Full Study Title:	At-home dermoscopy artificial intelligence for optimizing early triage of skin cancers and atypical melanocytic nevi with uncertain malignant potential
Protocol Number:	STUDY00023727
ClinicalTrials.gov ID	NCT05321784
Investigational Product:	Sklip System
Version Number:	5.05
Version Date:	09-15-2023
Replaces:	First Submission
Principal Investigator:	Sancy Leachman MD, PhD
	Department of Dermatology Oregon Health & Science University 3181 SW Sam Jackson Park Road Portland, OR 97239 Phone: 503-418-9356 Fax: (503) 494-6968 Email: leachmas@ohsu.edu
Investigational Product Evaluation Site	Participants will test the Sklip System at their home address using the Sklip dermatoscope device hardware, the Sklip Mole Scanning Algorithm (SMSA) and access to the research version of the Sklip App. Related training will be virtual.
Regulatory Sponsor: (if different)	Sklip Inc. 4800 Meadows Rd Ste 300 Lake Oswego, OR 97035 971-867-1069 Email: service@sklip.Ai Study Financing is described in a separate agreement(s) between the individual Sponsor and each Study Site.
Statistician:	Emile Latour, M.S Oregon Health and Science University Biostatistics Shared Resource Phone: (503) 223-1220 Fax: (503) 494-6968 Email: latour@ohsu.edu

SUMMARY OF CHANGES

#	Section	Summary of Changes	Justification
1	Synopsis, 3.1	Clarification that the Dermatology Provider performing the clinical full body skin exam will be blinded to the skin lesions that were selected by the study Participant at home. Addition of requirement for the Dermatology Provider to verbally inform the Study Coordinator the Participant's Fitzpatrick skin phototype (1,2,3,4,5 or 6) after leaving the patient room.	Clarification of how selection-bias will be avoided. How the Dermatology Provider assess the Participants Fitzpatrick skin phototype.
2	Synopsis, 5.3.1	Addition of the following text to clarify blinding procedures: Specifically, the dermatology provider will be instructed to say the following to each participant upon entering the patient room for the in-person FBSE: "Hello, my name is [name and title], the purpose of today's visit is to complete a full body skin examination as part of the at-home dermoscopy study. In order to avoid bias, please hold with any questions related to your moles of concern until I have verified that I completed your full body skin examination and all other study related activities. I will be happy to address your questions or concerns at that time."	Address FDA concerns regarding blinding and provide a uniform experience for the patient
3	Synopsis, 3.1	Addition of the following text to clarify situations where the Participant did not complete a part of at home tasks: 8) If the Participant has taken a set of SCI/DDI at home of a PSLC that is not intended (qualified because of anatomic body site) for the Sklip System, the Study Coordinator should still capture a set of control SCI/DDI and upload to REDCap Cloud. The Participant standard clinical care will not be changed. 9) If the Participant took a set of SCI/DDI of a PSLC at home but did not follow instructions – specifically uploading the DDI to the Sklip System - the Study Coordinator should remind the Participant to complete this task in the patient room (using the DDI from their mobile device gallery), upload to the Sklip System, and record the output on their Mole Log Sheet. If this situation occurs, the Study Coordinator should make a note in REDCap Cloud; If the Participant is/was concerned about a PSLC but did not take a set of SCI/DDI at home, this PSLC will not be included in the study.	Provide clarification

4	4.1, 14.3	Removed language regarding legally authorized representative (LAR)	This was discordant with the exclusion criteria and now updated

SYNOPSIS

Full Study Title	**At-home dermoscopy artificial intelligence for optimizing early triage of skin cancers and atypical melanocytic nevi with uncertain malignant potential**
Protocol #	**STUDY00023727**
Study Type	Prospective single-arm open-label multicenter research Study
Study Sample Size	310 Participants
Lead Study Site	Oregon Health and Sciences University (OHSU) in Portland, Oregon 3303 S Bond Ave CHH1 Ste 16 (Department of Dermatology) PI: Sancy Leachman MD, PhD (leachmas@ohsu.edu)
Satellite Study Site(s) Governance	OHSU IRB will not be responsible for governing any of the Satellite Study Sites. Their governance will be a third-party IRB using this IRB Protocol for guidance.
Study Site #2	Skin Cancer Center 3024 Burnet Ave, Cincinati, OH 45219 PI: Michael Tassavor MD FAAD (mtassavor2@gmail.com)
Study Site #3	The Skin Center Dermatology Group 200 East Eckerson Rd, New City, NY 10956 PI: Peter Friedman MD, PhD FAAD (pbc9@cumc.columbia.edu)
Study Site #4	The Private Practice of Johnny Gurgen D.O. P.A. 1340 Citizens Blvd, Leesburg, FL 34748 PI: Johnny Gurgen DO FAOCD (johngurgen@gmail.com)
At-Home Phase Duration	Up to 14 days, completed by Participants at their home address
In-Person Phase Duration	Up to 28 days, completed by Participants and Study Coordinators in-office
Enrollment Duration	Up to 90 days
Abbreviated Definitions in Sequential Order	Sklip System (Sklip dermatoscope device and SMSA (used in the Sklip App)) SMSA: Sklip Mole Scanning Algorithm SCI: Smartphone clinical images (non-medical-device assisted) DDI: Digital dermoscopy images PSLC(s): Pigmented skin lesion(s) of concern FDA: United States Food and Drug Administration PMLS: Participant Mole Log Sheet SaMD: Software as a Medical Device API: Application Program Interface DP: Dermatology Provider APP: Advanced Practice Practitioner (Physicians Associate or Nurse Practitioner) PCP: Primary Care Provider MD3PC: Modified dermoscopy three-point checklist DRFs: Dermoscopic remarkable features (based on the MD3PC)

	SSE(s): Self-skin-exam(s) performed by Participants at-home FBSE(s): Full body skin exam(s) performed by DPs in-office SCI-TD: Expert dermatologist consensus SCI triage decision DDI-GT: Expert dermatologist consensus DDI dermoscopic diagnosis DHI: Digital histologic image of a target PSLC biopsied during the In-person Phase EMR: Electronic medical record
Study Device Hardware	The **Sklip dermatoscope** device hardware will be provided to Participants to take DDI of their self-selected PSLCs using their smartphone or tablet. The Sklip dermatoscope is publicly (commercially) available and registered as a Class 1 Medical Device (FDA Reg. 3017732705).
Study Site Secure Smartphone and Sklip	The sponsor will provide one (1) smartphone to each Study Site, one (1) unique passcode access to the SMSA within the Sklip App, one (1) Sklip dermatoscope (with charging cable, instructions, and dermoscopy oil) for use with Participants in-office. Clear instructions will be given to delete all images from the native smartphone photo App gallery after Study Site Coordinators upload required data and images to the OHSU secure cloud, prior to returning the smartphone to the Sponsor. This will ensure no patient health information leaves the Study Site on physical hardware.
Study App	The **Sklip App** is a publicly available smartphone App to download on the Apple iOS and Google Play app stores. The Sklip App is non-FDA regulated and part of the approved protocol for the Melanoma Community Registry (OHSU IRB# 10561). A security review of the Sklip App has been performed as part of that Study and is transferred to this Study protocol.
Sklip Mole Scan Algorithm (SMSA)	The proprietary SMSA sensitivity triage performance is: 97.4% for melanoma and atypical melanocytic nevi with uncertain malignant potential, 97.0% for squamous cell carcinoma, 97.3% for basal cell carcinoma.
Synopsis of the Sklip System	The Sklip System is a SaMD that received breakthrough designation by the FDA on June 22, 2021. The Sklip System is intended to record, store and transfer DDI. The Sklip System consists of the Sklip App (used on a smartphone or tablet) and SMSA, that accept DDI taken by dermatoscope hardware. The Sklip System also displays DDI and non-diagnostic output of DDI analysis from the Sklip System software library that implements various DDI processing and artificial intelligence (Ai) analysis. This SaMD computes various digital parameters from DDI and provides these capabilities in the form of an API library. DDI can be incorporated into the Sklip System software to enable algorithmic analysis and analytics of DDI by the SMSA. The SMSA, is a software workflow tool designed to aid the assessment of DDI data input intended to conduct an initial screening of DDI for features suggestive of skin cancer and flag suspicious DDI for expedited review by appropriate medical personnel, such as a dermatology Provider (Dermatologist or dermatology trained APP), or primary care Provider (PCP). Specifically, the SMSA, via the Sklip System " Scan Moles with Ai" function, uses a Sklip Inc. proprietary Ai algorithm to provide DDI filtering, detection of noisy (non-qualified) DDI and detection of skin lesions containing qualified pigment that may be remarkable for MD3PC features ((DRFs): dermoscopic asymmetry, dermoscopic round structures and/or dermoscopic blue-white colors), which may be indicative of skin cancer.
Brief Description Of Study Intervention	This is a new protocol to analyze how the use of the Sklip System enables laypersons to safely triage self-selected PSLCs from home with the same or better accuracy than pre-specified performance goals* for the detection of PSLCs that require biopsy (**Melanoma and atypical melanocytic nevi with uncertain malignant potential** (moderate, severe, and high grade atypia; those with

	pathology reports that include notes such as: borderline, cannot exclude melanoma, cannot exclude early evolving melanoma, unusual features, atypical spitz nevi, suspicion for melanoma, re-excision (or further removal) should be considered or is recommended in the pathologist management comment), **Squamous cell carcinoma**, **Basal cell carcinoma**). The Study protocol will also compare the accuracy of the Sklip System when used by a layperson (Participant) versus near-perfect Sklip System user (Study Coordinator), assess whether Sklip System improves triage of PSLCs < 6 mm in diameter and triage of thin melanomas with <0.8 mm Breslow depth as suspicious, as compared to the current medical provider virtual triage method that relies on store-and-forward of smartphone clinical images (SCI), and assess accuracy of layperson-performed self-skin-exams (SSEs) at-home in the identification of all suspicious PSLCs present on their body as compared to the same layperson (Participant) evaluated with a full body skin examination (FBSE) by a dermatology Provider (DP) in-person.
Primary Objective	The Sklip System enables laypersons to safely triage self-selected pigmented skin lesions of concern (PSLCs) from home with the same or better accuracy than pre-specified performance goals* for detection of PSLCs that require biopsy and are malignant: **Melanoma and atypical melanocytic nevi with uncertain malignant potential** (moderate, severe, and high grade atypia; those with pathology reports that include notes such as: borderline, cannot exclude melanoma, cannot exclude early evolving melanoma, unusual features, atypical spitz nevi, suspicion for melanoma, re-excision (or further removal) should be considered or is recommended in the pathologist management comment) (≥95% sensitivity, ≥30% specificity), **Squamous cell carcinoma** (≥80% sensitivity, ≥30% specificity), **Basal cell carcinoma** (≥80% sensitivity, ≥30% specificity).
Exploratory Objectives	1. To compare the accuracy of Sklip System triage when used by a layperson versus near-perfect Sklip System user 2. To assess whether Sklip System improves triage of pigmented skin lesions of concern < 6mm in diameter as suspicious as compared to the current medical provider virtual triage method that relies on store-and-forward non-medical-device assisted smartphone clinical images 3. To assess whether Sklip System improves triage of thin melanomas with < 0.8 mm Breslow depth as suspicious as compared to the current medical provider virtual triage method that relies on store-and-forward non-medical-device assisted smartphone clinical images 4. To determine the accuracy of layperson-performed self-skin-exam(s) at-home in the identification of all suspicious pigmented skin lesions of concern present on their body as compared to the same layperson evaluated with full body skin examination by a dermatology Provider in-office
***Pre-specified Performance Goals**	*Pre-specified performance goals have been reviewed with the FDA for testing the Sklip System (including SMSA) as a stand-alone device.
Participant activity prior to the At-home Phase	A copy of the Participant Mole Log Sheet (PMLS) will be provided to Participants at the beginning of the At-home Phase. All Participants will be administered a pre-survey at the start of the Study to assess baseline knowledge and comfort in performing a SSE as well as a post-survey at the end of the Study.
Blinding	The Study Site PIs and DPs will be fully blinded to all results of the At-home Phase, including the PMLS. Participants will be informed of the blinding activity prior to their FBSE to avoid DP selection-bias. Specifically, the dermatology provider will be instructed to say the following to each participant upon entering

	the patient room for the in-person FBSE: "Hello, my name is [name and title], the purpose of today's visit is to complete a full body skin examination as part of the at-home dermoscopy study. To avoid bias, please hold with any questions related to your moles of concern until I have verified that I completed your full body skin examination and all other study related activities. I will be happy to address your questions or concerns at that time."
Synopsis of the At-home Phase in sequential order	Participants will be asked to **review** the Sklip System instructions, **perform** a SSE at-home, and **identify** PSLCs based on the following: (a) General concern (self or partner-identified, or non-dermatology Provider identified requiring a referral to a dermatology Provider) (b) Concern because the PSLC is different than the rest (i.e. "ugly duck sign") Then, Participants will be instructed to carefully follow provided instructions and **complete** the following for each target PSLC: 1) Mark the target PSLC with a green surgical marker (horizontal line) and the number (#) corresponding to the mole log, one (1) inch away from the target lesion 2) Record the target PSLC with a number (#) and anatomic location in the PMLS 3) Create a new photo album titled: "Moles" in their native smartphone/tablet Photo App 4) Take one (1) smartphone clinical image (SCI) of the target PSLC, twelve (12) inches away from the target skin lesion 5) Save the SCI in the album titled: "Moles" album 6) Review Sklip dermatoscope instructions for proper use 7) Take one (1) digital dermoscopy image (DDI) of the target PSLC using the Sklip dermatoscope. 8) Save the DDI of the target PSLC in the "Moles" album 9) Upload the DDI to the SMSA ("Scan Moles with Ai") within the Sklip App once per target PSLC, until either a Suspicious or Unremarkable result is obtained, for a maximum of three attempts. If after three attempts the user still receives an "Error" result, they will be prompted to document this in the participant mole log sheet. 10) Take one (1) screenshot of the SMSA output per target PSLC 11) Save the SMSA output screenshot in the album titled: "Moles" 12) Record each SMSA output (SUSPICIOUS, UNREMARKABLE, ERROR) in the PMLS once per target PSLC 13) Contact the Study Site to schedule an in-person FBSE within 28 days, if the Participant does not already have a scheduled visit
Summary of Participant data acquisition for each target PSLC	One (1) smartphone clinical image (SCI) One (1) digital dermoscopy image (DDI) One (1) Sklip Mole Scanning Algorithm (SMSA) output recorded in the PMLS One (1) SMSA output screenshot
Synopsis of the In-person Phase in sequential order	**With dermatology Provider present:** The dermatology Provider (DP) will be blinded to the skin lesions that were selected by the study Participant at home. The DP will perform a FBSE as part of the normal clinical care pathway. All PSLCs identified by the DP as SUSPICIOUS will be marked with a vertical line one (1) inch away from the target PSLC using a green surgical marker. After completing the FBSE and

	marking all DP-selected suspicious PSLCs, the DP will verbally inform the Study Coordinator the Participant's Fitzpatrick skin phototype (1,2,3,4,5 or 6) after leaving the patient room. **Without dermatology Provider present,** **with Study Coordinator present:** The Participant will be asked to provide their Participant Mole Log Sheet (PMLS). Then, all PSLCs recorded in the PMLS will entered into REDCap Cloud by the Study Coordinator. Any Participant-selected PSLCs that match those identified earlier as SUSPICIOUS by the DP will be marked with a horizontal line one (1) inch away from the target PSLC using a green surgical marker. Therefore, PSLCs identified by both the DP and Participant will have a plus symbol. Next, the Study Coordinator will take and record (near-perfect) SCI and DDI for all PSLCs recorded in the PMLS and those PSLCs identified by the DP as SUSPICIOUS (not matching the Participant PSLCs). Then, the Study Coordinator will complete the following: 1) Take one (1) photo of the Participant identification sticker with a Study Site secure smartphone/tablet 2) Take one (1) smartphone clinical image (SCI) of each target PSLC recorded in the Participant Mole Log Sheet (PMLS) 3) Take one (1) digital dermoscopy image (DDI) of each target PSLC using the Sklip dermatoscope. 4) Save the DDI of the target PSLC in the Study Site smartphone/tablet native photo gallery 5) Upload the Study Coordinator-taken DDI to the SMSA ("Scan Moles with Ai") within the Sklip App 6) Take one (1) screenshot the SMSA output 7) Record each SMSA output (SUSPICIOUS, UNREMARKABLE, ERROR) in REDCap Cloud, per target PSLC 8) If the Participant has taken a set of SCI/DDI at home of a PSLC that is not intended (qualified because of anatomic body site) for the Sklip System, the Study Coordinator should still capture a set of control SCI/DDI and upload to REDCap Cloud. The Participant standard clinical care will not be changed. 9) If the Participant took a set of SCI/DDI of a PSLC at home but did not follow instructions – specifically uploading the DDI to the Sklip System - the Study Coordinator should remind the Participant to complete this task in the patient room (using the DDI from their mobile device gallery), upload to the Sklip System, and record the output on their Mole Log Sheet. If this situation occurs, the Study Coordinator should make a note in REDCap Cloud; If the Participant is/was concerned about a PSLC but did not take a set of SCI/DDI at home, this PSLC will not be included in the study.
Synopsis of Study Data Collection	Study Coordinators at each Study Site will conduct regular EMR chart reviews to track Participant requests to begin their In-person Phase, after the Participant has completed their the At-home Phase.

Study Coordinators will use the Participant mole log sheet (PMLS) and Participant-taken SCI/DDI (from the native smartphone gallery titled "MOLES") for guidance and **<u>create</u> the following Datasets**:

A) Total number of PSLCs identified by the Participant at-home

B) Total number of PSLCs identified by the DP in-office

C) One (1) SMSA output recorded in the PMLS, per target PSLC

D) One (1) Participant-taken SCI, per target PSLC

E) One (1) Participant-taken DDI, per target PSLC

F) One (1) Participant-taken SMSA output screenshot, per target PSLC

G) One (1) Study Coordinator-taken DDI (near-perfect image technical quality) for each PSLC recorded in the PMLS and suspicious PSLCs identified by the DP in-office that were not recorded in the PMLS

H) One (1) Study Coordinator-taken SMSA output for each PSLC, recorded in the PMLS, using Dataset (G)

I) All other SCI of suspicious PSLCs identified by the DP in-office that were not recorded in the PMLS

J) All other DDI of suspicious PSLCs identified by the DP in-office that were not recorded in the PMLS

K) Pathology reports for all PSLCs that were biopsied during the In-Person Phase

L) Number of adverse events reported during the Study

Satellite Study Sites will also complete the above activities and securely **<u>submit</u>** their Datasets (A-L) to the Lead Study Site via OHSU secure cloud storage services. The Lead Study Site will prepare individual Qualtrics surveys using images from the Datasets above to **<u>create</u> the following Datasets**:

Dataset M) <u>SCI triage decision</u> (SCI-TD) based on Datasets (D) and (I), when at least two of three expert dermatologist readers have a concordant triage decision (MONITOR or BIOPSY). If there is a lack of concordance, an internationally recognized dermoscopy expert (dermatologist) will act as a fourth reader to determine the final SCI-TD

Dataset N) <u>DDI dermoscopic diagnosis ground truth</u> (DDI-GT) for PSLCs that were not biopsied during the In-Person Phase, using images in Datasets (E) and (J), when at least two of three expert dermatologist readers have a concordant dermoscopic diagnosis. If there is a lack of concordance, an internationally recognized dermoscopy expert (dermatologist) will act as a fourth reader to determine the final DDI-GT

Dataset O) <u>Histologic diagnosis ground truth</u> (H-GT) for lesions that were biopsied during the In-Person Phase, based on evaluations using either physical or digital histologic slides (described in Sections below), when both independent expert dermatopathologists have a concordant histologic diagnosis. If there is a lack of concordance, a third internationally recognized expert dermatopathologist will determine the final H-GT.

The Study Sponsor will be responsible for Study costs (logistics, shipping, handling, research reading fees) associated with the use of either physical or

	digital histologic slides to create Dataset O. If digital histologic images (DHI) are chosen, the Lead Study Site will be asked to prepare DHI for their own Study Site Participants who received a biopsy during the In-person Phase. The Lead Study Site will have the option to prepare DHI for the Satellite Study Sites. In order to eliminate biopsy specimen evaluation-bias there will not be a request to confirm or rule out any specific dermatologic neoplasm entity. All biopsy specimen slides will be de-identified and presented in blind to expert dermatopathologists at an independent Study Site for evaluation with only the following information: Participant **age**, **sex**, skin lesion **anatomic location**, and a written dermatopathology request: "**Please evaluate for pigmented skin lesion**."
Study ground truth	The following method has been discussed with the FDA via Sklip Inc. Q-Submission Sprint Discussion (#Q211049/S002/A002) Dataset N) DDI dermoscopic diagnosis ground truth (DDI-GT) for PSLCs that were not biopsied during the In-Person Phase, and Dataset O) Histologic diagnosis ground truth (H-GT) for lesions that were biopsied during the In-Person Phase
Product Labelling	Product labelling for proper use of the Sklip System by users (Study Participants) interpretation of SMSA Outputs (SUSPICIOUS, UNREMARKABLE, ERROR) are described in Sections below.
Key Inclusion Criteria	Study Site patients >21 years of age, English-speaking, access to a smartphone, self-identified having Fitzpatrick Skin Types 1-4. The recruitment source will include running an electronic medical record (EMR) patient report for Study recruitment (i.e. EPIC at OHSU, ModMed EMA at other Study Sites, or other EMR type).
Key Exclusion Criteria	Participants who self-identify having Fitzpatrick Skin Types 5 and 6, visionally impaired adults, pregnant and breastfeeding mothers. Participants who have had a skin check visit with a dermatology Provider within the last 90 days will be excluded to avoid self-selection bias, unless the Participant identifies a new unexamined (not previously documented) spot of concern. Vulnerable populations including children, prisoners, and decisionally impaired adults, will not be eligible for this Study. The Sklip System output is currently only available in English language, therefore non-English speaking Participants are not eligible.
Skin lesions not applicable for SMSA evaluation	Sklip System instructions and product labelling clearly define specific device limitations and suggest the Participant (user) to contact their healthcare Provider with their PSLC as part of normal clinical care, when the target PSLC does not qualify, or if the user does not understand the SMSA output result. The following anatomical locations, Fitzpatrick Skin Types and skin lesion types are not applicable for SMSA evaluation: *Non-qualified anatomical areas*: images of skin lesions taken from a non-sun exposed area (eyes, mucosal membranes (eyelids, medial canthi, mouth, anus, genitals)), hidden or not flat areas (nails, ears, perinasal fold, conchal bowl, intergluteal cleft, perianal skin and interdigital spaces) and/or acral lesions (palms of hands and soles of feet). *Not applicable Fitzpatrick Skin Types*: 5 and 6

	Pink skin lesions: a skin lesion (mole) that does not contain any pigment, contains only white, pink, red or uniform-homogenous color similar to the surrounding skin within its surface area, contains less than five (5) percent pigment within the skin lesion surface area or clearly defined in-focus vasculature that can be visualized with a dermatoscope (i.e. actinic keratosis without pigment, clinically and dermoscopically pink melanocytic nevi, amelanotic melanoma, basal cell carcinoma or squamous cell carcinoma without any pigment).
Definition of Pigment qualified for Sklip System	Pigment is defined as any color other than the surrounding skin phototype that delineates a skin lesion from the background that can be visualized with a dermatoscope. This includes: light brown, dark brown, black, white, blue, grey, purple, red, pink, yellow, and orange (including clearly distinguishable vascular patterns within the skin lesion surface area).
Follow-up Duration	After conclusion of the Study intervention, the EMR(s) of all enrolled Participants will be monitored for any relevant data obtained from follow up (as part of standard clinical pathways). An attempt to contact Participants lost to follow-up will be made for up to 30 days.
Duration of Therapy	There is no therapy as part of this Study.
Sponsor Monitoring	The Sponsor will conduct periodic monitoring of the Study Site data handling practices on REDCap Cloud every 45 days on at least one (1) instance to verify the integrity of the source data. This will be done in person or virtually with an approved Study Site representative responsible for REDCap Cloud use and data handling. At the end of the Study, ten percent (10%) of the source data will be re-evaluated by the Sponsor to re-verify the integrity of the source data.
Interim Data Analysis	There will not be any interim data analysis during this Study.
Medical costs during the In-Person Phase	All medical services that fall under the normal clinical care pathway including: scheduling, triage, spot check, FBSE, biopsy, diagnosis and treatment (when applicable), will not be covered by the Study Sponsor and will be billed by Study Sites directly to patient insurance, or required to be paid out pocket.
Final Disposition of the Sklip dermatoscope and Sklip System access	All Participants will be able to keep their Sklip dermatoscope at the end of the Study, at no cost. SMSA access will expire within fourteen (14) days of confirmed delivery of the Sklip dermatoscope at the home address of the Participant.
Participant Safety	There remains the risk that a Participant may not identify a skin lesion on their body that is malignant (both a PSLC and a non-PSLC). However, all risks are associated with the current at-home standard of care protocol for SSEs and not increased by use of the Sklip System. All Participants are required to come for an in-person FBSE, regardless of if they identify a PSLC during the At-home Phase. The FBSE will ensure that no malignancies are missed.
Synopsis of Statistical Analysis	An intent-to-treat (ITT) analysis set will include those who are enrolled in the Study regardless of adherence. All primary analyses will be conducted using the intent-to-treat analysis set. Demographic and clinical characteristics will be summarized using descriptive statistics (e.g. proportions, mean/median, and standard deviation/range). The Ground Truth will be the combination of the following: Dataset N) DDI dermoscopic diagnosis ground truth (DDI-GT) for PSLCs that were not biopsied during the In-Person Phase, and

Dataset O) Histologic diagnosis ground truth (H-GT) for lesions that were biopsied during the In-Person Phase

For the Primary and Secondary endpoints, the SMSA output of "SUSPICIOUS" or "UNREMARKABLE" from Participant-taken digital dermoscopy images (DDI) will be compared to the Ground Truth.

Primary endpoints

For the Primary endpoints, the SMSA output of "SUSPICIOUS" or "UNREMARKABLE" from Participant-taken digital dermoscopy images (DDI) will be compared to the Ground Truth.

For **Melanoma and atypical melanocytic nevi with uncertain malignant potential**, Sensitivity ($TP \div (TP + FN)$) of the SMSA will be calculated with a lower one-sided 95% confidence interval using the Exact (Clopper-Pearson) method.

For **Squamous cell carcinoma** and **Basal cell carcinoma**, Sensitivity and lower one-sided confidence intervals will be estimated in the same manner as for Melanoma and atypical melanocytic nevi with uncertain malignant potential.

Specificity ($TN \div (FP + TN)$) will be the same for Melanoma and atypical melanocytic nevi with uncertain malignant potential, Squamous cell carcinoma, and Basal cell carcinoma. Specificity will be estimated with a lower one-sided 95% confidence interval using the Exact (Clopper-Pearson) method. Two-sided 95% confidence intervals for all sensitivities and specificity will also be calculated using the Exact (Clopper-Pearson) method.

Exploratory endpoint 1

Similar to the Primary endpoint, the accuracy of SMSA output using Participant-taken DDI will be assessed using a 2x2 table, where the SMSA output of "SUSPICOUS" or "UNREMARKABLE" will be compared to the SMSA output using Study Coordinator-taken DDI (near-perfect technical quality), simulating a laboratory-type environment where the SMSA is fed the near-perfect technical quality DDI.

The Sensitivity of the SMSA output from Participant-taken DDI will be compared to the Sensitivity of the SMSA output from Study Coordinator-taken DDI using McNemar's Test, given the paired nature of the data, using 0.05 significance level.

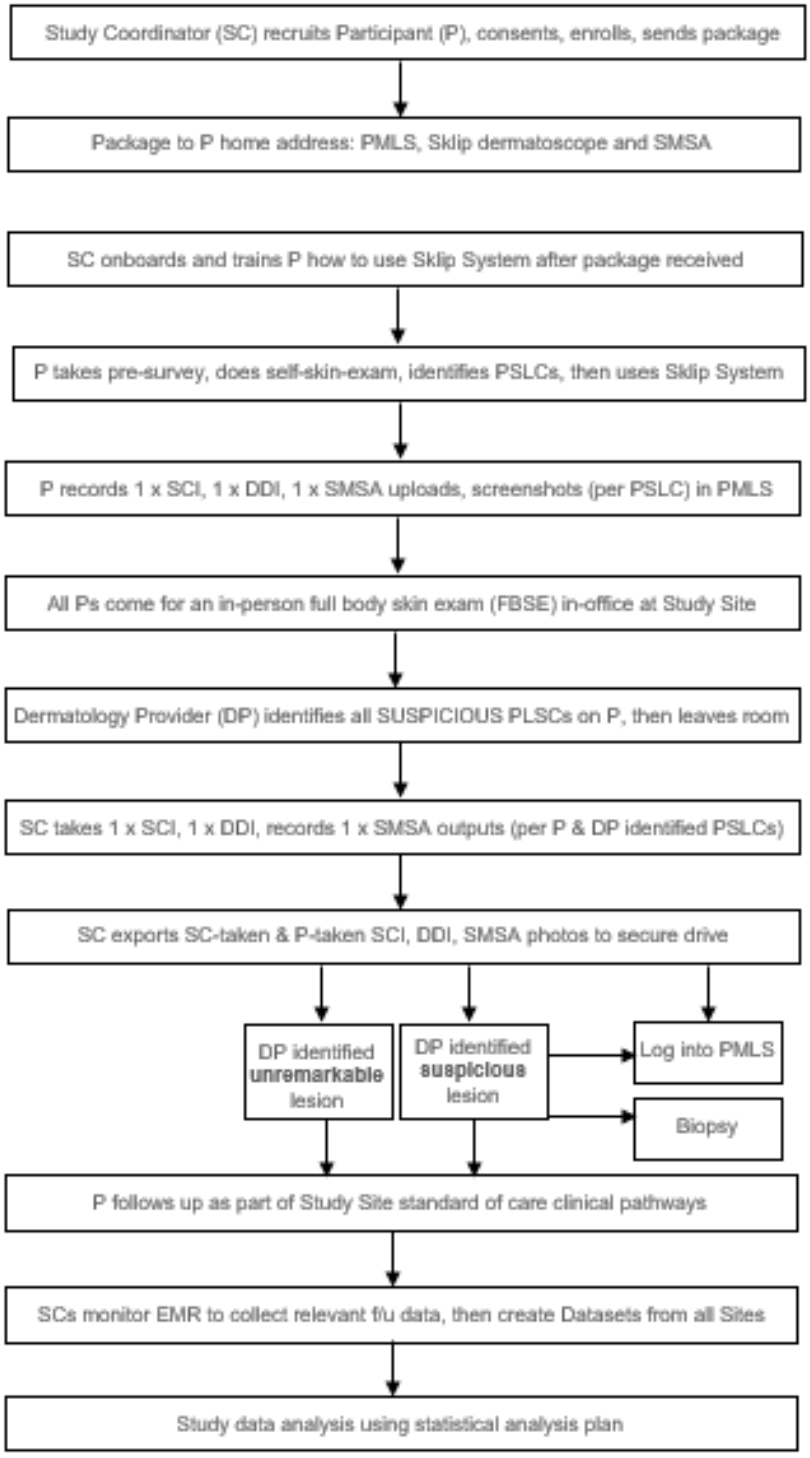
The Specificity of the SMSA output from Participant-taken DDI will be compared to the Specificity of the SMSA output from Study Coordinator-taken DDI using McNemar's Test, given the paired nature of the data, using 0.05 significance level.

This will be done for each disease entity:

- Melanoma **and atypical melanocytic nevi with uncertain malignant potential** (moderate, severe, and high grade atypia; those with pathology reports that include notes such as: borderline, cannot exclude melanoma, cannot exclude early evolving melanoma, unusual features, atypical

	spitz nevi, suspicion for melanoma, re-excision (or further removal) should be considered or is recommended in the pathologist management comment) • Squamous cell carcinoma, • Basal cell carcinoma *Exploratory endpoint 2:* Using only PSLs < 6 mm in diameter, the accuracy of the expert consensus triage decision using Participant-taken smartphone clinical images (SCI) will be assessed using a 2x2 table, where the expert consensus triage decision of "BIOPSY" or "MONITOR" will be compared to the intervention method, for both SMSA outputs recorded by Participants and SMSA outputs recorded by Study Coordinators for the same target PSLCs. The Sensitivity of the SMSA output will be compared to the Sensitivity of the expert consensus triage decision of Participant-taken SCI using McNemar's Test, given the paired nature of the data (i.e. the same PSLCs < 6mm), using 0.05 significance level. The Specificity of the SMSA output will be compared to the Specificity of the expert consensus triage decision of Participant-taken SCI using McNemar's Test using 0.05 significance level. This will be done for each disease entity listed above in Exploratory endpoint 1. *Exploratory endpoint 3:* Using only Melanomas < 0.8 mm Breslow depth, the accuracy of the expert consensus triage decision using Participant-taken smartphone clinical images (SCI) will be assessed using a 2x2 table, where the expert consensus triage decision of "BIOPSY" or "MONITOR" will be compared to the intervention method, for both SMSA outputs recorded by Participants and SMSA outputs recorded by Study Coordinators for the same target PSLCs. The Sensitivity of the SMSA output will be compared to the Sensitivity of the expert consensus triage decision of Participant-taken SCI using McNemar's Test, given the paired nature of the data (i.e. the thin melanomas < 0.8 mm Breslow depth), using 0.05 significance level. *Exploratory endpoint 4* We will calculate the following based on Participant self-skin exams (SSEs) performed during the At-home Phase: (a) the mean and standard deviation of the number of PSLCs identified by Participants performing a SSE, and (b) the mean and standard deviation of the number of PSLCs identified by the dermatology Provider during the In-person Phase full body skin exam (FBSE). The mean difference and 95% confidence interval will be calculated and assessed by paired t-test.

SCHEMATIC OF STUDY DESIGN



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LIST OF ABBREVIATIONS

CFR	United States Code of Federal Regulations
CoC	National Institutes of Health (NIH) Certificate of Confidentiality
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
Ecris	Electronic Clinical Research Information System
HIPPA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
N/A	Not applicable
OHSU	Oregon Health & Science University
[SKLIP SYSTEM]	[Sklip dermatoscope device and SMSA (used in the Sklip App)]
SMSA	Sklip Mole Scanning Algorithm
SCI	Smartphone clinical images (non-medical-device assisted)
DDI	Digital dermoscopy images
PSLC(s)	Pigmented skin lesion(s) of concern
FDA	United States Food and Drug Administration
PMLS	Participant Mole Log Sheet
SaMD	Software as a Medical Device
API	Application Program Interface
DP	Dermatology Provider
APP	Advanced Practice Practitioner (Physicians Associate or Nurse Practitioner)
PCP	Primary Care Provider
MD3PC	Modified dermoscopy three-point checklist
DRFs	Dermoscopic remarkable features (based on the MD3PC)
SSE(s)	Self-skin-exam(s) performed by Participants at-home
FBSE(s)	Full body skin exam(s) performed by DPs in-office
SCI-TD	Expert dermatologist consensus SCI triage decision
DDI-GT	Expert dermatologist consensus DDI dermoscopic diagnosis
DHI	Digital histologic image of a target PSLC biopsied during the In-person Phase
EMR	Electronic medical record

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 BACKGROUND

Reduced access: Appointment delays for skin lesion (mole) spot checks and FBSEs average 3-6 months nationally and were markedly increased during the COVID-19 Pandemic. Lack of access to a dermatology Provider (DP) is a result of limited number of DPs compared to the increasing population, low output of new DPs from MD/DO residency programs and NP/PA training programs compared to the rising population, understaffed clinics, and rising incidence of skin cancers that overwhelm the American healthcare system.

Shift to virtual care: There has been a monumental shift towards patient acceptance of virtual dermatology care in the last 36 months due to the Pandemic. Traditionally, virtual spot checks are performed using store-and-forward (SAF) patient-submitted SCI (non-medical-device assisted) that is evaluated by a DP. Accuracy of triage using SCI is lower than use of DDI for the same target skin lesion due dermoscopy inherently providing more visual information through magnification and visualization of surface and subsurface structures that are not detectable when using the naked-eye in-office or SCI virtually.[1]

Subjective selection bias of skin lesions (moles) of concern by patients at-home: Patients select PSLCs based on subjective concern and lack of professional triage training. A large portion of virtual visits initiated by patients result in reassurance by a DP that the PSLC is actually benign.

High conversion rate of virtual visits to in-person visits due to image clarity/selection bias: Evaluation of skin lesion images virtually using SCI typically results in low triage confidence by the DP. Provider uncertainty is largely due to limitations in image clarity and lack of medical-device assistance in an at-home environment. This often leads to a high conversion rate to an in-person evaluation by a DP. In the majority of cases the in-office DP, using a dermatoscope, will find that the PSLC is benign. This leads to patients being billed twice for triage for the same PSLC (1^{st} = virtual visit, 2^{nd} = in-person visit).

Packing the healthcare system can lead to delay of care for other patients: Layperson concern of unknowingly benign skin lesions can lead to overloading the healthcare system with unnecessary visits and increased delays for patients who may have an actual skin lesion that warrants biopsy, may be malignant, and ultimately requires equitable priority.

Interventional device: The Sklip System has been granted FDA Breakthrough Designation in 2021 (reported overall sensitivity of 94.47%) for its interpretation of DDI. The Sklip System will be made available to Study Participants via a non-commercial version of Sklip App with SMSA access via dedicated username and password (for research use only). The intended use of the Sklip System is stand-alone triage of PSLCs for skin cancer. Sklip System is intended for triage only (FDA Class 2). The Sklip System is not intended for diagnostic use (FDA Class 3). The reported Performance of SMSA for sensitivity of melanoma and atypical melanocytic nevi with uncertain malignant potential is 97.4%.[2]

Study protocol intervention: We will test SMSA output from Participant-taken DDI of Participant-selected PSCLs in an at-home environment and evaluate real world performance of the Sklip System.

Potential intervention outcomes: The Sklip System may safely reduce submission of technically unclear images to DPs through its two-step SMSA algorithm. Use of the Sklip System requires a medical-device-assisted image (DDI) where the first step of the SMSA is to identify if the image is a DDI, then if the DDI is clear, in-focus and free of artifacts. If the DDI passes the first step, the SMSA then evaluates the uploaded DDI for presence of modified dermoscopy three-point checklist criteria. **The average time to obtain a Sklip System result is 5 seconds.** If positive, the lesion is flagged as SUSPICIOUS and information signals the Sklip System user to contact a healthcare Provider with urgency through clear product labelling in the Sklip Mole Analysis Report.

Hence, the Sklip System could potentially identify a malignancy with high sensitivity, safety and help prioritize layperson-to-patient triage pathway. Furthermore, for the purpose of access equity, the current publicly available commercial version of the Sklip App (since 03-2023) has a free-access map of every dermatology office location

in the United States. The Sklip app provides free contact information (phone and website) for the layperson to request to schedule a visit. Using the Sklip Network filter in the Sklip App map, verified dermatology offices willing to accept new patients for spot checks from the Sklip app within fourteen (14) days and without a referral from a primary care Provider are highlighted to the App user.

Possible intervention impact on the healthcare system: U.S. based academic centers represent only a small fraction of access to dermatologic care for the American public and access to high quality skin cancer screening using medical grade tools (including dermoscopy) is limited. Outside of academic settings there is a greater than fifty (50) percent chance that a layperson (new patient) will be seen in a dermatology office by an advanced practice practitioner (APP) (nurse practitioner or physicians associate). APPs working in a dermatology setting typically have a short two (2) week to (1) month rotation in dermatology during their schooling, prior to obtaining licensure to practice. APPs neither receive focused general dermatology training (3 year dermatology residency) nor dermoscopy training (3 years in dermatology residency), yet are expected to provide independent, high quality dermatologic care to patients, specifically during mole spot checks and full body skin exams. Many times they do not even use a dermatoscope, which is considered a standard of care for all graduates of a formal ACGME dermatologic residency program. Due to this limitation in training and experience, sensitivity of triage and diagnosis of skin cancers is often lower than a MD/DO dermatologist and often lower than a MD/DO primary care provider (overall reported dermoscopy sensitivity of 79.2% when using a dermatoscope).[3,4]

The Sklip System can potentially empower both Providers and consumers that already have a concern about a pigmented skin lesion and do not have formal dermoscopy training, or multi-year experience, therefore offering the potential for safe improvement of triage accuracy in both office-based and home-based settings.

1.1.1 OVERVIEW OF STUDY DISEASE(S)

Incidence and cost to society: An estimated 1 in 5 Americans will develop skin cancer in their lifetime including melanoma, the deadliest form. Melanoma incidence rates have increased three times over the past three decades with two hundred thousand new cases reported in 2020. This number is expected to increase in 2023. When skin cancers are detected at an early stage, survival rates are 98% — compared to late detection of melanoma with metastasis, survival falls to 24% and becomes increasingly fatal.[5-8]

Skin cancer in the United States: Skin cancer is a problem in the United States with an incidence that has increased significantly in the last three decades. The Oregon Health and Science University Department of Dermatology and Knight Cancer Institute have initiated a War on Melanoma to combat it through early detection (IRB#10561). One crucial component of the War on Melanoma's early detection program is development and implementation of imaging technologies to enable earlier detection of melanomas before they become life-threatening.[9] Previous attempts to provide access to patients through virtual triage from home have relied on triage of PSLCs based upon patient selection – which is attune to subjective observation, bias and limitations. The current standard of care to evaluate a skin lesion of interest in-office (dermatology) is using a dermatoscope.[10,11]

1.1.2 OVERVIEW STUDY INTERVENTION(S)

All Participants of this single-arm prospective trial will be given up to 14 days to **review** the Sklip System instructions, **perform** a self-skin-exam (SSE) at-home, and **identify** pigmented skin lesions of concern (PSLCs). Then, Participants will be instructed to carefully follow provided instructions and **complete** a series of tasks described in Section 3.1 below.

1.2 **STUDY RATIONALE**

Limitations that we can overcome for layperson at-home self-selection of PSLCs:

a) **Layperson self-selection triage bias** using subjective selection criteria resulting in low sensitivity & specificity
b) **Lack of image quality verification prior to doctor consultation** which results in patients submitting low technical quality images (blurry) to DPs in a virtual communication, that are often difficult to evaluate
c) **DP low confidence when using SCI (non-medical-device assisted) to triage** PSLCs in a virtual setting
d) **Overuse of DP resources for benign self-selected PSLs and packing the healthcare system with visits** for PSLCs that are concerning for laypersons but often verified to be benign by a DP in-office using dermoscopy
e) **Reduced access and delay of care** due to increased wait times to see DPs in-office.

Current standard of care for layperson at-home self-selection of PSLCs:

In the current at-home SSE model, the layperson must first identify a specific PSL based on subjective observation. Then, the identified PSL must raise adequate concern to prompt communication with a DP through scheduling a virtual visit or requesting an in-person spot check. Currently, there is no objective prescreening method for PSLC selection or virtual visit image technical quality submission. If the layperson chooses to call and schedule an in-person visit for a new spot check appointment, the average national wait time to be seen in-person by a MD/DO dermatologist is 3 to 6 months, sometimes more. Alternatively, the layperson may choose to communicate with a DP, typically a MD/DO dermatologist, via virtual communication and send store-and-forwards SCI of their PSLC. Prior to submission, the PSLC SCI (non-medical-device assisted) image quality is not verified and often laypersons send images that are blurry, contain artifacts, or do not make it clear which PSLC is the one of concern amongst an image that contains several skin lesions (moles) in the field of view. This makes confident triage difficult for any DP in a virtual setting and often requires the DP or their team to contact the patient in order to request retaking the SCI again with better technical quality (clear image). Once an appropriate technical quality PSLC SCI is received, the DP uses non-medical-device assisted clinical judgement to make their triage decision into one of three categories:

1. **UNREMARKABLE** (no immediate concern with low clinical suspicion for malignancy, suggest the patient to self-monitor until the PSLC becomes unstable)
2. **SUSPICION** (concern with moderate to high suspicion for malignancy, recommendation to convert to an in-person visit to evaluate the PSLC with a dermatoscope, biopsy is possible)
3. **ERROR** (ask patient to retake a clear SCI image, if unsuccessful on the second attempt, convert to an in-person visit to evaluate with a dermatoscope, biopsy is possible).

Current evaluation of PSLCs by the Sklip System:

The Sklip System may safely improve triage of layperson self-selected PSLCs in an at-home environment by transitioning a regulated triage tool (FDA Class 2) into the hands of laypersons.

After a PSLC is initially identified by the layperson, the SMSA (Sklip Ai), an artificial intelligence tool, uses objective modified dermoscopy Three-Point Checklist (MD3PC): (asymmetry (including atypical network), round structures and blue-white color) to triage PSLs into one of three categories[12-15]:

1. **UNREMARKABLE** (no immediate concern, limited or no positive MD3PC, with low concern for malignancy or pre-malignancy, the SMSA output provides information and suggests the layperson to self-monitor the PSLC every three months, if the user does not understand the initial SMSA output result (Sklip Mole Scan Result) or the PSLC ever becomes unstable (changes), product labelling clearly instructs the user to contact a healthcare Provider for an in-person visit, biopsy is possible)
2. **SUSPICIOUS** (positive MD3PC with moderate to high concern for malignancy, the SMSA output result provides information and strongly suggests the layperson to contact a healthcare Provider for an in-person visit, biopsy is very possible)
3. **ERROR** (uploaded image does not meet SMSA criteria and an assessment of DDI cannot be made, the SMSA output result provides information how to properly retake DDI, if the user is unsuccessful after three (3) attempts, clear product labelling instructs the layperson to contact a healthcare Provider for an in-person visit, biopsy is possible)

How the Sklip System Improves Triage:

The Sklip System has the potential to improve triage of PSLCs and address the current limitations:

a) **Layperson self-selection triage bias** using subjective selection criteria resulting in low sensitivity & specificity.
Potential solution: Sklip System uses objective dermoscopy criteria (MD3PC) to evaluate a self-selected PSLC which may result in safe accuracy based on pre-specified performance goals by the FDA.

b) **Lack of image quality verification prior to doctor consultation** which results in patients submitting low technical quality images (blurry) to DPs in a virtual communication, that are often difficult to evaluate.
Potential solution: The Sklip dermatoscope is a medical grade device that enables the layperson user to take a medical grade in-office like quality image from home by controlling the light source, magnification and fixed placement of the device flat against the skin. The SMSA first verifies whether a digital dermoscopy image (DDI) is technically appropriate for evaluation, which may reduce the number of blurry DDI sent to a dermatology provider in a virtual communication. After the SMSA verifies technical quality of the DDI, the second step is the evaluation of the DDI based on trained MD3PC as described above.

c) **DP low confidence when using SCI (non-medical-device assisted) to triage** PSLCs in a virtual setting.
Potential solution: The Sklip System enables a layperson to take a medical grade DDI. It is well established in literature that the use of DDI improves both accuracy and confidence of PSLC triage. Additionally, the Sklip System will automatically categorize the PSL into: SUSPICIOUS, UNREMARKABLE, or ERROR, prior to the layperson contact with their dermatologist, which may result in safe accuracy based on pre-specified performance goals by the FDA.

d) **Overuse of DP resources for benign self-selected PSLs and packing the healthcare system with visits** for PSLCs that are concerning for laypersons but often verified to be benign by a DP in-office using dermoscopy.
Potential solution: Sklip System may help reduce layperson concerns about benign skin lesions due to safe and accurate triage based on pre-specified performance goals by the FDA. This may allow DPs to have more confidence not seeing the patient in person for an otherwise benign concern and improve access for patients with actual malignancies that may be detected by the SMSA. Additionally, in the case of SMSA SUSPICIOUS output, the user is clearly prompted to urgently contact a healthcare Provider.

e) **Reduced access and delay of care** due to increased wait times to see DPs in-office.
Potential solution: Sklip System would be used by laypersons as a stand-alone device to triage PSLCs. This could potentially improve access for persons with verified SUSPICIOUS PSLCs that require immediate in-person evaluation by a DP. FDA Clearance of the Sklip System could potentially streamline the time to treat for persons with skin malignancies who are currently delayed by the current medical system triage status quo.

The Sklip System has been reviewed by the FDA and received "Breakthrough Designation Status" with a reported overall sensitivity of 94.47% and specificity of 83.33%, compared to the highest reported accuracy by primary care providers using dermoscopy – sensitivity of 79.2% and specificity of 72.5%. The current SMSA Performance reported sensitivity for melanoma and atypical melanocytic nevi with uncertain malignant potential is 97.4% (2023).[16]

Of note, an estimated fifty (50) percent of PSLC biopsies occur in primary care settings. The functionality of DDI based triage using Sklip System by laypersons, that is the same, or superior, to an in-person spot check visit with a primary care Provider for a layperson self-selected PSLC, could have a significant impact on streamlining and improving the safety of current patient care access. This should be evaluated in a research setting.

1.3 RISK/BENEFIT ASSESSMENT

In alignment with the FDA guidance mentioned above and 21 CFR 812.3(m), Sklip Inc. has determined that a clinical Study utilizing the Sklip System constitutes a **Non-Significant Risk Device Study**. From a high level, and as described in more detail following, this is because:

1. The Sklip System is not of substantial importance in diagnosing, curing, mitigating or treating disease.
2. The Sklip System does not act in a manner that the FDA guidance flags as being considered significant risk.
3. The Sklip System is not included in the list of devices that the FDA considers to be significant risk.

Therefore, the Sklip System and the Study of it can be considered a Non-Significant Risk (NSR) Device Study. Our rationale is as follows, the Sklip System is not of substantial importance in diagnosing, curing, mitigating or treating disease. Instead, the Sklip System provides a stand-alone triage assessment according to a clinical accepted protocol, where the final decision to biopsy or not and diagnosis of a PSLC is intended for confirmation by a healthcare provider.

1.3.1 KNOWN POTENTIAL RISKS

There is a risk of loss of confidentiality in this Study. In addition, Participants in this Study are required to have any self-selected PSLCs to be further evaluated in-person and managed as part of normal clinical care pathways, which may result in the same increased risks associated with standards of clinical care. This includes possible increased identification of PSLCs that warrant conversion to a biopsy (as decided by a DP, not the interventional device, which may lead to increased physical biopsies and the risks associated with them. In addition, there remains the risk that a Participant in either group may miss identifying a skin lesion on their body that is malignant. However, these risks are all associated with current at-home standard of care protocol for SSEs and not increased by use of the interventional device. To provide each Participant with safety and peace-of-mind, a FBSE will be performed on each Study Participant during their in-person visit.

1.3.2 KNOWN POTENTIAL BENEFITS

Participants will receive a FBSE as part of this Study as part of normal patient care with their DP after completing the Study At-home Phase. The cost of in-person patient care will not be covered by this Study as described in the Participant consent form. Scheduling, triage, biopsy, diagnosis, surgeries, treatment and other medical care for suspicious or cancerous lesions are not covered as part of this Study. However, Participants may benefit by having access to expedited time to care with a dermatology Provider (DP) which may lead to earlier detection of skin cancer, and therefore may improve patient access and outcomes. Current national wait times for in-person dermatology visits average 3 to 6 months. Participant involvement in this Study may allow the Participant to receive care much earlier (within 28 days after completion of the At-home Phase). Participants will receive free education material and training that will increase the Participant's knowledge and awareness of skin cancer and also receive the Sklip dermatoscope at no cost and can keep the device after completion of the Study.

2. OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVES AND ENDPOINTS

Primary Objective	Endpoint	Start	End
Sklip System enables laypersons to safely triage self-selected pigmented skin lesions of concern from home with the same or better accuracy than pre-specified performance goals* for	Using all Participant PSLCs recorded in the Participant Mole Log Sheets, triage accuracy measures of the SMSA output of Participant-taken DDI will be assessed using a 2x2 table,	First day of enrollment	Up to 42 days after first day of enrollment

detection of pigmented skin lesions that require biopsy: **Melanoma and atypical melanocytic nevi with uncertain malignant potential** (moderate, severe, and high grade atypia; those with pathology reports that include notes such as: borderline, cannot exclude melanoma, cannot exclude early evolving melanoma, unusual features, atypical spitz nevi, suspicion for melanoma, re-excision (or further removal) should be considered or is recommended in the pathologist management comment): ≥95% sensitivity, ≥30% specificity **Squamous cell carcinoma**: ≥80% sensitivity, ≥30% specificity **Basal cell carcinoma**: ≥80% sensitivity, ≥30% specificity *Pre-specified performance goals have been reviewed with the FDA for testing the Sklip System (including SMSA) as a stand-alone device.	where the SMSA rating of "SUSPICIOUS" or "UNREMARKABLE" will be estimated to pre-specified accuracy metrics discussed with the FDA. The Sensitivity of the SMSA using Participant-taken DDI will be estimated to pre-specified performance goals described in sections above, using 0.05 significance level and 10% margin of error. Triage accuracy measures of the Sklip System (specificity, negative predictive value, positive predictive value, and accuracy) will also be calculated. The Ground Truth will be the combination of the following described in the Sections above: Dataset N) <u>DDI dermoscopic diagnosis ground truth</u> (DDI-GT) for PSLCs that were not biopsied during the In-Person Phase, <u>and</u> Dataset O) <u>Histologic diagnosis ground truth</u> (H-GT) for lesions that were biopsied during the In-Person Phase		

2.2 EXPLORATORY OBJECTIVES AND ENPOINTS

Exploratory Objectives	Endpoint	Start	End
1. To compare the accuracy of Sklip System triage when used by a layperson versus near-perfect Sklip System user	First, the Sensitivity of the SMSA using Study Coordinator-taken DDI (near-perfect technical quality) will be estimated to pre-specified performance goals described in sections above, using 0.05 significance level and 10% margin of error. Similar to the Primary endpoint, the accuracy of SMSA output	First day of enrollment	Up to 42 days after first day of enrollment

	using Participant-taken DDI will be assessed using a 2x2 table, where the SMSA output of "SUSPICOUS" or "UNREMARKABLE" will be compared to the SMSA output using Study Coordinator-taken DDI (near-perfect technical quality), simulating a laboratory-type environment where the SMSA is fed the best possible technical quality DDI.		
2. To assess whether Sklip System improves triage of pigmented skin lesions of concern < 6mm in diameter as suspicious as compared to the current medical provider virtual triage method that relies on store-and-forward non-medical-device assisted smartphone clinical images	Using only PSLs < 6 mm in diameter, the accuracy of the expert consensus triage decision using Participant-taken smartphone clinical images (SCI) will be assessed using a 2x2 table, where the expert consensus triage decision of "BIOPSY" or "MONITOR" will be compared to the intervention method, for both SMSA outputs recorded by Participants and SMSA outputs recorded by Study Coordinators for the same target PSLCs.	First day of enrollment	Up to 42 days after first day of enrollment
3. To assess whether Sklip System improves triage of thin melanomas with <0.8 mm Breslow depth as suspicious as compared to the current medical provider virtual triage method that relies on store-and-forward non-medical-device assisted smartphone clinical images	Using only Melanomas < 0.8 mm Breslow depth, the accuracy of the expert consensus triage decision using Participant-taken smartphone clinical images (SCI) will be assessed using a 2x2 table, where the expert consensus triage decision of "BIOPSY" or "MONITOR" will be compared to the intervention method, for both SMSA outputs recorded by Participants and SMSA outputs recorded by Study Coordinators for the same target PSLCs.	First day of enrollment	Up to 42 days after first day of enrollment
4. To determine the accuracy of layperson-performed SSEs at-home in the identification of all suspicious PSLs present on their body as compared to the same layperson evaluated with full body skin examination by a dermatology Provider in-person	We will calculate the following based on Participant self-skin exams (SSEs) performed during the At-home Phase: (a) the mean and standard deviation of the number of PSLCs identified by Participants performing a SSE, and (b) the mean and standard deviation of the number of PSLCs identified by the	First day of enrollment	Up to 42 days after first day of enrollment

	dermatology Provider during the In-person Phase full body skin exam (FBSE).		

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY DESIGN

Refer to Section 11*, Statistical Analysis for additional information regarding statistical methods used in this Study.*

All Participants of this single-arm prospective trial will be given up to 14 days to **review** the Sklip System instructions, **perform** a self-skin-exam (SSE) at-home, and **identify** PSLCs based on the following:

(a) General concern (self or partner-identified, or non-dermatology Provider identified requiring a referral to a dermatology Provider)
(b) Concern because the PSLC is different than the rest (i.e. "ugly duck sign")

Then, Participants will be instructed to carefully follow provided instructions and **complete** the following for each target PSLC:

1) Mark the target PSLC with a green surgical marker (horizontal line) and the number (#) corresponding to the mole log, one (1) inch away from the target lesion
2) Record the target PSLC with a number (#) and anatomic location in the PMLS
3) Create a new photo album titled: "Moles" in their native smartphone/tablet Photo App
4) Take one (1) smartphone clinical image (SCI) of the target PSLC, twelve (12) inches away from the target skin lesion
5) Save the SCI in the album titled: "Moles" album
6) Review Sklip dermatoscope instructions for proper use
7) Take one (1) digital dermoscopy image (DDI) of the target PSLC using the Sklip dermatoscope.
8) Save the DDI of the target PSLC in the "Moles" album
9) Upload the DDI to the SMSA ("Scan Moles with Ai") within the Sklip App once per target PSLC, until either a Suspicious or Unremarkable result is obtained, for a maximum of three attempts. If after three attempts the user still receives an "Error" result, they will be prompted to document this in the participant mole log sheet.
10) Take one (1) screenshot of the SMSA output per target PSLC
11) Save the SMSA output screenshot in the album titled: "Moles"
12) Record each SMSA output (SUSPICIOUS, UNREMARKABLE, ERROR) in the PMLS once per target PSLC
13) Contact the Study Site to schedule an in-person FBSE within 28 days, if the Participant does not already have a scheduled visit

In summary, for each target PSLC the Participant will acquire the following:

One (1) smartphone clinical image (SCI)
One (1) digital dermoscopy image (DDI)
One (1) Sklip Mole Scanning Algorithm (SMSA) output recorded in the PMLS
One (1) SMSA output screenshot
----------End of At-home Phase----------

Study Coordinators at each Study Site will conduct regular EMR chart reviews to track Participant requests to begin their In-person Phase, after the Participant has completed their the At-home Phase. These chart reviews will be conducted systematically every 7 days following Participant enrollment. Participant EMRs will be monitored for up to 28 days following conclusion of both Study Phases to account for any relevant data that may have not been collected during the Study.

----------Start of In-person Phase----------

With dermatology Provider present:
The dermatology Provider (DP) will be blinded to the skin lesions that were selected by the study Participant at home. The DP will perform a FBSE as part of the normal clinical care pathway. All PSLCs identified by the DP as SUSPICIOUS will be marked with a vertical line one (1) inch away from the target PSLC using a green surgical marker. After completing the FBSE and marking all DP-selected suspicious PSLCs, the DP will verbally inform the Study Coordinator the Participant's Fitzpatrick skin phototype (1,2,3,4,5 or 6) after leaving the patient room.

Without dermatology Provider present,
with Study Coordinator present:
The Participant will be asked to provide their Participant Mole Log Sheet (PMLS). Then, all PSLCs recorded in the PMLS will entered into REDCap Cloud by the Study Coordinator. Any Participant-selected PSLCs that match those identified earlier as SUSPICIOUS by the DP will be marked with a horizontal line one (1) inch away from the target PSLC using a green surgical marker. Therefore, PSLCs identified by both the DP and Participant will have a plus symbol. Next, the Study Coordinator will take and record (near-perfect) SCI and DDI for all PSLCs recorded in the PMLS and those PSLCs identified by the DP as SUSPICIOUS (not matching the Participant PSLCs). Then, the Study Coordinator will complete the following:

1) Take one (1) photo of the Participant identification sticker with a Study Site secure smartphone/tablet
2) Take one (1) smartphone clinical image (SCI) of each target PSLC recorded in the Participant Mole Log Sheet (PMLS)
3) Take one (1) digital dermoscopy image (DDI) of each target PSLC using the Sklip dermatoscope.
4) Save the DDI of the target PSLC in the Study Site smartphone/tablet native photo gallery
5) Upload the Study Coordinator-taken DDI to the SMSA ("Scan Moles with Ai") within the Sklip App
6) Take one (1) screenshot the SMSA output
7) Record each SMSA output (SUSPICIOUS, UNREMARKABLE, ERROR) in REDCap Cloud, per target PSLC
8) If the Participant has taken a set of SCI/DDI at home of a PSLC that is not intended (qualified because of anatomic body site) for the Sklip System, the Study Coordinator should still capture a set of control SCI/DDI and upload to REDCap Cloud. The Participant standard clinical care will not be changed.
9) If the Participant took a set of SCI/DDI of a PSLC at home but did not follow instructions – specifically uploading the DDI to the Sklip System - the Study Coordinator should remind the Participant to complete this task in the patient room (using the DDI from their mobile device gallery), upload to the Sklip System, and record the output on their Mole Log Sheet. If this situation occurs, the Study Coordinator should make a note in

REDCap Cloud; If the Participant is/was concerned about a PSLC but did not take a set of SCI/DDI at home, this PSLC will not be included in the study.

Schedule for data collection:
In order to avoid Participant PSLC recollection-bias, Study Coordinators will use the Participant Mole Log Sheet (PMLS) and Participant taken SCI/DDI for guidance and **record** the following Datasets in REDCap Cloud:

A) Total number of PSLCs identified by the Participant at-home
B) Total number of PSLCs identified by the DP in-office
C) One (1) individual SMSA output recorded in the PMLS, per target PSLC (SUSPICIOUS, UNREMARKABLE and ERROR)

Ensuring that no PHI is shared, Study Coordinators will **export** the following from the Participant smartphone/tablet gallery titled "Moles" to the Study Site smartphone/tablet gallery via Bluetooth or secure email:

D) One (1) Participant-taken SCI, per target PSLC
E) One (1) Participant-taken DDI, per target PSLC
F) One (1) Participant-taken SMSA output screenshot, per target PSLC

Then, Study Coordinators will **acquire** and **export** the following from the Study Site smartphone/tablet gallery to an OHSU secure cloud storage service:

G) One (1) Study Coordinator-taken DDI (near-perfect image technical quality) for each PSLC recorded in the PMLS and suspicious PSLCs identified by the DP in-office that were not recorded in the PMLS

Then, Study Coordinators will **upload** the DDI in Dataset (G) to the SMSA on a Study Site smartphone/tablet and **record** the following Datasets into REDCap Cloud:

H) One (1) Study Coordinator-taken SMSA output for each PSLC, recorded in the PMLS, using Dataset (G) (SUSPICIOUS, UNREMARKABLE and ERROR), including one (1) screenshots

Then, the Study Coordinator will **record** the following Datasets into REDCap Cloud:

I) All other SCI of suspicious PSLCs identified by the DP in-office that were not recorded in the PMLS
J) All other DDI of suspicious PSLCs identified by the DP in-office that were not recorded in the PMLS
K) Pathology reports for all PSLCs that were biopsied during the In-Person Phase
L) Number of adverse events reported during the Study

----------End of In-person Phase----------

Description of Satellite Study required activities
Satellite Study Sites will also complete the above activities and securely **submit** their Datasets (A-L) to the Lead Study Site via OHSU secure cloud storage services. The Lead Study Site will prepare individual Qualtrics surveys using images from the Datasets above to create the following Datasets:

Dataset M) SCI triage decision (SCI-TD) based on Datasets (D) and (I), when at least two of three expert dermatologist readers have a concordant triage decision (MONITOR or BIOPSY). If there is a lack of concordance, an internationally recognized dermoscopy expert (dermatologist) will act as a fourth reader to determine the final SCI-TD

Dataset N) DDI dermoscopic diagnosis ground truth (DDI-GT) for PSLCs that were not biopsied during the In-Person Phase, using images available in Datasets (E) and (J), when at least two of three expert dermatologist readers have a concordant dermoscopic diagnosis. If there is a lack of concordance, an internationally recognized dermoscopy expert (dermatologist) will act as a fourth reader to determine the final DDI-GT

Dataset O) Histologic diagnosis ground truth (H-GT) for lesions that were biopsied during the In-Person Phase, based on evaluations using either physical or digital histologic slides (described in Sections below), when both independent expert dermatopathologists have a concordant histologic diagnosis. If there is a lack of concordance, a third internationally recognized expert dermatopathologist will determine the final H-GT.

The Study Sponsor will be responsible for Study costs (logistics, shipping, handling, research reading fees) associated with the use of either physical or digital histologic slides to create Dataset O. If digital histologic images (DHI) are chosen, the Lead Study Site will be asked to prepare DHI for their own Study Site Participants who received a biopsy during the In-person Phase. The Lead Study Site will have the option to prepare DHI for the Satellite Study Sites.

In order to eliminate biopsy specimen evaluation-bias there will not be a request to confirm or rule out any specific dermatologic neoplasm entity. All biopsy specimen slides will be de-identified and presented in blind to expert dermatopathologists at an independent Study Site for evaluation with only the following information: Participant **age**, **sex**, skin lesion **anatomic location**, and a written dermatopathology request: "**Please evaluate for pigmented skin lesion**."

3.2 END OF STUDY DEFINITION

A Participant is considered to have completed the Study if he/she/they have remained a Participant for the entirety of the Study period and have completed the applicable end of Study REDCap Cloud survey. Therefore, up to 14 days for the At-home Phase, including Study intervention, is sufficient time to collect data and evaluate the interventional device. Since Study Sites are required to see all Participants after the At-home Phase, up to 28 days for the In-person Phase is sufficient time to see all Participants as patients through already scheduled visits, overbookings or separate dedicated clinics. Biopsy results typically take 7 days to follow up, however Study Coordinators will continue to monitor EMR of Participants to collect relevant data up to 30 days following the end of the Study.

3.3 STUDY DISCONTINUATION AND CLOSURE

This Study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification that documents the reason for Study suspension or termination will be provided by the suspending or terminating party to OHSU Coordinating Center, local IRB, and other regulatory authority. If the Study is prematurely terminated or suspended, the Investigator will promptly inform the IRB and provide the reason for the termination or suspension.

Reasons for terminating the Study may include the following:

- Unfavorable assessment of risk/benefit ratio
- Incidence or severity of adverse events, in this or other studies, that indicates a potential health hazard to Participants

- Demonstration of efficacy that would warrant stopping
- Data that are not sufficiently complete and/or evaluable
- Investigator not adhering to the Study protocol or applicable regulatory guidelines in conducting the Study
- Participant enrollment is unsatisfactory
- Submission of knowingly false information from the Study Site to OHSU Coordinating Center or regulatory authority
- Upon instruction by local or other regulatory or oversight authority.

The Study may resume once concerns about safety, protocol compliance, and/or data quality are addressed as applicable and requirements of the OHSU Coordinating Center, Study sponsor, IRB and/or other applicable regulatory authority are satisfied.

4. STUDY POPULATION

4.1 PARTICIPANT INCLUSION CRITERIA

To be eligible to participate in this Study, an individual must meet all of the following criteria:

1. Participant must provide written informed consent before any Study-specific procedures or interventions are performed.
2. Age ≥ 21 years with at least one pigmented skin lesion (PSL)/mole on their body. All genders and members of all races and ethnic groups will be included.
3. Participant self-identifies as having Fitzpatrick Skin Type 1 through 4.
4. Participant must be a current or new patient through self-referral or Provider-referral at the participating Study Site.
5. Participant must have access to a smartphone/tablet and be willing to set up virtual communication via direct message to a Study Site dermatology provider (i.e. MyChart in EPIC, direct message in ModMed EMA or other electronic medical record (EMR) type)
6. Participant must be English-speaking due to FDA Breakthrough Designation of the Sklip System in the English language. Therefore, we are unable to accommodate non-English speaking Participants.
7. Participant must be "Healthy", which is defined as someone considered not urgently sick or hospitalized. This will be determined by the Study principle investigator (PI) at each Study Site, a licensed dermatologist, who will be responsible for screening Participants to ensure eligibility criteria is met prior to enrollment.

4.2 PARTICIPANT EXCLUSION CRITERIA

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

1. Participant who self-identifies having Fitzpatrick Skin Type 5 or 6.
2. Participant who have had a skin check visit with a dermatology Provider within the last 90 days will be excluded to avoid self-selection bias, unless the Participant identifies a new unexamined (not previously documented) spot of concern.
3. Vulnerable populations including children, prisoners, and decisional impaired adults as well as vision impaired adults will not be eligible for this Study.
4. Pregnant individuals will be excluded in this Study. Since this is a minimal pregnancy risk category, no special precautions will be taken to determine that the patient is not pregnant

4.3 LIFESTYLE CONSIDERATIONS

During this study, Participants will not be asked to make any lifestyle changes or restrictions as we do not anticipate that these factors will impact the results of this study.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Proposed Study Sites have been discussed with the FDA via Sklip Inc. Q-Submission Sprint Discussion (#Q211049/S002/A002; completed on 03/31/23).

Four (4) Study Sites will participate in this Study. The Lead Study Site will be Oregon Health and Science University (OHSU) in Portland, Oregon.

Minimum recruitment per Site: 15% of the total Study sample size
Maximum recruitment per Site: 40% of the total Study sample size

Site #1: Oregon Health and Sciences University in Portland, Oregon
3303 S Bond Ave CHH1 Ste 16 (Department of Dermatology)
PI: Sancy Leachman MD, PhD (leachmas@ohsu.edu)

Governance of Satellite Study Sites: OHSU IRB will not be responsible for any of the Satellite Study Sites as they will be governed by a third-party IRB and use this IRB Protocol for guidance.

Site #2: Skin Cancer Center
3024 Burnet Ave, Cincinati, OH 45219
PI: Michael Tassavor MD FAAD (mtassavor2@gmail.com)

Site #3: The Skin Center Dermatology Group
200 East Eckerson Rd, New City, NY 10956
PI: Peter Friedman MD, PhD FAAD (pbc9@cumc.columbia.edu)

Site #4 Johnny Gurgen D.O. P.A.
1340 Citizens Blvd, Leesburg, FL 34748
PI: Johnny Gurgen DO FAOCD (johngurgen@gmail.com)

Participants for this Study will be recruited from participating Study Site dermatology practices. Participants may be identified by a member of the research team, the PI, or medical and surgical oncology clinics part of the Study Site. As a member of the treatment team, Investigator(s) will screen their patients' medical records for suitable research Study Participants and compile a list of eligible Participants to contact and discuss the Study and their potential for enrolling in the research Study. The Investigator(s) may also screen the medical records of potential Participants with whom the investigator does not have a treatment relationship. This will be done for the limited purpose of identifying patients who would be eligible to enroll in the Study and to record appropriate contact information in order to approach these potential individuals regarding the possibility of participating in the Study. Participants may also be recruited to the Study through existing primary care referrals wait lists for spot checks to rule out skin cancer, or FBSE due to the increased likelihood to identify a skin cancer, in particular the rarer form – melanoma, when there is an existing patient PSLC.

4.4.1 ACCRUAL ESTIMATES

Total accrual of all PSLCs based on sample size estimates is anticipated to take a total of up to 42 days from enrollment.

No OHSU Knight Cancer Institute Study will focus on any gender, racial or ethnic subset. No Participant will be excluded from the Study based on gender, racial or ethnic origin. Male, female and minority volunteers will be

recruited for this Study from the general patient population and approximately 50% men and 50% women will be studied. Gender-nonconforming and gender-fluid individuals will also be recruited.

The projected gender, racial and ethnic composition of the Study will include different proportions of patients with Fitzpatrick Skin Types 1—3 and Fitzpatrick Skin Type 4 because the prevalence of skin cancers differs between Fitzpatrick Skin Types. There are no available estimates of the prevalence of Fitzpatrick Skin Types in the general population and so estimates of White populations and Non-white populations will be used for accrual estimation purposes only[9–11]. Actual stratification will depend on participants' self-selected Fitzpatrick Skin Type.

Table 3. Population Demographics by gender and race

All histories	Female	Male	Total
White	29.7%	29.7%	59.3%
Non-white	20.4%	20.4%	40.7%
Total	50.0%	50.0%	100.0%

*Source: adapted from the 2017 U.S. Census Bureau

Table 4. Projected Accrual for the Present Study

All histories	Female	Male	Other/unknown	Total
Fitzpatrick 1-3	90	87	2-3	180
Fitzpatrick 4	65	62	2-3	130
Total	155	149	4-6	310

4.4.2 INCLUSION OF CHILDREN

This protocol does not include children for the following reasons:

1. The number of children with melanoma or non-melanoma skin cancer is limited
2. In order to be in alignment with FDA guidance where the intended use of the Sklip System is in persons 21 years or older.

5. PARTICIPANT SCREENING, ENROLLMENT, AND WITHDRAWAL

5.1 CONSENT AND SCREENING

In order to participate in this Study, signed informed consent must be obtained from the Participant. The current IRB approved informed consent form must be signed and dated by each Participant prior to undergoing any Study procedures. The informed consent discussion must be documented, and a copy of their signed IRB approved informed consent form must be scanned in the Participant's medical record.

The Participant will be contacted with a targeted virtual communication message (i.e. MyChart message) that includes a brief purpose and summary of the Study with an included embedded link to self-screen through an nPhase REDCap Cloud survey for recruitment or by phone for patients who already have a scheduled visit with a dermatology Provider at the Study Site and meet Study inclusion criteria. Participants may also be recruited at health and/or wellness events in the community using a printed version of the approved virtual communication message with the included link to nPhase REDCap Cloud self-screening survey.

During this time, the Study Coordinators, under the supervision of the PI, will screen the Participants on nPhase REDCap Cloud to ensure they meet our eligibility criteria. Participants that complete the survey and meet the eligibility criteria will be contacted using the phone number provided in the screening survey and have their personal and contact information confirmed. Then a nPhase REDCap Cloud e-consent will be sent to the email given by the Participant. The Participants will be given ample time to review the consent form thoroughly and privately to avoid feeling pressured. If they indicate interest to participate in the Study and submit the nPhase REDCap Cloud screening and e-consent, they will be contacted by a Study Coordinator by phone to discuss in detail the consent form, what the Study entails, and answer any additional questions the Participant may have. If the Participant is unable to sign the e-consent form, they may be invited in-person to obtain written consent. If the subject does not respond after at least two call attempts made during the screening process over the span of a week, we will consider the subject as screen failed.

5.1.1 SCREENING PERIOD

When a Study Coordinator reaches out to a potential Participant to discuss the Study and obtain informed consent, the Study Coordinator, who is supervised by our PI, will ensure the Participant meets our eligibility criteria. The inclusion criteria for this Study does not require consistent screening or monitoring and therefore initial screening period at time of consent is sufficient. Most of the eligibility criteria for Participants can be decided via chart review (i.e. age, no recent visit with a dermatology Provider) however, Study Coordinators will still additionally ensure this via verbal confirmation that will be documented during the screening and consenting period.

5.1.2 RE-TESTING DURING SCREENING

There are no laboratory tests or baseline imaging required for screening, therefore re-testing is not applicable.

5.2 **ENROLLMENT PROCEDURES**

This is a prospective single-arm open-label multicenter research Study. After recruitment, those who have indicated interest in enrolling in the Study will be contacted by one of the Study Site Coordinators to further explain the Study and consent the Participant. Participants will be enrolled on a continuous rolling basis until the target number of Participants have been met.

5.2.1 ENROLLMENT PROCEDURES FOR THE OHSU SITE

Eligibility must be confirmed and documented by a Study Coordinator, under the supervision of the Study PI, prior to enrollment. Materials required to complete the eligibility review include, at minimum:

- Current IRB-approved consent form and HIPAA Authorization for the Study signed & dated by the Participant
- Documented (signed and dated) attestation by the PI confirming Participant's eligibility based on available source documentation and authorizing enrollment

Once eligibility is confirmed and consent forms have been signed by the Participant, the Participant is considered 'enrolled' and Study intervention may begin.

5.2.2 ENROLLMENT PROCEDURES FOR SUB-SITES

Once interested Participants have been identified at Satellite Study Sites, the list of potential recruits to screen will be given to the Lead coordinating Site (OHSU) to contact via E-mail, phone or text message. Communications during the screening process will use IRB-approved text or phone scripts and will include a message with the URL to the nPhase REDCap Cloud Survey to screen for inclusion and exclusion criteria. Upon completion of the screening survey and phone call and meeting inclusion and exclusion criteria, recruits will be sent a link to e-consent for enrollment.

5.3 MEASURES TO MINIMIZE BIAS

5.3.1 RANDOMIZATION/MASKING PROCEDURES

Blinding is considered unnecessary to reduce bias for all the observations because follow up evaluation for all Participants will follow standard clinical care pathways and is not affected by this interventional Study. The Study Site PIs and DPs will be fully blinded to all results of the At-home Phase, including the Participant Mole Log Sheet. Participants will be informed of the blinding activity prior to their FBSE to avoid DP selection-bias. Specifically, the dermatology provider will be instructed to say the following to each participant upon entering the patient room for the in-person FBSE: "Hello, my name is [name and title], the purpose of today's visit is to complete a full body skin examination as part of the at-home dermoscopy study. To avoid bias, please hold with any questions related to your moles of concern until I have verified that I completed your full body skin examination and all other study related activities. I will be happy to address your questions or concerns at that time."

5.4 SCREEN FAILURES

Any Participant that has signed the consent form but does not meet all the Study eligibility criteria or meets Study eligibility criteria but terminates their participation prior to receiving Study interventional materials, will be considered a screen failure and not counted towards total number of planned enrollments. The reason for screen failure will be captured in the research record for each Participant who fails to meet all the eligibility criteria.

5.4.1 RE-SCREENING ALLOWANCE / PROCEDURES

This Study permits the re-screening of a Participant that has discontinued the Study as a screen failure (i.e. early termination prior to receiving intervention, lack of proper medical records that confirm criteria eligibility). If re-screened, the Participant must be re-consented.

5.5 PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Participants are free to withdraw consent and discontinue participation in the Study at any time and without prejudice to further treatment. If a Participant withdraws consent, they should be asked to specify if they are withdrawing consent to all further participation in the Study or if they are choosing to withdraw only from further Study intervention, meaning that further follow-up and data collection about their disease and health status is allowable. The Participant should also be asked about their consent to the future use of their Study-generated data and any biological samples, as applicable.

No further Participant contact will be made if the Participant withdraws consent for participation in the Study. Information about the reason(s) for discontinuation will be collected at the time the Participant withdraws consent.

A Participant may also be withdrawn from the Study by the Investigator, local IRB, or regulatory authorities.

Reasons for a Participant to discontinue the Study may include the following:

- Participant dies or is lost to follow-up
- Participant withdraws consent for any further participation
- The end of Study is reached
- Significant Study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the Study would not be in the best interest of the Participant
- If the Participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further Study participation

In the event of a pregnancy, the Study intervention will be immediately reported to the appropriate committees and their participation in the Study will be discontinued. Refer to Section 10.6.6 regarding reporting of pregnancy

In the event a Participant withdraws early from the Study, Investigator(s) will attempt to find a replacement to enroll in the Study to meet target number of Participants.

5.5.1 HANDLING PARTICIPANT DISCONTINUATION FROM STUDY

When a Participant discontinues participation in the Study, the reason the Participant is no longer participating, the Study Site, Study name, IRB Study number, and the date of discontinuation will be documented in the Participant's medical record. The change in Study status will be documented in the appropriate clinical trial management system for the applicable Study Site (i.e. eCRIS) per OHSU policy.

Subjects who sign the informed consent form but do not receive the Study intervention may be replaced. Subjects who sign the informed consent form and receive the Study intervention, and subsequently withdraw, or are withdrawn or discontinued from the Study may be replaced.

5.6 **LOST TO FOLLOW-UP**

A Participant will be considered lost to follow-up if the individual fails to submit the REDCap Cloud survey administered at the end of each Phase.

The following actions must be taken if a Participant fails to complete the end of Study survey:

- A Study Coordinator will attempt to contact the Participant and counsel Participant on importance of completing the survey
- Before a Participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the Participant (2 attempts to contact via virtual communication message, text messages, email, or phone call). All contact attempts made by the Study team will be documented in the Participant's medical record or Study file
- Should the Participant continue to be unreachable, he or she will be considered to have withdrawn from the Study with a primary reason of lost to follow-up

6. STUDY INTERVENTION

A list of the adverse events and potential risks associated with the study intervention administered in this study can be found in Section 10.4, Adverse Events.

6.1 NAME OF STUDY INTERVENTION

6.1.1 STUDY INTERVENTION DESCRIPTION

Device Study Risk Evaluation
Please refer to Section 1.3 RISK/BENEFIT ASSESSMENT.

Device Description
The **Sklip dermatoscope** device hardware will be provided to Participants to take DDI of their self-selected PSLCs using their smartphone or tablet. The Sklip dermatoscope is publicly (commercially) available and registered as a Class 1 Medical Device (FDA Reg. 3017732705).

The **Sklip App** is a publicly available smartphone App to download on the Apple iOS and Google Play app stores. The Sklip App is non-FDA regulated and part of the approved protocol for the Melanoma Community Registry (OHSU IRB# 10561). A security review of the Sklip App has been performed as part of that Study and is transferred to this Study protocol.

The proprietary **SMSA** evaluation of DDI has a reported Melanoma and atypical melanocytic nevi with uncertain malignant potential sensitivity Performance of 97.4% (2023).

The **Sklip System** is a SaMD that received breakthrough designation by the FDA on June 22, 2021. The Sklip System is intended to record, store and transfer DDI. The Sklip System consists of the Sklip App (used on a smartphone or tablet) and SMSA, that accept DDI taken by dermatoscope hardware. The Sklip System also displays DDI and non-diagnostic output of DDI analysis from the Sklip System software library that implements various DDI processing and artificial intelligence (Ai) analysis. This SaMD computes various digital parameters from DDI and provides these capabilities in the form of an API library. DDI can be incorporated into the Sklip System software to enable algorithmic analysis and analytics of DDI by the SMSA. The SMSA, is a software workflow tool designed to aid the assessment of DDI data input intended to conduct an initial screening of DDI for features suggestive of skin cancer and flag suspicious DDI for expedited review by appropriate medical personnel, such as a dermatology Provider (Dermatologist or dermatology trained APP), or primary care Provider (PCP). Specifically, the SMSA, via the Sklip System " Scan Moles with Ai" function, uses a Sklip Inc. proprietary Ai algorithm to provide DDI filtering, detection of noisy (non-qualified) DDI and detection of skin lesions containing qualified pigment that may be remarkable for MD3PC features ((DRFs): dermoscopic asymmetry, dermoscopic round structures and/or dermoscopic blue-white colors), which may be indicative of skin cancer.

The Sklip System (SMSA component) is not currently commercially available in the United States. Sklip Inc. is currently discussing ultimate classification and premarket submission type with the FDA.

Clear SMSA output graphic language is provided to the Sklip System user: [SUSPICIOUS, UNREMARKABLE, or ERROR]. Additionally, more specific information and guidance is available by clicking the informational ("i") button graphic clearly visible in the Sklip App "Mole Scan Analysis Result." The following language has been reviewed with the FDA and will be included in the Sklip System during this Study:

SMSA Output: [SUSPICIOUS]:

"A **SUSPICIOUS** Sklip MOLE SCAN RESULT means that the proprietary Sklip Ai (artificial intelligence) has detected a possible presence of at least one remarkable feature in the dermoscopy photo uploaded for scan. This result is not a diagnosis, it is a possible finding.

What should you do?
a) **Consult** this result in person with your established local healthcare provider, or

b) **Consult** this result in person with a dermatology provider by searching your geographic location within the Sklip network map. Click the **TAKE ACTION** button in this result to find a local dermatology office in the Sklip map.
c) **Consult** this result in person and **get a prioritized office visit within 14 days without the need for a referral**. *Click the* **TAKE ACTION** button in this result to find local dermatology offices in your area. Then *click the* **SKLIP NETWORK** filter button to identify a Sklip verified dermatology office.

Costs associated with consulting your mole scan result with a healthcare provider are your financial responsibility and Sklip is not responsible for costs associated with medical care or verifying insurance coverage"

SMSA Output: [UNREMARKABLE]:

"An **UNREMARKABLE** Sklip MOLE SCAN RESULT means that the proprietary Sklip Ai (artificial intelligence) has not detected a possible presence of at least one remarkable feature in the dermoscopy photo uploaded for scan. This results is not a diagnosis, it is a possible finding.

What should you do?
a) **Self-monitor** the color, size or shape of this mole (skin lesion) after 1 month, then every 3 months. If you find that the mole changes at any time in the future you may re-scan the mole with Sklip Ai or consult with your local healthcare provider in person.
b) **Submit** this mole today for a Sklip anonymous informational, non-diagnostic second opinion by a real dermatologist (additional fees may apply), or
c) **Consult** this result in person with your established local healthcare provider if you do not understand this result or are still concerned about the mole. If you do not have an established provider *click the* **TAKE ACTION** button in this result to find a local dermatology office in the Sklip map.

Costs associated with consulting your mole scan result with a healthcare provider are your financial responsibility and Sklip is not responsible for costs associated with medical care or verifying insurance coverage"

SMSA Output: [ERROR]:

"An **ERROR** Sklip MOLE SCAN RESULT means that the proprietary Sklip Ai (artificial intelligence) has detected that you have not uploaded a qualified Sklip dermoscopy photo. This may be because you uploaded a photo taken **without** a Sklip dermatoscope (not applicable), or you uploaded a photo with a Sklip dermatoscope that is not qualified due to **artifacts**. This results is not a diagnosis, it is a possible finding. Please review the below requirements to take a clear Sklip dermoscopy photo and minimize artifacts.

What should you do?

1. **Open** your smartphone/tablet native camera App
2. **Clip** (attach) the Sklip dermatoscope to your rear facing smartphone/tablet camera
3. **Turn ON the Sklip light** by pressing the external oval button on the Sklip dermatoscope front side
4. **Center** the Sklip dermatoscope image view (you will see either a circle or rectangle)
5. **Zoom the image 1.5X to 2.0X** (maximum) until you eliminate the black border created from the circle or rectangle
6. **Apply THREE drops** of dermoscopy oil (Sklip provided) on the target skin lesion (mole)
7. **Press** the Sklip contact plate (clear front window) flat to the skin surface (ensure there is no angle)
8. **Apply** gentle pressure to eliminate artifact air bubbles from the field of view
9. **Capture** the Sklip digital dermoscopy (DDI) image in your native phone camera App
10. **Open** the Sklip App, then **Click** "***SCAN MOLE WITH Ai***" to access the SMSA (Sklip Ai)
11. **Click** the gallery icon in (bottom left screen), **Upload** the DDI from native photo App gallery
12. **Press SCAN** to initiate the SMSA (Sklip Ai) and obtain the Sklip Ai Mole Analysis Report

13. REPEAT PROCESS FOR EACH MOLE

TECHNICAL SUGGESTIONS FOR PIGMENTED SKIN LESIONS OF CONCERN (PSLCs)
*****Apply Sklip System to a target PSLC without hair (remove hair with a shaver if needed)
*Apply Sklip System to a target PSLC that can be flattened by Step #7 above, nodular lesions are not applicable
*Apply Sklip System to a target PSLC that has at least 3 mm of diameter

If you fail to obtain a result other than ERROR (i.e. UNREMARKABLE or SUSPICIOUS) after 3 attempts, please **Consult** this result in person with a healthcare provider. Click the **TAKE ACTION** button in this result to find a local dermatology office in the Sklip map."*

***Reason for maximum of 3 attempts:**
The number of SMSA attempts on the same target PSLC that result in an output of ERROR will be recorded up to the third attempt. The reason for this is to prompt users of the Sklip System to seek medical care from a healthcare Provider if they cannot obtain a binary output (SUSPICIOUS or UNREMARKABLE) within the first three attempts.

6.1.2 ACQUISITION

The brand new Sklip dermatoscope devices used in this Study will be shipped by the Study Sponsor to the OHSU Department of Dermatology in order to prepare, sanitize, and ensure all materials are packaged prior to sending to Participants. The devices will be provided on a rolling basis for enrolled Participants enrolled for a targeted goal of 310 total devices used. The Sklip dermatoscope device and access to the SMSA will be provided at no cost to all Study Participants. The OHSU Department of Dermatology will offer shipping to Study Participants at other Study Sites. Costs for shipping will be covered by the Study Sponsor.

6.1.3 FORMULATION, APPEARANCE, PACKAGING AND LABELING

The description of the proposed device, indications for use, manufacturing process, device storage, handling, accountability, and access (limited to appropriate personnel and only by appropriate Study subjects) are provided in this document above in *Section 6.1.1 Study Intervention Description.* The device has been granted FDA Breakthrough Designation record number Q211049. Sklip System instructions for use that include safety instructions and warnings are included in the devices sent out to Study Participants.

1. *Sklip dermatoscope device hardware* is currently registered as a Class 1 Medical Device with the FDA.
2. *Sklip Mole Scanning Algorithm (SMSA)* has been evaluated by the FDA and received FDA Breakthrough Designation. The intended use for the Sklip System is a stand-alone triage tool (FDA Class 2). The Sklip System is not intended for diagnostic use (FDA Class 3)

6.1.4 PRODUCT STORAGE AND STABILITY

The SMSA will be available to Participants for research use only using a dedicated username and password on a non-commercial version of the Sklip App. Use of the Sklip System is completely anonymous. Sklip dermatoscope device storage will be on the CHH1 14th floor in a secure location dedicated to the Department of Dermatology.

6.1.5 COMPATIBILITY

Not applicable. Our Study does not involve any drug or therapeutic agent.

6.1.6 HANDLING

Access to Sklip dermatoscope devices will be limited to appropriate personnel within the OHSU Department of Dermatology and other Study Sites. Access to the non-commercial version of Sklip app for the purpose of research will be limited to enrolled Study Participants. OHSU dedicated employees will have access to the master list to match patient MRN to the anonymous username for the purpose of this Study. An OHSU Study team member will provide usernames and passwords to the additional Study Sites. Since this Study is anonymous the Sponsor will not receive any patient health information (PHI) during this Study. All Sklip dermatoscope devices will be sent one way to Participants via USPS or UPS.

6.1.7 PREPARATION

Once a Participant is officially enrolled in the Study, a designated Study Coordinator will properly sanitize and prepare a package of the necessary materials the Participant will need for the Study. The following are items that will be prepared to be shipped to the Participant via USPS or UPS:

- Instructions for Participants
- One (1) printed Participant Mole Log Sheet
- One (1) Sklip dermatoscope device (charging cable and dermoscopy oil)
- One (1) username/password enabling SMSA access using the Sklip App

6.1.8 ADMINISTRATION

1) All necessary materials will be shipped to all Participants via USPS or UPS as described in 6.1.7 PREPARATION.

2) Study Coordinators will provide specific onboarding training:

    a. The Participants will be trained on how to log their SSE self-selected PSLCs in their Participant Mole Log Sheet. They will also be asked to submit a copy of their Participant Mole Log Sheet using nPhase REDCap image upload, or email (athomederm@ohsu.edu). Participants will be reminded to bring it in person during their in-person visit.
    b. The Participants will be informed on the requirement to follow up in-person for a FBSE with a Study Site dermatology Provider within 28 days of completing the At-home Phase.
    c. The Participant will be informed that all costs associated with normal medical care activities will not be covered by the Study Sponsor as described in the sections above.

At the end of the Study, the Participants will be sent an nPhase REDCap Cloud survey that will document Participant responses to the number of self-selected PSLCs and the number of suspicious PSLCs identified by the dermatology Provider during the Study.

6.1.9 SPECIAL CONSIDERATIONS FOR ADMINISTRATION

N/A

6.1.10 ACCOUNTABILITY

The Investigators, or a responsible party designated by the Investigators, will maintain a careful record of the inventory and disposition of the Study agent.

Responsibility for device accountability at Study Sites rests with its Investigator; however, the Investigator may assign some of the device accountability duties to an appropriate designee. Inventory and accountability records

will be maintained and readily available for inspection by the Study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies.

The Investigator or designee will collect and retain all used, unused, and partially used containers of the Study device or devices unwanted by Participant at the end of the Study until full accounting has been completed. The Investigator or designee will maintain records that document:

- Investigational product delivery to the Study Site.
- The inventory at the Site.
- Number of investigational products shipped to Participant and date of shipment
- Any return of investigational product to the Investigator or designee.

These records will include dates, quantities, and the unique code numbers assigned to the investigational product and Study Participants.

The investigational product must be used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the Participants were provided the correct Study materials specified based off the Participants randomly assigned group. Completed accountability records will be archived by the Site.

6.1.11 DESTRUCTION AND RETURN

At the completion of the Study, the Investigator or designee will oversee repurposing or redistribution of any remaining Study product to be used in other applicable studies. There is no indication for destruction of unused Study devices.

6.2 DEVICE-SPECIFIC CONSIDERATIONS

Device Description

Please refer to 6.1.1 (Device Description)

7. TREATMENT PLAN

7.1 DOSAGE AND ADMINISTRATION

N/A

7.1.1 DEFINITION OF DOSE-LIMITING TOXICITY (DLT)

N/A

7.1.2 DEFINITION OF MAXIMUM TOLERATED DOSE (MTD)

N/A

7.1.3 DOSE DELAYS

N/A

7.1.4 DOSE ESCALATION

N/A

7.1.5 DOSE DE-ESCALATION

N/A

7.1.6 GENERAL DOSE MODIFICATION GUIDELINES

N/A

7.2 DISCONTINUATION FROM STUDY INTERVENTION

Discontinuation from the Study intervention (reported discontinued use of Sklip System by Participants) does not mean discontinuation from the Study, and remaining Study procedures (nPhase REDCap Cloud survey, chart reviews) should be completed as indicated by the Study protocol.

The data to be collected at the time of Study intervention discontinuation will include the following:

a) Anonymous Sklip App analytics per Study Participant (frequency of use)
b) Data obtained from chart reviews to track the number of submitted PSLCs, the number of PSLCs identified as SUSPICIOUS by the dermatology Provider during the in-person FBSE, the chosen method of follow-up, and any relevant pathology results for each Participant.
c) Data from the end of Study REDCap Cloud survey.

Participants MUST discontinue investigational product for any of the following reasons:

- Participant's request to stop Study intervention. Participants who request to discontinue using the provided Sklip System will remain in the Study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a Participant specifically withdraws consent for any further contact (refer to Section 5.2)
- Loss of ability to freely provide consent through imprisonment, or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

All Participants who discontinue Study intervention should comply with protocol specified follow-up procedures as outlined in Section 8. If Study intervention is discontinued prior to the Participant's completion of the Study, the reason for the discontinuation must be documented in the Participant's medical records and entered on the appropriate CRF.

7.3 TREATMENT PERIOD AND MAINTENANCE

Interventional treatment will not be provided in this Study. All treatment and management for Participants will follow standard OHSU clinical care protocol.

7.4 CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

N/A

7.5 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

There are no restrictions on specific medications, treatments, or procedures for this study.

7.7 OTHER TREATMENT MODALITIES

N/A

8. STUDY PROCEDURES/EVALUATIONS AND SCHEDULE

8.1 STUDY-SPECIFIC PROCEDURES

8.1.1 MEDICAL HISTORY

The Participant's medical history will be obtained from their medical records. Relevant medical history for this Study include:

- Demographic information (age, gender, race, location of residence)
- History of melanoma skin cancer confirmed by pathology report
- History of non-melanoma skin cancer confirmed by pathology report
- Whether the Participant has had a virtual communication (MyChart encounter, virtual video visit, direct message, e-visit) or in-person visit with a dermatology Provider within the last 90 days.

8.1.2 DISEASE ASSESSMENT

All Participants will be required to obtain an in-person FBSE. Since PSLCs will be evaluated per standard clinical care pathways, the evaluating dermatology Provider may or may not be involved in the Study. The dermatology Provider will be blinded to Participant activity, including the Participant Mole Log Sheet. The dermatology Provider may choose to perform biopsy, when applicable, independent of Participant at-home findings.

Biopsies may be performed for suspicious lesions identified by the dermatology Provider during the FBSE and will be assessed by histologic assessment as part of current standards of care for diagnosis, independent of the Study. **The use of the Sklip System is for <u>triage only</u> and is not intended to act as a substitute for official diagnosis via pathology results, and all subsequent management and treatment of disease will be based off official histologic diagnosis and in accordance current guidelines.**

8.1.3 MEDICATION REVIEW

N/A

8.1.4 PHYSICAL EXAMINATION

In-person Phase activity is described in Section 3.1 above.

8.1.5 RADIOGRAPHIC OR OTHER IMAGING ASSESSMENTS

Not applicable. All Participant-identified suspicious lesions that require further evaluation will be assessed with digital dermoscopy.

8.1.6 ADVERSE EVENT EVALUATION

The device does not pose a serious risk to the health, safety, or welfare of subjects. The clinical trial design is such that the potential risk of not flagging a suspicious lesion is appropriately mitigated and the trial itself does not pose a potential for serious risk to the health, safety, or welfare of a subject.

8.1.7 COUNSELING PROCEDURES

The results of this Study will not be made available to Participants. Participants will receive direct dermatology Provider care after visit summaries and biopsy results, when applicable, as part of standard of care according to their individual case.

8.1.8 ASSESSMENT OF STUDY AGENT ADHERENCE

Participants are not required to adhere to the interventional product. Frequency of use of the Study agent is measured and recorded (via Sklip analytics or nPhase REDCap Cloud survey), however use of the Study intervention is voluntary and at the discretion of the Participant.

8.1.9 ASSESSMENT OF PARTICIPANT-REPORTED OUTCOMES

Study Coordinators will provide specific onboarding training for all Participants on how to record each self-selected PSLC in their Participant Mole Log Sheet. Participants will be asked to record this information and self-report it at the end of the Study in the nPhase REDCap Cloud survey.

8.2 **LABORATORY PROCEDURES AND EVALUATIONS**

8.2.1 PREGNANCY TEST

N/A

8.3 **BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES**

N/A

8.3.1 LABORATORY CORRELATIVE STUDIES

N/A

8.3.2 SPECIAL STUDIES

N/A

8.4 **SCREENING ASSESSMENTS**

Screening will be done once during the initial contact by a Study Coordinator to have informed consent explained and signed. Since the eligibility criteria measurements are unlikely to change (of age, English speaking, access to smartphone, etc.) during the Study, only an initial baseline screening is required.

8.5 **BASELINE ASSESSMENTS**

After confirming whether the Participant meets the eligibility criteria, no further baseline screening or assessment is necessary to obtain prior to beginning the Study.

8.6 **ASSESSMENTS DURING TREATMENT**

Not applicable. There is no interventional treatment or therapies in this Study. The number of submitted PSLCs, the number of PSLCs qualified for follow-up, the chosen method of follow-up, and any relevant pathology results for each Participant will be recorded and analyzed as part of period retrospective chart reviews conducted by a Study Coordinator as described in Sections above.

8.7 EARLY TERMINATION OR END OF TREATMENT VISIT

EARLY TERMINATION – N/A; PARTICIPANTS DO NOT HAVE A PHYSICAL STUDY VISIT

END OF TREATMENT – N/A

8.8 FOLLOW-UP

There will be no scheduled follow-up after completion of the Study. Any follow up for Participants after conclusion of the 42 day Study will be part of the Participant's standard clinical care pathways and not the responsibility of Study Coordinators or the Study Sponsor.

8.9 UNSCHEDULED VISITS

All Participants will be requested to engage in an in-person visit at their Study Site within 28 days of completing the at-home Phase to obtain a FBSE. If the Participant does not already have a scheduled visit, Study Site dermatology providers will agree to accommodate overbookings to ensure that each participant can obtain an in-person visit within the

8.10 SCHEDULE OF EVENTS

Table 3. Schedule of events

Days (± 3 Days)	Recruitment	Enrollment	Data Entry	Phase 1 Survey
	Days -28 to -1	Day 1	Continuously	Day 42
Invite Participants	X			
Screening, Inclusion/exclusion criteria	X			
Informed Consent	X	X		
Onboard training		X		
MyChart, Direct message, Calls, Email, or Text	X	X		X
EMR Chart Review			X	X
Participant nPhase REDCap Cloud Survey	X	X		X

9. EFFICACY MEASURES

Assessment of any Participant self-selected PSLCs as part of the intervention in this Study will be conducted by the Sklip System. The Sklip System incorporates proprietary artificial intelligence (Ai) DDI analysis (SMSA) of PSLCs based on a modified dermoscopy Three-Point Checklist (MD3PC). PSLs presented to the SMSA are triaged into three categories: UNREMARKABLE, SUSPICIOUS or ERROR, and its performance has been verified and validated in alignment with expectations necessary for the safety and effectiveness of the device aligned with its intended use.

9.1 DEFINITION OF EFFICACY MEASURES

Measurable disease: Measurable PSLCs are defined as those that can be accurately measured in at least one dimension as > 3 mm diameter by naked-eye examination and confirmed using a medical ruler or professional dermatoscope (i.e. Heine D30) with a fixed measurement ruler in the field of view. There is no therapy introduced or evaluated in this Study, therefore parameters for determining disease response are unnecessary.

9.2 DISEASE EVALUATION

Any suspicious skin lesions (including PSLCs) that get further evaluated in this Study will be via Study Site normal clinical care pathways. Per current guidelines, all definitive diagnosis of dermatology Provider verified suspicious skin lesions with concern for malignancy must be made via biopsy and histologic assessment by the Study Site.

9.3 EFFICACY CRITERIA FOR TUMOR RESPONSE

N/A.

10. SAFETY

10.1 SPECIFICATION OF SAFETY PARAMETERS

The investigational device being assessed in this Study (Sklip System) is not of substantial importance in diagnosing, curing, mitigating, or treating disease. Instead, it provides a triage assessment according to a clinically accepted protocol, which is intended for confirmation by a healthcare professional. Therefore Participants enrolled in the Study are not exposed or introduced to any additional medical safety risks that would warrant scheduled screening assessments. The Participants have the option to be evaluated by a dermatology Provider via standard clinical care pathways, not part of the Study, and would be considered an unscheduled visit (Section 8.9 Unscheduled Visits).

There is minimal risk of psychological or behavioral effects that may be experienced by the Participant during the Study. At the start of enrollment for each Participant, he/she/they will have onboarding training by a Study Coordinator on how to contact a research team member to report any adverse psychological or behavioral effects throughout the duration of their enrollment.

If a Participant reports any adverse events, the investigator will immediately be informed of the event. The investigator will be responsible for assessing the reported adverse events and will be followed by a member of the Study team until resolution/stabilization. The Participant will be offered the voluntary option to withdraw from the Study and discontinue any intervention. The report will be documented in the Participant's record.

10.2 DEFINITIONS

10.2.1 ADVERSE EVENT (AE)

An adverse event is defined as any undesirable physical, psychological or behavioral effect experienced by a Participant during their participation in an investigational Study, in conjunction with the use of the investigational

product (Sklip System). In general, this includes signs or symptoms experienced by the Participant from the time of signing the informed consent to completion of the Study. Although we do not anticipate that the intervention in this Study poses significant risk to Participants, the following AEs for this Study may include but are not limited to:

- Subjective reports of increased psychological stress induced by self-skin-examinations (SSEs)
- Subjective reports of significant changes in behavior experienced by the Participant
- Allergic reaction to the Sklip provided dermoscopy oil (not reported to date)

10.2.2 SERIOUS ADVERSE EVENT (SAE)

In alignment with the FDA guidance and 21 CFR 812.3(m), Sklip has determined that a clinical Study utilizing the Sklip System constitutes a **Non-Significant Risk Device Study**. Please refer to Section 1.3 RISK/BENEFIT ASSESSMENT.

10.2.3 UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers UPs involving risks to Participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the Participant population being studied;
2. Related or possibly related to participation in the research ("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); and
3. Suggests that the research places Participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Our Study additionally includes an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of Participants (21 CFR 812.3(s))

10.2.4 SEVERITY OF EVENT

The Investigator will grade the severity of each AE using, when applicable, the current version of the CTCAE v5.0. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as defined below:

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE.

10.2.5 ASSESSMENT OF CAUSALITY RELATIONSHIP TO STUDY INTERVENTION

For all collected AEs, the clinician who examines and evaluates the Participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Related – The AE is known to occur with the Study intervention, there is a reasonable possibility that the Study intervention caused the AE, or there is a temporal relationship between the Study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the Study intervention and the AE.

Not Related – There is not a reasonable possibility that the administration of the Study intervention caused the event, there is no temporal relationship between the Study intervention and event onset, or an alternate etiology has been established.

10.3 EXPECTEDNESS

The Investigator 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 agent.

10.4 ADVERSE EVENT LIST(S)

10.4.1 ADVERSE EVENT LIST FOR SKLIP DEVICE AND SKLIP SYSTEM

Detailed information about the risks and expected AEs of the Sklip System may be found in the current edition of the manufacturer's instruction manual.

In alignment with the FDA guidance mentioned above and 21 CFR 812.3(m), Sklip has determined that a clinical Study utilizing the Sklip System constitutes a **Non-Significant Risk Device Study.** Please refer to Section 1.3 RISK/BENEFIT ASSESSMENT.

10.4.2 ADVERSE EVENT LIST FOR

N/A

10.4.3 KEY SAFETY CONCERNS AND/OR ADVERSE EVENTS OF SPECIAL INTEREST

All Participants			
Key safety concern/AESI:	**Threshold for action:**	**Participant management:**	**Special reporting requirements:**
Increased psychological stress/burden	Participant reports significant increase in psychological stress and requests for additional action	Participant will be offered the option to discontinue the Study or be offered a referral to an appropriate provider within the Study Site provider network	N/A

10.5 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an UP, AE or SAE may come to the attention of Study personnel during Study visits and interviews of a Study Participant presenting for medical care, upon review by a Study monitor, or during an audit. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, seriousness, expectedness, relationship to Study product (assessed only by those with the training and authority to make a diagnosis), and date 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 after enrollment. 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 Investigator will record all reportable events with start dates occurring any time after enrollment until the last day of Study participation. AEs will be evaluated using the current version of the CTCAE v5.0. If a Participant electively schedules a follow up visit with a provider, the investigator will inquire about the occurrence of AE/SAEs. Events will be followed for outcome information until resolution or stabilization.

10.6 REPORTING PROCEDURES

10.6.1 OHSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Unanticipated Problems (UP) and Adverse Events (AE) at the coordinating Study Site will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB website.

Fatal and life-threatening UP will be reported to OHSU IRB no later than 7 days of notification of the event. All other UP reports will be submitted to OHSU IRB no later than 15 days of occurrence or notification of the event. Copies of the report documents will be kept on REDCap.

Unanticipated Problems and AEs at the satellite Study Site(s) will be reported to their respective IRB according to their respective policies, procedures and guidelines and to OHSU study Site members.

Events that must be reported by the Investigator to the IRB are detailed in the OHSU IRB **Investigator Guidance: Prompt Reporting Requirements (HRP-801)**. Events that meet the criteria for OHSU RNI must be reported to the IRB within 5 days of learning of the event. At a minimum, events requiring reporting to the IRB include:

- Any new or increased risk related to the research, including AEs or IND safety reports that require a change to the protocol or consent,
- New FDA black box warning,
- Publications identifying new risks,
- Data Safety Monitoring Board/Committee letters recommending changes or discussing new risks
- Unanticipated adverse device effect
- Unauthorized disclosure of confidential Participant information

10.6.2 CENTRAL REPORTING OF ADVERSE EVENTS FOR MULTI-SITE STUDIES

All Adverse Events (AE) should be reported as soon as possible but no later than 7 days of notification of the event. AEs should be reported to the respective Site's IRB accordance to their policies, procedures and guidelines and to OHSU study Site members.

10.6.3 FDA REPORTING

Some events must be reported to the FDA through the MedWatch Voluntary reporting program, even if the trial involves a commercially available agent. Events to be reported include any UPs and any SAEs with a suspected association to the Study intervention. An eligible person at the OHSU Coordinating Center will evaluate any reported UADE at the coordinating Study Site or satellite Study Site(s). The sponsor will provide to the FDA, all reviewing IRB's, and all sub-investigators an IDE Safety Report for any UADE that meets all of the following criteria: 1) an adverse effect caused by or associated with the device, 2) serious, and 3) Unanticipated. The sponsor will provide this no later than 10 working days after first notice of the effect. Thereafter, the sponsor will report any additional information concerning the effect per FDA request, and as warranted.

If the sponsor determines that the UADE presents an unreasonable risk to subjects, the sponsor will terminate all

investigations or parts of investigations that present risk as soon as possible (no later than 5 working days after the sponsor makes this determination), and no later than 15 working days after the sponsor first receives notice of the effect.

10.6.4 SUSPECTED UNEXPECTED ADVERSE REACTIONS (SUSARS)

Per regulatory requirements, if an event is assessed by the Sponsor Institution as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor Institution to submit the SUSAR to Regulatory Authorities according to applicable regulations. In addition, the SUSAR will be distributed to the Investigators/Sites utilizing a Council for International Organizations of Medical Sciences (CIOMS) report form, or the MedWatch 3500A form). The Investigator will submit a copy of the report to their respective IRB or IEC per the governing institutional requirements and in compliance with local laws and guidelines.

10.6.5 SKLIP INC REPORTING REQUIREMENTS

All events reported to the FDA will also be reported to Sklip Inc. as provided in the Research Agreement within 24 hours of reporting.

10.6.6 REPORTING OF PREGNANCY

N/A

10.7 **STUDY STOPPING RULES**

The overall Study will be paused and appropriate authorities notified if indicated by statistical stopping rules in this protocol.

11. STATISTICAL CONSIDERATIONS

11.1 **STATISTICAL AIM**

The statistical aim of this pivotal trial is the estimation of diagnostic accuracy of the Sklip System estimated to pre-specified criteria: 95% sensitivity and 30% specificity for **Melanoma and atypical melanocytic nevi with uncertain malignant potential** (moderate, severe, and high grade atypia; those with pathology reports that include notes such as: borderline, cannot exclude melanoma, cannot exclude early evolving melanoma, unusual features, atypical spitz nevi, suspicion for melanoma, re-excision (or further removal) should be considered or is recommended in the pathologist management comment), 80% sensitivity and 30% specificity for **Squamous cell carcinoma**, 80% sensitivity and 30% specificity for **Basal cell carcinoma**.

11.2 **SAMPLE SIZE DETERMINATION**

Sample size was calculated using formulas based on normal approximation to the binomial distribution. Previously recorded historical biopsy results for Melanoma, Squamous cell carcinoma, and Basal cell carcinoma across the proposed Study Sites averaged 2.3%, 12.5% and 29.2% of in-person dermatology Provider visits (i.e. cases), respectively. This represents disease prevalence rates in this pivotal Study target population of interest (i.e. patients who visited a Study Site within a 365 day period specifically for a mole spot check with concern for skin cancer, or a full body skin exam (FBSE) for the purpose of skin cancer prevention. This calculation presumes the exclusion of all other dermatology visits not related to a concern for skin cancer. Formulae (1) and (2) were used to estimate the sample size needed to evaluate the sensitivity (Se) and specificity (Sp), based on the diagnostic performance data available for melanoma from the SMSA Performance Study, and the target population case prevalence rates. The following values are inserted: $Z_{\alpha/2} = 1.96$ for $\alpha = 0.05$ level of significance, and $d = 10\%$ margin of error for 95% Confidence Interval.

$$n_{\text{Se}} = \frac{Z^2_{\frac{\alpha}{2}}\widehat{\text{Se}}(1-\widehat{\text{Se}})}{d^2 \times \text{Prev}} \quad (1)$$

$$n_{\text{Sp}} = \frac{Z^2_{\frac{\alpha}{2}}\widehat{\text{Sp}}(1-\widehat{\text{Sp}})}{d^2 \times (1-\text{Prev})} \quad (2)$$

Table 4 and Table 5 below summarizes the sample size estimates for cutaneous diseases of interest to evaluate the sensitivity and specificity of the investigational device (Sklip System). As can be seen from the table, the size estimate calculated using the sensitivity value for detecting melanoma (423 cases [lesions]) yields the largest number. The expected numbers of lesions that will be accordingly captured during the Study are summarized in Table 6.

Considering the larger number of cases required for evaluation of sensitivity (423 for Melanoma; based on SMSA performance of sensitivity for melanoma of 97.4%) as opposed to specificity (114 for SCC), a 49% specificity can be estimated from the hypothetical sample data. Previous peer-reviewed studies, exclusive to virtual visits, showed that participants submitted an average of 1.02 to 1.9 images per participant.[1] Considering the aforementioned and average case submission rates reported by the proposed Study Sites, we expect a case submission rate of 1.5 per Study Participant. Assuming a 10% drop-out rate a total number of 310 Participants (dropout-inflated sample size) will be needed for the current study (310 = 423 ÷1.5 × 1.10).

Table 4. Sample size estimates for cutaneous diseases of interest to evaluate the sensitivity of Sklip System based on the available target population prevalence data.

	Sample Size Estimate to Test for Sensitivity											
	Melanoma			*BCC*			*SCC*			*AMN*		
Lesions	Confirmed	Excluded	Total	Confirmed	Excluded	Total	Confirmed	Excluded	Total	Confirmed	Excluded	Total
Suspicious	9	248	257	17	89	107	17	31	48	17	243	260
Non-Suspicious	1	165	166	1	38	39	1	13	14	1	104	105
Total Scanned	10	413	**423**	18	128	**146**	18	44	**63**	18	347	**365**
Prevalence	2.3%			12.5%			29.2%			5.0%		
Sensitivity	97.4%			95%			95%			95%		
Specificity	40%			30%			30%			30%		

The sample size was estimated using formulae (1) and (2) to test for sensitivity and specificity, respectively, with α = 0.05 significance level and 10% margin of error for 95% Confidence Interval. The respective sensitivity and specificity values were used to estimate the numbers of suspicious and non-suspicious lesions confirmed or excluded by the Ground Truth as described in the Sections above. BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, AMN: Atypical melanocytic nevi with uncertain malignant potential.

Table 5. Sample size estimates for cutaneous diseases of interest to evaluate the specificity of Sklip System based on the available target population prevalence data.

Sample Size Estimate to Test for Specificity

Melanoma			*BCC*			*SCC*			*AMN*		
Confirmed	Excluded	Total	Confirmed	Excluded	Total	Confirmed	Excluded	Total	Confirmed	Excluded	Total
2	55	57	11	56	67	32	56	88	4	56	61
0	37	37	1	24	25	2	24	26	0	24	24
2	92	**94**	12	81	**92**	33	81	**114**	4	81	**85**
2.3%			12.5%			29.2%			5.0%		
97.4%			95%			95%			95%		
40%			30%			30%			30%		

The sample size was estimated using formulae (1) and (2) to test for sensitivity and specificity, respectively, with $\alpha = 0.05$ significance level and 10% margin of error for 95% Confidence Interval. The respective sensitivity and specificity values were used to estimate the numbers of suspicious and non-suspicious lesions confirmed or excluded by the Ground Truth as described in the Sections above. BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, AMN: Atypical melanocytic nevi with uncertain malignant potential.

Table 6. Numbers of PSLCs expected to be captured in the estimated sample from the target population.

Lesions	Melanoma Confirmed	Melanoma Excluded	BCC	SCC	AMN	Total non-Melanoma Cancers	Total Malignant Lesions	Total Negative for Malignancy Lesions	**Total**
Suspicious	9	248	36	84	14	135	144	113	257
Non-Suspicious	0	165	15	36	6	58	58	107	166
Total	10	413	52	121	21	193	203	220	**423**
Prevalence	2.3%	97.7%	12.5%	29.2%	5.0%	46.7%	49.0%	51.0%	100%
Lesions per Melanoma	1	42	5	13	2	20	21	22	43

A review of all histologically confirmed Melanoma diagnosis made at OHSU within the past 10 years revealed over 3,500 cases. A review of all histologically confirmed non-Melanoma skin cancer diagnosis made at OHSU within the past 5 years revealed over 30,000 cases. Based off these findings, since three (3) additional Satellite Study Sites are each required to contribute at least fifteen (15) percent of the total sample size each, a maximum of 124 Participants at Site #1 OHSU (FDA suggested maximum enrollment cap of 40%) and a minimum of 47 participants (FDA suggested minimum enrollment of 15%) at each additional Site is feasible.

11.3 POPULATIONS FOR ANALYSIS

An intent-to-treat (ITT) analysis set will include those who are enrolled in the Study regardless of adherence. All primary analyses will be conducted using the intent-to-treat analysis set.

11.4 DESCRIPTION OF STATISTICAL METHODS

11.4.1 GENERAL APPROACH

This is a new statistical protocol to analyze how the use of the Sklip System enables laypersons to safely triage self-selected pigmented skin lesions of concern (PSLCs) from home with the same or better accuracy than pre-specified performance goals* for detection of PSLCs that require biopsy and are malignant: **Melanoma and atypical melanocytic nevi with uncertain malignant potential** (moderate, severe, and high grade atypia; those with pathology reports that include notes such as: borderline, cannot exclude melanoma, cannot exclude early evolving melanoma, unusual features, atypical spitz nevi, suspicion for melanoma, re-excision (or further removal) should be considered or is recommended in the pathologist management comment) (≥95% sensitivity, ≥30% specificity), **Squamous cell carcinoma** (≥80% sensitivity, ≥30% specificity), **Basal cell carcinoma** (≥80% sensitivity, ≥30% specificity).

*Pre-specified performance goals have been reviewed with the FDA for testing the Sklip System (including SMSA) as a stand-alone device.

The Study protocol will also compare the accuracy of the Sklip System when used by a layperson (Participant) versus near-perfect Sklip System user (Study Coordinator), assess whether Sklip System improves triage of PSLCs < 6 mm in diameter and triage of thin melanomas with <0.8 mm Breslow depth as suspicious, as compared to the current medical provider virtual triage method that relies on store-and-forward of smartphone clinical images (SCI), and assess accuracy of layperson-performed self-skin-exams (SSEs) at-home in the identification of all suspicious PSLCs present on their body as compared to the same layperson (Participant) evaluated with a full body skin examination (FBSE) by a dermatology Provider (DP) in-person.

The following method has been discussed with the FDA via Sklip Inc. Q-Submission Sprint Discussion (#Q211049/S002) to **establish the Study Ground Truth, described in the full IRB protocol**:

Dataset N) DDI dermoscopic diagnosis ground truth (DDI-GT) for PSLCs that were not biopsied during the In-Person Phase, and
Dataset O) Histologic diagnosis ground truth (H-GT) for lesions that were biopsied during the In-Person Phase

For Primary and Secondary endpoints below, the first SMSA output for each target PSLC will be used. If the first SMSA output for the target PSLC yields ERROR, then the second SMSA output for the same target PSLC will be used. If the first and the second SMSA outputs for the same target PSLC yield ERROR, then the third SMSA output for the same target PSLC will be used. If all three SMSA outputs yield ERROR, then the SMSA outputs for the target PSLC will be excluded. In other words, for each PSLC, there will be one SMSA output for analysis with a binary outcome "SUSPICIOUS" or "UNREMARKABLE." Else, that target PSLC may be excluded from some analyses.

Descriptive statistics will be used to describe the demographic and clinical characteristics of the Study Participants. Categorical data will be summarized using counts and percentages; continuous data will be summarized using means and standard deviations. Underlying statistical assumptions will be checked with the analysis. We do not anticipate a need to transform any of the data; if assumptions are violated, then alternative methods will be considered.

11.4.2 ANALYSIS OF PRIMARY ENDPOINT(S)

For the Primary Endpoints, the SMSA outputs of "SUSPICIOUS" or "UNREMARKABLE" from Participant-taken DDI will be compared to the Ground Truth, described in the Sections above. For **Melanoma and atypical melanocytic nevi with uncertain malignant potential** (moderate, severe, and high grade atypia; those with pathology reports that include notes such as: borderline, cannot exclude melanoma, cannot exclude early evolving melanoma, unusual features, atypical spitz nevi, suspicion for melanoma, re-excision (or further removal) should be considered or is recommended in the pathologist management comment), a 2x2 table consisting of the following counts (number of PSLCs):

- True Positives (TP): the SMSA output of SUSPICIOUS agrees with the Ground Truth for PSLCs that were

biopsied and were diagnosed as Melanoma or atypical melanocytic nevi with uncertain malignant potential, using Dataset (O) (Histologic diagnosis ground truth (H-GT)),

- False Positives (FP): the SMSA output of SUSPICIOUS does not agree with the benign Ground Truth using Dataset (N) (DDI dermoscopic diagnosis ground truth) and Dataset (O)
- False Negatives (FN): the SMSA output of UNREMARKABLE does not agree with the Ground Truth for PSLCs that were biopsied and diagnosed as Melanoma or atypical melanocytic nevi with uncertain malignant potential using Dataset (O)
- True Negatives (TN): the SMSA output of UNREMARKABLE agrees with the benign Ground Truth, using both Dataset (N) and Dataset (O)

For **Melanoma and atypical melanocytic nevi with uncertain malignant potential**, Sensitivity ($TP \div (TP + FN)$) of the Sklip System will be calculated with a lower one-sided 95% confidence interval using the Exact (Clopper-Pearson) method. For **Squamous cell carcinoma** and for **Basal cell carcinoma**, Sensitivity and lower one-sided confidence intervals will be estimated in the same manner as for Melanoma and atypical melanocytic nevi with uncertain malignant potential.

Specificity ($TN \div (FP + TN)$) will be the same for Melanoma and atypical melanocytic nevi with uncertain malignant potential, SCC, and BCC, where:

- False Positives (FP): the SMSA output of SUSPICIOUS does not agree with the benign Ground Truth, using Dataset (N) and Dataset (O)
- True Negatives (TN): the SMSA output of UNREMARKABLE agrees with the benign Ground Truth, using Dataset (N) and Dataset (O)

Specificity will be estimated with a lower one-sided 95% confidence interval using the Exact (Clopper-Pearson) method. Two-sided 95% confidence intervals for all Sensitivities and Specificities will also be calculated using the Exact (Clopper-Pearson) method.

We also will estimate the following measures of triage accuracy for each cutaneous disease entity with two-sided 95% confidence intervals using the Exact (Clopper-Pearson) method :

- $Accuracy\ (P) = (TP + TN) \div (TP + FP + FN + TN)$
- $Positive\ predictive\ value\ (PPV) = TP \div (TP + FP)$
- $Negative\ predictive\ value\ (NPV) = TN \div (FN + TN)$
- $Prevalence = (TP + FN) \div (TP + FP + FN + TN)$

11.4.3 ANALYSIS OF THE EXPLORATORY ENDPOINTS

Exploratory endpoint 1

Similar to the Primary endpoint, the accuracy of SMSA output using Participant-taken DDI will be assessed using a 2x2 table, where the SMSA output of "SUSPICOUS" or "UNREMARKABLE" will be compared to the SMSA output using Study Coordinator-taken DDI (near-perfect technical quality), simulating a laboratory-type environment where the SMSA is fed the near-perfect technical quality DDI.

The Sensitivity of the SMSA output from Participant-taken DDI will be compared to the Sensitivity of the SMSA output from Study Coordinator-taken DDI using McNemar's Test, given the paired nature of the data, using 0.05 significance level.

The Specificity of the SMSA output from Participant-taken DDI will be compared to the Specificity of the SMSA output from Study Coordinator-taken DDI using McNemar's Test, given the paired nature of the data, using 0.05 significance level.

This will be done for each disease entity:

- Melanoma and atypical melanocytic nevi with uncertain malignant potential,
- Squamous cell carcinoma,
- Basal cell carcinoma

Exploratory endpoint 2

Using only PSLs < 6 mm in diameter, the accuracy of the expert consensus triage decision using Participant-taken smartphone clinical images (SCI) will be assessed using a 2x2 table, where the expert consensus triage decision of "BIOPSY" or "MONITOR" will be compared to the intervention method, for both SMSA outputs recorded by Participants and SMSA outputs recorded by Study Coordinators for the same target PSLCs.

The Sensitivity of the SMSA output will be compared to the Sensitivity of the expert consensus triage decision of Participant-taken SCI using McNemar's Test, given the paired nature of the data (i.e. the same PSLCs < 6mm), using 0.05 significance level.

The Specificity of the SMSA output will be compared to the Specificity of the expert consensus triage decision of Participant-taken SCI using McNemar's Test using 0.05 significance level.

Estimates with two-sided 95% confidence intervals will be calculated using the Exact (Clopper-Pearson) method.

This will be done for each disease entity:

- Melanoma and atypical melanocytic nevi with uncertain malignant potential,
- Squamous cell carcinoma,
- Basal cell carcinoma

Exploratory endpoint 3

Using only Melanomas < 0.8 mm Breslow depth, the accuracy of the expert consensus triage decision using Participant-taken smartphone clinical images (SCI) will be assessed using a 2x2 table, where the expert consensus triage decision of "BIOPSY" or "MONITOR" will be compared to the intervention method, for both SMSA outputs recorded by Participants and SMSA outputs recorded by Study Coordinators for the same target PSLCs.

The Sensitivity of the SMSA output will be compared to the Sensitivity of the expert consensus triage decision of Participant-taken SCI using McNemar's Test, given the paired nature of the data (i.e. the thin melanomas < 0.8 mm Breslow depth), using 0.05 significance level.

Estimates with two-sided 95% confidence intervals will be calculated using the Exact (Clopper-Pearson) method.

Exploratory endpoint 4

We will calculate the following based on Participant self-skin exams (SSEs) performed during the At-home Phase:

(a) the mean and standard deviation of the number of PSLCs identified by Participants performing a SSE, and
(b) the mean and standard deviation of the number of PSLCs identified by the dermatology Provider during the In-person Phase full body skin exam (FBSE).

The mean difference and 95% confidence interval will be calculated and assessed by paired t-test.

11.4.4 SAFETY ANALYSIS

Adverse events will be tabulated by the Medical Dictionary for Regulatory Activities. The severity of the AE will be assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 criteria. Descriptive statistics using the safety evaluable population, will be used to report on all on-Study AEs, grade 3-4 AEs, treatment-related AEs, grade 3-4 treatment-related AEs, SAEs, treatment-related SAEs, and AEs

leading to discontinuation per CTCAE v5.0. Grade 3-4 laboratory abnormalities will be summarized using worst grade NCI CTCAE v 5.0 criteria.

11.4.5 BASELINE DESCRIPTIVE STATISTICS

Summaries of demographics, baseline characteristics, and baseline disease characteristics will be presented for Participants will include the following:

1. Demographics: Sex (Male, Female); Age (continuous); Ethnicity; Race; Region
2. Baseline Characteristics: Height (cm); Weight (kg);

11.4.6 ADDITIONAL SUB-GROUP ANALYSIS

If actual sample size will permit sub-group analysis, the analysis of the primary and secondary endpoints will be repeated but stratified by Fitzpatrick Skin Types 1—3 and 4. Additional sub-group, analysis by Site may also be performed.

11.5 HANDLING OF MISSING DATA

Missing data will not be imputed. Whenever possible, the analysis will be conducted using all available data. Missing data will be reported in the descriptive summary, and it will be noted if Participants were excluded from the analysis due to missing data.

12. CLINICAL MONITORING

12.1 OHSU KNIGHT CANCER INSTITUTE DATA & SAFETY MONITORING PLAN

All clinical trials at the Knight are required to have Data and Safety Monitoring Plan (DSMP). This Study is under the oversight of the Knight Cancer Institute's DSMC as described in the Knight institutional DSMP. The Knight DSMP outlines the elements required to ensure the safety of clinical trial Participants, the accuracy and integrity of the data, and the appropriate modification of cancer-related clinical trials for which significant benefits or risks have been discovered or when the clinical trial cannot be successfully concluded. The Knight DSMP also describes the methods and procedures for ensuring adequate, risk-based oversight of cancer-related research at OHSU.

As described in the Knight DSMP, regardless of a trial's risk level and any specific Knight oversight in place, the Investigator is singularly responsible for overseeing every aspect of the design, conduct, and final analysis of his/her investigation.

12.2 CLINICAL DATA & SAFETY MONITORING

As part of the Quality Assurance plan and in full agreement with NIH policy (NIH Guide, NIH Policy for Data and Safety Monitoring, June 10, 1998) that states all clinical trials require monitoring to ensure the safety of Study Participants and the validity and integrity of the data, monitoring will be a continuous, ongoing and multifaceted process. This includes external review by the DSMC and IRB(s), as well as internal data quality control, review and evaluation. Site monitoring visits are central to this process, and will include reporting to appropriate individuals with oversight responsibilities.

Details of monitoring activities, including designation of assigned monitoring entities, scope of monitoring visits, timing, frequency, duration of visits, and visit reporting, will be included in a separate Data and Safety Monitoring Plan (DSMP).

The Study Site Investigator is ultimately, singularly responsible for overseeing every aspect of the investigation, including design, governing conduct at all sub-Sites, and final analysis of Study data.

In the absence of a formal monitoring plan, the Investigator may work with his/her Study team to conduct and document internal monitoring of the Study to verify protection of human Participants, quality of data, and/or ongoing compliance with the protocol and applicable regulatory requirements.

If at any time Investigator noncompliance is discovered at OHSU or the satellite Study Site the corresponding Investigator shall promptly either secure compliance or end the Investigator's participation in the Study.

Independent audits will be conducted by the Knight DSMC to verify that the rights and well-being of human Participants are protected, that the reported trial data are accurate, that the conduct of the trial is in compliance with the protocol and applicable regulatory requirements, and that evidence of ongoing investigator oversight is present.

12.3 QUALITY ASSURANCE & QUALITY CONTROL

The investigational Study Sites will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring by the monitor and/or sponsor, and auditing by the Knight DSMC and/or regulatory authorities.

All clinical trials at the Knight Cancer Institute are required to have a Data and Safety Monitoring Plan (DSMP). All clinical work conducted under this protocol is subject to ICH GCP guidelines. This includes inspection of Study-related records by the lead Site, Sponsor, its designee, or health authority representatives at any time.

QA audit activities will occur as detailed in the Knight's institutional DSMP. All discrepancies, queries, deviations, observations, and findings of non-compliance will be compiled into a final audit report. The PI must review and assess each finding, and generate a response to the audit report that incorporates Corrective and Preventative Action (CAPA). A CAPA must approach analyzes root cause(s) of noncompliance in order to identify and determine changes to correct and resolve issues, and prevent recurrence.

Quality Control (QC) activities will occur to monitor and ensure the safety of Study Participants and the validity and integrity of data. Monitoring will be a continuous, ongoing and multifaceted process. This includes review by the Knight DSMC and applicable IRB(s), as well as internal data quality control, review and evaluation. Site monitoring visits are central to this process, and will include reporting to appropriate individuals with oversight responsibilities.

The Sponsor-Investigator, or Study monitor, will verify that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1 SOURCE DATA/DOCUMENTS

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. The Investigator will maintain adequate case histories of Study Participants, including accurate CRFs, electronic (e)CRFs and relevant electronic data capture (EDC) system and all relevant source documentation.

13.1.1 PARTICIPANT & DATA CONFIDENTIALITY

The information obtained during the conduct of this clinical Study is confidential, and unless otherwise noted, disclosure to third parties is prohibited. Information contained within this Study will be maintained in accordance with applicable laws protecting Participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Participant confidentiality is strictly held in trust by the Site Investigator(s) and Study team. This confidentiality is extended to cover testing of biological samples and genetic tests 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. No information concerning the Study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The Study monitor, other authorized representatives of the sponsor, representatives of the IRB or manufacturer 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 each 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 within the Knight Cancer Institute per OHSU's Information Security Directives. 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 Knight Cancer Institute research staff will be secured and password protected per OHSU's Information Security Directives. At the end of the Study, or after the appropriate period of record retention stated in Section 13.1.4, all Study databases will be de-identified and archived within the Knight Cancer Institute.

13.1.2 DATA COLLECTION & STORAGE: PRIVACY, CONFIDENTIALITY & SECURITY

Data collection is the responsibility of the clinical trial staff at the Site under the supervision of the Study Site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Standard institutional practices will be followed as described in the OHSU's Information Security Directives to maintain the confidentiality and security of data collected in this Study. Study staff will be trained with regard to these procedures.

Confidentiality: Loss of Participant confidentiality is a risk of participation. Efforts will be made to keep Study Participant identities confidential except as required by law. Participants' samples will be identified by code only. Specifically, each consenting Participant will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the Participant throughout the duration of their participation in the trial. The coded identifier will also be used to identify any Participant specific samples.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical research information system (eCRIS), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing Participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Data for this project will be stored in nPhase REDCap Cloud, a highly secure and robust web-based research data collection and management system. Study outcome data will be captured in electronic CRFs (eCRFs) using the electronic data capture (EDC) system nPhase REDCap Cloud. nPhase REDCap Cloud EDC is a web-hosted application hosted by nPhase (located in Encinitas, CA), and is an approved EDC system that has been reviewed by OHSU Security. To further preserve confidentiality, PHI in the EDC system will be limited to just birth date and visit dates. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the database are assigned a unique username and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

13.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

After the Study is completed, the de-identified, archived data will be transmitted and stored in a secure database on OHSU computers with encryption. A Study Coordinator will enter data from Participant surveys or charts into the secure database only for the purposes of this Study. In order to provide security for data and specimens, all Study members will be familiar with this protocol and the procedures and analyses described herein. Access to the nPhase

REDCap database will be limited to the PI, co-investigators and Study personnel. We have no plans at this time to accept data from sources other than those described in this protocol. Permission to transmit data to the data repository will be included in the consent form.

13.1.4 MAINTENANCE OF RECORDS

Records and documents pertaining to the conduct of this Study, source documents, consent forms, laboratory test results and medication inventory records, will be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the device being investigated. It is the responsibility of the sponsor to inform the Investigator when these documents no longer need to be retained.

If the Investigator relocates or for any reason withdraws from the Study, the Study records will be transferred to an agreed upon designee, such as another institution or another investigator at OHSU. Records must be maintained according to institutional or FDA requirements.

13.2 MULTI-SITE GUIDELINES

Once interested Participants have been identified at Satellite Study Sites, the list of potential recruits to screen will be given to the OHSU Lead Study Site to contact via E-mail, phone or text message. Communications during the screening process and further activities are described in the Sections above. The OHSU Lead Site will administer all Study activities, outside of the in-person FBE, and any data collected will be stored on the nPhase REDCap Cloud database.

13.3 PUBLICATION AND DATA SHARING POLICY

This Study will adhere to the requirements set forth by the ICMJE and FDAAA that requires all clinical trials to be registered in a public trials registry (e.g., ClinicalTrials.gov) prior to Participant enrollment.

13.3.1 DATA SHARING POLICY FOR GENOME-WIDE ASSOCIATION STUDIES (GWAS)

N/A

13.4 CONFLICT OF INTEREST POLICY

Two researchers associated with this Study are Dr. Joanna Ludzik MD, PhD and Dr. Alexander Witkowski MD, PhD. They have developed the interventional device used in this Study and have a company that sells the hardware component (Sklip dermatoscope). The nature of this potential conflict of interest and the design of this Study have been reviewed by two committees at OHSU and a management plan is in place to help ensure that this research is not affected by these financial interests. Dr. Ludzik and Dr. Witkowski will be exclusively providing normal clinical care to Study Participants, when applicable for an in-person visit, and will not be involved in communication with Study Participants or data collection. If you would like more information, please contact the OHSU Research Integrity Office at (503) 494-7887.

13.5 DELIVERY OF PROGRESS REPORTS TO STUDY FUNDER

Upon the request of Sklip Inc. the Institution will submit oral or written reports on the progress of the Study as provided by this protocol. Within thirty (30) days following the completion or termination of the Study, Institution will furnish Study Funder with a final report detailing the results of the Study.

14. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

14.1 ETHICAL STANDARD

The Investigator will ensure that this Study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR 812, and/or the ICH E6.

14.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent forms, 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.

14.3 INFORMED CONSENT

Written informed consent will be obtained from all Participants participating in this trial, as stated in the Informed Consent section of 21 CFR Part 50. Documentation of the consent process and a copy of the signed consent shall be maintained in the Participant's medical record.

14.3.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreement 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 as appropriate. Consent forms will be IRB-approved and the Participant will be asked to read and review the document. 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/benefits of the Study, alternatives to participation, 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 prior to any procedures being done specifically for the Study. The Participants may withdraw consent at any time throughout the course of the trial. A copy of the 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.

14.3.2 PARTICIPANT INCENTIVES

There will be direct payment incentive to participate in this Study. At the end of this Study each Participant will be able to keep their commercially available Sklip dermatoscope device hardware (research value: $99.99). The ability for Study Participants to keep or obtain a Sklip device at the end of the Study is not considered coercive neither expected to create any bias for a Participant to choose to participate in this Study.

14.4 PROTOCOL REVIEW

The protocol and informed consent form for this Study must be reviewed and approved in writing by the OHSU Knight Cancer Institute's Clinical Research Review Committee (CRRC) and the appropriate IRB prior to any Participant being consented on this Study.

14.5 CHANGES TO PROTOCOL

Any modification of this protocol must be documented in the form of a protocol revision or amendment submitted by the Investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the Participant. In that event, the Investigator must notify the IRB/FDA/or sponsor within 5 business days after the implementation. An Investigator who holds an IND or IDE application must also notify the FDA of changes to the protocol per 21 CFR 812.

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