A Prospective Multicenter Randomized Controlled Clinical Study to Investigate the Safety and Effectiveness of RES (Regenerative Epidermal Suspension) Prepared with the RECELL® Device Compared to Conventional Care for Healing of Donor Sites in Infants, Children and Adolescents (Aged 1–16 Years)

Investigational Plan

Study Number:	CTP006-1
Device:	RECELL Autologous Cell Harvesting Device
Study Type:	Pivotal Study
IDE Reference Number:	13053
Issue Date/Version:	October 30, 2018 / Revision 3
Sponsor:	AVITA Medical Americas, LLC 28159 Avenue Stanford, Suite 220 Valencia, CA 91355

PRINCIPAL INVESTIGATOR'S STATEMENT

This statement is to certify that I have received the above-referenced investigational plan, which has been approved for initiation at my investigational site by the Institutional Review Board on the date of _____. As Principal Investigator, I will ensure that all personnel who have been delegated responsibilities for this study will be trained on the investigational plan and associated responsibilities prior to study participation. I agree to conduct this clinical study in compliance with the investigational plan and applicable requirements of the U.S. Code of Federal Regulations (21 CFR Parts, 50, 54, 56, 812 and 45 CFR Part 46).

Signature: _____ Date: _____

Principal Investigator

PROTOCOL SYNOPSIS

Title	A Prospective Multicenter Randomized Controlled Clinical Study to Investigate the Safety and Effectiveness of RES (Regenerative Epidermal Suspension) Prepared with the RECELL® Device Compared to Conventional Care for Healing of Donor Sites in Infants, Children and Adolescents Aged 1–16 Years
Protocol No.	CTP006-1
Sponsor	AVITA Medical Americas, LLC 28159 Avenue Stanford, Suite 220 Valencia, CA 91355
Funding	Funded by the Biomedical Advanced Research and Development Authority (BARDA) within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services
Investigational Donor Site Treatment	Application of RES prepared using the RECELL® Autologous Cell Harvesting Device + Telfa™ Clear primary and Xeroform™ secondary wound dressings
Control Donor Site Treatment	Telfa™ Clear primary and Xeroform™ secondary wound dressings
Phase of Study	Pivotal Study
Proposed Indication	The RECELL Device is indicated for use to aid healing of split-thickness donor sites created in treatment of complex skin defects requiring autografting in patients 1 year of age or greater.
Primary Objectives	To evaluate whether time to complete closure is superior for RECELL-treated split-thickness donor sites, compared with Control (standardized dressings only). The mean time to donor site healing will be compared between treatments.
Planned Enrollment	Randomized Accrual: It is anticipated that a minimum of 50 randomized subjects will be enrolled in the study to evaluate the primary endpoint and to gain additional RECELL device experience for the proposed indication. Roll-In, Non-Randomized Accrual: Additionally, up to 2 roll-in subjects may be treated with the RECELL device at each of up to 5 investigational sites prior to commencement of randomization at that site to assure proficiency with the investigational device and study procedures. Thus, up to 10 roll-in subjects may be enrolled in addition to the randomized subjects. All roll-in subjects must meet the same eligibility criteria and will undergo the same follow-up assessment as the randomized subjects; however, data from this cohort of subjects will be analyzed separately from the randomized cohort. Therefore, the total planned subject accrual within this study including both the non-randomized and randomized cohorts is anticipated to be a minimum of **60 subjects**. This study utilizes an adaptive design with sample size re-estimation. The maximum enrollment in the randomized phase will be set to 100 subjects, thus the total maximum enrollment in the study with inclusion of the non-randomized cohort will be **110 subjects**.
Trial Design	This is a prospective, within-subject, paired, randomized (1:1), blinded evaluator, multicenter trial to investigate whether application of RES can be safely and effectively used to promote wound healing of donor sites created when harvesting skin for autografting. Additionally, the impact of the use of RECELL will be investigated with respect to pain, itching, subject and investigator treatment preference and donor site scar outcomes, and RECELL device safety. Infants, children and adolescents aged from 1 through 16 years, both males and females, with complex skin defects over a total body surface area (TBSA) of between 5% and 25% (inclusive) which require autografting will be considered for participation in this study. Subject consent, and assent (as applicable), will be obtained prior to conduct of any study-related procedures. This study utilizes a matched pairs design, where each subject will have two designated donor sites of similar surface area (representing a minimum of 1%

	TBSA each) randomized to receive treatment with RECELL or control dressing. The primary and secondary dressing for each study donor site (RECELL and Control) should be distinct, without any overlap. In addition to the study donor sites, other areas (partial-thickness defects, meshed autografts and non-study donor sites) may have RES applied at the discretion of the investigator. ***Only the randomized donor sites (designated study donor sites) will be part of the study area for evaluation of all endpoints.*** Subjects and their parent/guardian will be blinded to treatment assignment. Subjects should be seen 2 days post-treatment for secondary dressing changes, as clinically indicated. Follow-up visits will be scheduled Monday, Wednesday and Friday until complete healing is confirmed. The first follow-up visit will be on Friday for subjects who are treated Monday or Tuesday, on Monday for subjects treated Wednesday, Thursday or Friday, and on Wednesday for subjects who are treated Saturday or Sunday. Study donor sites will also be evaluated at Week 4. Longer-term follow-up visits will be performed at Weeks 8, 16, 24, 36 and 52. Study donor site healing will be evaluated via direct visualization by the treating investigator (non-blinded investigator) and by a qualified clinical investigator blinded to treatment allocation (i.e., Blinded Evaluator). The blinded assessment will serve as the primary healing assessment. During the early assessments, pain, itching, and subject and investigator treatment preference will be documented. Study donor sites will be documented using digital photography. At longer term visits, study donor site scar outcomes will be rated using the Patient and Observer Scar Assessment Scale (POSAS) questionnaire which includes components for both the Blinded Evaluator and the subject (or parent/guardian as appropriate). A sample size re-estimation will be conducted after approximately 50% of total randomized enrollment has completed the primary effectiveness endpoint (i.e., 25 subjects have reached the healing endpoint) and the sample size adjusted upwards as necessary.
Number of Trial Centers	It is planned that eight (8) US trial centers with a specialty in pediatric burn/injury care will participate. No site will contribute more than 30% of the total randomized subjects without written Sponsor permission.
Duration of Participation	Each subject will participate in the trial for 52 weeks post-treatment.
Primary Effectiveness Endpoint	The primary effectiveness endpoint is time (in days) to complete closure of study donor sites confirmed at two consecutive visits. It is anticipated that time to complete closure will be superior for application of RES on donor sites compared to conventional treatment (Control). Wound closure will be defined as complete when ≥95% epithelialization has been achieved as assessed by the blinded evaluator. This definition for donor site healing (i.e., complete closure), is consistent with FDA guidance[1] and consensus standards established by the American Burn Association (ABA)[2].
Safety Endpoints	All treatment-related adverse events will be documented. Safety variables compared between the two treatments are: incidence of donor site specific adverse events including but not limited to infection, allergic reaction, delayed healing, pain, and scars requiring intervention.

[1] Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment (June 2006).

[2] Singer, Adam J., et al. "Burn Wound Healing Outcomes." *Journal of Burn Care & Research* 34.4 (2013): 381-385.

Secondary Effectiveness Endpoints	The following secondary endpoints will be evaluated for superiority of RECELL over Control: 1. Donor Site Treatment Preference at Week 4 (reported by subjects 8 years of age or older, or by parent/guardian if subject is less than 8 years of age). 2. Investigator Donor Site Treatment Preference at Week 4. 3. Comparative Itching of study donor sites during 1st week post-treatment (Day 7 ± 1 day). 4. Comparative Pain of study donor sites during 1st week post-treatment (Day 7 ± 1 day). 5. Blinded Evaluator Overall Opinion POSAS Score of study donor sites at Week 24. 6. Patient Overall Opinion POSAS Score of study donor sites at Week 24 (reported by subjects 8 years of age or older, or by parent/guardian if subject is less than 8 years of age). Each endpoint will be tested in a fixed hierarchical method at a one-sided 0.025 significance level in the above order. These secondary endpoints/hypotheses will only be evaluated if the null hypothesis for the primary endpoint is rejected in the appropriate direction, and each secondary endpoint will only be evaluated if the null hypothesis of equality, for the endpoint preceding it in the list above, is rejected in the appropriate direction.
Tertiary Endpoints/ Data Collection	Other tertiary endpoints: 1. Investigator's (unblinded) assessment of healing at all RECELL-treated areas including study donor sites will be documented for all visits. 2. Subject (or parent/guardian) reported study donor site pain prior to and during dressing changes. 3. Subject (or parent/guardian) reported study donor site itching score prior to dressing changes (Itch Man Scale). 4. Pain score associated with dressing changes at study donor sites assessed by the health care provider performing the dressing change using the Face, Legs, Activity, Cry, Consolability (FLACC) scale. 5. Blinding effectiveness at Week 4 and Week 24.
Inclusion Criteria	Subjects must meet all the follow criteria to be eligible: 1. Male or female patients aged 1 through 16 years (inclusive) with a skin defect for which split-thickness autografting is indicated. 2. The area of total injury or planned defect (excluding donor sites) is 5% to 25% Total Body Surface Area (TBSA), inclusive. 3. Two discrete split-thickness donor sites of similar size (±25%) can be created in a similar non-articulating location (excluding the scalp) with each donor site representing a minimum of 1% TBSA. 4. The patient and family member/parent/guardian are able to complete all follow-up evaluations required by the study protocol. 5. In the opinion of the investigator, the patient and/or parent/guardian must be able to: a. Understand the full nature and purpose of the study, including possible risks and adverse events, and b. Provide informed consent/assent as appropriate for study participation. 6. The patient and/or parent/guardian agrees to abstain from any other treatment of the wound(s) for the duration of the study unless medically necessary and comply with all compulsory study procedures. 7. The patient and/or parent/guardian agrees to abstain from enrollment in any other interventional clinical trial for the duration of the study. 8. The patient and/or parent/guardian can understand instructions and give informed, voluntary, written consent. 9. Life expectancy greater than 52 weeks.
Exclusion Criteria	Subjects who meet any of the following criteria are not eligible for participation in the study:

	1. Prior autograft harvest at planned study donor sites. 2. Patients with sepsis or hemodynamic instability. 3. The patient has an infection under active management or other dermatologic condition at the planned donor sites or treatment areas. 4. Patient (of reasonable age) or parent/guardian is unable to follow the protocol requirements. 5. The patient has other concurrent conditions that in the opinion of the investigator may compromise patient safety or study objectives. 6. Patients with a known hypersensitivity to trypsin or compound sodium lactate for irrigation. 7. In post-pubescent girls, pregnant or breast-feeding (*pregnancy test should be performed in accordance with local institutional requirements*). 8. Enrollment in a concurrent study in which the study treatment may confound the endpoints of this study.
Statistical Consideration	As the primary effectiveness outcome is an acute outcome and it is anticipated that healing data will be available for all (if not most) subjects, the sample size calculation is based on the paired t-test for inequality rather than a survival method. Survival estimates are generally applicable to longer-term wound healing studies such as studies of chronic wounds where there is the expectation for missing outcomes (wounds not healing) and where the follow-up to observe the primary outcome of interest is prolonged raising concerns for a greater number of withdrawals; which is not the case for this study. After approximately 50% of the subjects have achieved healing on both wounds, a sample size re-estimation will be performed by an independent statistician and will be presented to the independent data monitoring committee (DMC). The sample size re-estimation analysis will be performed according to the Mehta & Pocock Promising Zone approach and the DMC may recommend adjusting the sample size upwards as indicated by the sample size re-estimation analysis, as long as the conditional power for success by the protocol-specified final sample size is in the promising zone (38% - 80%). The standard deviation is based on literature in which it is reported that the standard deviation for time to re-epithelialization of partial thickness injuries in children was four days. Thus, the standard deviation of the treatment difference could be as large as 5.6 days depending on the within-patient correlation on the primary endpoint (the lower the correlation, the larger the standard deviation). Assuming the true mean difference is 2.8 days and conservatively assuming the standard deviation is 5.6 days, then with a sample size of 37 subjects, there is an 80% probability that the null hypothesis will be rejected at a significance level of 0.025 (one-sided). The randomized sample size will be increased to 50 subjects primarily to gain additional RECELL device experience for the proposed indication as well as to account for missing endpoint data which is anticipated to be minimal. The primary effectiveness endpoint is time (in days) to complete closure of study donor sites. It is anticipated that RECELL treatment of donor sites will be superior to conventional treatment (Control) for the primary effectiveness endpoint. The Intent to Treat (ITT) population will consist of all enrolled subjects who are randomized with data analyzed according to randomized treatment assignment. This population will be utilized as a primary analysis population for the effectiveness endpoints. The Per Protocol (PP) population will consist of ITT subjects who do not have major protocol deviations with data analyzed according to treatment received. This population will be utilized as a secondary analysis population for the primary effectiveness endpoints.