hansen M, Argenziano G. How good are skin cancer clinics at melanoma detection? Number needed to treat variability across a national clinic group in Australia. J Am Acad Dermatol 2009;61:599-604.
18. Althunian TA, de Boer A, Groenwold RHH, Klungel OH. Defining the noninferiority margin and analysing noninferiority: An overview. *Br J Clin Pharmacol*. 2017;83(8):1636–1642. doi:10.1111/bcp.13280

19 Supplemental Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments

A. Nevisense Summary of Safety and Effectiveness (PMA)
B. Nevisense Administration & Service Instructions
C. Nevisense Instructions for Use
D. Study Print Advertisement
E. Study Online Advertisement
F. Sample Certified Letter For Malignancy Diagnosis
G. Sample Certified Letter For Skin Biopsy Recommendation
H. Emergency Patient Card (samples)
I. Nevisense Acquisition Commitment Letter from SciBase
J. DermLite Cam Instructions for Use
K. Enrollment Patient Questionnaire
L. Participant Experience Questionnaires (After data acquisition, Visit 1, Visit 3)
M. Teledermatologist Biopsy Recommendation Phone Script
N. Teledermatologist No Biopsy Recommendation Phone Script
O. Pre-screening Questionnaire
P. Pre-screening and Scheduling Phone Script
Q. Key Information Sheet (for participant)
R. Wound Care (take-home patient sheet)
S. Wound Care Assessment & Biopsy Result Communication Phone Script
T. In-Person Dermatologist Data Collection Form
U. Teledermatologist Data Collection Form

20 Schedule of Events

Activity	Pre-Screening Visit	First Visit [1]	Teledermatologist Report Phone Call* [4+/-2]	Skin Biopsy Visit* [7 +/-2]	Biopsy Pathology Result Phone Call* [17 +/- 3]	Suture Removal Visit* [21+/- 3]
Study team procedures						
Recruitment Survey and possible scheduling for first visit	X					
Eligibility Screening		X				
Informed Consent		X				
Enrollment Questionnaire with Medical History		X				
Physical Exam		X				
Procedural Intervention (Image acquisition, Nevisense measurement)		X				
Control Intervention (in-person dermatologist evaluation)		X				
Skin biopsy procedure		X*		X*		
Teledermatologist report communicated			X*			
Scheduled for biopsy			X*			
Wound Check					X*	X*
Suture removal (if necessary)						X*
Communicate Biopsy result					X*	
Scheduled for suture removal (if necessary)				X*	X*	
Subject Study Completion Questionnaire			X*		X*	
Laboratory Assessments						
Skin Biopsy Processing Initiated		X*		X*		

*For Select Participants

This material is the property of the NYU School of Medicine and Langone Medical Center. Do not disclose or use except as authorized in writing by the study sponsor