Team-Based Connected Health to Improve Clinical Outcomes and Access in Atopic Dermatitis

National Clinical Trial (NCT) Identified Number: NCT03981926

September 23, 2019

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (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. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

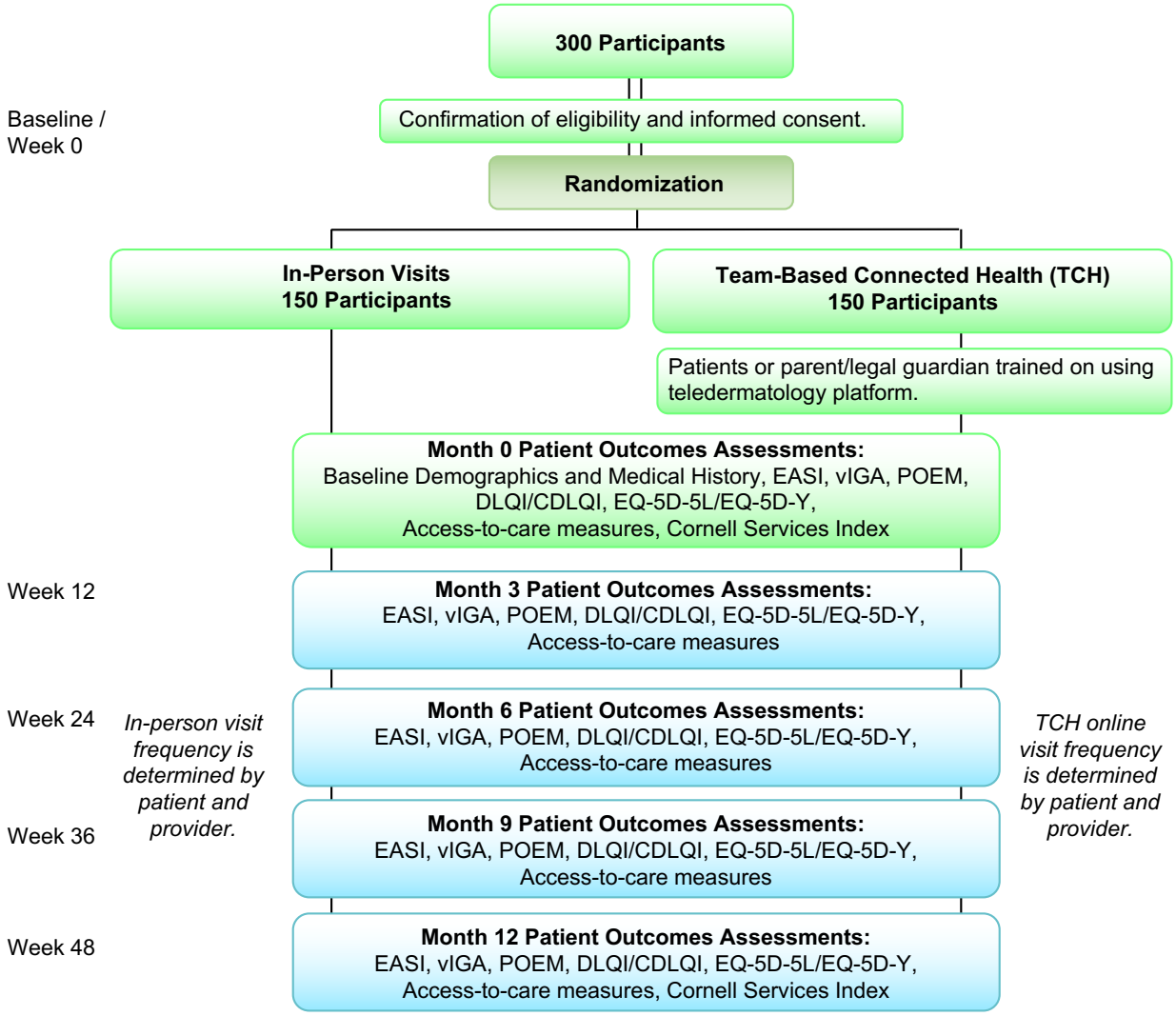
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Team-Based Connected Health to Improve Clinical Outcomes and Access in Atopic Dermatitis
Study Description:	This is a pragmatic, randomized, controlled, equivalency trial. This 12-month trial will evaluate the impact of an online, team-based connected health (TCH) model for management of atopic dermatitis (AD) as compared to in-person care. 300 patients will be randomly assigned to the online TCH model or the in-person control arm stratified by two factors: age (<18 years vs. 18+ years) and study site. This pragmatic, randomized trial will compare AD disease severity (Aim 1), quality-of-life and access-to-care measures (Aim 2), and costs (Aim 3) between the two models.
Objectives:	The primary goal of the protocol is to evaluate whether an online, team-based connected (TCH) health model results in equivalent improvements in disease severity and quality of life, provides better access to specialist care, and is cost-saving compared to usual in-person care for AD management. We will perform a pragmatic randomized equivalency trial to compare the online, TCH model versus in-person care. The specific aims of the study are as follows: <u>Primary Objective (Aim 1)</u>: Compare differences in AD severity, as measured by the Eczema Area and Severity Index (EASI), Patient-Oriented Eczema Measure (POEM), and validated Investigator Global Assessment (vIGA), between patients randomized to Team-Based Connected Health and in-person care in a 12-month pragmatic, randomized equivalency trial.

	Secondary Objectives (Aim 2): Compare differences in quality of life as measured by dermatology-specific instruments (Dermatology Life Quality Index / Children's Dermatology Life Quality Index) and a generic instrument (European Quality of Life-5 Dimensions) between patients randomized to Team-Based Connected Health and in-person care. Furthermore, we will compare differences in access-to-care measures such as transportation and time needed for evaluation between patients randomized to Team-Based Connected Health and in-person care. Secondary Objectives (Aim 3): Compare differences in healthcare costs from a societal perspective between Team-Based Connected Health and in-person care through cost-minimization analysis.
Endpoints:	The primary and secondary endpoints are as follows: Primary Endpoint: ● Change in EASI from baseline averaged across 12 months. Secondary Endpoints: ● Change in vIGA from baseline averaged across 12 months ● Change in POEM from baseline averaged across 12 months ● Change in DLQI and CDLQI from baseline averaged across 12 months ● Change in EQ-5D-5L and EQ-5D-Y from baseline averaged across 12 months ● Patient reported access-to-care outcomes, including transportation and time needed for evaluation ● Healthcare utilization and costs from a societal perspective
Study Population:	The study population consists of children and adults (age 1 year and older) with atopic dermatitis (AD). We plan to enroll 300 patients representing the full spectrum of AD disease severity in southern California.
Description of Sites/Facilities Enrolling Participants:	Ambulatory clinics associated with Keck Medicine of University of Southern California and LAC+USC Medical Centers will participate in enrolling participants.
Description of Study Intervention:	The Team-Based Connected Health (TCH) model enables structured online interactions among patients, primary care providers (PCPs), and dermatologists. The goal of TCH is to provide patients and PCPs with high-quality online communication with specialists that would otherwise occur in person.
Study Duration: **Participant Duration:**	60 months 12 months

1.2 SCHEMA


300 Participants
Baseline / Week 0
Confirmation of eligibility and informed consent.
Randomization
In-Person Visits
150 Participants
Team-Based Connected Health (TCH)
150 Participants
Patients or parent/legal guardian trained on using teledermatology platform.
Month 0 Patient Outcomes Assessments:
Baseline Demographics and Medical History, EASI, vIGA, POEM, DLQI/CDLQI, EQ-5D-5L/EQ-5D-Y,
Access-to-care measures, Cornell Services Index
Week 12
Month 3 Patient Outcomes Assessments:
EASI, vIGA, POEM, DLQI/CDLQI, EQ-5D-5L/EQ-5D-Y,
Access-to-care measures
Week 24
Month 6 Patient Outcomes Assessments:
EASI, vIGA, POEM, DLQI/CDLQI, EQ-5D-5L/EQ-5D-Y,
Access-to-care measures
Week 36
Month 9 Patient Outcomes Assessments:
EASI, vIGA, POEM, DLQI/CDLQI, EQ-5D-5L/EQ-5D-Y,
Access-to-care measures
Week 48
Month 12 Patient Outcomes Assessments:
EASI, vIGA, POEM, DLQI/CDLQI, EQ-5D-5L/EQ-5D-Y,
Access-to-care measures, Cornell Services Index
In-person visit frequency is determined by patient and provider.
TCH online visit frequency is determined by patient and provider.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures/Assessments	Month 0 / Baseline	Month 3	Month 6	Month 9	Month 12
	+ 28 days	-7 days, +21 days	-7 days, +21 days	-7 days, +21 days	--7 days, +28 days
Informed Consent	X				
Randomization	X				
Patient or parent/legal guardian training on utilization of the teledermatology platform	X				
Baseline Demographics and Medical History	X				
Atopic Dermatitis Severity Assessments					
EASI	X	X	X	X	X
vIGA	X	X	X	X	X
POEM	X	X	X	X	X
Quality of Life Assessments					
DLQI / CDLQI	X	X	X	X	X
EQ-5D-5L / EQ-5D-Y	X	X	X	X	X
Access to Care					
Access to Care (Baseline)	X				
Access to Care (Follow-up)	X	X	X	X	X
Healthcare Costs Assessments					
Cornell Services Index	X				X
Safety Assessments					
Adverse Event Collection Form	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Chronic skin diseases are associated with markedly decreased quality of life and financial consequences.[1-2] In the U.S., access to dermatologists remains a significant challenge, especially for those in underserved or rural communities.[3-7] Even after an initial evaluation by a dermatologist, many patients have difficulties maintaining regular access to dermatologists for follow-up care. Consequently, many patients experience worse clinical outcomes and reduced quality of life.[8]

With the maturation in communication technology to facilitate healthcare, now is the critical time to determine how technology-enabled healthcare delivery models impact patient outcomes, access, and costs in the real world.

We will evaluate an online, team-based connected health (TCH) model that enables structured asynchronous online interactions among patients, primary care providers (PCPs), and dermatologists. The goal of TCH is to provide patients and PCPs with high-quality online communication with specialists that would otherwise occur in person. TCH leverages innovative health services model and technology to bring expert care to patients and PCPs in a location-independent and asynchronous manner.

Atopic dermatitis (AD) is the ideal disease model to evaluate TCH because it is common, chronic, and can inflict substantial morbidity if not managed effectively.[9-11] To address skin inflammation, itch, and psychosocial consequences, PCPs and dermatologists need to adopt a team-based approach to effectively manage all aspects of the disease.

2.2 RISK / BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

As with all electronic health information exchange and record platforms, potential risks include loss of confidentiality. Our research team has extensive experience protecting privacy and maintaining confidentiality of our patients' personal information on telemedicine platforms. The teledermatology platform is secure and HIPPA compliant, and it has been used for online telemedicine visits and for telemedicine studies. We deem the probability of experiencing loss of confidentiality of protected health information low. Specific mitigation strategies to ensure data security and confidentiality are discussed below in the section 10.1.3 "Confidentiality and Privacy".

Because we are recruiting patients with AD across the spectrum of disease severity, potential risks remain with either arm of the study with regards to adverse events related to AD or its associated treatments. Because the study is pragmatic in design, it enables in-person or online visits at frequencies that are individualized and deemed medically necessary by the provider. Thus, providers and patients in both arms can follow up at frequencies that are necessary to manage AD and any treatment-related adverse events. Furthermore, the patients randomized to the online arm could seek in-person care if the patient or the provider deem that online care is insufficient to address a problem. Thus, we deem the probability of experiencing untoward events by the study participants not higher than what would otherwise be expected via routine care.

2.2.2 KNOWN POTENTIAL BENEFITS

The TCH model offers several distinctive benefits. The model offers multiple ways for both patients and PCPs to access dermatologists online asynchronously that are responsive to real-world needs. The patients can also upload clinical images and history online and obtain asynchronous evaluation and recommendations from the dermatologists. PCPs can upload patient's photos and history online and access dermatologists asynchronously for consultations or to request a dermatologist to assume care of a patient's atopic dermatitis.

Overall, the TCH model not only increases patient and provider engagement; it also provides comprehensive specialist support to both PCPs and patients. TCH eliminates the need for patients to find a local healthcare facility with telemedicine capabilities to engage dermatologists via telemedicine. After careful consideration of the benefits and risks associated with the study, we deem the benefit-risk assessment to be acceptable to research participants. The accessibility of quality and timely specialist care for atopic dermatitis patients outweighs the potential adverse risks associated with the study.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Evidence supports accuracy and reliability of diagnosis by asynchronous teledermatology. Furthermore, multiple studies have demonstrated concordance in management plans between care delivered through asynchronous teledermatology versus in person. However, potential risks remain with either arm of the study with regards to adverse events related to AD exacerbation or adverse events arising from AD treatment. Because the study is pragmatic in design, it enables in-person or online visits at frequencies that are individualized and deemed medically necessary by the provider. Thus, providers and patients in both arms can follow up at frequencies that are necessary to manage AD and any treatment-related adverse events. Thus, we deem the probability of experiencing untoward events beyond what would otherwise be expected via routine care for this population to be low.

Protection against Adverse Events during Management of Atopic Dermatitis

To mitigate risks of adverse events related to AD or the treatment, the PI and the study staff will continuously monitor patients for adverse events. Patients can report adverse events using two methods: (1) using the "Adverse Event Collection Form", which is captured at quarterly intervals, or (2) reporting AEs spontaneously to the study at any time 24/7. The study team or the patient's provider will address adverse events as they occur.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Aim 1: Compare differences in atopic dermatitis disease severity, as measured by Eczema Area and Severity Index (EASI), and validated Investigator Global Assessment (vIGA), and Patient-Oriented Eczema Measure (POEM) between patients randomized to TCH and in-person care in a 12-month pragmatic, randomized equivalency trial.	The primary endpoint of the study is the mean improvement from baseline in EASI averaged across 12 months. The mean improvement in EASI is defined as the difference in EASI between baseline and the average of the follow-up visits (months 3-12). Secondary endpoints for Aim 1 include: ● Change in vIGA from baseline averaged across 12 months ● Change in POEM from baseline averaged across 12 months	EASI is a validated, granular assessment of AD patient disease severity. It is commonly used in clinical trials, including trials for therapeutic approvals. By using EASI, we will be able to compare the results of this study with other studies in AD patients. The 5-point IGA is a valid measure of disease severity and meets the need for a clinically meaningful measure for atopic dermatitis. POEM is a validated patient-reported outcome used to

		monitor AD severity that focuses on the illness as experienced by the patient.
Secondary		
Aim 2: Compare differences in quality of life as measured by dermatology-specific instruments (Dermatology Life Quality Index (DLQI)/ Children's Dermatology Life Quality Index (CDQI)) and a generic preference-based instrument (European Quality of Life-5 Dimensions), between patients randomized to TCH and in-person care. Compare differences in access-to-care measures such as transportation and time needed for evaluation between patients randomized to TCH and in-person care.	The secondary endpoints for Aim 2 include: • Change in DLQI or CDLQI from baseline averaged across 12 months between the in-person and online groups • Change in EQ-5D-5L or EQ-5D-Y from baseline averaged across 12 months between the in-person and online groups. • Transportation and time needed for evaluation between the in-person and online groups.	The DLQI and the CDLQI are validated, 10-question questionnaires that can be used to assess dermatology-specific quality of life in adults and children with atopic dermatitis. EQ-5D-5L and EQ-5D-Y are validated measures of health status. The EQ-5D-5L and EQ-5D-Y provide a single index value that can be used for QoL and economic evaluations. Transportation and time needed for evaluation are measures of access.
Secondary		
Aim 3: Compare differences in healthcare costs between TCH and in-person care.	The secondary endpoints for Aim 3 are: • Healthcare utilization • Healthcare costs	The Cornell Services Index is a validated method to assess health service use. The measure provides a reliable snapshot of service use patterns across types, providers, and sites of service among adults who seek medical care.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is testing the hypothesis that team-based connected health (TCH) model results in equivalent improvements in disease severity and quality of life, provides better access to specialist care, and is cost-saving as compared to usual in-person care for management of patients with atopic dermatitis (AD).

This is a 12-month, pragmatic, randomized, controlled, equivalency trial to evaluate the impact of an online, team-based connected health (TCH) model for management of atopic dermatitis (AD) as compared to in-person care. A total of 300 participants will be randomly assigned to the online TCH model or the in-person control arm.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The rationale for proposing this 12-month pragmatic trial is to test whether the TCH model works in the real world. This design allows for a large spectrum of everyday clinical settings in order to maximize applicability and generalizability. These pragmatic approaches are especially pronounced along the Pragmatic Explanatory Continuum Indicator Summaries (PRECIS) domains of experimental intervention flexibility, usual in-person care as control, and outcomes being highly relevant to patients.

4.3 RATIONALE FOR INTERVENTION

Lack of access to dermatologic care and problems with traditional teledermatology models: In the U.S., access to dermatologists remains a significant challenge for many patients. Many patients have difficulties maintaining regular access to dermatologists due to factors such as lack of transportation or the inability to take time away from work for medical visits. Consequently, these patients with chronic skin diseases suffer from poor clinical outcomes and reduced quality of life.

Teledermatology is a specialty-care delivery model in which skin diseases are diagnosed and treated remotely by means of telecommunications technology.[12] While ample evidence supports accuracy and reliability of asynchronous teledermatology, few studies have examined patient outcomes.
To develop more effective methods for specialty-care delivery, it is important to first recognize why traditional models of teledermatology have not worked well. [13-21] Several key limitations exist with traditional consultative teledermatology. First, patients must find a nearby healthcare facility with telemedicine capabilities in order to access dermatologists online. Second, there is no direct contact between patients and the specialists, and this is the key reason for patient dissatisfaction. Third, the PCPs are variably effective in conveying and implementing specialists' recommendations.

Team-based connected health (TCH) model to provide expert care online. In this proposal, we will evaluate an online TCH model that provides high-quality, asynchronous online care for AD patients. Specifically, TCH will bring quality specialist care to patients and PCPs in a location-independent and asynchronous manner. Importantly, because dermatologists are central to the sustainability of this online model, the intervention is designed to maximally support the dermatologists.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

- Age 1 year or older
- Physician-diagnosed atopic dermatitis (AD)
- Access to a digital-photo capturing device (mobile phone or camera) capable of capturing images with a minimum resolution of 1024x768 pixels
- Access to internet
- Able to establish care or have established care with providers
- Provision of signed and dated informed consent and youth assent form

5.2 EXCLUSION CRITERIA

- Unable to fulfill study-related tasks by adult AD patients or parent/legal guardian of pediatric AD patients

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. To ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, we will include demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

5.4.1 RECRUITMENT PLAN

In this pragmatic, randomized equivalency trial, we will recruit pediatric and adult patients with AD from both genders, diverse racial and ethnic groups, and across the full spectrum of AD severity. Patients will be randomized 1:1 stratified by age and study site to either the online TCH model or in-person visits for management of AD.[22]

Medical records of patients with AD or eczema who had presented to the study sites since 2013 will be reviewed by the study staff to prescreen for eligibility. For patients who are potentially eligible, the study team will send these patients or their parents a letter that introduces the study. Following the letter, the study team will call these patients to inquire about their interest in the study.

In addition, the study team will also examine the clinic schedule and identify patients with visits for “eczema”, “atopic dermatitis”, “dermatitis”, or other related terms. The study staff will contact these patients prior to their appointment to alert them that a study member may speak to them about the study on the day of their visit.

Other recruitment methods include flyers placed at the study sites, online and social media advertisements, ResearchMatch, local newspapers, and referral from colleagues. Selection is based solely on the participant's ability to meet the criteria stated in the protocol and his/her willingness to participate in the study.

5.4.2 RETENTION PLAN

Prior to study initiation, we will conduct pre-trial retention training for the study staff. Prior to enrollment, the study staff will communicate with eligible patients regarding the importance of completing all outcome assessments. We will emphasize the importance of full participation during screening, enrollment, and throughout the trial.

It is important to note that, for online and in-person visits between the provider and patients, these visits occur at an individualized frequency based on medical necessity. However, the collection of outcome assessments (disease-severity, quality-of-life endpoints, and selected access-to-care measures) occurs at a quarterly basis for all participants.

All subjects will be reminded via email, text, or telephone to submit their quarterly outcome assessments beginning 7 days prior to the due date. If a subject fails to submit the quarterly outcome assessments within 2 days of the due date, the subject will be contacted using telephone and/or electronic methods to remind them to submit the assessments. The study staff will also discuss with the participant strategies to improve adherence with the study requirements. If the participant cannot be contacted after at least five attempts, a certified return receipt letter will be sent to encourage continuation in the trial.

If a participant fails to complete a quarterly assessment within 21 days of the due date, the study staff will make at least five attempts to contact (at least three telephone calls, two emails, and, if necessary, a certified return receipt letter to the participant's last known mailing address or local equivalent method). These contact attempts will be documented in the participant's study file.

If a participant wishes to withdraw from the study, the study coordinators will attempt to collect the Month 12 visit data as well as detailed data on the reasons for the discontinuation from the study. The study coordinators are encouraged to share their ideas and experiences to promote participant retention via regular communication during staff meetings.

5.4.3 VULNERABLE SUBJECTS

While the study does not specifically target pregnant women, we will not exclude pregnant women from participation. Pregnant women who meet eligibility criteria and are willing to participate will be enrolled in the study, and their AD will be managed by their providers on an individualized basis.

Children that meet the eligibility requirements will be able to enroll. Assent from the child and written consent from the parent or authorized legal guardian will be obtained in accordance with the provisions of Subpart D, 45 CRF 46.

Prisoners, fetuses, or neonates will not be included in the study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION ADMINISTRATION

6.1.1 INTERVENTION DESCRIPTION AND ADMINISTRATION

We will evaluate an online team-based connected health (TCH) model that facilitates high-quality, efficient, and accessible care for patients with AD in a location-independent and asynchronous manner. Specifically, TCH enables dermatologists, PCPs, and patients to conduct structured and efficient online visits that would otherwise occur in person. TCH offers several ways of online communication: (1) PCP-dermatologist, (2) Patient-dermatologist, and (3) Patient-PCP interactions. For example, either PCPs or patients can upload clinical images and history online to obtain dermatologist expertise for evaluation and management of AD. TCH is responsive to real-world workflow needs, and it focuses on team-based care by fostering multidirectional, informed communication among patients, PCPs, and dermatologists.

6.1.1.1 WHAT DEFINES AN ONLINE VISIT?

In the TCH model, online communication is classified as either "online visits" or "follow-up questions." An online visit contains photos of appropriate quality, history of present illness, medications, allergies, review of systems, and a provider's assessment and plan.

In contrast, a follow-up question refers to an *ad hoc* question from a patient that is submitted within 30 days following a prior online visit.

6.1.1.2 WHAT HAPPENS DURING AN ONLINE VISIT?

When the patient initiates an online visit, the platform begins a process with "required fields" to ensure completion of all required elements of an online visit before transmission to the dermatologist. Specifically, the patient uploads images of skin lesions and submits clinical history.

Within three business days, the dermatologist reviews the patient's history and images. The dermatologist then communicates the recommendations to the patient, prescribes the medications, and where appropriate, provides standard-care educational materials to patients online asynchronously.

The frequency of the follow-up online visits will be determined by the dermatologists and patients based on medical necessity.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

A total of 300 participants will be randomly assigned to the online, TCH arm or the in-person control arm. To ensure balance of demographic and clinical characteristics between the two arms across the recruitment sites, we will perform randomization stratified by two factors: age and study site. Age will be dichotomized into two categories indicative of adulthood: < 18 years vs. 18+ years.

A randomization schema for each site, with blocks ranging from 6 to 12 will be created by the study statistician and uploaded to REDCap in accordance with the REDCap Randomization Model.[22] Then, the randomization will be predicated on the participant age and study site and provided to research staff. In this study, blinding of patients and providers is not possible due to the nature of the intervention. However, the randomization schema will not be known to the staff until revealed at time of randomization. Only the statistician, who has no interactions with the patients, will have access to the full randomization schema to check for balance between groups.

6.3 STUDY INTERVENTION COMPLIANCE

We will ensure compliance in delivering the telemedicine intervention via continuous monitoring of interventional fidelity throughout the study. If patients or providers face difficulties with online visits or completion of assessments, they are able to access the study staff 24/7 to obtain assistance. Additionally, throughout the study, the study staff will also ensure providers' compliance in using TCH intervention by monitoring online communications "in the background" and provide feedback and/or assistance when necessary.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The criteria for discontinuing the online intervention include (1) the patient expresses desire to discontinue study intervention, (2) the provider expresses desire to discontinue patient from study intervention for any reason, which include AD exacerbation or adverse events that cannot be managed online *for the remainder of the study*. We will record the reasons for discontinuing the study intervention in detail via structured data capturing.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

The study team will ensure that participants are fully informed and understand the study commitments as presented in the informed consent form to minimize patient withdrawal. Patients are encouraged to complete the study regardless of their response. Participants may withdraw from the study at any time without impact to their care. In the event a participant discontinues study treatment before study completion, the study team will attempt to collect the Month 12 visit data. They may also be discontinued from the study at the discretion of the PI if patient's participation poses a safety concern to himself/herself or to the study staff.

The reason for participant discontinuation or withdrawal from the study will be documented on the Enrollment Status eCRF. Subjects who sign the informed consent form and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced, nor will they be eligible for rescreening.

7.3 LOST TO FOLLOW-UP

All attempts will be made to minimize lost to follow-up. A participant will be considered lost to follow-up if he or she fails to complete a quarterly assessment according to the Schedule of Activities within 6 weeks of scheduled date of completion.

If a participant fails to complete a quarterly assessment within 2 days of the due date, the subject will be contacted by phone and electronically to submit the assessments. The study staff will also discuss with the participant strategies to improve adherence with the study requirements.

If a participant fails to complete a quarterly assessment within 7 days of the due date, the following steps to will be initiated:

- The study staff will make *at least* five attempts to contact (at least three telephone calls, two emails, and, if necessary, a certified return receipt letter to the participant's last known mailing address or local equivalent methods.) These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable within 6 weeks of the scheduled date of completion, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- The Principal Investigator will have the ultimate discretion on the final determination of whether additional attempts should be made to contact the participant or if the participant should be declared lost to follow up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Study investigators and designated study staff will determine patient eligibility during the screening period, using a screening checklist form. Screening can occur on the same day the patient is enrolled if the participant meets the specified inclusion and exclusion criteria.

Outcomes data will be collected using patient-reported, validated instruments as described below.

Assessments and Evaluations (Patient-Report Measures)

- Eczema Area and Severity Index (EASI): the EASI is a validated scoring system that grades the physical signs of atopic dermatitis/eczema. EASI is a core outcome for measuring the clinical signs of eczema in all trials.
- Validated Investigator's Global assessment (vIGA): This is a three-item measure that assesses the thickness, redness, and scale of atopic dermatitis lesions.
- Patient Oriented Eczema Measure (POEM): POEM is a 7-item tool for patient and/or proxy self-completion used to monitor atopic dermatitis severity, focusing on the illness as experienced by the patient.
- Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI): DLQI/CLDQI is a 10-item survey that asks patients questions about their health-related quality of life on a 0-3 scale. DLQI and CDLQI are routinely used in clinical trials of dermatology treatments and can also be used routinely in clinical practice.
- EQ-5D-5L or EQ-5D-Y: These are generic and utility-based health-related quality of life measures that capture outcomes based on 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is measured based on 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.
- Patient reported access-to-care outcomes, including transportation and time needed for evaluation.
- Cornell Services Index: The Cornell Services Index (CSI) assesses the frequency and duration of use of a range of services over the past three months. Services are aggregated into four types: outpatient psychiatric or psychological, outpatient medical, professional support, and intensive services. Each service use includes information on the discipline of the primary provider, the location of the service, and the reason for the service. Finally, the CSI collects information on out-of-pocket cost to the individual and the primary method of payment (for example, Medicare, Medicaid, or self-pay).

8.2 SAFETY AND OTHER ASSESSMENTS

The patients will contact their healthcare provider for any significant problems related to their atopic dermatitis. Patients will also be asked to complete quarterly forms that capture any AEs/SAEs that may have occurred over the past three months of the study. Importantly, patients can spontaneously report Aes/SAEs at any point during the study.

Safety Assessments

- AE/SAE occurrence form (patient-reported)

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (Aes) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

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

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (Aes) will have their relationship to study intervention assessed by the principal investigator or authorized designee who examines and evaluates the participant 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.

8.3.3.3 EXPECTEDNESS

The principal investigator or designee will be responsible for determining whether an adverse event (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 intervention.

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

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All Aes including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All Aes occurring while on study must be documented appropriately regardless of relationship. All Aes will be followed to adequate resolution.

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

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 principal investigator or designated study staff member will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious Aes) or 30 days (for SAEs) after the last day of study participation. During each scheduled assessment, study subjects will be asked to complete a form to capture any occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Patients can report adverse events using two methods: (1) using the "Adverse Event Collection Form", which is collected at quarterly intervals, or (2) reporting Aes spontaneously to the study staff at any time 24/7. All adverse events reported during the course of the study will be reported to the PI.

Each week, the study team will review the quarterly AE Collection Forms and Aes that were spontaneously reported. In accordance with IRB regulations, reportable adverse effects arising from any research procedures will be submitted promptly to University of Southern California's Office of Human Research Protection (OHRP) within 10 working days after the investigator becomes aware of the event. All adverse events will be collected and reported in aggregate to the DSMB.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Any AE that meets any criterion for a SAE requires the completion of an SAE Report Form in addition to being recorded on the AE pages of the CRF. The principal investigator is required to ensure that the data on these forms is accurate and consistent. This applies to all SAEs, regardless of relationship to study intervention, that occur after informed consent has been obtained.

All SAEs regardless of relatedness of expectedness will be reported immediately (within 48 hours of the principal investigators' knowledge of the event) to the NIAMS and the Data and Safety Monitoring Officer through the Executive Secretary (KAI).

The SAE report must provide a detailed description of the SAE. If a subject has died and an autopsy has been performed, copies of the autopsy report and death certificate will be sent to the NIAMS and Data and Safety Monitoring Board (DSMB) as soon as the information becomes available. Any follow-up data will be detailed in a subsequent SAE Report Form and sent to the NIAMS and DSMB accordingly.

The principal investigator or designee is responsible for informing the Institutional Review Board/Ethics Committee (IRB/IEC) of the SAE and providing them with all relevant initial and follow-up information about the event. The principal investigator or designee will keep copies of all SAE information, including correspondence with the NIAMS, DSMB and the IRB, on file. All SAEs that have not resolved upon discontinuation of the subject's participation in the study will be followed until either the event resolves completely, stabilizes/resolves with sequelae, or returns to baseline (if a baseline value is available).

8.3.7 REPORTING EVENTS TO PARTICIPANTS

If any adverse or serious adverse event results in a change to the risk/benefit ratio of the study, participants will be notified immediately, and asked to re-consent to participating in the study by signing an updated informed consent form

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UPs)

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

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- 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
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The principal investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the NIAMS Data and Safety Monitoring Board (DSMB). The UP report will include the following information:

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

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

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the NIAMS and DSMB through the Executive Secretary (KAI) within **48 hours** of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the NIAMS DSMB within **10 working days** of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within **10 working days** of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be notified of any unanticipated problems via emailed letter from the Principal Investigator.

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

We consider $\boldsymbol{\delta_U}$ **= ±6.5 as the equivalence limit for our primary outcome, SA-EASI**, which is half of a clinically significant difference and much more conservative than prior studies.[11] We computed sample size estimates for equivalency comparison of means for the primary endpoint and secondary endpoints from Aim 1 and Aim 2 using one-sided α = 0.05 and 80% power (PASS version 14). 272 patients randomized are sufficient to determine equivalency with 80% power for the primary endpoint of EASI given the range of SD (15-20), with anticipated 15% attrition. This N is larger than that required for any

of the other outcomes.[23-25] Thus, enrolling 300 patients provides adequate power to evaluate primary and all secondary outcomes and accounts for attrition.

9.2 POPULATIONS FOR ANALYSES

We will use an intent-to-treat (ITT) approach to evaluate equivalency of changes between the two arms across 12 months for AD-disease-severity and quality-of-life endpoints using longitudinal linear mixed modeling.

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

For this pragmatic, randomized trial, we will compare patients randomized to the online, team-based connected health (TCH) versus patients receiving in-person care across one year. The overall analytical strategy is to use linear mixed or generalized estimating equations, depending on the outcome variable, to account for repeated measures within patients. Random effects for patients will be included in the model so that the estimates of any patient-level variables will be appropriately calculated. Additionally, we will adjust *a priori* for the randomization stratification factors site and age group (<18 years, and 18+ years) in all models. While we do not anticipate a site-level main effect, random effects for site will be included in the model in case there are factors common to patients within a site that affect the outcome.

For comparison of AD disease severity (Aim 1) and quality of life (Aim 2), we will test an equivalence hypothesis between the interventions using longitudinal linear mixed effects modeling; this allows for the estimation of intra-individual variance. Using this same technique, we will test the hypothesis of improved access to specialist care (Aim 2) and cost-saving (Aim 3) with the TCH model compared to the in- person model.

9.3.2 ANALYSIS OF THE PRIMARY EFFICAY ENDPOINTS

The primary endpoint of the study is the mean improvement from baseline in EASI versus the follow-up visits (months 3-12). The comparison of improvement in EASI will incorporate all available post-intervention follow-up visits. Our primary goal will be to compare the mean difference in improvement between groups to examine if they are equivalent.

We will use an intent-to-treat (ITT) approach to evaluate equivalency of changes between the two arms across 12 months for AD-disease-severity and quality-of-life endpoints using longitudinal linear mixed modeling. This modeling allows us to account for intra-individual variability and the possibility of different numbers of follow-up measurements inherent in this pragmatic research design. For these analyses, the null hypothesis is that there is a differential treatment effect between the groups: H_0: $\mu_{In\text{-}person} \neq \mu_{TCH}$. The alternate hypothesis is H_A: $\mu_{In\text{-}person} = \mu_{TCH}$, where μ represents the average change from baseline across the follow-up visits (3 months – 12 months).

For the primary comparison of baseline versus average of follow-up visits, a dummy-coded time variable will be coded with 0 = baseline and 1 for all follow-up visits, so that the estimate of the effect will indicate the difference between baseline and the average of follow-up visits. In addition, a group

variable will be added to the model (coded 0 for in-person and 1 for TCH) along with a group x time effect.

We consider $\delta_U = \pm 6.5$ as the equivalence limit for the primary endpoint of EASI. This equivalence limit of 6.5 was selected for EASI because it represents the minimal clinically important difference in the AD literature.[28] It is also more conservative than equivalency limits of 12-20 from pilot studies.[29]

9.3.3 ANALYSIS OF THE SECONDARY ENDPOINTS

Analysis of Disease Severity (Aim 1)

In Aim 1, we will assess a secondary endpoint, vIGA, which is an ordinal scale that provides a global assessment of the patient's AD disease severity. vIGA is scored on a 5-point ordinal scale ranging from 0 (clear) to 4 (severe). We will apply the same general modeling procedure using generalized estimating equations with the ordinal outcome of vIGA. The reference category will be 0 = clear. The equivalence margin for vIGA is 0.5, which is smaller than the minimal clinically important difference and considered a conservative equivalence margin by AD experts.

We will also assess a secondary endpoint of patient-reported symptoms using the validated instrument POEM. For POEM, we will use the same modeling method as the one described for EASI. The scores for the POEM instrument range from 0 to 28. The equivalence margin for POEM is 3.4, which is the minimal clinically important difference defined in the AD literature.[28]

Analysis of Health-Related Quality of Life and Access-to-Care Measures (Aim 2)

In Aim 2, we will compare health-related quality of life between patients from practices randomized to the two interventions. The hypothesis is that the TCH model results in *equivalent* improvement in health-related quality of life as that in the in-person arm, as measured by DLQI and Children's DLQI (CDLQI), and EQ- 5D-5L/EQ-5D-Y.

DLQI and CDLQI are validated dermatology-specific quality-of-life instruments for adults and children, respectively. The scores range from 0 to 30, with higher scores indicating more severe impact on quality of life. The equivalence margin for DLQI and CDLQI is ± 4, which corresponds to the established minimal clinically important difference.[29]

EQ-5D-5L and EQ-5D-Y are valid and reliable, generic preference-based quality of life instruments. In dermatology, EQ-5D-5L has been used in numerous AD trials. The equivalence margins for the utility index (± 0.15) and VAS (± 10) of the instrument are no larger than half of SD (Cohen's d = 0.5) and are considered the minimal clinically important difference.

The same repeated-measures, equivalency-evaluation approach described above for Aim 1 "Analysis of Atopic Dermatitis Disease Severity" will be used to compare responses to DLQI/CDLQI, and EQ-5D-5L/EQ-5D-Y between patients from practices randomized to the TCH model and in-person care across time.

The hypothesis for access-to-care measures is that TCH provides *superior* access to specialist care than in- person model. For these analyses, access-to-care measures include transportation and time needed for evaluation.

Linear regression models will be used to test whether there is a difference between the groups.

Analysis of Costs (Aim 3)

Cost analysis in healthcare research is essential for evaluating the financial impact of different treatment models on both patients and healthcare systems.[26-27] For this aim, out-of-pocket (OOP) costs represent a significant factor in determining the feasibility and accessibility of team-based connected health (TCH) compared to traditional in-person care for atopic dermatitis (AD). By analyzing OOP expenditures, this study will provide insights into whether TCH offers a cost-effective alternative while maintaining equivalent clinical outcomes.[31-38]

Healthcare utilization will be analyzed using the Cornell Services Index (CSI), which quantifies visit frequency, duration, and associated costs for medical, psychological, and professional consultations.[30] CSI data will be collected at baseline and again at 12 months, with ITT analysis requiring baseline values to be duplicated for patients missing follow-up data. Visit counts for different service categories will be analyzed through linear models, with treatment status as the primary predictor. Mean visit duration per patient and visit type will be compared across the two groups using Welch's two-sample t-tests and linear regression models incorporating total visit count as a covariate. The impact of TCH on visit duration will be further assessed using analysis of variance (ANOVA) models to determine potential treatment group differences. Additionally, sub-analyses will be conducted to explore whether utilization patterns differ by age or baseline disease severity. Given the pragmatic design of the study, an emphasis will be placed on real-world applicability, ensuring that findings account for the variability seen in routine clinical settings.

Out-of-pocket (OOP) costs will be evaluated using a combination of t-tests, ANOVA, least squares regression, and random-effects gamma regression. Initial analyses will compare total OOP costs per visit and overall OOP costs between the two treatment groups using simple t-tests. Subsequently, multiple linear regression models will be used to assess the impact of TCH on total OOP costs while adjusting for relevant covariates such as treatment site, age, sex, baseline EASI score, and history of asthma. A sensitivity analysis will be performed using gamma regression models. Given that cost data often exhibit a skewed distribution, appropriate transformations or robust estimation methods will be applied where necessary to improve model fit and interpretability.[32] Statistical significance for all analyses will be set at $p<0.05$, and all statistical computations will be conducted using standard statistical software such as R.

9.3.4 SAFETY ANALYSES

All safety data will be descriptively summarized by treatment groups and analyzed using the safety population.

Treatment Emergent Adverse Events (TEAE)s are defined as Aes that first occurred or worsened in severity after the initiation of online or in-person visits. The number of TEAEs as well as the number and percentage of patients who experienced at least 1 TEAE will be summarized using Medical Dictionary for Regulatory Activities for each system organ class (or a body system) and each preferred term by intervention group. SAEs and Aes that lead to discontinuation of the study intervention will also be summarized by the intervention group.

9.3.5 BASELINE DESCRIPTIVE STATISTICS

Demographic and baseline characteristics will be summarized descriptively by treatment group. Descriptive statistics including number of patients, mean, standard deviation, median, minimum, and maximum will be provided for continuous measures, and frequency counts and percentages will be tabulated for categorical measures.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATION

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Electronic consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and electronic documentation of informed consent is required prior to starting intervention/administering study intervention. The following electronic consent materials are submitted with this protocol: Adult Informed Consent Form and Youth Assent Form.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document.

Only the trained study staff listed on the protocol will obtain informed consent. Specifically, the study staff will explain the study procedures, benefits, and risks in detail to the interested adult patients. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the electronic consent form through the NORA® platform and ask questions prior to providing an electronic signature. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document electronically prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the electronically-signed informed consent document will be available to the participants to print for their records via an emailed link. The informed consent process will be conducted and documented in the electronic source document (including the date), and the form electronically signed, before the participant undergoes any study-specific procedures. 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.

We take special care with the assent process for minors and will adhere to all applicable institutional, state, and federal guidelines. Following the established USC IRB guidelines, we will review the study process with all minors below age 18 and his/her parent(s). For minors between 13-17 years of age and who agree to participate in the study, we will utilize the University of Southern California (USC) IRB-

approved Adult Informed Consent/Youth Assent/Parental Permission Form to be electronically signed by both the minor and the parents or legal guardian. If the minor is between the ages of 7 to 12 years of age, the study staff will review the IRB- approved "Assent to be in Research" with the minor (to be electronically signed by the minor), and his or her parents or legal guardian will electronically sign the Adult Informed Consent/Youth Assent/Parental Permission Form. If the minor is between ages 4 to 6, the study staff will speak with the minor in age-appropriate language to explain the details of the study. This discussion will occur in the presence of the parent(s) and one other staff member serving as a witness. The study staff will thoroughly document the details of the discussion. If the minor expresses any hesitation to participating in the study, the minor will not be enrolled in the study. If the minor expresses willingness to participate in the study, his or her parents or legal guardian(s) will electronically sign the Adult Informed Consent/Youth Assent/Parental Permission Form. For minors between ages 1 to 3, the study staff will obtain parental permission using a USC IRB-approved the Adult Informed Consent/Youth Assent/Parental Permission Form. In all cases, both parents must give their permission via electronic signature unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Determination that the primary endpoint has been met

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the funding agency. 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.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor and representatives of the Institutional Review Board (IRB) 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 the reviewing IRB, Institutional policies, or sponsor requirements.

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

10.1.4 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including dermatology, teledermatology, and inflammatory skin diseases. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet semi-annually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. The DSMB will provide its input to the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

10.1.5 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Structured research data will be captured electronically into NORA®, a secure, HIPAA compliant electronic data capture system powered by Science 37, Inc. Similarly. The study-specific database will be designed such that only data meeting certain criteria and ranges will be accepted. Additionally, missing values and incongruent or potentially erroneous data will be flagged atomically for study site review.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

10.1.6 DATA HANDLING AND RECORD KEEPING

10.1.6.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

Data Collection

The study staff will enter all structured research data into NORA®, which is a secure, HIPAA compliant electronic data capture system powered by Science 37, Inc. Similarly, all subject questionnaires will be entered electronically and captured directly in the NORA® database. The study-specific database will be used to collect patient-reported outcomes as well as nature and severity of adverse events.

The database will be designed such that acceptable ranges for input will be included for all subject data points. Data not meeting the specified parameters will not be accepted. All database data capture will be validated and response parameters will be included to minimize the risk of erroneous entries, missing fields, and data discrepancies. Automatically triggered error messages will allow the users to correct the entry instantaneously online. The study team will perform data quality checks at monthly intervals. The PI and designated study staff will review the data entered in to NORA® to assess completeness and accuracy. Data queries generated from the data quality checks will be addressed by the research study staff in a timely manner.

In the unlikely event of noncompliance, the PI will speak directly with the study staff to identify the cause of noncompliance and develop strategies to prevent such noncompliance in the future. Immediate and frequent reassessment will be done by the research team to ensure compliance.

Data Confidentiality and Subject Privacy

All HIPAA, IRB, State and Federal policies and guidelines will be followed to ensure confidentiality. Research data collected in NORA® will be labeled with a code that the research team can link to protected health information (PHI). All protected health information (PHI) in electronic format will be safeguarded by password-protected files and computers. Any hardcopies of PHI will be stored in secured drawers in locked offices. Only the PI and study staff will have access to hard-copy materials in the locked locations.

Only data specified in the protocol will be collected from the study participants. All research data will be kept in the password-protected, encrypted database NORA®. Only the PI, trained study staff, IRB, and other authorized individuals specified in the protocol will be allowed access to the database. Electronic access to the secured drive is automatically logged by Science 37.

Data Lock

Data will be verified prior to data lock. Once the data has been locked, the dataset will be considered complete and accurate. The dataset will be de-identified prior to analysis. The study findings will be reported using common data elements to enable comparison with other studies. Finally, we will follow all NIH guidelines regarding data sharing as outlined in:
http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm.

10.1.6.2 STUDY RECORDS RETENTION

Study documents should be retained until at least 3 years have elapsed since the formal discontinuation of clinical development of the study intervention.

10.1.7 PROTOCAL DEVIATIONS

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

These practices are consistent with ICH GCP:

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

It is the responsibility of the PI to use continuous vigilance to identify and report deviations within 30 days of identification of the protocol deviation, or within 30 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the NIAMS Program Official, the DSMB, and the University of Southern California. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOOP.

10.1.8 CONFLICT OF INTEREST POLICY

Any conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Institutional Review Board and NIAMS has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

AD	Atopic Dermatitis
AE	Adverse Event
CDLQI	Children's Dermatology Life Quality Index
CEA	Cost Effectiveness Analysis
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
CRC	Clinical Research Coordinator
CRF	Case Report Form
CSI	Cornell Services Index
DCC	Data Coordinating Center
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
EASI	Eczema Area and Severity Index
EC	Ethics Committee
eCRF	Electronic Case Report Forms
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRQol	Health-related Quality of Life
ICER	Incremental Cost Effectiveness Rations
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NMB	Net Monetary Benefit
NORA®	Network Oriented Research Assistant
OHRP	Office for Human Research Protections
PCP	Primary Care Physician
PI	Principal Investigator
POEM	Patient Oriented Eczema Measure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QA	Quality Assurance
QALY	Quality Adjusted Life Years
QC	Quality Control
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SC CTSI	Southern California Clinical Translational Science Institute
SD	Standard Deviation
SOA	Schedule of Activities
SOP	Standard Operating Procedure
TCH	Team-Based Connected Health
UP	Unanticipated Problem
US	United States

USC	University of Southern California
VAS	Visual Analog Scale
vIGA	Validated Investigator's Global Assessment
WTP	Willingness to Pay

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