Adaptive Deployment of DermAI to Evaluate Human Factors of Testing

NCT06387472

15Sep2024

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Protocol Number: (IRBe)	23-007636
Clinical Trial Registration Number:	NCT06387472
Internal Study Number	DermAI-005

Initial version: January 16, 2024
Revision number and date: Version 1.1 - March 29, 2024
Revision number and date: Version 1.2 – September 15, 2024

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Study Summary

Title	Adaptive deployment of DermAI to evaluate human factors of testing
Running Title	User Adaptation
Protocol Number	DermAI-005
Phase	Other
Methodology	Prospective randomized controlled trial
Overall Study Duration	12 months
Subject Participation Duration	Participation will take approximately 1 week.
Single or Multi-Site	Single
Objectives	To develop the performance characteristics and human factor considerations to support fully remote patch testing.
Number of Subjects	Up to 10 pilot subjects followed by 150 Adaptive Patients
Diagnosis and Main Inclusion Criteria	The condition being studied is allergic contact dermatitis Inclusion Criteria: • Adults aged 18 or older • Able to provide consent
Study Product, Dose, Route, Regimen	Device: AI algorithm to evaluate photographs of skin test patch regions Drug: Allergens used in the testing protocol
Statistical Methodology	The analysis plan will focus on comparing the AI predictions of reactions with the interpretation of a human review of the photographs documented during the study visits. The reference criterion will be the expert, in person review as is currently performed with standard clinical operations.

Summary of Protocol Changes

Protocol Version	Summary of Key Changes
1.0	• Original Protocol
1.1	• Addition of 10 pilot subjects • Minor refinements to protocol details throughout
1.2	• Addition of allergens and updates on Phase III activities.

1. Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1. Background

Allergic contact dermatitis is a common inflammatory skin disorder. The disorder is characterized by pruritus, erythema, vesicles and scaling of the skin. Contact dermatitis can be further divided into allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD). ACD is a type of IV-mediated hypersensitivity to a specific allergen, resulting in an inflammatory response with exposure. ICD is a non-immunologically driven, inflammatory reaction to an irritating substance.

ACD is common, with some studies demonstrating prevalence rates as high as 20% of the general population (Alinaghi, Bennike, Egeberg, Thyssen, & Johansen, 2018). It can be difficult to distinguish ACD from other forms of dermatitis. History, patch testing, and other forms of assessments may help to clarify the diagnosis.

The cause of allergic contact dermatitis is determined by patch testing performed by dermatologists.

1.2. Investigational Agents

This protocol is in preparation of the creation of an integrated test kit consisting of a novel physical patch design, custom allergen panels, digital photography, and a computer vision-based algorithm to interpret the patch test results. These innovations represent a future state of technology. Within scope of this protocol is an adaptation of existing patch testing supplies and a test of the performance of the AI algorithm performance in a manner that does not inform or alter the routine clinical diagnostic practice to minimize risk.

The prospective data collection will involve multiple digital photography technologies. The primary photography device is an iOS-based custom application that allows for automated photograph capture and scheduling. This smartphone application will be used by the participant enrolled in the study using a study-specific iPhone 12 or newer device. The application in its current state only photographs the test site region and uploads the images to a secure, Firebase database on Google Cloud. The software as a medical device aspect of the AI processing will not be involved in the capture or transfer of the data in the current configuration. The models will be run asynchronously using the data captured during the study. In addition to this smart phone application, we will also use additional cameras, including a full-spectrum (infrared + ultraviolet + visible light spectrums), to ensure the model performance is not contingent upon the iPhone model used in the study along with providing new data to potentially enhance the detection of contact dermatitis in the future.

1.2.1. Camera technologies under study

Visible Light Digital Photography ("regular" photography): A standard iOS camera system will be the primary camera used in the study. This camera will be supplemented with cameras used during routine clinical documentation of the testing (i.e., a combination of Mayo Clinic owned and operated smartphones and interchangeable lens cameras.

Full Spectrum Photography: A full-spectrum digital photography system is one where the digital sensor has had the Bayer filter removed. This allows all wavelengths of light to reach the imagining sensor, including the ultraviolet spectrum (not visible with the unaided eye). A "Wood's light" (or black light) uses ultraviolet light to accentuate different aspects of the skin, particularly pigmentation profiles. The study will also need to incorporate infrared light sources to best utilize the spectrum of light energy a camera can capture. A full spectrum camera can photograph the same wavelength of light, particularly if a glass filter that allows only a narrow range of wavelengths to pass is used. Likewise, infrared is used by many animals (and door sensor technologies) to identify subtle differences in heat profiles in objects. We are hypothesizing that the combination of ultraviolet and infrared spectra will improve the detection of allergic contact dermatitis by the computer vision algorithms.

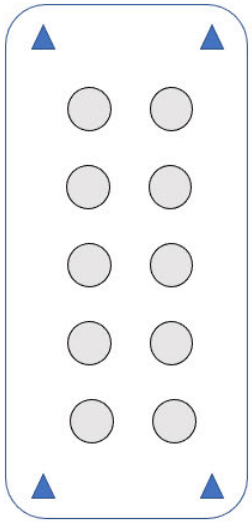
Photogrammetry: While a single photograph may characterize the appearance of raised textures on the skin surface, photogrammetry allows for direct modeling of the surface of the skin. Briefly, photogrammetry is an established technique where an object (e.g., a suspicious skin lesion) is photographed from 30 or more angles. Computer algorithms assemble the set of photographs into a 3D mesh object that is a digital representation of the surface of the skin. We hypothesize that this 3D representation of the skin lesion will convey important "tactile" information about the test sites that is not otherwise present in standard 2D digital photographs.

1.2.2. Allergens

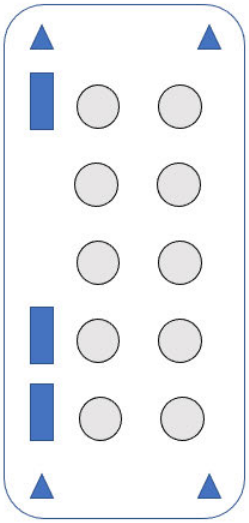
The use of the allergens are in accordance with standard clinical practice. However, the allergens are not FDA approved for this purpose. As such, they will be considered as investigational agents in the context of this study.

1.2.3. Test Patch

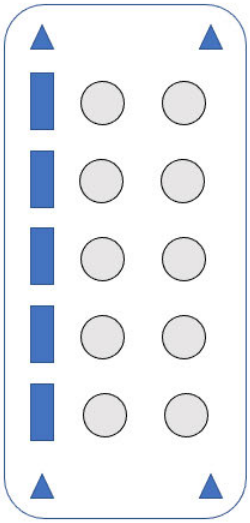
The physical patch test device is a clinical standard apparatus manufactured by Finn Chamber. The allergens are applied to the skin by means of direct contact when the patch test device is applied for testing. Allergens are contained in an inert metal well. For the purpose of this study, the paper-like border surrounding these metal wells will be modified to allow for specific visual patterns to be drawn onto the skin using a standard surgical marker (blue shaded regions in the figure below). These markings will allow for the finalized AI workflow to identify unique allergen placement profiles based on markings drawn on the skin.



Binary mathematical marker indicating Patch #1



Binary mathematical marker indicating Patch #26



Binary mathematical marker indicating Patch #32

Fiducial marker noting orientation and boundaries

Binary mathematical marker to identify patch and allergen profiles.

Double-rimmed allergen disk

Patch ID	Hole Sequence	Patch ID	Hole Sequence
1	0-0-0-0-0	17	0-0-0-0-1
2	1-0-0-0-0	18	1-0-0-0-1
3	0-1-0-0-0	19	0-1-0-0-1
4	1-1-0-0-0	20	1-1-0-0-1
5	0-0-1-0-0	21	0-0-1-0-1
6	1-0-1-0-0	22	1-0-1-0-1
7	0-1-1-0-0	23	0-1-1-0-1
8	1-1-1-0-0	24	1-1-1-0-1
9	0-0-0-1-0	25	0-0-0-1-1
10	1-0-0-1-0	26	1-0-0-1-1
11	0-1-0-1-0	27	0-1-0-1-1
12	1-1-0-1-0	28	1-1-0-1-1
13	0-0-1-1-0	29	0-0-1-1-1
14	1-0-1-1-0	30	1-0-1-1-1
15	0-1-1-1-0	31	0-1-1-1-1
16	1-1-1-1-0	32	1-1-1-1-1

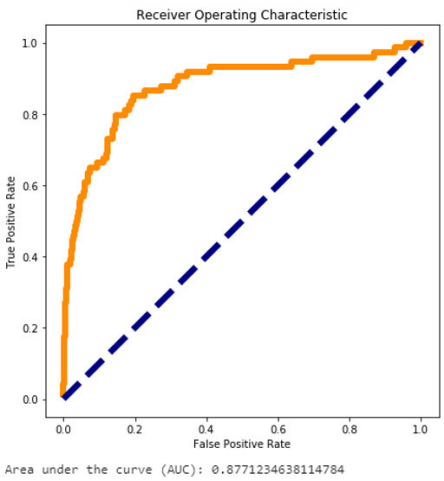
1.3. Preliminary Data

1.3.1. Study #1: IRB 19-012164

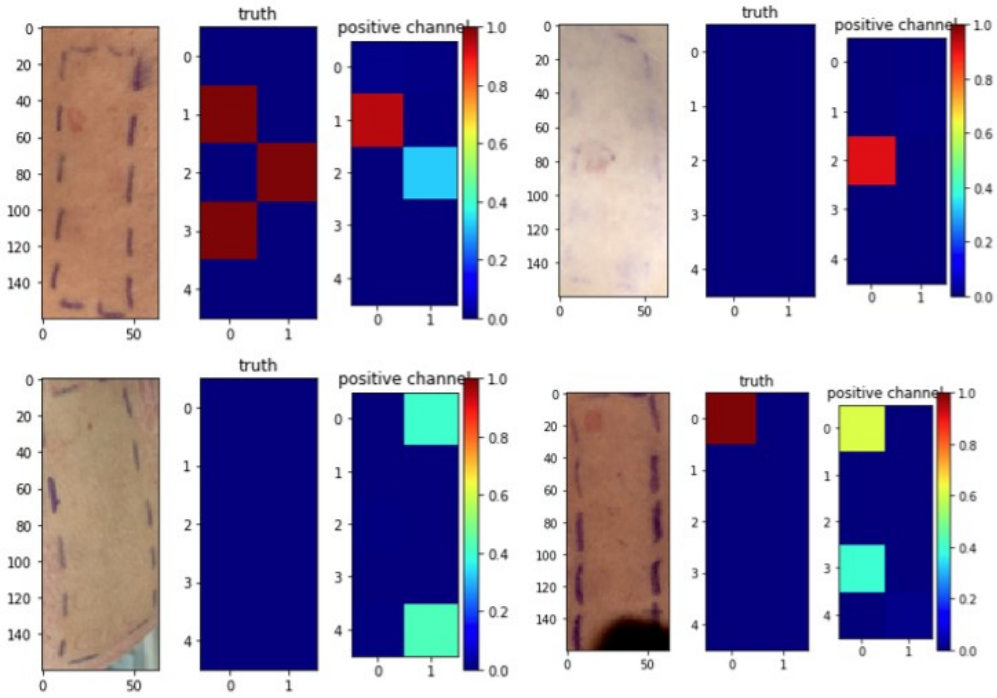
To-date, retrospective data collection under IRB 19-012164 has enrolled 310 subjects with 5,417 reaction photographs (approximately 54,170 individual reaction sites) which includes images taken both from the prior patch design as well as the new, fiducial patch design.

We have designed a deep learning classifier to predict the presence of allergic reaction from smartphone images of patch test reaction sites. The model was tested on a dataset of 260 patches (2,600 individual reactions) from several dozen individuals.

On the test dataset, the model displayed area under the ROC curve of 0.877. At a prediction cutoff of 10%, the model had an accuracy of 0.942, a sensitivity (true positive rate) of 0.540, and a specificity (true negative rate) of 0.956. The ROC curve is shown below, along with several examples of correct and incorrect predictions.



ROC curve for model performance at the reaction level



Examples of model prediction. For each of the four examples, the smartphone image of the reaction site is shown on the left, the true reaction label (based on the clinical report) is shown in the middle, and the model prediction is shown on the right. Positive and negative predictions are shown on a continuous color scale, where 1 (red) indicates the presence of reaction and 0 (blue) indicates the absence.

1.3.2. Study #2: Prospective Clinical Trial (IRB 21-011596)

A prospective, pragmatic clinical trial was designed to advance the technologies associated with a democratized skin patch testing approach that leveraged novel patch designs and an integrated smartphone-based application to capture and upload photographs of the patch testing sites to the cloud. The study incorporated an in person, clinical assessment at all three study visits to establish the reference criterion according to current clinical protocol. Photographs were captured at each visit to provide means to evaluate a novel deep learning model for the detection of allergic contact dermatitis. While the deep learning algorithm's performance could be established relative to the in-clinic reference reading, it was unknown just how well a human reader could function when only exposed to the photographs of the test sites (i.e., not able to palpate suspicious regions). To address this, the study incorporated a human reading protocol where the same photographs, void of any data collected about the patient or information obtained during the clinical visit, were reviewed by humans to determine what the accuracy of the machine learning approach in the context of human readers.

A total of 232 participants consented to participate and 206 reached the day five assessment. A specific purpose of this study was to enroll 50% of participants with Fitzpatrick Skin Types IV – VI. This objective was achieved as the distribution of skin types over the six types were as follows: 46.6% were classified as types IV-VI. The mean (SD) participant age was 39.1 (13.5) years, and 66% (136/206) of the participants were female. A total of 32.0% (66/206) of participants self-identified as being Black or African American, 16.5% (34/206) as Asian (34/206), and 40.3% as White (83/206). A total of 23 participants self-identified as Other (11.2%) or of Hispanic origin (73.9%, 17/23).

The overall incidence of allergic contact dermatitis in the sample was 6.4% (132/2,060) using the panel of allergens to be tested in the present study. The 206 images yielded 2060 test sites that were expertly evaluated during the in clinic (Day 5) evaluation. The only input to the neural network was the cropped image of the patch test site sites. The CNN model diagnosed the presence or absence of reaction with an AUROC of 0.861 (95% CI, 0.824 – 0.897). Using the previously selected cutoff of 4.88%, this generated an accuracy of 91.0% (95% CI, 89.7%-92.2%), a sensitivity of 58.3% (95% CI, 49.4%-66.8%), and a specificity of 93.3% (95% CI, 92.0%-94.3%).

1.4. Risks and Benefits

The risks of this research study are minimal. The most common side effect of skin testing is slightly swollen, red, itchy bumps (wheals). These wheals may be most noticeable during the test. In some people, though, an area of swelling, redness and itching may develop a few hours after the test and remain for a couple of days.

Rarely, allergy skin tests can produce a severe, immediate allergic reaction.

The patches are placed on the forearm for 48 hours. During this time, bathing and activities that cause heavy sweating need to be avoided. Irritated skin at the patch site may indicate an allergy.

As with all research, there is a chance that confidentiality could be compromised; however, we will take all appropriate precautions to minimize this risk.

2. Study Objectives

2.1. Primary Objective

- To test if interpretation using novel AI algorithms analysis of photographs of skin patch tests is concordant with in person skin patch test interpretation.

2.2. Secondary Objectives

- To test if human review of photographs of skin patch tests are concordant with in person examination results.
- To demonstrate performance of DermAI application usage by the participant.
- To develop a database on novel photography modalities and explore performance advantages full spectrum photography and photogrammetry may bring to detecting contact dermatitis reactions.
- To explore novel combinations of allergens to lessen the burden of testing.
- To refine and optimize the lighting characteristics for photographing with visible spectrum and full spectrum lighting.

3. Study Design

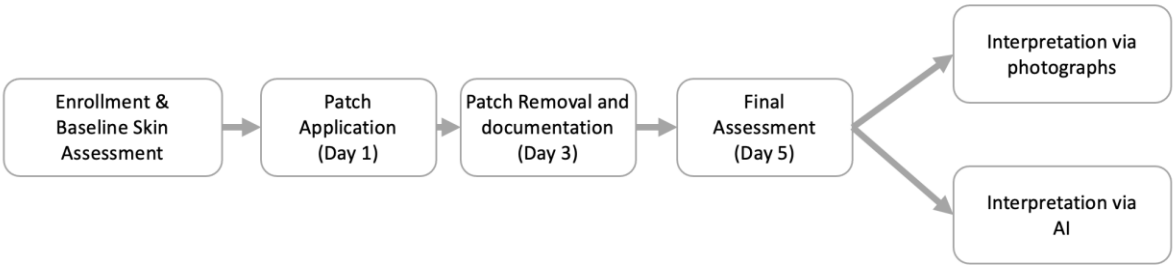
3.1. General Description

The overall adaptive study is designed to include three consecutive phases. Prior to the start of the adaptive study, a pilot cohort of up to 10 participants are planned to optimize the study protocol logistics, including camera usage, image capture parameters and documentation, and lighting conditions. This pilot phase is to ensure that the data captured during the adaptive study are as optimal as possible based on all study procedures. Pilot subjects will undergoing the same overall protocol scheme shown below and receive remuneration. The data collected will be used to refine the protocol, with amendments as necessary.

Each of the phases in the adaptive study is intended to advance the technologies and evaluate how scalable the technologies will be outside the clinical practice. The phases described below cover the primary intended workflow using the Mayo Clinic owned iPhone. Additional protocol actions including additional photography and ascertainment of other clinical study data (including adverse events) will occur to enrich the study data.

Common study flow for all phases of the study:

On day 1 a routine skin examination will be conducted. This will include photographic documentation of the condition of the skin region to be tested. Afterwards, the test patches will be applied to commence the testing. On day 3, the patients will return to remove the patch tests and document the test sites using the study iPhone app and the additional camera setups as specified in the protocol. On day 5, the final photographic documentation will be acquired and the final clinical assessment for allergic contact dermatitis will be provided by a medical professional with training in patch testing to establish the reference criterion.



Specific adaptation according to each phase of the study:

Phase 0 (n <=10): This pilot phase will study up to 10 participants to optimize the study manual of operations, ensuring the logistics and timing of all study visits to optimally conduct the three main phases of the study.

Phase 1 (n=100): Phase 1 initiates where the prior pragmatic clinical trial (NCT053339750, IRB 21-011596) concluded. This phase of the study will advance the technology in material ways through shifting day 3 (patch removal) and day 5 (final photographic documentation of test site) to the participant in the study. Participants will be guided in the use of the application and primary iOS/iPhone photographic documentation; the study team will provide additional photographic documentation and review of the test site to establish the reference criterion.

Phase 2 (n=25): For phase 2, the patch will be placed on the inside of the arm by the participant The study documentation will proceed identical to Phase 1.

Quality Checkpoint Decision: Patch able to be successfully applied by patient in >90% of the cases (fewer than 3 placement errors).

Phase 3 (n=25): In phase 3, the entire study will be patient-led, although on-campus visits will be required to obtain the allergen panel and evaluate the reference criterion. This phase will use a prototype novel test kit with printed instructions and necessary supplies to clean the arm, assemble the patch application jig, install the app, and perform the patch testing. Human observation and patient surveys will be conducted to evaluate the human factors aspects of the test kit.

For both Phases 2 and 3, participants will be invited to complete the Patient Journey questionnaire at least a week ahead of the scheduled visit 1 appointment by email. Responses will be summarized to suggest allergens that would be recommended based on past exposures. The recommendations will be constrained to only the set of allergens tested in this protocol (See Section 5.2). Participant will have the option to select the standard allergens used in Phase 1 of the study or use up to 10 of the recommended allergens based on the Patient Journey.

3.2. Number of Subjects

Up to a total of 160 participants will be enrolled and tested as part of the pilot (n<=10) or adaptive study (n=150).

3.3. Duration of Participation

An individual participant will require three visits to the study site on Days 1, 3 and 5.

3.4. Identification of Source Data

Study-specific case report forms (CRFs) will be used to document all of the following:

1. Demographics and medical history including assessment of Fitzpatrick skin types
2. Patient will be assigned to one of the randomized allergen templates that will be used for the study.
3. Documentation of the randomized location of the allergens on the test patch used with the participant
4. Documentation of the reference criterion (in person assessment by medical professional with training in patch testing Day 5) as well as the initial impression of reactions at Day 3 immediately following the removal of the patches.
5. Participant feedback on the user experience of the test patching
6. Documentation of the blinded human review of the photographs acquired on Day 3 and Day 5
7. Adverse events

The following source data will not be directly collected in the CRFs, but will be integrated into the master database:

- Test site photographs
- AI predictions on the photographs

4. Subject Selection Enrollment and Withdrawal

4.1. Inclusion Criteria

- Adults aged 18 or older
- Willing and able to provide informed consent

4.2. Exclusion Criteria

- Under 18 years of age
- Has used topical or oral steroids two weeks prior to patch testing
- Currently taking immunosuppression agents or is immunocompromised due to medical condition
- No sunburn or rash at site of testing
- Women who are breastfeeding or pregnant.
- Treatment with ultraviolet (UV) light (including tanning) during the two weeks prior to visit.
- Subjects unable to comply with patch test study requirements including multiple return visits and activity restrictions (e.g., protecting patch test area from excess moisture due to showering)

4.3. Subject Recruitment, Enrollment and Screening

The recruitment for this study will include participants from Mayo Clinic Florida patients and staff, and collaboration with the University of North Florida.

In 2019, approximately 284 patients had skin patch tests performed at Mayo Clinic Department of Dermatology in Jacksonville Florida. Among these patients, 17 were identified Black or African American with a Fitzpatrick score of 5-6, and 32 were identified as Hispanic or Latino with a Fitzpatrick score of 3-6.

Additionally, we will advertise for a healthy control group throughout Mayo Clinic Florida campus as well as the University of North Florida. In 2019, the University of North Florida student population enrollment was reported at approximately 17,117 students. The distribution of population for minority population of interest is 10% (1,684) Black or African American, 13.3% (2,280) Hispanic or Latino, and 5% (853) two or more races. Potential participants can contact the study coordinator listed in the flyer and/or electronic display to further inquire on eligibility criteria and study questions.

Thus, we estimate that from a pool of 49 eligible patients in Mayo Clinic Florida per year, the robust minority population of employees at Mayo Clinic and student population at University of North Florida, we can achieve full enrollment.

We will monitor enrollment bi-weekly and will hold calls with the study team to clarify questions about eligibility and ensure robust recruitment. If recruitment falls short of numerically defined targets, we will assess reasons for slow accrual and adjust the protocol accordingly.

Patients who have undergone previous patch testing will be screened by an experienced study coordinator for participants with a Fitzpatrick skin types 4 through 6 and eligibility criteria. This study coordinator will call the patient to discuss the study, eligibility, and study logistics, and then will plan to meet the patient at their next visit to the clinic to review and sign the consent (if the patient wishes to participate and is eligible).

Potential participants who answer the advertisement will have a call scheduled with the study coordinator to discuss the study, eligibility, and study logistics. Based on the potential participant's agreement, the study coordinator will schedule a research visit, as well coordinate with the Dermatology medical assistants to schedule the patch testing procedures.

The study coordinators are skilled in presenting the trial information without bias or pressure and in a culturally appropriate manner. Translators will be used as needed. Study coordinators will ask those patients who remain initially undecided if they may contact them again at a determined timeframe to review again and ask further questions. Screening and enrollment failures and related reasons for same will be discussed at the monthly review meetings and potential actions will be taken as need. Attention will be paid to adhering to regulatory issues.

4.4. Early Withdrawal of Subjects

4.4.1. When and How to Withdraw Subjects

Participants may withdraw at any point in the study. In the event the test patch is removed early due to possible reaction to an allergen or for another other reason (e.g., removed while bathing), the study team will be notified of the event.

4.4.2. Data Collection and Follow-up for Withdrawn Subjects

Participation is strictly voluntary. The participant will be followed according to protocol to document the reactions if the participant is willing. If the participant is unable or unwilling to continue with protocol procedures, the study records will be noted as such.

5. Test Patch and Allergen Details

5.1. Description of test patch vehicle

The test patch (Finn Chamber) is a non-sterile aluminum chamber mounted on Scanpor tape, which is a hypoallergenic surgical tape with a non-latex adhesive. The tape is made of rayon and polyester fibers.

5.2. Investigational allergens

5.2.1. Primary Test Site (arm 1)

The following ten allergens manufactured by AllergEAZE will be used for patch testing during the study. Potential adverse reactions include pruritus, irritation, skin discoloration, erythema, induration, blistering and ulceration. Pruritus can be managed over-the-counter antihistamines.

While most reactions self-resolve, more severe skin reactions would be managed with topical steroids.

1. Nickel sulfate hexahydrate, 2.5% (18.3%)
2. M. Pereirae resin, 25% / Balsam of Peru (9.2%)
3. Neomycin sulfate, 20% (7.8%)
4. Fragrance mix, 8% (6.7%)
5. Bacitracin, 20% (6.4%)
6. Carba mix, 3% (5.8%)
7. Quaternium-15, 1% (4.4%)
8. Benzoic acid, 5% (3.7%)
9. Propolis, 10% (3.5%)
10. Thiuram mix, 1% (2.8%)

5.2.2.Secondary Test Site (arm 2)

As part of the technology development program, two secondary tests will be used. Each participant will be randomized to one of these two patches.

Combination Patch #1: Standard Panel Array of 10 Allergens Combined into 4 Wells

1: Metals: Nickel sulfate hexahydrate

2: Fragrance & Taste Enhancers: M. Pereirae resin, 25% / Balsam of Peru + Fragrance mix + Quaternium-15

3: Topical/Homeopathic: Neomycin sulfate + Bacitracin + Propolis

4: Fungicides: carba mix + Thiuram mix + Benzoic acid

Combination Patch #2: Common Jewelry & Cosmetic Patch

1: Common metal allergy: Nickel sulfate hexahydrate

2: Cosmetics: M. Pereirae resin, 25% / Balsam of Peru

3: Cleaners: Methylchloroisothiazinoline / methylisothiazinolone

4: Fragrance: Fragrance mix

Combination Patch #3: Patient Identified Allergen Profiles

For Phase II and III of the study, the following ten allergens will be added to the pool of 10 unique allergens tested in the primary patch and the combination of allergens offered as a part of the two combination patches.

- Linalool
- P-phenylenediamine
- Benzisiothiazolinone, 0.1p
- Methylchloroisothiazinoline / methylisothiazinolone
- Paraben mix
- Formaldehyde
- Tea Tree Oil
- Cobalt Chloride
- Disperse Dye (Blue Mix)
- Gold Sodium Thiosulfate

This patient-driven combination of allergens can have between 1 and 10 individual test sites allowing for measurement of preference for "body burden" and patch test configurations.

5.3. Method for Assigning Allergens to Test Site Regions

To minimize complexity of the randomization process and preparation of the patch test for the primary test site, a total of four randomized placement sequences will be generated. Participants will be assigned to these sequences in consecutive order. This same randomization sequence will be used to randomize the secondary patch option to the participants with participants holding an odd study number receiving Combination #1 and even study numbers receiving #2. Note these two patches are largely identical except for how the allergens are combined with the exception that Combination #2 has methylchloroisothiazinoline / methylisothiazinolone added to it.

5.4. Preparation and Application of Test Patches

The application of the allergens to the test patch will be conducted according to the Study Operation Manual. This manual will include the documentation of safe storage and handling practices of the allergens, templates of the randomized allergen locations, and guidelines for the application of the patch to the participant's arm.

5.5. Subject Compliance Monitoring

The primary compliance consideration for this study is the maintenance of the test patch over the first three days. The participant will be given information on showering and other personal hygiene considerations while the patches are worn. Early removal or contamination of the test patch will be documented on Day 3 during the participant's visit. Deviations from the expected protocols will be documented on study case report forms.

5.6. Masking/Blinding of Study

The medical professional that reads the photographs of the test sites will be blinded to all clinical information including, but not limited to, the allergen's randomized locations, the in-person assessment of the reactions, and any AI predictions on the images. Effectively, the human read of the photograph will only have the photograph available to form all impressions about the reactions.

The reading of the human interpretation of the photographs will occur at least 1 month after the clinical visit to maintain blinding and washout in the event study staff provide a visual impression of the reaction sites via photographic review.

6. Study Procedures

6.1. Prior to Visit 1 and after study consent, the participant will have an opportunity to complete the Patient Journey. For Phases II and III of the study, this patient journey will be distributed to the patient prior to Visit 1 to allow for the data to be summarized. The summarization will include qualitative and quantitative approaches to quantify the self-reported employment profiles, ancestry, and known allergens to identify which allergens that may be more allergenic to the participant. Visit 1 (Day 1)

Informed consent will be obtained as well as demographic information, medical history, and current medications questionnaire (see Schedule of Events).

A limited physical exam focused on the forearm will be conducted as well as assessment of participant's Fitzpatrick skin type.

A baseline photo will be taken using the smart phone application and the additional camera systems including the full spectrum documentation and photogrammetry acquisition.

A member of the study team will place the primary test patch on the volar aspect of participants' forearm. The patch contains allergens placed in dime-sized wells. The location of the allergens within the patch will be randomized between participants. The study team member will document the location of each allergen.

The smaller, 4 well patch, on the secondary arm will be placed similar manner to the primary test patch.

Tape or waterproof dressing may be used to secure the patch strips. Participant will be given instructions to avoid water contact with patch, and avoidance of sun exposure.

Participants will be allowed to take over the counter histamine blockers to alleviate pruritus.

6.2. Visit 2 (Day 3)

Participant will be asked to return after 48 hours (Day 3) for patch removal and preliminary reaction assessment.

Skin will be assessed and documented for reactions which may include irritation, redness, and/or swelling localized to the patch test area.

The reaction will be documented as negative, irritation, or positive contact allergic reaction using the scale described below in section 6.6.

Participant will be encouraged to let the study team know if there was any itching or burning while the patches were in place.

A complete set of photos will be taken to document any reactions with the smart phone application and other camera systems.

6.3. Visit 3 (Day 5)

After about 96 hours (Day 5), the participant will return for a final assessment.

This assessment time is the final (reference criterion) assessment as it is necessary to allow for up to five days for a skin reaction to appear.

At the visit, the medical professional with training in patch testing will review the skin for any reaction and document in the CRF.

A complete set of photos will be taken to document the reactions using the smart phone application and other camera systems.

Participant feedback on the patch testing experience will be documented.

Severe contact dermatitis will be treated with topical steroids if needed.

6.4. Photographic Documentation

At each study visit with photographs taken, a comprehensive set of images will be captured. This will include the primary acquisition using the study's smartphone application but also novel imaging including:

Full spectrum analysis:

1. Unfiltered (clear)
2. Filtered to specific wavelengths: 590nm, 665nm, 720nm, and 850nm
3. Additional (wide range) filters: Blue IR (excluding visible light spectrum, except blue, and including infrared) and Hot Mirror (~100nm – 700nm; i.e., visible light)

4. Lighting conditions – routine clinical lighting, exposed with a Wood's Lamp ("black light"), exposed with

Live video clips: Short videos using the iPhone's live capture

Photogrammetry: A series of 20 or more images of each test site will be captured from all angles. These images are reconstructed using software to form a three-dimensional rendering of the test site.

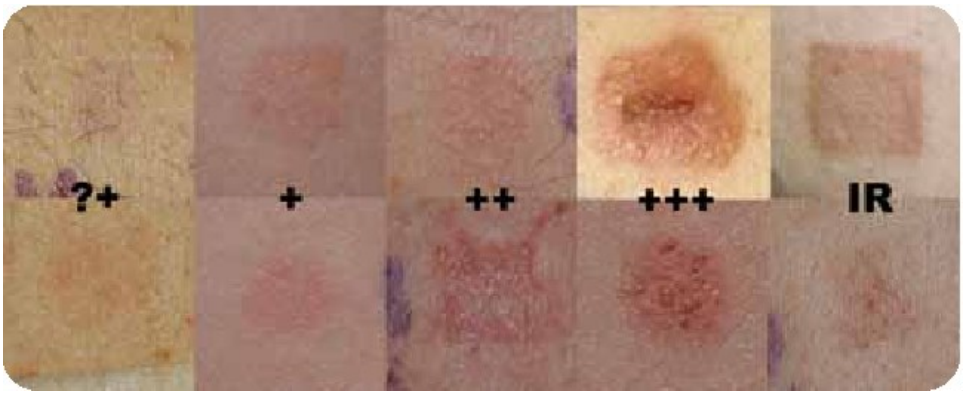
Tripod / camera assist device: The smartphone will be supported with a phone cradle during the photographic documentation. This device includes a shell to block ambient light while allowing for the phone to be securely supported during the documentation process. This device is to standardize the distance and lighting while removing artifacts from the background of the image that could be identifiable data.

6.5. Off study evaluation (post reaction care, if applicable)

In the event of a positive allergic reaction that should be treated with topical steroids, the participant will be provided over-the-counter hydrocortisone. If prescription strength steroids are required, a prescription will be made.

6.6. Reaction Grading Scale

Reactions will be graded as negative, irritant, or positive. Positive reactions will be rated as doubtful (1), weak (2), strong (3), or extreme (4) depending on their physical appearance. Doubtful reactions only have faint erythema, weak reactions are those with non-vesicular erythema, strong reactions are raised and have vesicular or non-vesicular erythema, extreme reactions are bullous or ulcerative in nature.



(Spiewak et al)

Symbol	Morphology	Assessment
–	No reaction	Negative reaction
?+	Faint erythema only	Doubtful reaction
+	Erythema, infiltration, possibly papules	Weak positive reaction
++	Erythema, infiltration, papules, vesicles	Strong positive reaction
+++	Intense erythema, infiltrate, coalescing vesicles	Extreme positive reaction
IR	Various morphologies, e.g. soap effect, bulla, necrosis	Irritant reaction

(Johansen et al)

6.7. Participant Remuneration

Participants will be remunerated $125 / visit ($375 total for completing the study).

Schedule of Events

Study Activity	Day 1	Day 2	Day 3	Day 4	Day 5	Off Study Evaluation
Informed consent	X					
History [a]	X					
Concurrent meds	X					
Limited physical exam [b]	X					
Patch placement [e]	X					
Documentation of allergen location	X					
Photographic Documentation [c]	X		X		X[d]	
Patch Removal			X			
Reaction Assessment			X		X	
Participant feedback					X	
Adverse Event Assessment			X		X	X

a. Demographic information, medical history
b. Fitzpatrick skin type assessment, arm inspection
c. Photographic documentation of volar aspect of forearm (primary and optional secondary test sites) taken with the approved photographic assessment
d. In person assessment on Day 5 used as reference criterion
e. Phase 1 & 2 will be done by provider. Phase 3 done by patient.

7. Statistical Plan

7.1. Sample Size Determination

The primary sample size is determined based on Phase I of the study. With an expectation that 15% of the test sites will be positive, based on the selection of allergens with the highest incidence of reactions, and a target sensitivity of 95%, 90% power, and a minimum clinically relevant difference of 5 percentage points, a total of 130 positive test sites needs to be present in the study to achieve the design specifications. Given the assumption that most participants will only exhibit 1 to 2 reactions and the intraclass correlation of detections remains unknown, the design effect (or variance inflation effect) is not applied to account for potential clustering of reactions per participant. Therefore, with the assumption that each participant will have 1.5 positive reactions on average, we anticipate a requirement for 100 participants.

The sample sizes for Phase II and III have been administratively set based on feasibility of recruitment and testing.

7.2. Study Endpoints

7.2.1. Primary Study Endpoints

The accuracy for the classification of regions within the test panel that either were a reaction (reaction grade 1+) or not (grade 0).

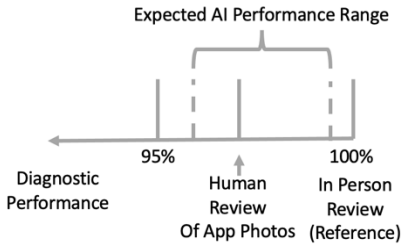
7.2.2. Secondary Study Endpoints

- The accuracy for the classification of the test site region using a 5-point scale: Grades 0 – 4.
- Sensitivity
- Specificity
- False positive rate
- False negative rate
- Percentage early termination of testing
- Percentage of participants that removed patches early
- Adverse events related to allergen exposure
- Patient feedback on the testing process

Primary Hypothesis:

The AI algorithm will provide non-inferior performance measured by binary classification accuracy relative to the human performance.

To test the primary hypothesis, The primary hypothesis to be tested is the "agreement" between the clinical (in person) evaluation and the human review and AI predictions of the app captured images. Generalized estimating equations (GEE) will be structured to estimate the clustered accuracy using an identity link and robust variance estimator to account for the clustering within the database. The model will have a single predictor that indicates which reader (AI vs. human) is associated with the accuracy determination (a 1/0 with 1 indicating the "reader" reached the same conclusion as the expert, in person review). For the purpose of the primary outcome measure, the prediction from either the human or AI algorithm will be dichotomized into no reaction (grade 0) vs. any reaction (grades 1 – 4). The estimate and 95% CI for the "reader" effect will summarize the differential performance between the human and AI interpretations. For the AI algorithm to be considered non-inferior, a limit of inferiority of 5 percentage points will be used. The fitted model will be used to estimate the overall performance and 95% CI for the two readers. As shown in the figure, we desire both the human and AI performance to provide greater than 95% accuracy.



To supplement this analysis, the area under the receiver operating characteristic curve (AUC ROC) will be computed using the visual analog scale by test site determined by the human observer and the AI model's output. DeLong's test will be used to compare the differences in performance between these two approaches.

Secondary Hypothesis 1:

For the secondary endpoint of agreement on the 5 point clinical scale, unweighted and weighted Kappa will be used to estimate the degree to which the human and AI interpretations agree. The unweighted analysis will focus on the direct match on grade assigned to each of the test sites.

There is a block of standard measures of diagnostic performance (e.g., sensitivity, specificity). These statistics will be computed as is customary for similar studies. The calculations will be performed two ways when possible. First, each test site will be assumed to be statistically independent in the rating. For the neural network, this is how the algorithm functions. For the human reading, there may be some correlation among the ratings based on the reactions, if any, that are observed. To address this, an exploratory analysis will be conducted using generalized estimating equations to examine the impact empirically the intercorrelations may have on the estimated precision of the estimates (i.e., confidence interval width).

Safety data will be summarized by tabulating adverse events for the study. These will be categorized according to allergen related or study protocol related.

The secondary test sites include allergens, in novel combinations, that were tested in the primary test site. A secondary analysis will be conducted to quantify the agreement of reactions to the same allergens alone (primary test patch) and in combination (secondary test patch). Kappa will be used to quantify this agreement.

Finally, participant feedback on the study including the wearability of the patch on the forearm will be summarized using standard qualitative methods. This will include the extraction of key themes as well as listing open ended feedback provided to the study team by the participants.

7.3. Additional Statistical Considerations

7.3.1. Descriptive Statistics

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate for all variables. Baseline values for demographic, clinical, and outcome variables (primary and secondary) will be tabulated for the enrolled participants. These summaries will be summarized for the overall sample and by Fitzpatrick Skin Type.

7.3.2. Handling of Missing Data

Missing data may occur throughout the study. The primary analysis, which is based on the AI and human interpretation of the images relative to the in-person assessment, will require that all test site regions have an interpretation of the reaction grade. If missing data is not able to be obtained by re-assessing the data, a "worst case" imputation strategy will be used. With this missing data will be included in the denominator of test sites tested but none of the regions will be included in the numerator for measurement of accuracy or concordance between AI and human interpretation (i.e., is counted as a "miss" in the analysis). For demographic and medical history data, any missing data will be reported as such in the final analysis.

7.3.3. Multiplicity

There will be no adjustment to the level of significance for multiple testing. All results will be reported unadjusted at the alpha=0.05 level of significance using estimates and 95% confidence intervals.

7.3.4. Interim Analysis

There is no planned interim analysis.

7.3.5. Analysis Sets

The analysis set for this study will follow the modified intention to treat principle. To be included in the analysis, the participant needs to be randomized and complete at least the day 5 assessment (final documentation of the skin reactions). Participants that study the allergen exposure challenge early are still eligible for the final analysis provided they consent to a day 5 assessment (see schedule of assessment early in the event the day 5 assessment occurs earlier).

8. Safety and Adverse Events

8.1. Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e., unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of a medical product (i.e., drug, device, biologic) in a patient or research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity
- substantial disruption of the ability to conduct normal life functions
- birth defect/congenital anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

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

Adverse Event Reporting Period

Adverse events that occur between the time of the test patch application (Day 1) and Day 5 should be reported on the study CRFs.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

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

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

8.2. Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3. Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1. Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

8.3.2. Sponsor-Investigator reporting: Notifying the FDA

The sponsor-investigator will report to the FDA all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats, and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA-on-FDA Form 3500A, no later than 7 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA-on-FDA Form 3500A, no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA-on-FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

The sponsor-investigator must also notify the FDA (and sponsors must notify all participating investigators) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under § 312.32(c)(1)(i)-(iv).

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA-on-FDA Form 3500A, no later than 15 calendar days after the sponsor-investigators initial receipt of the information about the event.

8.4. Unmasking/Unblinding Procedures

In the event of a reaction to one of the allergens, the primary medical professional performing the in-person evaluation will have access to the unblinding information (i.e., identification of the allergens for each test site). The cause of any reactions will be denoted in the study records and communicated to the participant.

8.5. Stopping Rules

No study stopping rules are proposed based on the risk profile for the study. In the event the feasibility of the study is not tenable due to challenges in recruitment or other study operational considerations, the study may be terminated at the request of the study sponsor in conjunction with the institutional review board of record.

8.6. Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above.

9. Data Handling and Record Keeping

9.1. Confidentiality

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

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

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

9.2. Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and

records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3. Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF is expected to be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in ink. If any entry error has been made, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management

Data recorded on CRFs will be entered into a password protected, change-audited electronic data management system (REDCap or equivalent). Data will be structured to document missing data, when appropriate. All changes to data saved to the database will have a timestamp indicating the user account that made the change to the data.

Standard reports on data quality will be configured to identify possible errant data elements. In the event a questionable data is identified, the data will be confirmed using original study records.

9.4. Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

Case report forms will be designed to identify each subject-by-subject entry number and, where appropriate, subject's initials, the product being evaluated, and the results observed. All entries to the CRFs must be made as instructed by the study investigator. Data on subjects collected on CRFs during the study will be documented in an anonymous fashion, and the subject will only be identified by the subject number, and by his/her initials, if also required.

All records will be kept in conformance to applicable national laws and regulations. The original signed ICF will be attached to each subject's file. When the study treatment is completed, the ICF will be kept in the appropriate file folder; otherwise, a note indicating where the records can be located will be made. Documents will be stored in a password protected Mayo secure server as well as in a locked cabinet, where the study team is the only ones to have access to.

The investigator will retain the specified records and reports for

- Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and

delivery of the drug for investigational use is discontinued and the FDA has been so notified OR

- As outlined in the Mayo Clinic Research Policy Manual – "Retention of and Access to Research Data Policy" [redacted]

whichever is longer.

10.Study Monitoring, Auditing, and Inspecting

10.1. Study Monitoring Plan

The Investigator will allocate adequate time for such monitoring activities. The investigator will also ensure the monitor or other compliance, or quality assurance reviewer has access to all study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2. Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11.Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

11.1. Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

11.2. Subject Stipends or Payments

Participants will receive $125.00 for each study visit completed. If the participant completes the entire study, they will receive payment up to $375.00

12.References

1. Spiewak R, Pietowska J, Curzytek K. Nickel: a unique allergen - from molecular structure to European legislation. Expert Rev Clin Immunol. 2007 Nov;3(6):851-9. doi: 10.1586/1744666X.3.6.851. PMID: 20477134.
2. Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M, Cannavó A, Giménez-Arnau A, Gonçalo M, Goossens A, John SM, Lidén C, Lindberg M, Mahler V, Matura M, Rustemeyer T, Serup J, Spiewak R, Thyssen JP, Vigan M, White IR, Wilkinson M, Uter W. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. Contact Dermatitis. 2015 Oct;73(4):195-221. doi: 10.1111/cod.12432. Epub 2015 Jul 14. PMID: 26179009.