A Pilot Study to Evaluate a Temporary Skin Substitute (Spincare® Matrix) for Wound Healing in RDEB Patients

Study Protocol and Statistical Analysis Plan

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Jean Y Tang
Clinical Research Protocol

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Protocol Number:	IRB-69575
Version Date:	05 JUNE 2024
Investigational Device:	Spincare
Study Phase:	Phase 1 (pilot study)
Sponsor-Investigator:	Jean Y Tang 450 Broadway St, Stanford School of Medicine North Campus, [redacted] Redwood City CA 94063
Funding Organization:	EB Research Partnership
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LIST OF ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
QC	Quality Control
PI	Principal Investigator
UADE	Unanticipated Adverse Device Effect

PROTOCOL SYNOPSIS

TITLE	A Pilot Study to Evaluate a Temporary Skin Substitute (Spincare™ Matrix) for Wound Healing in RDEB patients
REGULATORY SPONSOR	Jean Y Tang, MD, PhD
FUNDING ORGANIZATION	EB Research Partnership
NUMBER OF SITES RATIONALE	Single site Of the various EB subtypes, it is well known that recessive dystrophic epidermolysis bullosa (RDEB) patients suffer from the most severe skin wounds. In this pilot study we will enroll RDEB patients due to their need for specialized wound care, which is typically more complex and frequent than other types of EB. Therapies that reduce pain and the size and severity of wounds have also been reported as the main priorities for RDEB patients and caregivers. There are limited therapies approved in the US for the treatment of EB and there has been an exponential rise in EB-related studies. The mainstay of treatment is supportive with non-adhesive wound dressings. With the lack of therapies available to address the multitude of RDEB needs and the slow pace of EB research, we propose to evaluate the matrix device as a suitable and safe device for application of a matrix wound dressing to EB wounds. This study is looking at preliminary wound efficacy signals and tolerability. Results of this pilot study would inform the design of larger trials evaluating the suitability of the device as a vehicle in delivering *COL7A1* gene-corrected skin cells for healing of RDEB wounds. This is currently under research development by Dr Anthony Oro's Lab at Stanford.
STUDY DESIGN	This is a single-center, randomized feasibility study that offers an Open-Label Phase upon completion of the Randomized Phase.
PRIMARY OBJECTIVE	To assess the preliminary efficacy of matrix treatment in RDEB wound To assess safety profile of matrix treatment in RDEB wound

SECONDARY OBJECTIVES NUMBER OF SUBJECTS	To assess improvement in wound pain with matrix treatment in RDEB wound To assess improvement in wound itch with matrix treatment in RDEB wound To assess caregiver responses on wound dressing ease of use with matrix treated wounds To compare the change in wound cultures between matrix treated wounds vs control wounds 6-10 subjects for enrollment of at least 20 wound pairs
SUBJECT SELECTION CRITERIA	Inclusion Criteria: Clinical and/or genetic diagnosis of RDEB by a dermatologist, age 6 years or older willing and able to give consent/assent and have at least 6 wounds (3 wound pairs) each with an area of 10cm2 or greater located at any site (excluding face and genital skin). The first patient that will be enrolled is an adult patient before the recruitment of pediatric patients. Wounds must be present for at least 4 weeks and able to be classified as recurrent wounds (wounds that heal within 12 weeks but then re-blister) vs chronic open (older than 12 weeks). Exclusion Criteria: Actively infected wounds with pus (colonized wounds are eligible), areas that have had squamous cell carcinoma (SCC), areas on the face and genitals, and areas that have been treated with investigational therapies in the past 3 months.
INVESTIGATIONAL DEVICE / INTENDED USE	Spincare The Spincare matrix is delivered from a portable, hand-held device that produces an electrospun healing matrix made of biocompatible materials that attaches directly to the wound bed.
CONTROL GROUP OR OTHER STUDY ARMS (if applicable)	Standard of care non-adhesive wound dressings and bandage changes currently used.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 4 months **Screening:** performed over phone and then virtually (up to 30 days before Day 0 treatment day) **Treatment:** 1-3 days (subjects to attend clinic) **Follow-up:** 4 months **Open-Label Phase:** 4 months The total duration of the study is expected to be 1 year. 4 months for subject recruitment and 6 months for final subject follow-up is anticipated.

CONCOMMITANT MEDICATIONS	Allowed: current EB medications (i.e., pain meds, vitamins, iron infusions, antibiotic ointments, oral antibiotics if needed). Prohibited: none
Efficacy Evaluations	Greater than 90% wound closure, patient reported outcomes in pain and itch sensation
Primary endpoint	Comparison of the duration of wound closure (weeks) of matrix treated wounds vs control wounds from baseline to Month 4. Wound photos will be captured at least every 2 weeks by the patient and/or caregivers. The matrix will be applied initially in clinic and afterwards patients/caregivers are allowed to apply the Spincare treatment (up to once a week) to the designated treatment wounds if required. They will receive adequate training at the in-person and/or remotely visits before applying it.
Secondary endpoints	1. Comparison of application site adverse events (burning, erythema, pain) between matrix treated wounds vs control wounds after application. 2. Comparison of wound pain (Wong-Baker FACES scale) between matrix treated wounds vs control wounds at Month 1, Month 2, Month 3, Month 4 (prior to application). More frequent timepoints may be requested. 3. Comparison of wound itch [Itch Severity Scale (adults) / Itchy Man scale (minors)] between matrix treated wounds vs control wounds at Month 1, Month 2, Month 3, Month 4 (prior to application). More frequent timepoints may be requested. 4. Comparison of wounds that reach >50% healing from baseline in matrix vs control wounds at month 1, 2, 3, 4. 5. Comparison of wounds that reach >70% healing from baseline in matrix vs control wounds at month 1, 2, 3, 4.
Other Evaluations	1. Comparison of caregiver responses on wound dressing ease of use on matrix treated wounds vs control wounds with the Caregiver Global Impression of Change survey (CaGI-C) at Month 3 and Month 4.

	2. Comparison of change in wound cultures between matrix treated wounds vs control wounds at Month 2 and Month 4.
Safety Evaluations	Wound evaluation e.g. presence of infection or skin cancer and documentation of adverse events.
Planned Interim Analyses	None. 1 adult subject to be enrolled first to ensure tolerability and safety before treating pediatric EB subjects > 6 years of age.
STATISTICS Primary Analysis Plan	**Sample size calculation:** We calculated that a sample size of 40 wounds (20 matrix-treated vs 20 untreated) would give us 90% power to detect a difference of 8.5 vs 6 weeks (SD=3) of wound closure duration between matrix treated vs untreated wounds with a two-sided alpha of 0.05. **Recruitment plan:** We will recruit our cohort of 6-10 patients from various settings including the Stanford EB clinic (~100 RDEB patients), our clinical research database (75 RDEB patients), and the Epidermolysis Bullosa Clinical Research Consortium (EBCRC) (290 RDEB patients). Many of these patients have already received a clinical and/or genetic diagnosis of RDEB and have detailed medical and wound histories recorded
Rationale for Number of Subjects	This sample size calculation is based on our prior natural history study of 720 RDEB wounds for 6 months in 13 RDEB adult and pediatric participants. We anticipate that the majority of pediatric wounds will be the recurrent type. If the Spincare matrix decreases the duration of wound closure, then this clinical trial would show a novel wound healing device that may improve wound closure duration in difficult to heal RDEB wounds. We would assess the secondary endpoints to determine if a 2.5 week longer wound closure is clinically meaningful and associated with wound specific decreases in pain and itch.

1.0 PURPOSE OF THE INVESTIGATION

1.1 Name of investigational device

Spincare matrix

1.2 Intended use of the investigational device

The Spincare device, developed by Nanomedic, is the first portable tool that delivers an electrospun, nanofibrous matrix dressing to wounds to promote healing that is approved in Europe. The aim of this pilot study is to determine the suitability of this device in RDEB wounds and assess its wound healing properties, safety and tolerability, particularly in the EB population.

1.3 Objectives of the clinical investigation

1.3.1 Primary objective

1. Evaluate the efficacy and safety of the device on wounds in patients with recessive dystrophic epidermolysis bullosa.

1.3.2 Secondary objective(s)

2. To evaluate the improvement in patient reported pain and itch sensation with the matrix treatment.

3. To evaluate patient and caregiver responses on wound dressing ease of use on matrix treated wounds vs control wounds with the Caregiver Global Impression of Change survey (CrGI).

4. To compare the change in wound cultures between matrix treated wounds vs control wounds at Month 2 and Month 4.

1.4 Anticipated duration of the clinical investigation: 10 months

2.0 CLINICAL PROTOCOL

2.1 Protocol number and title

IRB-69575: A Pilot Study to Evaluate a Temporary Skin Substitute (Spincare™ Matrix) for Wound Healing in RDEB patients

2.2 Protocol version number and date

Version 4.0, 05 June 2024

2.3 Study design

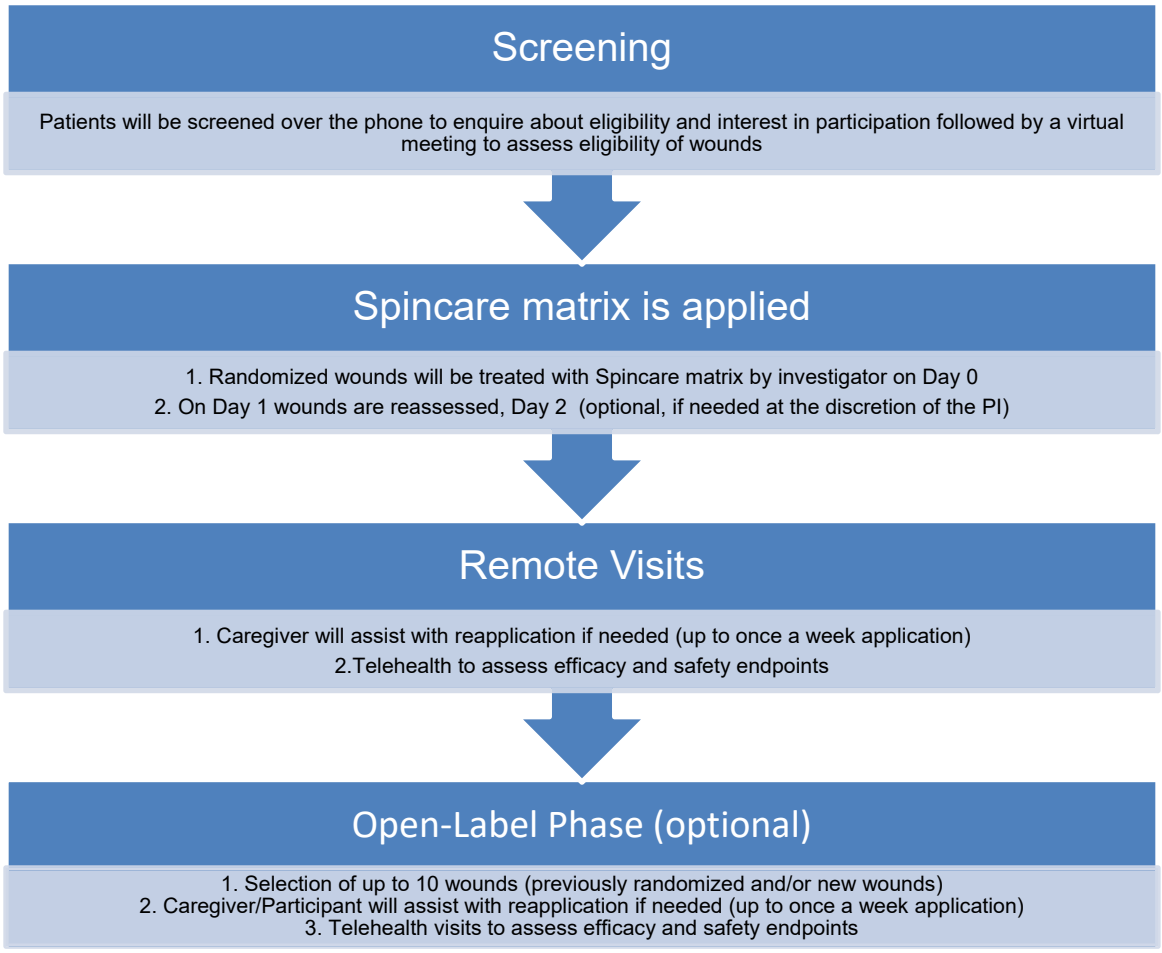
2.3.1 General study design

Pilot study in 6-10 subjects where wounds will be randomized 1:1 to matrix or no treatment (control): Patients will be asked to review and sign the informed consent form. The matrix will be applied to randomized treatment wounds (computer generated randomization), along with a non-adhesive bandage as a protective layer. At the time of matrix application, the investigator will score amount of wound burning, pain, or other adverse events. Non-treated wounds will have the patient's standard of care, and the non-adhesive bandage applied. Reapplication of matrix treatment may be required soon after the initial application depending on how well the matrix has propagated with the first application. Subjects and caregivers will be trained on how to take photos. We will ensure that photos of the face are NOT included to protect patients' confidentiality. One day after a wound examination will be performed in clinic. The investigator will assess the adherence of the matrix, and any adverse events (AEs).

Thereafter a caregiver may travel to the participants home to apply the matrix device to randomized, treated wounds once a month or more frequently if required (up to once-a-week application is allowed, the patient will record when they have applied the matrix treatment at home and the reason). Spray application(s) may be skipped at the discretion of the PI to address any concerns or adverse events. Investigators will perform remote monitoring (via phone call or virtual platform) at Week 1, Week 2, Month 1, Month 2, Month 3 and Month 4 (additional interim visits may be required) to assess for adverse events and track progress. Additional photographs will be taken, and investigators will use Telehealth to monitor for healing and safety reporting. Compliance is verified by bi-weekly photographs. Wound swabs of treated and untreated wounds will be taken prior to spray treatment and at Month 2 and Month 4. After Month 1, patients are given the option to not put any dressings on their wounds if this is medically acceptable and in line with the patient preference. Throughout the visit wound closure assessments may not be always possible if the Spincare matrix is still intact and this will be indicated on the source document. No Spincare treatment is to be applied 2 weeks prior to the end of the visit to allow for wound size measurement.

After the completion of the 4-month randomized phase, patients will be allowed to choose to enroll in an Open-Label Phase for an additional 4 months. Investigators will conduct remote monitoring on a monthly basis to assess adverse events and wound healing.

2.3.2 Study design schematic



2.4 Subject selection

2.4.1 General characteristics of the proposed subject population(s)

Patients aged 6-65 years old with a clinical and/or genetic diagnosis of recessive dystrophic epidermolysis bullosa. This target population was chosen as they suffer from large painful wounds usually resistant to conventional treatment and would benefit the most from matrix treatment with the Spincare device.

2.4.2 Anticipated number of research subjects

6-10 patients are planned to be recruited in the study.

2.4.3 Inclusion criteria

1. Subject has a clinical and/or genetic diagnosis of RDEB by a dermatologist;
2. Subject is age 6 years or older willing and able to give consent/assent;
3. Subject has at least 6 wounds (3 wound pairs) each with an area of 10cm^2 or greater located at any site (excluding face and genital skin);
4. Subject wounds must be present for at least 4 weeks.

2.4.4 Exclusion criteria

1. Actively infected wounds with pus (colonized wounds are eligible);
2. Wound areas that have had squamous cell carcinoma (SCC);
3. Wound areas on the face and genitals;
4. Wound areas that have been treated with investigational therapies in the past 3 months.

2.5 Study procedures

2.5.1 Screening procedures

Patients will be screened based on the inclusion and exclusion criteria. This will be initially performed over the phone. If eligible a virtual meeting will be organized, and patients will be asked to review and sign the informed consent form after which the wounds would be assessed in terms of suitability.

2.5.2 Study treatment or diagnostic product procedures

The Spincare device produces a wound dressing matrix that is sprayed to the wound bed. It uses a laser system to help with correct distance position to produce a uniform matrix that is electrospun to the wound bed. The device is currently available in Israel and 11 European countries but is not FDA-approved or cleared on any indications. In the current literature the main indications are acute and chronic wounds, partial thickness burns and ulcers and the matrix treatment has been used in more than 20 countries so far. A case study of Spincare treatment in EB has been described.

A full body wound examination will be performed by the investigator and target wound areas will be identified. All eligible wound sites will be randomized for matrix treatment versus standard of care wound dressings (6 wounds, or 3 wound pairs). The matrix will be applied to randomized treatment wounds, along with a non-adhesive bandage (e.g. Telfa, Mepitel, Rylon, etc.) as a protective layer. At the time of matrix application, the investigator will ask about any potential wound burning sensations, pain, or other adverse events. Non-treated wounds will have the patient's standard of care and non-adhesive bandage applied. Subjects and caregivers will be trained on how to take photos. Wound pain and itch are captured at least every 2 weeks.

The matrix treatment will be applied on Day 0 in clinic. Day 1 visit will be mandatory to assess for any adverse events (Day 2 is optional and may be required particularly if AEs have occurred and this will be at the discretion of the

PI). Subsequent applications will be performed by a caregiver if needed up to once a week.

Detailed Schedule:

Randomized phase:
Day 0 – Spincare would be applied to wounds after randomization process and covered with a non-adhesive dressing. Reapplication of matrix treatment may be required depending on how well the matrix has adhered with the first application. The need for this will be assessed by the investigators.
Day 1 – A wound examination will be performed in clinic one day after the initial application. The investigator will assess the adherence of the matrix, and any adverse events (AEs).
Day 2 is optional and may be required if medically indicated at the discretion of the PI.
Week 1, Week 2, and Months 1, 2, 3, 4 – Investigators will arrange telehealth assessment at Week 1, Week 2, Month 1, Month 2, Month 3 and Month 4 (additional interim phone call visits/telehealth assessment at **Week 6, Week 10 and Week 14**, or more frequently, if deemed necessary). A caregiver may travel to the participants home to apply the matrix device to randomized, treated wounds (up to once a week if needed, they will record the date of application and the reason). Additional photographs will be taken, and investigators will use Telehealth to monitor for healing and safety reporting. At the time of matrix application, the caregiver will score amount of wound burning, pain, or other adverse events. Matrix will not be applied after **Week 14** to ensure the final wound assessment at Month 4.
Month 4 – Telehealth (End of Randomized Phase) Visit: The investigator will virtually assess wound healing compared to baseline photographs in the treated and control wounds. Digital photographs of the treatment and control wounds will be taken with a ruler by the caregiver/participant and sent to the investigator. All wound photos will be stored and reviewed on the REDCap. The participant's preference to enroll on the Open-Label Phase will be assessed.

Open-Label Phase:
Participants who are eligible for the Open-Label Phase, at the discretion of the investigators (taking into consideration participant's prior documented adverse events, current medical status, and adherence to trial protocol), and who choose to participate, will be provided with the Spincare matrix and will be instructed to apply it once a week at most. Participant will be allowed to treat previously randomized wounds (treated and control wounds) and new wounds, up to a max of 10 individual wounds; there won't be control nor randomized wounds. The wounds would be selected at the Open-Label Baseline remote visit and will need to meet the same wound criteria as the Randomized phase. At minimum during each monthly visit, participants will be required to provide digital photos taken with a ruler before and after the application of the Spincare matrix. Additionally, they will complete surveys regarding their pain and itch, offer updates on their

medical history, provide information about concurrent medications, and report any adverse events. No blood draws, wound cultures and in person visits will be required during the Open-Label phase.

This extension phase will be 4 months long and will take place after the participants complete the Randomized phase.

Participants who elect to participate in the Open-Label Phase will undergo remote visits at **Open-Label Baseline** (could be done during the Month 4 of the Randomized Phase), **Open-Label Month 1**, **Open-Label Month 2**, **Open-Label Month 3**, and **Open-Label Month 4**.

Open-Label Baseline visit – Telehealth visit. Participant will have up to two weeks after the end of the Randomized Phase to enroll in the Open-Label Phase. At the Open-Label Baseline visit the Investigator will select up to 10 wounds from previously randomized (treated and control) wounds and new wounds (that meet the initial wound criteria). Medical history, con-medications, and adverse events will be reviewed. Spincare matrix will be applied on the new wounds, digital photographs of the wounds from before and after will be taken with a ruler by the caregiver/participant and sent to the research team. Participant will complete baseline pain and itch surveys.

Open-Label Months 1, 2, 3, 4 – Investigators will arrange telehealth assessment visits at Open-Label Month 1, Open-Label Month 2, Open-Label Month 3 and Open-Label Month 4 (additional interim remote assessments if deemed necessary). A caregiver may travel to the participant's home to apply the matrix device to the treated wounds (up to once a week if needed, they will record the date of application and the reason). Photographs will be taken, and investigators will use Telehealth to monitor for wound healing and safety reporting. At the time of matrix application, the caregiver will notate any wound burning sensations, pain, or other adverse events. Matrix will not be applied after **Open-Label Week 14** to ensure the final wound assessment at Open-Label Month 4.

Open-Label Month 4 – Telehealth (End of Open-Label Phase) visit. The investigator will virtually assess wound healing compared to baseline photographs in the treated wounds. Photos of the treated wounds will be collected by the caregiver/participant and sent to the research team. All wound photos will be stored and reviewed on the REDCap.

2.5.3 Allocation to treatment

Intra-patient randomization and allocation of treatment is planned. Wounds will be matched according to wound characteristics e.g. size, severity, and location. Randomization will be computer generated.

2.5.4 Unblinding

Clinical study is not blinded.

2.5.5 Treatment/matrix adherence

Treatment will be applied by investigator (initial application and reapplication on Day 0). Subsequent treatment will be applied by caregiver during the scheduled visit for Week 1, Week 2, Months 1, 2 and 3 if needed. More frequent application to the treatment wounds is allowed (up to once a week).

2.5.6 Withdrawal of subjects due to non-compliance

Subjects are allowed to withdraw at any time during the entire study period. They should contact the PI directly and attend an early study termination clinic visit to assess for adverse events and discuss ongoing treatment.
Subjects may withdraw from study participation due to non-compliance or patients may choose to discontinue. Recruitment of subjects will continue until the minimum number of wounds is met (20 treated and 20 control wounds).

2.5.7 Procedures to assess efficacy

Wounds will be assessed by investigator review of photographs for achievement of >90% healing from baseline every two weeks for a total of 16 weeks (4 months). Wound photos will be captured every two weeks by the subject or caregiving using mobile phone photographs uploaded into REDCap. Patient reported pain and itch surveys (Wong-Baker FACES scale and Itch Severity Scale (adults) / Itchy Man scale (minors) will be analyzed.

The aim is to analyze all data using an intention to treat analysis method. Further sub-analysis will be undertaken e.g. analyze data from patients who have applied the Spincare matrix 80% of the expected number of times or greater.

2.5.8 Procedures to assess safety

Safety assessments for dermal tolerability such as erythema, inflammation and ulceration will be made by investigators. Adverse events will be documented and analyze.

2.5.9 Schedule of study visits

	Randomized Phase											Open-Label Phase				
	Day 0	Day 1	Week 1	Week 2	Month 1	Week 6	Month 2	Week 10	Month 3	Week 14	Month 4[a]	Baseline[b]	Month 1	Month 2	Month 3	Month 4
	Clinic Visit		Phone Call									Phone Call				
Medical History	X	X	X	X	X		X		X		X	X	X	X	X	X
Adverse Events		X	X	X	X		X		X		X	X	X	X	X	X
Vital Signs	X	X														
Direct Skin examination	X	X														
IGA grading			X		X		X		X		X	X	X	X	X	X
Wound selection and randomization	X											X[c]				
Application of matrix in clinic	X	X														
Application of matrix at home			X	X	X	X	X	X	X			X	X	X	X	X
Wound culture	X						X				X					
Itch and pain scores	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Caregiver survey									X		X					
Wound size measurements	X	X	X		X		X		X		X	X	X	X	X	X
Photographs by investigator	X	X														
Photographs at home			X		X	X	X	X	X	X	X	X	X	X	X	X

Study timeline:
Randomized Phase:
Day 0: in person visit; randomization of wounds with wound photography, application of matrix and monitoring of adverse events (matrix application within 30 days of screening).
Day 1: in person assessment of wounds.
Day 2 (optional): review of wounds with photographs.
Telehealth assessment at **Week 1, Week 2, Month 1, Month 2, Month 3 and Month 4** (a window of ±7 days for the monthly scheduled visits is expected). Participant will provide pain and itch surveys and photographs every two weeks.
Additional visits (over secure video platform or phone calls), and reapplication of matrix by caregiver may be scheduled if deemed necessary.
Open-Label Phase:
Baseline Open-Label: telehealth assessment; selection of wounds and baseline wound photography, application of matrix and monitoring of adverse events.
Telehealth assessment at **Open-Label Month 1, Open-Label Month 2, Open Label Month 3** and **Open-Label Month 4** (a window of ±7 days for the monthly scheduled visits is expected). Participant will provide pain and itch surveys and photographs at every Open-Label Month visit. Participants can reapply up to once a week. Additional visits (over secure video platform or phone calls), and reapplication of matrix by caregiver may be scheduled if deemed necessary.

a The **Baseline Open-Label** visit could be done during the **Randomized Phase Month 4**.
b The **Baseline Open-Label** visit could be done up to two weeks after the **Randomized Phase Month 4** visit.
c During the **Baseline Open-Label** visits the investigator will select the wounds to be treated during the Open-Label Phase. No randomization will be required.

2.6 Study outcome evaluations

2.6.1 Study endpoints

Primary endpoint:
Comparison of the duration of wound closure (weeks) of matrix treated wounds vs control wounds from baseline to Month 4. Wound photos will be captured bi-weekly by caregivers.

Secondary endpoints:
1. Comparison of application site adverse events (burning, erythema, pain) between matrix treated wounds vs control wounds after application;
2. Comparison of wound pain (Wong-Baker FACES scale) between matrix treated wounds vs control wounds at month 1, month 2, month 3, month 4 (prior to matrix application);
3. Comparison of wound itch (Itch NRS/Itchy Man scale) between matrix treated wounds vs control wounds at month 1, month 2, month 3, month 4 (prior to matrix application;
4. Comparison of wounds that reach >50% healing from baseline in matrix vs control wounds at month 1, 2, 3, 4;
5. Comparison of wounds that reach >70% healing from baseline in matrix vs control wounds at month 1, 2, 3, 4.

Exploratory endpoints:
1. Comparison of caregiver responses on wound dressing ease of use on matrix treated wounds vs control wounds with the Caregiver Global Impression of Change (CrGI);
2. Comparison of change in wound cultures between matrix treated wounds vs control wounds at Month 2 and Month 4,

2.6.2 Sample size determination
We calculated that a sample size of 40 wounds (20 matrix-treated vs 20 untreated) would give us 90% power to detect a difference of 8.5 vs 6 weeks (SD=3) of wound closure duration between untreated vs matrix treated wounds respectively a two-sided alpha of 0.05. This sample size calculation is based on our prior natural history study of 720 RDEB wounds for 6 months in 13 RDEB adult and pediatric participants. We anticipate that the majority of pediatric wounds will be the recurrent type. If the Spincare matrix reduces the duration of wound closure, then this clinical trial would show a novel wound healing device that may improve wound closure duration in difficult to heal RDEB wounds. We would assess the secondary endpoints to determine if a 2.5-week shorter wound closure is clinically meaningful and associated with wound specific decreases in pain and itch.

2.6.3 Outcome data and data analysis

We anticipate that a higher number of wounds achieving >90 % wound closure would be achieved with the matrix treatment. Furthermore, we anticipate that patient reported wound pain and itch will be reduced with matrix treatment. This study would also provide pivotal data in designing future larger studies e.g. determination of wound type, wound location, wound size suitable for matrix treatment.

3.0 RISK ANALYSIS

3.1 Anticipated risks.

1. Irritation including burning, pain and itch when the matrix treatment is applied to the wound bed;
2. Potential allergic reaction to the matrix material.

3.2 Adverse event reporting

3.2.1 Adverse event definitions

Unanticipated adverse device effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Associated with the investigational device: There is a reasonable possibility that the adverse effect may have been caused by the investigational device.

Serious adverse effect: An adverse effect is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

1. Death;
2. A life-threatening AE;
3. Inpatient hospitalization or prolongation of existing hospitalization;
4. A persistent or significant disability/incapacity;
5. A congenital anomaly/birth defect;
6. Required intervention to prevent permanent impairment or damage.

3.2.2 Eliciting adverse effect information

Clinical study subjects will be questioned about adverse effects at each study visits including clinic visit.

3.2.3 Recording and assessment of adverse effects

All adverse effects (serious or non-serious) will be recorded in the subjects’ case report forms. For all adverse effects, sufficient information will be pursued and/or

obtained to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a *serious adverse effect*) and; 2) an assessment of the casual relationship between the adverse effect and the investigational device.

3.2.5 Causality and severity assessment

The sponsor-investigator will promptly review documented adverse effects to determine if there is a reasonable possibility that the adverse effect was caused by the investigational device or other study treatments; and if the adverse effect meets the criteria for a *serious adverse effect*.

3.2.6 Reporting adverse effects to the FDA

For any adverse event that is determined to be a UADE, the sponsor-investigator will submit a safety report to the FDA.
The completed Form FDA 3500A will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the sponsor-investigator first receives notice of the adverse event.
Subsequent to the initial submission of a completed Form FDA 3500A, the sponsor-investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

3.2.5 Reporting adverse effects to the responsible IRB

For any adverse event determined to be a UADE, the sponsor-investigator will submit the completed Form FDA 3500A to the IRB as soon as possible and, in no event, later than 10 working days after the sponsor-investigator first receives notice of the adverse event.
Other events and information that will require prompt reporting to the IRB using the eProtocol form include:
(1) Unanticipated problems involving risks to participants and others (UPs) as defined by Stanford University's HRPP Policy Guidance (GUI-P13, 07/22)
(2) New Information that indicates a change to the risks or potential benefits of the research in terms of severity or frequency or impacts the subjects' willingness to participate
(3) Noncompliance of the investigator, study staff or others that are possible serious and possibly continuing
(4) Complaint unresolved by the research team
(5) Incarceration when in the opinion of the PD it is in the best interest of the participant to remain on the study
Items 1 to 5 will be reported by the PD directly to the IRB within 10 days working days from when the PD learns of the event or new information. Unexpected deaths or life-threatening experiences related to the research will be reported to the IRB within 5 working days from PD learning of the event.

3.3 Withdrawal of subjects due to adverse effects

Adverse events that are deemed serious or life-threatening will be reasons for withdrawal at the discretion of the investigator. Subjects will not be replaced and patients will be assessed as per intention to treat analysis.

4.0 DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The Spincare System is comprised of a hand-held, battery-operated, portable device and a pre-filled, sterile, disposable, single patient, single use ampule; it contains a sterile, biocompatible, biodegradable polyester-based polymer solution. The matrix is created and applied using the help of an electrode and laser pointers that will guide with the appropriate distance that is required between the device and wound to achieve uniform matrix. *No changes to the device are anticipated.*

5.0 MONITORING PROCEDURES

Monitoring of the study for compliance with the clinical protocol will be conducted every 4 months or when the first subject completes the trial. Monitoring will be done by a qualified staff of Stanford (e.g. Stanford Dermatology Project Manager of clinical trials with Dr. Peter Marinkovich, EB investigator not affiliated with this study). Dr. Marinkovich will also review the wound healing and AE results after the first 2 adult subjects complete the trial before any pediatric subjects will be enrolled.

The sponsor-investigator will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

6.0 LABELING

The labeling will contain the statement "CAUTION - Investigational Device. Limited by Federal (or United States) Law to Investigational Use." [§ 812.5(a))].

7.0 INFORMED CONSENT

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Sponsor-Investigator will prepare the informed consent form and HIPAA authorization and provide the documents to IRB for approval. The Sponsor-Investigator will retain an IRB-approved copy of the Informed Consent Form in the study master file. A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records (EPIC).

8.0 IRB INFORMATION

The protocol, consent form, and other study documents including patient recruitment material will be reviewed and approved by Stanford IRB before the study is initiated. UADEs will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study.

9.0 ADDITIONAL RECORDS AND REPORTS

9.1 Data handling and record-keeping

A paper Case Report Form (CRF) will be completed for each subject enrolled into the clinical study. The sponsor-investigator will review, approve and sign/date each completed CRF; the sponsor-investigator's signature serving as attestation of the sponsor-investigator's responsibility for ensuring that all clinical data entered on the CRF are complete, accurate and authentic.
Subjects will have the option to complete documents and upload photos electronically to Stanford REDCap. Data collected at remote visits may be entered directly into Stanford REDCap.

9.2 Record maintenance and retention

The sponsor-investigator will retain the study records and reports as per the local and federal regulatory requirements.