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 Standard of Care Dressings for Treatment of Partial-thickness Burns in Infants, Children and Adolescents (Aged 1 – 16 Years)

Investigational Plan

Study Number:	CTP006-2
Device:	RECELL® Autologous Cell Harvesting Device
Study Type:	Pivotal Study
IDE Reference Number:	13053
Issue Date/Version:	December 11, 2020 / Revision 5
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. 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).

Print Name: _____
Principal Investigator

Signature: _____ Date: _____
Principal Investigator

TABLE OF CONTENTS

0.0 TABLE OF REVISIONS

Date/Revision	Changed from	Changed to	Comment
11DEC2020 / Revision 5	Synopsis – Trial Design A random selection of digital tracings will be reviewed by an Independent Medical Monitor to confirm the correct tracing of healed vs. unhealed areas (used to calculate percent re-epithelialization) reported by a third-party centralized image vendor.	A random selection of digital tracings will be reviewed by an Independent Medical Monitor to confirm the correct tracing of ~~healed vs. unhealed areas (used to calculate percent re-epithelialization)~~ re-epithelialized areas reported by a third-party centralized image vendor.	Clarification
	Synopsis – Number of Trial Centers Up to 18 US trial centers with a specialty in pediatric burn care will participate.	Up to ~~18~~ 25-US trial centers with a specialty in pediatric burn care will participate.	Delayed study start-up and enrollment
	4.5 Study Design This is a prospective, parallel-arm, randomized (1:1), blinded evaluator, multicenter trial. Infants, children, and adolescents (aged from 1 through 16 years), male and female, with a burn injury at least 5% and no more than 30% of their total body surface area (TBSA) where no more than 10% of the burn injury represents a full-thickness burn will be considered for participation.	This is a prospective, parallel-arm, randomized (1:1), blinded evaluator, multicenter trial. Infants, children, and adolescents (aged from 1 through 16 years), male and female, with a burn injury ~~at least 5% and~~ that is no more than 30% of their total body surface area (TBSA) and no more than 10% TBSA is full-thickness burn injury, ~~of the burn injury represents a full-thickness burn~~ will be considered for participation.	Clarification
	5.2.1 Primary Effectiveness Endpoint 9.3 Primary Effectiveness Variable and Statistical Hypotheses The primary effectiveness endpoint is incidence of Index Burns with Day 10 healing. Day 10 healing is defined as the presence of ≥95% skin epithelialization without drainage or dressing required for healing. To be deemed healed, Day 10 (or earlier) healing must be confirmed at the Day 28 visit. If the Index Burn undergoes a secondary surgical treatment for closure (including conventional	The primary effectiveness endpoint is incidence of Index Burns with Day 10 healing, ~~Day 10 healing is defined as the presence of ≥95% skin epithelialization without drainage or dressing required for healing. To be deemed healed, Day 10 (or earlier) healing must be confirmed at the Day 28 visit.~~ post treatment, evaluated by an observer blinded to treatment allocation, with confirmation at Day 28. Healing is clinically-evaluated wound closure, i.e., skin re-epithelialization without drainage or dressing	FDA's recommendation to revise the study's primary effectiveness endpoint.

Date/Revision	Changed from	Changed to	Comment
	autografting) prior to the Day 28 visit, this will be considered an endpoint failure. The primary effectiveness endpoint will be assessed by a blinded evaluator. Per consensus standards established by the American Burn Association (ABA) and FDA guidance wound healing has been defined as complete when ≥95% epithelialization has been achieved confirmed at two consecutive visits. The hypothesis to be evaluated is whether the incidence rate of confirmed Day 10 healing is greater (superior) with RECELL treatment vs. Control treatment.	requirements for healing. Note that *protective* dressings are advised after initial healing with RECELL treatment while the newly healed skin matures (RECELL Instructions for Use, PMA 170122). If the Index Burn undergoes a secondary surgical treatment for closure (including conventional autografting) prior to the Day 28 visit, this will be considered an endpoint failure. ~~The primary effectiveness endpoint will be assessed by a blinded evaluator.~~ ~~Per consensus standards established by the American Burn Association (ABA) and FDA guidance wound healing has been defined as complete when ≥95% epithelialization has been achieved confirmed at two consecutive visits.~~ The hypothesis to be evaluated is whether the incidence of ~~confirmed~~ Day 10 healing post-treatment (confirmed at Day 28) is greater (superior) with RECELL treatment vs. Control treatment. Post-treatment in the Investigational Treatment Group is defined as post-RECELL treatment and in the Control Treatment Group is post baseline photos and (re)placement of Mepilex Ag.	
	<u>5.2.2 Secondary Effectiveness Endpoints</u> <u>9.5 Secondary Effectiveness Variables and Statistical Hypotheses</u> 1. Incidence of healing (≥95% skin epithelialization) of the Index Burn on or before Day 21, confirmed on Day 28.	1. Incidence of Index Burn Day 21 post-treatment healing ~~(≥95% skin epithelialization) of the Index Burn on or before Day 21,~~ (confirmed on Day 28).	FDA recommendation

Date/Revision	Changed from	Changed to	Comment
	6.1.1. Inclusion Criteria 2.TBSA (exclusive of superficial areas) of 5 to 30% (inclusive) where ≤10% of the burn injury is full-thickness. 3.The Index Burn must be no less than 160 cm^2 clean partial-thickness burn injury between 2-20% BSA (inclusive).	2. The patient has a thermal burn injury that is: a. ≤ 30% TBSA (exclusive of superficial areas) and b. ≤ 10% TBSA is a full-thickness burn. 3.The Index Burn must be a clean partial-thickness burn injury ≥160 cm^2 and between 2-20% BSA (inclusive).	Clarification and removal of lower TBSA requirement
	7.3.3. Point of Randomization Randomization will be stratified by investigational site and total burn area (5 to <10% TBSA and ≥10% TBSA).	Randomization will be stratified by investigational site and total burn area (~~5 to~~ <10% TBSA and ≥10% TBSA).	Removal of lower TBSA requirement
	7.7.2 Longer-Term Follow-Up Visits	Added: *During the longer-term follow-up visits, the preferred method is in-person clinical visits, however (if necessary), these follow-up visits may be conducted remotely (e.g., via telemedicine) with the exception of the Week 52 visit.*	Option for remote longer-term follow-up visits as necessary per "FDA Guidance on Conduct of Clinical Trials of Medical Products during. COVID-19 Public Health Emergency"
	7.7.3.1 Post-Autografting Follow-Up Index Burns requiring conventional autografting will be seen for follow-up visits on Days 7 and 14 post-autografting and every two weeks thereafter until the Index Burn is healed as confirmed via direct observation by the investigator of ≥95% epithelialization at two consecutive visits.	Index Burns requiring conventional autografting will be evaluated as clinically indicated.	To better align with standard clinical follow-up per medical advisory input
	7.8.1.1. Index burn Healing Assessment by Investigator and Blinded Evaluator Index Burn healing will be evaluated via direct visualization by the investigator at each study visit and by the Blinded Evaluator (on or before Day 10, Day 21 (if not healed by Day 10), and Day 28). Healing is defined as	Index Burn healing will be evaluated via direct visualization by the investigator at each study visit and by the Blinded Evaluator on or before Day 10, Day 21 (if not healed by Day 10), and Day 28 post-treatment. ~~Healing is defined as ≥95% epithelialization confirmed at two consecutive visits.~~	FDA 15JUL2020 and 10SEP2020 recommendation

Date/Revision	Changed from	Changed to	Comment
	≥95% epithelialization confirmed at two consecutive visits. The healing assessment will be captured categorically as follows: • ≥ 95% to 100% re-epithelialized • ≥ 90% to 94% re-epithelialized • ≥ 80% to 89% re-epithelialized • ≥ 70% to 79% re-epithelialized • ≥ 50% to 69% re-epithelialized • ≥ 25% to 49% re-epithelialized • < 25% re-epithelialized	The healing assessment will be captured categorically as follows: • ~~≥ 95% to 100% re-epithelialized~~ • ~~≥ 90% to 94% re-epithelialized~~ • ~~≥ 80% to 89% re-epithelialized~~ • ~~≥ 70% to 79% re-epithelialized~~ • ~~≥ 50% to 69% re-epithelialized~~ • ~~≥ 25% to 49% re-epithelialized~~ • ~~< 25% re-epithelialized~~ • Healed – skin re-epithelialization without drainage or dressing requirements for healing • Not healed – presence of drainage and/or dressings required for healing	
	7.8.1.2 Percent Re-epithelialization of the Index Burn via Photographic Planimetry Re-epithelialization values ≥95% will be classified as healed.	~~Re-epithelialization values ≥95% will be classified as healed.~~	FDA recommendation
	Informed Consent Form Following the skin grafting procedure, you will have to return to see your doctor 7 and 14 days after the skin grafting procedure and then every 2 weeks until the grafted area has healed. After you complete the initial healing assessment period (through 28 days after your treatment), you will need to return for study visits 8, 16, 24, 36 and 52 weeks after your initial study treatment (unless you required skin grafting in which case the post-grafting visit schedule identified above is applicable).	Following the skin grafting procedure, you will ~~have to return to see your doctor 7 and 14 days after the skin grafting procedure and then every 2 weeks until the grafted area has healed.~~ continue to see your doctor until the grafted area has healed. After you complete the initial healing assessment period (through 28 days after your treatment or following your skin grafting procedure), you will need to see your study doctor 8, 16, 24, 36 and 52 weeks after your initial study treatment ~~(unless you required skin grafting in which case the post-grafting visit schedule identified~~	Option for remote longer-term follow-up visits as necessary per "FDA Guidance on Conduct of Clinical Trials of Medical Products during. COVID-19 Public Health Emergency"

Date/Revision	Changed from	Changed to	Comment
		~~above is applicable).~~ These visits will occur in-person or may be conducted remotely (e.g., via telemedicine) if necessary. Your last study visit (Week 52) will be conducted in-person.	
15-JUN-2020/ Revision 4	-	-	Revisions throughout associated with secondary and tertiary endpoints, follow-up schedule, statistical considerations, in addition to general clarifications. Revisions made in light of COVID-19 as early and frequent follow-up visits are clinically non-essential and unable to be conducted at investigational sites.
09-JAN-2019/ Revision 3	The primary effectiveness endpoint is incidence of Index Burns with confirmed Day 10 healing. Day 10 healing is defined as the presence of ≥95% epithelialization with a contiguous layer of viable epithelium (as determined by a Blinded Evaluator) AND without the need for secondary surgical treatment (including conventional autografting) to achieve initial healing. Factors considered during the healing assessment include color, presence of granulation tissue, and whether the wound is covered with a contiguous layer of viable epithelium. Using this definition, some small degree of blistering is acceptable as long as the wound is ≥95% epithelialized. To be deemed healed, ≥95% epithelialization must be confirmed at the Day 28 visit.	The primary effectiveness endpoint is incidence of Index Burns with Day 10 healing. Day 10 healing is defined as the presence of ≥95% skin epithelialization without drainage or dressing required for healing. To be deemed healed, Day 10 healing must be confirmed at the Day 28 visit. If the Index Burn undergoes a secondary surgical treatment (including conventional autografting) prior to the Day 28 visit, this will be considered an endpoint failure. The primary effectiveness endpoint will be assessed by a blinded evaluator.	Per FDA request 9-Jan 2019
07-DEC-2018/ Revision 2	-	-	Substantial changes throughout prior to initiation of enrollment
09-Jul-2018/ Revision 1	ReCell; RES-treated; Avita; Caregiver;	RECELL; RECELL-treated; AVITA; Parent/guardian;	Modified for consistency throughout protocol

Date/Revision	Changed from	Changed to	Comment
	Study treatment; Treating physician-investigator	Investigational device; Investigator	
	Control Treatment: Mepilex® Wound Dressing (Mölnlycke Health Care)	Mepilex® Ag Wound Dressing (Mölnlycke Health Care)	Use of dressings with antimicrobial properties is part of standard care for this type of burn injury
	Section 1.0 Section 5.2.2 Intra-operative Eligibility Criteria Patient requires staged procedures for treatment of partial-thickness burns.	Added exclusion criteria: *Superficial / trivial burns or burns that in the investigator's opinion appear to be healing sufficiently such that care under this protocol would be inappropriate.* Patient requires *immediate or staged autograft* procedures *for treatment of planned index burn, which has been determined, after debridement, to be of deep partial-thickness burns*.	Exclusion criteria #5 also included in intra-operative exclusion criteria. Clarification of intra-operative exclusion criteria #2.
	Section 2.0 Principal Contacts	Added: *Quantificare*	Centralized Image Review contact
	Table 1 Screening/Baseline	Screening~~/Baseline~~	Clarification
	Table 1 & Section 6.7.1	Added *holiday* to: "when assessment falls on a weekend or *holiday"*	Clarification when the assessments are to be performed in the event of a holiday
	Section 4.2.4 All treatment-related and device-related SAEs occurring at during the course of the clinical study (beginning from the initiation of study treatment), will be recorded on the AE Case Report Form.	~~All treatment-related and device-related SAEs occurring at during the course of the clinical study (beginning from the initiation of study treatment), will be recorded on the AE Case Report Form.~~	AE reporting detailed in Section 7.2 Adverse Events
	Section 5.1.1 Inclusion Criteria	~~Note: Due to referral patterns from tertiary centers, the study will accept that some subjects may already have a dressing in place and/or prior application of silver sulfadiazine at the time of arrival for their definitive care.~~	Redundant statement
	Section 6.4.1	*The method of harvest, depth setting*, size, *and anatomical*	Clarified to specify depth setting of harvesting tool vs. donor site depth.

Date/Revision	Changed from	Changed to	Comment
	Skin sample size, location and depth will be recorded in the eCRF.	*location of the donor site(s)* will be recorded in the eCRF.	
	Section 6.6 Section 6.7.1 The primary dressing should remain in place for a minimum of 6-8 days and is not to be manipulated unless medically necessary. Following initiation of study treatment, silver-impregnated dressings are not to be used **pro-actively or prophylactically**.	The primary dressing should remain in place *and is not to be manipulated unless medically appropriate, until the dressing releases from the wound due to underlying epithelialization.* Following initiation of study treatment, silver-impregnated dressings or *topical antibiotics* are not to be used ~~**pro-actively or**~~ **prophylactically**.	Clarification to allow for adequate assessment of study areas and topical antibiotic use
	Section 6.7.1 Section 6.7.2, & Table 1	Added: *Non-Index Burn Area healing assessment, if applicable* *Photography of total burn injury (all areas) at Treatment and Week 52*	Clarification healing assessments for Non-Index Burn Areas and photography for total burn injury
	Section 6.8.2.1 Pain Scoring Prior to and After Dressing Changes	Added: *Based on the age the subject at the time of consent*	Clarification
	6.8.4 For the purposes of this study, the BOQ will be presented in 3 versions, administered based on the age the subject will be at the end of the study	For the purposes of this study, the BOQ will be presented in 3 versions, administered based on the age of the subject *at the time of consent*	Clarification
	Section 6.8.6 After the last subject's last visit is performed at the participating institution, the treating-physician investigator will be requested to respond to the following question and the response documented within the eCRF.	Investigator(s) at each institution will be requested to respond to the following question based on the subjects they treated and followed throughout the study. Their response will be collected and documented within the eCRF after the investigator's last subject last visit is performed.	Clarified multiple investigators may respond from a site based on the subjects they treated
	Section 7.2.5.3 Any treatment area undergoing a subsequent surgical intervention for scar revision will also be considered a major treatment-related adverse event.	~~Any treatment area undergoing a subsequent surgical intervention for scar revision will also be considered a major treatment-related adverse event.~~ Added: *Scar requiring surgical revision to mitigate functional*	Clarification on how to report and classify surgical scar intervention vs. cosmesis laser scar intervention

Date/Revision	Changed from	Changed to	Comment
		issues will be considered a treatment-related adverse event and should be reported as serious if the event meets the criteria outlined in Section 7.2.8. Rate and severity of scars requiring surgical intervention will be compared for RECELL versus Control for the purposes of evaluating safety. *Cosmetic issues, including those requiring laser procedures will also be documented as treatment-related adverse events, however these will not be considered as part of the safety evaluation (i.e., laser treatment for cosmesis will not be considered as a surgical intervention).*	
	Section 7.2.6 Relationship of Adverse Events to the RECELL Investigational Device	Categories refined to align with CDISC standards	Clarification
	Section 13.0 Reports "fax"	"~~fax~~ email"	Method of notification may be made initially by email
	Appendix C	Aftercare Instructions updated	Updated to align with current guidance
8-Mar 2018/ Original	NA -original	NA -original	NA -original

1.0 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 Standard of Care Dressings for Treatment of Partial-thickness Burns in Infants, Children and Adolescents (Aged 1–16 Years)
Protocol No.	CTP006-2
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 Treatment	Application of RES® prepared using the RECELL® Autologous Cell Harvesting Device to partial-thickness burns (dressed with Telfa™ Clear primary and Xeroform™ secondary wound dressings)
Control Treatment	Mepilex® Ag Wound Dressing (Mölnlycke Health Care) is a standardly employed dressing for second-degree/partial-thickness burns due to its non-adherent and antimicrobial properties. The layered dressing includes a flexible, absorbent polyurethane foam pad embedded with silver sulfate compound and vapor permeable film backing with a silicone layer covered with a polyethylene release film.
Phase of Study	Pivotal Study
Proposed Indication for Use	The RECELL Device is indicated for treatment of partial-thickness burns in patients 1 year of age or greater.
Primary Objectives	To demonstrate that RECELL treatment of partial-thickness burn injuries, can safely and effectively increase the incidence of Day 10 healing compared with a standardized wound dressing. Also, the effects of both treatments on the incidence of conventional autografting, pain, itching, scarring, health-related quality of life and resource utilization will be investigated.
Planned Enrollment	To evaluate the primary endpoint, enrollment of **160 subjects** is planned. This study utilizes an adaptive design with interim analysis for early stopping due to futility or positive outcome and, if necessary, sample size re-estimation in order to maintain adequate condition power. The maximum enrollment will be **300 subjects**.
Trial Design	This is a prospective, parallel-arm, randomized (1:1), blinded evaluator, multicenter trial. Infants, children, and adolescents (aged from 1 through 16 years), male and female, with a burn injury that is no more than 30% of their total body surface area (TBSA) and no more than 10% TBSA is full-thickness burn injury, will be considered for participation. Randomization and assigned treatment must be performed within 72 hours of the burn injury for a subject to be treated within this study. Qualifying subjects will be randomized 1:1 either to treatment with RECELL or to Control (Mepilex® Ag Wound Dressing). Randomization will be stratified by investigational site and total burn area (<10% TBSA and ≥10% TBSA). If there is more than one partial-thickness burn wound, the largest partial-thickness burn wound meeting eligibility requirements will be identified as the Index Burn (the burn wound that will be compared for effectiveness outcomes). The Index Burn will be a contiguous area at least 160 cm^2 that excludes the face, hands, feet and genitalia.

	In order to evaluate the impact of study treatment on quality of life and health economic outcomes, unless clinical circumstances dictate otherwise, all of the subject's partial-thickness burn wounds, including any non-index burn(s), should be treated at the initial procedure according to the randomized treatment assignment. For subjects randomized to RECELL, skin sample harvesting and treatment should be performed in accordance with the RECELL Instructions for Use. Prior to application of RES, necrotic tissue is to be excised. The skin sample size required for processing is approximately 1/80th of the area to be treated. RES may be applied to the RECELL donor site at the investigator's discretion. For subjects randomized to Control, burn wounds should be cleaned per local standard practice prior to application of Mepilex® Ag Wound Dressing. Mepilex® Ag Wound Dressing will be applied in accordance with the manufacturer's Instructions for Use. Subjects should be seen for dressing changes as clinically indicated. Primary Effectiveness Assessments: Day 10 and Day 28 post-treatment, the Index Burn will be evaluated via direct visualization by a qualified local clinical investigator blinded to treatment allocation (Blinded Evaluator) to assess Index Burn healing, unless the Index Burn has been autografted. At all follow-up visits, the Index Burn will be photographically documented using standardized digital imaging. From these images, the percent re-epithelialization will be determined via photographic planimetry by a third-party centralized image vendor. A random selection of digital tracings will be reviewed by an Independent Medical Monitor to confirm the correct tracing of re-epithelialized areas reported by a third-party centralized image vendor. During the acute follow-up period, the investigator will determine whether autografting of the Index Burn is required. Autografting is typically indicated when there are no signs of improvement or healing, when the investigator expects no further wound healing in the next 7 to 11 days, or when a contiguous area greater than 0.5% TBSA is unhealed. Index Burns requiring conventional autografting will be evaluated as clinically indicated. Standardized digital images of Index Burns taken during acute follow-up, including images taken the day the investigator made a decision to autograft will be presented, out of time sequence, to an Independent Medical Monitor (blinded to treatment allocation and investigator's determination) to review. Longer-term follow-up visits will be performed at Weeks 8, 16, 24, 36 and 52 post-treatment (irrespective whether a subject had conventional autografting of the Index Burn). At the Week 16, 24, 36 and 52 post-treatment visits, scar outcomes and disease-specific quality of life will be assessed. Scar outcomes will be measured 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). Patient- and family-reported quality of life outcomes will be captured via the age-specific Burn Outcomes Questionnaire (BOQ). The BOQ evaluates several domains specific to longer-term burn outcomes including physical function, appearance, satisfaction and emotional health among

	others. Investigator treatment preference will be documented for each treating investigator, at each burn center, following the investigator's last subject's last visit. During the longer-term follow-up visits, the preferred method is in-person clinical visits, however (if necessary), these follow-up visits may be conducted remotely (e.g., via telemedicine) with the exception of the Week 52 visit. Treatment-related adverse events (e.g., infection, wound breakdown, etc.) are to be recorded for the Index and Non-Index Burn wounds as well as for donor sites. An interim analysis will be conducted after approximately 50% of total enrollment has reached the primary effectiveness endpoint (i.e., 80 subjects have completed the primary endpoint evaluation including confirmation of healing at Day 28). At that time, study enrollment may be discontinued due to futility or demonstration of effectiveness. If enrollment continues, a sample size re-estimation will be performed, and the sample size may be adjusted upwards to at most 300 subjects. Safety data will be reviewed and adjudicated by an Independent Medical Monitor. A Data Monitoring Committee will be responsible for interim review of safety and effectiveness data and will be responsible for reviewing data from the interim and sample size re-estimation analyses.
Number of Trial Centers	Up to 25 US trial centers with a specialty in pediatric burn care will participate. No center will contribute more than 25% 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 incidence of Index Burns with Day 10 healing post-treatment, evaluated by an observer blinded to treatment allocation, with confirmation at Day 28. If the Index Burn undergoes a secondary surgical treatment for closure (including conventional autografting) prior to the Day 28 visit, this will be considered an endpoint failure. The hypothesis to be evaluated is whether the incidence of Day 10 healing post-treatment is greater (superior) with RECELL treatment vs. Control treatment.
Safety Endpoints	Safety will be evaluated in terms of treatment-related adverse events and serious device-related adverse events.
Secondary Effectiveness Endpoints	Specific secondary endpoints to be investigated for potential labeling claims include the following: 1. Incidence of Index Burn Day 21 post-treatment healing (confirmed on Day 28). 2. Percent area of Index Burn requiring autografting. 3. Incidence of conventional autografting to achieve Index Burn healing. 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	1. Absolute area (cm^2) of Index Burn requiring autografting. 2. Index Burn pain scores at dressing changes assessed by the health care provider performing the dressing change using the Face, Legs, Activity, Cry, Consolability (FLACC) Scale. 3. Subject reported Index Burn pain scores at dressing changes. 4. Percent epithelialization of the Index Burn per digital planimetry. 5. Index Burn POSAS scar ratings.

	6. BOQ Outcomes (raw scores and recovery curves for all domains), with baseline at Day 10. 7. Investigator treatment preference. 8. Health economics/medical resource utilization (determined using CRF data in conjunction with UB-04/CMS-1500 and/or similar hospital and physician claim forms for billing purposes to collect data associated with the initial hospital care and readmissions during follow-up as applicable). 9. Index Burn Itch Man Scale ratings.
Pre-Randomization Inclusion Criteria	1. Male or female patients aged 1 through 16 years (inclusive) with a partial-thickness thermal burn injury. 2. The patient has a thermal burn injury that is: a. ≤ 30% TBSA (exclusive of superficial areas) and b. ≤ 10% TBSA is a full-thickness burn. 3. The Index Burn must be a clean partial-thickness burn injury ≥160 cm^2 and between 2-20% BSA (inclusive). 4. The Index Burn may not cover the face, hand, foot or the perineum/genitalia (Note: a patient with wounds in these areas may be enrolled but the Index Burn Area may not include these areas). 5. The patient and/or parent/guardian agrees to comply with all compulsory study procedures and visit schedule. 6. The patient and/or parent/guardian agrees to abstain from any other treatment for closure of the Index Burn for the duration of the study unless medically necessary. 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. 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, b. Understand instruction, and c. Provide voluntary informed written consent/assent as appropriate for study participation.
Pre-Randomization Exclusion Criteria	1. Not able to understand English or Spanish. 2. Burns caused by chemicals, electricity or radiation. 3. Patients presenting with only 3rd-degree/full-thickness wounds which require immediate autografting. 4. Burn injury has had prior treatment for definitive closure. 5. Patients for whom use of sedation/general anesthesia is not medically appropriate. 6. Superficial/trivial burns or burns that in the investigator's opinion appear to be healing sufficiently such that care under this protocol would be inappropriate. 7. Patient requires immediate or staged surgical procedures for closure of their partial-thickness burns. 8. Conditions, e.g., previous burn injury to study area, poor nutritional status, poorly controlled diabetes mellitus (HbA1c >9%), that in the investigator's opinion may compromise subject safety or trial objectives. 9. Current use of medications, e.g., immunosuppressive agents (excluding inhaled corticosteroids), that in the investigator's opinion may compromise subject safety or trial objectives. 10. Inhalation injury. 11. Active infection, cellulitis or need for immediate grafting at the planned treatment areas. 12. Concerns for parent/guardian's ability to provide appropriate follow-up care. 13. Subjects with a known hypersensitivity to trypsin or compound sodium lactate for irrigation solution.

	14. Subjects with a known sensitivity to silver. 15. In post-pubescent girls, pregnant or breast-feeding (pregnancy test should be performed in accordance with local institutional requirements). 16. Immediate life-threatening condition or life expectancy less than one year. 17. Previous randomization within this investigation.
Post-Randomization (Prior to treatment) Eligibility Criteria	Post-Randomization Inclusion: 1. Patient randomized (and will be treated) within 72 hours from the time of the burn injury. 2. Patient continues to meet all pre-randomization inclusion criteria. Post-Randomization Exclusion: 1. Incidental finding of any pre-randomization exclusion criteria. Consented subjects who do not meet the post-randomization eligibility criteria and did not receive study treatment will be followed through the Day 28 visit and then withdrawn from the study. The criteria for which exclusion was based will be documented.

Table 1. SCHEDULE OF ASSESSMENTS

			ACUTE POST-TREATMENT FOLLOW-UP			INDEX BURN AUTOGRAFTING		LONGER-TERM FOLLOW-UP				
	Screening (Prior to Treatment) *May be conducted on same day as Treatment*	**Treatment** Initial wound cleaning & Randomization (RECELL or Mepilex® Ag) ***within 72 hours of initial injury***	**Day 10** (prior to or +1 day) *May be conducted on or before Day 10*	**Day 21** (±2 days) *Required only if Index Burn is not healed by Day 10*	**Day 28** (3 days) *Required unless Index Burn auto-grafted*	**Autograft Procedure**	**Post-Autograft** *Follow-up as clinically indicated*	**Week 8** (±5 days)	**Week 16** (±5 days)	**Week 24** (±14 days)	**Week 36** (±14 days)	**Week 52** (±28 days)
Informed Consent / Assent	X	-	-		-	-	-	-	-	-	-	-
Demographics / Medical History / Overall Burn Injury Assessment	X	-	-		-	-	-	-	-	-	-	-
Vital Signs (BT=body temperature only)	X	X	BT		BT	X	BT	X	X	X	X	X
Complete Physical Exam / Fitzpatrick Skin Type	X	-	-		-	-	-	-	-	-	-	-
Risks for Impaired Wound Healing	X	-	-		-	-	-	-	-	-	-	-
Eligibility Assessment	X pre-randomization	X post-randomization	-		-	-	-	-	-	-	-	-
ASA Physical Classification Score	-	X	-		-	-	-	-	-	-	-	-
Targeted Physical Assessment (changes from prior visit noted)	-	X	-		-	X	-	X	X	X	X	X
Treatment Details (All Burn Injury Area(s) & Donor Site(s))	-	X	-		-	X	-	-	-	-	-	-
Index Burn Dressing Regimen	-	X	X	X	X	X	X	-	-	-	-	-
Investigator Healing Evaluation Index Burn	-	-	X	X	X	-	X	X	X	X	X	X
Blinded Evaluator Healing Evaluation Index Burn	-	-	X		X	-	-	-	-	-	-	-
Assessment of Requirement for Conventional Autografting of Index Burn	-	-	X	X	X	-	-	-	-	-	-	-
Subject (or parent/guardian) Pain at Index Burn prior to and during Dressing Change (FPS-R/NRPS)	-	-			X	-	X	-	-	-	-	-
Pain at Index Burn during Dressing Change by HCP performing dressing change (FLACC)	-	-	X		X	-	X	-	-	-	-	-

Table 1. SCHEDULE OF ASSESSMENTS *(continued)*												
			ACUTE POST-TREATMENT FOLLOW-UP			**INDEX BURN AUTOGRAFTING**		**LONGER-TERM FOLLOW-UP**				
	Screening (Prior to Treatment) *May be conducted on same day as Treatment*	**Treatment** Initial wound cleaning & Randomization (RECELL or Mepilex® Ag) ***within 72 hours of initial injury***	**Day 10** (prior to or +1 day) *May be conducted on or before Day 10*	**Day 21** (±2 days) *Required only if Index Burn is not healed by Day 10*	**Day 28** (3 days) *Required unless Index Burn auto-grafted*	**Autograft Procedure**	**Post-Autograft** *Follow-up as clinically indicated*	**Week 8** (±5 days)	**Week 16** (±5 days)	**Week 24** (±14 days)	**Week 36** (±14 days)	**Week 52** (±28 days)
Subject (or Parent/guardian) Itching at Index Burn prior to Dressing Change (Itch Man Scale)	-	-	X		X	-	X	-	-	-	-	-
Subject Quality of Life Questionnaire (BOQ)	-	-	X		X	-	-	-	X	X	X	X
POSAS Blinded Evaluator & Subject or Parent/guardian – Index Burn	-	-	-		-	-	-	-	X	X	X	X
Investigator Treatment Preference ([2]after each treating investigator's last subject last visit)	-	-	-		-	-	-	-	-	-	-	X[2]
Photography – Index Burn Donor Site, as applicable (donor site(s) associated with treatment of the Index Burn)	-	X	X		X	X	X	-	-	-	-	-
Photography – Index Burn ([a]pre- and post-debridement; [b]pre-excision, post-excision and post-autografting)	-	X[a]	X	X	X	X[b]	X	X	X	X	X	X
Photography –Complete burn injury (*Screening *or* Treatment visit)	X*	X*	-		-	-	-	-	-	-	-	X
Concomitant Medications, Procedures & Therapies ([3]document prior 7-days' medications at screening)	X[3]	X	X		X	X	X	X	X	X	X	X
Treatment-Related Adverse Events (AEs) & Serious Adverse Events (SAEs) (including photography of ***any*** involved burn/donor areas)	-	X	X		X	X	X	X	X	X	X	X

2.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

3D	Three-Dimensional
AE	Adverse event
ABA	American Burn Association
ADE	Adverse Device Effect
ASA	American Society of Anesthesiology
BARDA	Biomedical Advanced Research and Development Authority
BOQ	Burn Outcome Questionnaire
BSA	Burn Surface Area
CDC	Center for Disease Control
CFR	Code of Federal Regulations
CRF /eCRF	Case report form / electronic Case Report Form
DMC	Data Monitoring Committee
FDA	Food and Drug Administration (of the US)
FLACC	Face, Legs, Activity, Cry, Consolability
FPS-R	Faces Pain Scale-Revised
HbA1c	Glycosylated hemoglobin
HCP	Healthcare provider
HSRRB	Human Patients Research Review Board
HRPO	Human Research Protection Office
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IMM	Independent Medical Monitor
IRB	Institutional Review Board
ITT	Intent to Treat
mITT	Modified Intent to Treat
N/A	Not applicable
NRPS	Numeric Rated Pain Scale
PI	Principal Investigator
POSAS	Patient and Observer Scar Assessment Scale
PP	Per Protocol
RES	Regenerative Epidermal Suspension
SAE	Serious adverse event
SAS	Statistical Analysis System
SSD	Silver Sulfadiazine
STMSG	Split-thickness Meshed Skin Graft
TBSA	Total body surface area
TEAE	Treatment emergent adverse event
UADE	Unanticipated (unexpected) adverse device event
US	United States

3.0 PRINCIPAL CONTACTS

Sponsor Contacts:	Elizabeth Kirshner Vice President, Clinical Research AVITA Medical Americas, LLC 28159 Avenue Stanford, Suite 220 Valencia, CA 91355 Telephone Number: 661-877-6869 Email: ekirshner@avitamedical.com Andrew Quick Chief Technology Officer AVITA Medical Americas, LLC 28159 Avenue Stanford, Suite 220 Valencia, CA 91355 Telephone Number: 661-367-9159 Email: aquick@avitamedical.com
Clinical Monitoring:	Avania 100 Crowley Drive, Suite 216 Marlborough, MA 01752
Data Management:	Avania 100 Crowley Drive, Suite 216 Marlborough, MA 01752
Centralized Image Review:	QuantifiCare 4020 Old Milton Parkway, Suite 210 Alpharetta, GA 30005
Quality of Life:	Colleen M. Ryan, MD, FACS Shriners Hospitals for Children 51 Blossom St Boston, MA 02114

4.0 INTRODUCTION

4.1 BACKGROUND

One of the leading causes of accidental home injuries in children is burns.[1] The 2016 National Burn Repository report from the American Burn Association indicates that 30% of burns from 2006 to 2015 occurred in pediatric patients (ages 1 – 15 years).[2] Because they have thinner skin, children burn more quickly and deeply at lower temperatures, putting young children especially at high risk for burn injury. Young children also may not perceive danger as readily, may have less control over their environment and may lack the ability to escape a life-threatening burn situation.[3, 4]

Management of burn injuries is based largely on assessment of depth, likelihood of healing within a timeframe associated with less chance of hypertrophic scarring, and availability of healthy donor skin for the harvesting of autografts. In deep partial-thickness and full-thickness injuries, surgical intervention, typically autografting is used to heal the wound to optimize outcome. However, the autograft donor site is frequently a source of morbidity and scarring. Superficial injuries, such as scalds, are often treated acutely (approximately 7 to 10 days) with conservative treatment including debridement and dressings. Since skin defects taking longer than 3 weeks to heal have a much higher rate of hypertrophic scar, it is usual that wounds initially treated conservatively that do not completely heal in 7 to 10 days, proceed to excision and autografting with the goal of achieving healing within the 3-week period.[5,] From the patient's perspective, ideally their second-degree burn will heal without conventional autografting, as surgical management for treatment of burns in smaller, younger patients represents a compromise, leaving a second-degree injury to heal with time increases likelihood of hypertrophic scarring. However, harvesting of donor skin required for conventional autografting creates the potential for autograft scar and donor site scar.

The RECELL® Autologous Cell Harvesting Device (RECELL), the device to be evaluated within this study, is an autograft-sparing technology intended to maximize the effective treatment area of a burn injury, while minimizing the amount of donor skin needed. The RECELL Device provides a novel but simple technique that enables a clinician to process a split-thickness skin sample to prepare autologous Regenerative Epidermal Suspension (RES®, also known as Spray-On Skin™ Cells suspension) for immediate application to the wound bed. The process involves use of enzymatic and mechanical disaggregation. The disaggregated skin cells are suspended in a Buffer solution for delivery to the wound. This technique allows for expansion of up to 80 times the area of split-thickness donor skin. The end effect is that the donor site defect is minimized while maximizing wound coverage.

The overall purpose of this study is to evaluate the safety and effectiveness of use of the RECELL Device for treatment of partial-thickness burns compared with conventional dressing in infants, children, and adolescents to aid healing of these injuries and potentially avoid the progression to conventional autografting. It is recognized that early surgical intervention with use of RECELL represents a paradigm shift in the care of partial-thickness burns, however, for infants and children, the minimal harvesting of skin for creation of skin cell suspension (typically a 2cm x 2cm skin sample) poses limited risk relative to the intended benefit of averting conventional autografting altogether. In addition to evaluating incidence of healing, the impact that use of RECELL may have on requirement for autografting, pain, scar, health-related quality of life and health economics will also be evaluated.

[1] http://www.hopkinsmedicine.org/healthlibrary/conditions/pediatrics/burns_in_children_90,P01887/ accessed on May 18, 2017.
[2] American Burn Association NBR Advisory Committee, National Burn Repository 2016 Report, http://www.ameriburn.org/2016ABAFull.pdf accessed on May 19, 2017.
[3] World Report on Child Injury Prevention, World Health Organization accessed at https://www.ncbi.nlm.nih.gov/books/NBK310640/ on May 19, 2017
[4] Preventing Injuries to Children by Residential Fires published by Safe Kids Worldwide at safekidscobbcounty.org/safety-tips/fire_tips.pdf accessed on May 19, 2017
[5] Chipp E, Charles L, Thomas C, Whiting K, Moiemen N, Wilson Y. A prospective study of time to healing and hypertrophic scarring in paediatric burns: every day counts. Burns & Trauma 2017; 5:3. Published online 2017 Jan 19.

4.2 RECELL (THE INVESTIGATIONAL DEVICE)/JUSTIFICATION FOR INVESTIGATION

The RECELL® Device (Figure 1) is provided sterile as a stand-alone, disposable (single use) unit that equips a healthcare provider with the necessary items to safely prepare RES from donor skin and to deliver the skin cell suspension to the burn injury. The device is designed for point-of-care use. The suspension of primarily single, viable cells is a mixed population of predominantly keratinocytes and fibroblasts, with a small presence of melanocytes. Preparation of RES does not require culturing, amplification or expansion prior to application. Preparation of RES commences with availability of a harvested skin sample. Incubation in Enzyme is complete in 20-25 minutes, with the mechanical scraping and filtering of each skin sample taking 5-10 minutes, which fits within the typical time required for wound bed preparation (See Figure 1 for RECELL Process Overview). As such, RECELL application integrates well with the current standard practices for autografting.

Figure 1. RECELL Device

The disaggregated skin cells are suspended in a Buffer solution for delivery to the wound (Figure 2.).

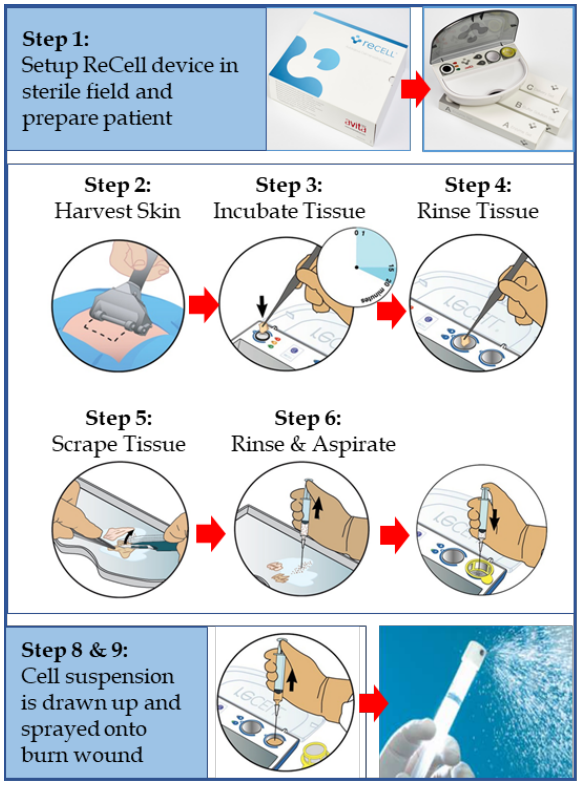


Figure 2. RECELL Process Overview

Safety and effectiveness of the RECELL Device in the treatment of acute partial-thickness burn injuries in adults have been evaluated in a prospective randomized **study (results presented below in 4.3.2).**

4.3 PRIOR INVESTIGATIONS AND MARKET EXPERIENCE

The safety of RECELL has been demonstrated with greater than 8,500 treatment procedures conducted worldwide. RECELL has Conformité Européenne (CE) Marking in Europe, Therapeutic Goods Administration (TGA) clearance in Australia, RECELL has been marketed in China and Canada, as well as other markets (e.g., Taiwan, Hong Kong, Mexico, Brazil and Venezuela). Also, RECELL has secured FDA PMA approval (BP170122) for the treatment of acute thermal burn wounds in patients 18 years or older. There have been no reports of adverse events associated with the use of RECELL that have met the requirements for safety vigilance reporting to regulatory authorities.

A study performed by Wood et al, the use of RECELL and a biosynthetic dressing (Biobrane) was compared to standard treatment (dressings every 2–3 days with conventional autograft surgery 10–14 days after the injury). [6] A total of 13 children were included and followed up over 6 months; 5 received RECELL with Biobrane, 4 received Biobrane alone and 4 received standard treatment. At 10 days after the initial burn, none of the patients in the RECELL plus Biobrane group were assessed as requiring autografting; 1 patient in the Biobrane group required autografting, and 3 out of 4 patients in the standard treatment group required autografting. The median time to complete healing for RECELL group was similar to the time for the Biobrane group and the median time was longer in the standard treatment group (median [interquartile range] 16.0 [11.5–18.0], 16.0 [14.25–23.0] and 36.5 [18.5–47.7] days respectively; no statistical analysis provided). The patients treated with RECELL plus Biobrane showed a higher proportion of wound area healing at both 10 and 21 days after the burn (95% and 100% respectively) compared with Biobrane alone (83.2% and 97.7%) or with standard treatment (71.2% and 90.1%).

Furthermore, the RECELL Device has been evaluated within 2 controlled clinical trials sponsored by AVITA Medical Americas evaluating the use of the device for treatment of burn wounds. Summaries of the 2 studies are presented below.

4.3.1 Demonstration of the Safety and Effectiveness of RECELL combined with Meshed Skin Graft for Reduction of Donor Area in the Treatment of Acute Burn Injuries (Mixed Depth Burns-Protocol CTP001-6)

Within protocol CTP001-6, RECELL was evaluated as a treatment for acute mixed-depth burn injuries. The study was designed to demonstrate the safety and effectiveness of the RECELL® device combined with meshed skin graft for reduction of donor area. This was a prospective, randomized, multicenter, evaluator blinded, within patient-controlled study where 30 patients were treated at 7 investigational sites in the U.S. There were no device-related treatment emergent adverse events reported. RECELL treatment was non-inferior to control treatment (conventional autografting) for the healing of burn injuries, required significantly less donor skin area to cover the same-sized treatment area, and was similar to control treatment in terms of patient satisfaction, scar outcome, and safety profile.

Results of this study demonstrated non-inferiority of RECELL relative to control for recipient site healing using the pre-specified non-inferiority margin of 10%. Confirmed treatment area closure by Week 8 was 92.3% for RECELL vs. 84.6% for the control treatment areas. The treatment difference was -7.7% (1-sided 97.5% CI upper bound of 9.55%). The progression of healing was similar between treatments, with both RECELL and control treatments achieving 100% re-epithelialization for approximately 50% and 80% of treatment areas at Week 4 and Week 6, respectively. Superiority of RECELL was established with respect to relative reduction in donor site harvesting ($p<0.001$). The mean donor site areas for RECELL and control were 270.5 ± 123.7 cm^2 and 368.0 ± 150.1 cm^2, respectively. Despite the more widely meshed autograft and use of less skin, the long-term outcomes with RECELL were no different than control. There was no statistically significant difference between treatments observed for the secondary effectiveness endpoints (patient satisfaction, Week 24 blinded observer overall opinion on POSAS, and Week 24 patient overall opinion on POSAS). Furthermore, there was no statistically significant treatment difference for these endpoints at any study visit. No unanticipated adverse device effects or device-related events were reported. The number of subjects with any treatment-emergent adverse event (TEAE) at the RECELL treatment site was the same as the number of subjects with any TEAE at the control treatment area (17/30, 56.7%). Most subjects experienced TEAEs that were mild (26.7%) or moderate (36.7%). There was no statistically significant difference ($p>0.05$) between RECELL and control in the incidence of TEAEs at the treatment area (impaired healing, pain, graft loss, skin abrasion,

[6] Wood F, Martin L, Lewis D, Rawlins J, McWilliams T, Burrow S, Rea S. A prospective randomized clinical pilot study to compare the effectiveness of Biobrane® synthetic wound dressing, with or without autologous cell suspension, to the local standard treatment regimen in paediatric scald injuries. Burns 2012; 38:830-839.

and skin graft failure). The most common TEAE at both the RECELL and control treatment areas was pruritus experienced by 7 (23.3%) subjects. One or more severe TEAE was experienced by 7 (23.3%) subjects; however, no TEAE was considered related to the RECELL Device. Twelve subjects had SAEs and one died as a result of the SAEs (acute respiratory distress syndrome and subarachnoid hemorrhage, both of which were severe and not related to the study device). There was no difference in the incidence and types of SAEs at the RECELL and control treatment areas.

Results of the CTP001-6 study provide favorable evidence for the RECELL Device as an autograft-sparing technology indicated for use at the patient's point-of care for preparation of an autologous skin cell suspension to be applied to a prepared wound bed.

4.3.2 A Comparative Study of RECELL Device and Autologous Split-thickness Meshed Skin Graft in the Treatment of Acute Burn Injuries (Deep Partial-Thickness Burns Protocol - CTP001-5)

The safety and effectiveness of the RECELL Device for coverage of deep partial-thickness burn wounds was investigated within an adult population. This was a prospective, randomized, within patient-controlled study that enrolled 101 subjects with second-degree thermal burn injuries. Subjects were enrolled at 12 U.S. clinical sites. The clinical performance of the RECELL Device was compared with that of conventional split-thickness meshed skin graft (STMSG). The study was overseen by the U.S. Army Medical Research and Materiel Command (USAMRMC) via the Office of Research Protection (ORP) and the Human Research Protection Office (HRPO) or Human Patients Research Review Board (HSRRB).

Within the primary analysis population (per protocol population, PP), at Week 4, 94.3% of the RECELL recipient sites achieved healing vs. 100% of the control recipient sites. Although comparable numbers were achieved, the primary endpoint of non-inferiority of RECELL relative to control for recipient site healing was not established using the pre-specified non-inferiority margin of -10% (RECELL-Control; difference -5.7%, 95% CI: -12.8%, -0.4%). At Week 4, mean percent epithelialization of the recipient site was 97.7 ± 12.0% and 100.0 ± 0.07%, for the RECELL and control recipient sites, respectively (p=0.0761). The failure to demonstrate non-inferiority was attributed to the lack of explicit wound care instructions for RECELL grafts and the resulting use of cytotoxic medication (e.g., silver sulfadiazine) which interferes with epithelialization. When evaluating a defined Modified PP population (MPP) (*post-hoc* analysis) excluding the subjects managed with silver sulfadiazine at Week 4, only 1 subject did not achieve wound healing in the RECELL group (98.8%) and the difference in proportions between the RECELL and control recipient areas was -2.4% (95% CI: -8.4 to 2.3%). The MPP analysis provides evidence that if RECELL-treated sites are properly dressed and protected, healing is non-inferior to those sites treated with meshed autografts. Donor site healing was superior at Week 1 for the RECELL donor sites versus the control donor sites (p = 0.0042). Subjects reported less pain at the RECELL donor site compared to the control donor site within the 8 weeks following treatment ($p \leq 0.0005$ at each interval). Similarly, subjects expressed significantly greater satisfaction with the visual appearance of the RECELL donor site compared with the control donor site at all longer-term follow-up visits ($p \leq 0.005$ at each interval). The mean donor site size for burn injuries randomized to RECELL treatment was significantly less than that of the control: 4.7 ± 3.19 cm^2 vs 194.1 ± 158.5 cm^2 ($p<0.0001$).

Results from this study demonstrate the use of the RECELL Device appears to be safe and well tolerated. With proper aftercare, use of RECELL results in non-inferior wound healing to standard of care. Moreover, RECELL treatment has smaller skin harvesting requirements (forty-fold less than standard technique), and is associated with less donor site pain, superior donor site healing, and improved appearance of healed donor sites.[7]

[7] Holmes, J.H., Molnar, J.A., Carter, J.E., Hwang, J., Cairns, B.A., King, B.T., Smith, D.J., Cruse, C.W., Foster, K.N., Peck, M.D. and Sood, R., 2018. A Comparative Study of the ReCell® Device and Autologous Spit-thickness Meshed Skin Graft in the Treatment of Acute Burn Injuries. *Journal of Burn Care & Research*.

4.4 INTENDED USE OF THE INVESTIGATIONAL DEVICE (PROPOSED INDICATION)

The proposed indication for use for the RECELL Device is as follows:

The RECELL Device is indicated for treatment of partial-thickness burns in patients 1 year of age or greater.

4.5 STUDY DESIGN

This is a prospective, parallel-arm, randomized (1:1), blinded evaluator, multicenter trial to demonstrate that RECELL treatment of partial-thickness burn injuries can safely and effectively increase the incidence of Day 10 healing post-treatment compared with a standardized, conventional wound dressing, i.e., Mepilex® Ag Wound Dressing (Mölnlycke Health Care). The effects of both treatments on healing, the incidence of conventional autografting, pain, itching, scar outcomes, investigator treatment preference and health economics. Additionally, longer-term disease-specific health-related quality of life will be evaluated.

Infants, children, and adolescents (aged from 1 through 16 years), male and female, with a burn injury of no more than 30% of their total body surface area (TBSA) where no more than 10% TBSA represents a full-thickness burn injury will be considered for participation in this study. Enrollment of 160 subjects is planned. A Data Monitoring Committee will be responsible for interim review of safety data and will be responsible for reviewing data from the sample size re-estimation analysis.

The study will be conducted in the United States following Institutional Review Board (IRB) approval. Written informed consent will be obtained prior to conducting any study-related procedures. Only patients who can be consented, randomized and treated within 72 hours of their burn injury may participate in this study. Each subject will participate in approximately 10 to 15 assessments/visits (depending on rate of healing or if conventional autografting is required) over a period of 12 months. Enrollment of 160 (80/treatment group) is planned at up to 18 institutions. All subjects will be followed for 52 weeks post-treatment.

4.5.1 Control of Bias

The following aspects of study design will minimize bias:

- The study design is a parallel arm, prospectively controlled study.
- Subjects will be randomly allocated to treatment assignment AFTER initial wound cleaning to prevent selection bias.
- The primary endpoint of Day 10 healing will be assessed by a Blinded Evaluator (burn specialist blinded to treatment assignment).
- The requirement for autografting will be verified via centralized review by an Independent Medical Monitor (IMM) without knowledge of the investigators' decision, participating institution, subject or post-treatment time interval.
- The study design utilizes multiple investigators/institutions.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 STUDY OBJECTIVES

The primary objective of this study is to demonstrate that RECELL treatment of partial-thickness burn injuries can safely and effectively increase the incidence of Day 10 healing compared with a standardized wound dressing. Also, the effects of both treatments on the incidence of conventional autografting, pain, itching, and scarring will be investigated for the Index Burn while health-related quality of life and resource utilization will be investigated for the patient as a whole.

5.2 STUDY ENDPOINTS (EFFECTIVENESS AND SAFETY)

5.2.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is incidence of Index Burns with Day 10 healing, post-treatment, evaluated by an observer blinded to treatment allocation, with confirmation at Day 28. Healing is clinically-evaluated wound closure, i.e., skin re-epithelialization without drainage or dressing requirements for healing. Note that *protective* dressings are advised after initial healing with RECELL treatment while the newly healed skin matures (RECELL Instructions for Use, PMA 170122). If the Index Burn undergoes a secondary surgical treatment for closure (including conventional autografting) prior to the Day 28 visit, this will be considered an endpoint failure.

The hypothesis to be evaluated is whether the incidence of Day 10 healing post-treatment (confirmed at Day 28) is greater (superior) with RECELL treatment vs. Control treatment. Post-treatment in the Investigational Treatment Group is defined as post-RECELL treatment and in the Control Treatment Group is post baseline photos and (re)placement of Mepilex Ag.

5.2.2 Secondary Effectiveness Endpoints

Secondary endpoints to be investigated for potential labeling claims include the following four hypotheses:

1. Incidence of healing of the Index Burn wound on or before Day 21 post-treatment (confirmed on Day 28). The hypothesis to be evaluated is that the incidence of Day 21 healing will be superior in the RECELL treatment group.
2. Percent area of Index Burn requiring autografting. The hypothesis being evaluated is that the percent area of the Index Burn requiring autografting will be less in the RECELL treatment group.
3. Incidence of conventional autografting to achieve Index Burn healing. The hypothesis being evaluated is that subjects in the RECELL group will less frequently require conventional autografting.

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.

5.2.3 Tertiary Endpoints/Additional Data Collection

Other endpoints/data collection:

1. Absolute area (cm^2) of Index Burn requiring autografting.
2. Index Burn pain scores at dressing changes assessed by the health care provider performing the dressing change using the Face, Legs, Activity, Cry, Consolability (FLACC) scale.
3. Subject reported Index Burn pain scores at dressing changes.
4. Percent epithelialization of the Index Burn per digital planimetry.
5. Index Burn POSAS scar ratings.
6. BOQ Outcomes (raw scores and recovery curves for all domains), with baseline at Day 10.
7. Investigator treatment preference
8. Health economics/medical resource utilization (determined using CRF data in conjunction with UB-04/CMS-1500 and/or similar hospital and physician claim forms for billing purposes to collect data associated with the initial hospital care and readmissions during follow-up as applicable).
9. Index Burn Itch Man Scale ratings.

5.2.4 Safety

Safety of the RECELL Device will be based on the evaluation of the incidence of treatment-related and serious device-related adverse events (AEs). AEs will be documented for both the Index and Non-Index Burn as well as donor sites. For all AEs, the investigator must provide an assessment of the event, treatment resolution, and relationship to the investigational device. See also Section 8.2.

6.0 SELECTION OF SUBJECTS

6.1 PRE-RANDOMIZATION ELIGIBILITY CRITERIA

6.1.1 Inclusion Criteria

Subjects must meet all the following pre-randomization criteria to be eligible for participation in the study:

1. Male or female patients aged 1 through 16 years (inclusive) with a partial-thickness thermal burn injury.
2. The patient has a thermal burn injury that is:
    a. ≤ 30% TBSA (exclusive of superficial areas) and
    b. ≤ 10% TBSA is a full-thickness burn.
3. The Index Burn must be a clean partial-thickness burn injury ≥160 cm^2 and between 2-20% BSA (inclusive).
4. The Index Burn may not cover the face, hand, foot or the perineum/genitalia (Note: a patient with wounds in these areas may be enrolled but the Index Burn Area may not include these areas).
5. The patient and/or parent/guardian agrees to comply with all compulsory study procedures and visit schedule.
6. The patient and/or parent/guardian agrees to abstain from any other treatment for closure of the Index Burn for the duration of the study unless medically necessary.
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. 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,
    b. Understand instruction, and
    c. Provide voluntary informed written consent/assent as appropriate for study participation.

6.1.2 Exclusion Criteria

Subjects who meet any of the following pre-randomization criteria are not eligible for participation in the study:

1. Not able to understand English or Spanish.
2. Burns caused by chemicals, electricity or radiation.
3. Patients presenting with only 3rd-degree/full-thickness wounds which require immediate autografting.
4. Burn injury has had prior treatment for definitive closure.
5. Patients for whom use of sedation/general anesthesia is not medically appropriate.
6. Superficial/trivial burns or burns that in the investigator's opinion appear to be healing sufficiently such that care under this protocol would be inappropriate.
7. Patient requires immediate or staged surgical procedures for closure of their partial-thickness burns.
8. Conditions, e.g., previous burn injury to study area, poor nutritional status, poorly controlled diabetes mellitus (HbA1c >9%), that in the investigator's opinion may compromise subject safety or trial objectives.
9. Current use of medications, e.g., immunosuppressive agents (excluding inhaled corticosteroids), that in the investigator's opinion may compromise subject safety or trial objectives.
10. Inhalation injury.
11. Active infection, cellulitis or need for immediate grafting at the planned treatment areas.
12. Concerns for parent/guardian's ability to provide appropriate follow-up care.
13. Subjects with a known hypersensitivity to trypsin or compound sodium lactate for irrigation solution.
14. Subjects with a known sensitivity to silver.
15. In post-pubescent girls, pregnant or breast-feeding (pregnancy test should be performed in accordance with local institutional requirements).
16. Immediate life-threatening condition or life expectancy less than one year.
17. Previous randomization within this investigation.

6.2 POST-RANDOMIZATION ELIGIBILITY CRITERIA

Consented subjects who do not meet the post-randomization eligibility criteria and did not receive study treatment will be followed through the Day 28 visit and then withdrawn from the study. The criteria for which exclusion was based will be documented.

6.2.1 Post-Randomization Inclusion Criteria

1. Patient randomized (and will be treated) within 72 hours from the time of the burn injury.
2. Patient continues to meet all pre-randomization inclusion criteria.

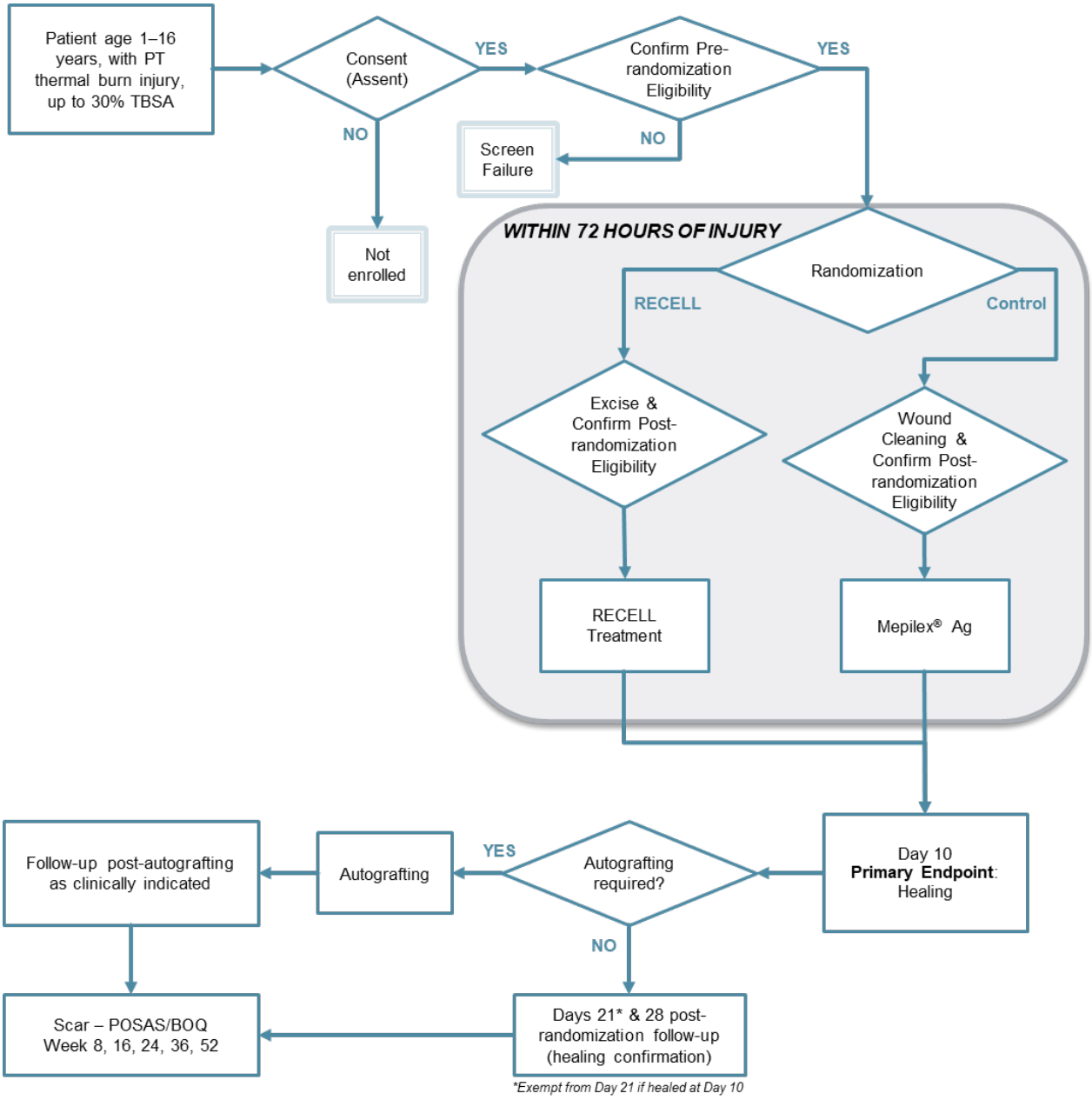
6.2.2 Post-Randomization Exclusion Criteria

1. Incidental finding of any pre-randomization exclusion criteria.

7.0 STUDY PROCEDURES

Study procedures are standardized to the extent possible and are summarized in Table 1and Figure 3.

Figure 3. Study Flow



7.1 INVESTIGATOR TRAINING

Investigators treating burn injuries will be board-certified surgeons. Investigators will be trained in the use of the RECELL Device by an AVITA Medical representative. All study staff and providers participating in the care of subjects will be provided with instruction concerning appropriate post-operative care. In some cases, it will be the responsibility of the investigators to ensure proper education and training of those involved with the follow-up care of their subjects. Aftercare Guidelines will be provided for the subjects and/or parents/guardians. The AVITA Medical representative will evaluate the investigator's skill in processing skin samples with the RECELL Device. RECELL Devices may not be used until investigator training is satisfactorily completed. Investigators with prior training and experience with the RECELL Device may be waived from this requirement.

7.2 SCREENING AND ENROLLMENT

Prior to enrollment in the study, subjects will be evaluated to determine potential eligibility. The parent/guardian of subjects who meet all eligibility criteria and none of exclusion criteria will be asked to sign the study-specific Institutional Review Board approved Informed Consent Form (ICF) and subjects may be asked to sign the ICF or Assent Form, as applicable, before any study-specific procedures are conducted. The sample ICF is provided as Appendix B.

A subject is considered enrolled once written informed consent has been obtained. If a subject is determined to be ineligible following consent signing but prior to randomization, the subject will be considered a screen failure. The reason for the screen failure will be documented. Standard care for treatment and follow-up should ensue. Only subjects who are randomized will be included in the analysis populations.

The following screening assessments are to be performed.

- Eligibility Assessment: Evaluation of compliance with pre-randomization inclusion and exclusion criteria
- Demography and medical history information
- Injury etiology/history including documentation of any prior treatments used on the partial-thickness burn wounds
- Complete physical examination including weight, height, vital signs and Fitzpatrick skin type
- Record all medications taken within 7 days prior to the screening visit

Prior to randomization, initial wound care may be performed in accordance with local standard practice (e.g., wound cleaning, dressings).

7.3 STUDY TREATMENT

A targeted physical assessment is to be performed and any changes in the subjects' physical parameters/health status from the screening assessment shall be documented. The subjects' vital signs and ASA Physical Classification score are to be recorded.

7.3.1 Burn Wound Cleaning

Burn wounds are to be cleaned in accordance with standard medical practices at the institution. This may be performed on initial admission per local practice or prior to randomization.

7.3.2 Index Burn Selection

The Index Burn (the area that will be evaluated for primary effectiveness outcomes) is to be identified in accordance with the pre-randomization inclusion/exclusion criteria. If a subject has multiple partial-thickness burns meeting the eligibility criteria, the largest partial-thickness burn will be designated as the Index Burn. The Index Burn must be at minimum 160 cm^2 and is to be a contiguous area excluding the face, hand, foot and genitalia, in order to minimize parameters that may confound healing and other outcomes.

A description of the anatomical location and size of all burns, including the Index Burn and any Non-Index burn(s), will be documented in the medical record of each subject.

7.3.3 Point of Randomization

Following wound cleaning per local standard practices, pre-randomization inclusion/exclusion criteria will be confirmed to ensure the subject continues to be eligible for the study. If the subject remains eligible, the subject will be randomized (1:1) to either RECELL or to Control (Mepilex® Ag). Randomization will be stratified by investigational site and total burn area (<10% TBSA and ≥10% TBSA).

The Index Burn will be digitally photographed using standardized digital photography following randomization (post-wound cleaning).

Unless clinical circumstances dictate otherwise, all of the subject's partial-thickness burn wounds, including any non-index burn(s), should be treated at the initial procedure according to the randomized treatment assignment. Subjects randomized to RECELL will have their partial-thickness burn wounds treated in accordance with the procedures outlined in Section 7.4 and subjects randomized to Control will have their partial-thickness burn wounds dressed in accordance with Section 7.5.

Before proceeding with assigned study treatment, the post-randomization inclusion/exclusion criteria must be confirmed. Any subject determined not to meet the post-randomization eligibility criteria *prior* to treatment will be followed through Day 28 and then withdrawn from the study.

7.4 RECELL TREATMENT

7.4.1 Wound Bed Preparation

Under monitored anesthesia care (MAC) or general anesthesia, burn injury areas are to be excised in accordance with standard medical practices at the institution to remove non-viable tissue.

7.4.2 Skin Sample Acquisition and Processing

With the subject in a suitable position allowing for easy access to both the RECELL skin sample donor site and the Index Burn, a sterile field will be established. The skin sample(s) to be harvested are to be clean and show no evidence of surrounding cellulitis or infection. Skin samples for processing with the RECELL Device will be harvested with the harvesting tool set between 0.006" and 0.008" (inclusive). The skin sample (Index Burn donor site) should provide adequate coverage for the Index Burn, any other partial-thickness treatment areas (Non-Index Burn(s)), and the RECELL Index Burn donor site(s).

The RECELL Index Burn donor site(s) will be digitally photographed post-harvest.

Please refer to the RECELL Instructions for Use. In summary, 1 ml of RES physically covers a treatment area of 80 cm^2. Each milliliter of cell suspension contains cells harvested from a square centimeter of a thin, split-thickness skin sample. Treatment area sizes and cell suspension volumes are to be recorded. The method for harvest, harvesting tool setting, size, and anatomic location of the donor sites will also be recorded. The reagents and components of the RECELL Device are used, in a scalable fashion, to facilitate disaggregation of cells from skin samples into filtered cell suspension.

7.4.3 RES Application

Before proceeding with the application of RES, ensure that the prepared primary and secondary dressings are ready for immediate application. Apply the Telfa™ Clear wound dressing to the inferior margin of the wound. Attach the spray nozzle supplied with the RECELL Device to the syringe containing the cell suspension using firm pressure. Check that the aperture of the attached spray nozzle faces the wound. Invert the syringe several times prior to application to ensure an even suspension. Hold the spray applicator approximately 10 cm from the most elevated point of the wound surface and apply moderate pressure to the plunger of the syringe. Start spraying at the most elevated part of the wound so that any run-off helps to cover the more dependent areas of the wound. One application of a fine mist of cells should be delivered to the entire wound. To cover the area, carefully move the spray applicator in one continuous motion

from one side of the wound to the other as you spray. Alternative methods of dripping the suspension are also described in detail in the RECELL Instructions for Use.

Complete coverage (wetting with RES) of the wound is essential. If there is insufficient RES to cover the area, another skin sample is to be taken and the process repeated to create additional RES.

RES is to be applied to the Index Burn, any other partial-thickness burn areas (Non-Index Burn) and may also be applied to the RECELL Index Burn donor site at the investigator's discretion.

Any full-thickness area (Non-Index Burn) should be treated with conventional autografting and RECELL. RES should also be applied to donor sites.

After RECELL treatment, treated areas are to be covered with Telfa™ Clear wound dressing (primary) and with a secondary dressing of Xeroform™ Occlusive Petrolatum Gauze (Covidien) placed over the primary dressing. Additional padding of gauze and a crepe bandage will be placed over the Xeroform for added protection.

The dressing should overlap the wound bed by at least 2 cm onto the surrounding skin.

Treatment details for all treated areas and donor sites in addition to the dressing regimen for the Index Burn will be documented and collected in the eCRF.

7.5 CONTROL TREATMENT

Apply the Mepilex® Ag dressing (primary) in accordance with the institution's standard procedures and consistent with the manufacturer's instructions. The dressing is to be applied with the adherent side to the partial-thickness injury. When used on an extremity, position Mepilex® Ag slightly below the center of the wound to avoid leakage caused by gravitation. When necessary, Mepilex® Ag may be fixated with a bandage or other fixation.

Mepilex® Ag is to be applied to the Index Burn and any other partial-thickness burn areas (Non-Index Burn). This use will be documented within the eCRF.

Any full-thickness area (Non-Index Burn) should be treated with conventional autografting (without RECELL).

The dressing should overlap the wound bed by at least 2 cm onto the surrounding skin. Treatment details for all treated areas and donor sites, if applicable, will be documented and collected in the eCRF.

7.6 POST-TREATMENT CARE

Personnel responsible for performing dressing changes must be skilled in atraumatic pediatric dressing changes. Care must be taken to not disrupt new skin.

Subjects should be seen for dressing changes as clinically indicated.

It is important that the wound sites not be exposed to shear forces in the immediate post-op period as this may disrupt healing. Careful positioning of the subject may be required to avoid wound trauma. Use of supports or splints for stabilization should be used as appropriate.

7.6.1 RECELL-Treated Areas

For all Index Burns, Non-Index Burns (partial- and full-thickness), and donor sites treated with RECELL, the Telfa™ Clear (primary dressing) should remain in place and is not to be manipulated unless medically appropriate, until the dressing releases from the wound due to underlying epithelialization. On Day 10, any Telfa™ Clear dressing remaining on a RECELL-treated area should be removed. It is essential that any dressing not easily removed be soaked in aqueous or oil-based solutions to prevent trauma upon removal.

7.6.2 Control-Treated Areas

For all Index Burns, Non-Index Burns (partial- and full-thickness), and donor sites the Mepilex® Ag (primary dressing) may be left in place for up to 7 days or as indicated by accepted clinical practice, dependent on the exudate, condition of the wound and surrounding skin, per manufacturer's instructions.

Index Burns randomized to Control should have the Mepilex® Ag dressing gently lifted and/or changed, as clinically appropriate, to assess healing.

7.6.3 Prohibited Medication and Dressing

Post-treatment use of silver sulfadiazine (SSD) is prohibited, regardless of treatment assignment. Application of SSD *prior to* study treatment is acceptable.

Following initiation of study treatment, topical antibiotics are not to be used **proactively or prophylactically on the Index Burn**.

Additionally, silver-impregnated dressings are not to be used proactively or prophylactically on an Index Burn treated with RECELL. However, containment of infection within large treatment areas is crucial. Secondary dressings are to be replaced with silver-impregnated dressings (e.g., Acticoat, Smith & Nephew) over any malodorous or moist areas. Microbiological assessment of suspicious areas should be conducted. If the infection is microbiologically confirmed or worsens, the affected area should be debrided and treated topically. If the malodorous or moist area resolves, silver-impregnated dressings should be replaced with dressings that do not contain silver.

7.6.4 Instructions for All Treated Areas

Important Note: All healed areas are to be protected for a minimum of two weeks after closure, using light hydrophobic compression garments/sleeves or dry gauze and elastic bandaging (e.g., ACE™). Dressings used for protection at this stage of care are not to be considered 'dressings required for healing' as referenced by the primary endpoint definition. It is mandatory that the treated areas be protected such that the areas will not be subjected to secondary trauma. During this time, avoid vigorous cleansing or excessive application of topical creams, so as not to damage the newly formed skin.

Subjects and parent/guardians should be instructed that the treatment areas may be relatively fragile and require approximately 2 weeks (following closure) to mature. Rigorous cleansing and rigorous application of topical creams or lotions may cause damage to new skin and should be avoided. Appropriate measures, such as continued use of a secondary dressing, changed as appropriate (to prevent the dressing from drying and adhering) should be used until the treatment area has approximately 2 weeks (following closure) to mature.

Thereafter, aftercare should be consistent with the standard of care for the clinical site. All therapies related to wound healing will be documented and collected within the eCRF.

If blistering is present, a dry dressing should NOT be used. If the blisters rupture, exudate will dry and bond the dry dressing to the newly healed area. Removal of the dressing may result in removal of the new skin.

Following healing and wound maturation, moisturizer can be applied as required and sunscreen should be used on exposed treatment areas and donor site areas (if applicable) to prevent hyperpigmentation.

A copy of the Aftercare Instructions (Appendix C) is to be provided to the subject or their parent/guardian.

7.7 FOLLOW-UP ASSESSMENTS/VISITS

Subjects should be instructed to immediately contact the clinical site with any dressing issues, questions, or concerns during the healing period.

Subjects returning outside of the visit window for their scheduled visit will have their information collected according to the protocol and recorded within the eCRFs. These visits will be documented as protocol deviations and taken into consideration during the data analysis. Subjects may return for visits other than the study schedule above, and these will be recorded as unscheduled visits.

At all follow-up visits, the subject or parent/guardian will be asked to list any medications pertaining to pain, itching, and/or wound healing (i.e., antibiotics, steroids, topical wound treatments, etc.) taken and/or concomitant procedures and/or therapies performed since the last visit.

The investigator or other designated study personnel will ascertain whether the subject has experienced any reportable adverse events since the last visit. All treatment-related and serious adverse events will be documented regardless of their relationship to the RECELL Device. Photography, healing assessments, documentation of pain, itching and completion of study questionnaires will be performed as shown in Table 1. Photographs should be taken of the Index Burn, Non-Index Burn, and/or Index Burn Donor Site when there is a treatment-related adverse event.

7.7.1 Acute Follow-Up Visits

Day 10, Day 21 (if not healed by Day 10), and Day 28 post-treatment, the Index Burn will be evaluated via direct visualization by a qualified local clinical investigator blinded to treatment allocation (Blinded Evaluator) to assess Index Burn healing, unless the Index Burn has been autografted.

Blinded evaluators must have a minimum of 2 years clinical experience in assessing and treating acute burn wounds. Prior to the healing assessment by the Blinded Evaluator, subjects will be draped so that only the Index Burn to be evaluated is available to view.

An unscheduled visit will be documented for subjects seen at timepoints other than Days 10, 21 and 28. If a subject is seen prior to Day 10 and the Index Burn is healed per the Blinded Evaluator's assessment, the subject is not required to return on Day 10, assuming all Day 10 protocol required assessments were completed. If the Index Burn is healed on or before Day 10, the subject is not required to return on Day 21.

Subjects with Index Burn healing on or before Day 10 will return on Day 28. The Day 28 visit serves as the healing confirmation for Day 10 and Day 21.

Subjects not healed by Day 10 will return on Day 21 and may return more frequently at the discretion of the investigator. Index Burns should be assessed for healing at all scheduled and unscheduled visits.

The Day 28 visit should be conducted, unless the Index Burn was autografted, regardless of healing status on Day 10.

Index Burn dressing changes are to be performed *prior to* any other dressing changes.

At each acute follow-up visit the following will be performed, unless otherwise indicated:

- Body temperature
- Photography of Index Burn and RECELL Index Burn donor site, as applicable
- Index Burn healing evaluation by investigator and Blinded Evaluator
- Assessment of requirement for conventional autografting at Index Burn by investigator
- Assessment of Index Burn pain before and during dressing change (as applicable) by subject or parent/guardian and health care professional*
- Assessment of Index Burn itch severity by subject or parent/guardian*
- Index Burn dressing type(s) and frequency of changes since prior visit (if applicable)*
- Burn Outcome Questionnaire (Day 10 and 28 only)*
- Concomitant medications (including medication for pain and/or itching), therapies and procedures related to wound healing
- Treatment-related adverse events (including photography of any involved burn injury area or donor site)
- Any serious adverse events whether related to study treatment or not

*Not required for subjects who were randomized and did not receive study treatment.

7.7.2 Longer-Term Follow-Up Visits

The following procedures will be performed, or information collected during the Weeks 8, 16, 24, 36 and 52 post-treatment visits. (see also Table 1 Study Visits/Procedures). At each visit the following will be performed, unless otherwise indicated.

- Vital signs
- Targeted physical assessment
- Index Burn healing assessment by investigator
- Photography of Index Burn
- Photography of total burn injury (all areas) at Week 52
- Index Burn POSAS Scar assessment (subject or parent/guardian and Blinded Evaluator) at Weeks 16, 24, 36 and 52
- Burn Outcome Questionnaire at Weeks 16, 24, 36 and 52
- Concomitant medications (including medication for pain and/or itching), therapies and procedures related to wound healing
- Treatment-related adverse events (including photography of any involved burn injury area or donor site)
- Any serious adverse events whether related to study treatment or not

During the longer-term follow-up visits, the preferred method is in-person clinical visits, however (if necessary), these follow-up visits may be conducted remotely (e.g., via telemedicine) with the exception of the Week 52 visit.

Investigator treatment preference will be documented for each treating investigator, at each burn center, following the investigator's last subject's last visit. Refer to Section 7.8.6.

7.7.3 Conventional Autografting Procedure (if clinically necessary)

During acute follow-up visits, the investigator will evaluate the Index Burn to determine the requirement for autografting. Autografting is typically indicated when there are no signs of improvement or healing, when the investigator expects no further wound healing in the next 7 to 11 days, or when a contiguous area greater than 0.5% TBSA is unhealed.

Unless medically necessary, autografting should not be performed until after 9 days post-burn to provide sufficient time for healing to occur (autografting prior to this time point will be considered a major protocol deviation). Conversely, autografting when deemed necessary, ideally should be performed no later than approximately 3 weeks from the initial burn injury to lower the risk of hypertrophic scarring which has been shown to increase when epithelialization is delayed beyond 3 weeks[5].

Autografting will be performed, and wounds will be dressed in accordance with the investigator's standard practices. Additionally, if the subject was randomized to the RECELL group, RECELL may be used with conventional autografting based on the investigator's discretion. The following data are to be collected before or during the conventional autografting procedure of the Index Burn:

- Vital signs
- Targeted physical assessment
- Burn excision/preparation for autografting
- Pre-excision, post-excision, and post-autografting photography of Index Burn
- Autograft treatment details (e.g., location and amount of donor skin harvested, mesh expansion, area autografted (in cm^2))
- Index Burn dressing
- Index Burn donor site photography
- Concomitant medications (including medication for pain and/or itching), therapies and procedures related to wound healing
- Treatment-related adverse events (including photography of any involved burn injury area or donor site)
- Any serious adverse events whether related to study treatment or not

Note: As the requirement for autografting is considered an endpoint outcome and/or anticipated event and will be appropriately documented within the eCRFs, the initial autografting procedure for the Index Burn and/or Non-Index is NOT to be documented as an AE or SAE.

7.7.3.1 Post-Autografting Follow-up

For subjects who undergo conventional autografting, post-operative follow-up visits will be performed as clinically indicated.

The following procedures will be performed, or information collected during the post-autografting assessments (see also Table 1. Study Visits/Procedures).

- Body temperature
- Photography of Index Burn and Index Burn autograft donor site
- Index Burn healing assessment by investigator
- Assessment of Index Burn pain before and during dressing change (as applicable) by subject or parent/guardian and health care professional
- Assessment of Index Burn itch severity by subject or parent/guardian
- Index Burn dressing type(s) and frequency of changes since prior visit (if applicable)
- Concomitant medications (including medication for pain and/or itching), therapies and procedures related to wound healing
- Treatment-related adverse events (including photography of any involved burn injury area or donor site)
- Any serious adverse events whether related to study treatment or not

Note: Additional surgical intervention required for definitive closure of conventionally autografted Index Burns is to be documented as an AE and/or SAE.

7.8 STUDY ASSESSMENTS

7.8.1 Index Burn Healing and Requirement for Autografting

7.8.1.1 Index Burn Healing Assessment by Investigator and Blinded Evaluator

Index Burn healing will be evaluated via direct visualization by the investigator at each study visit and by the Blinded Evaluator on or before Day 10, Day 21 (if not healed by Day 10), and Day 28 post-treatment.

The healing assessment will be captured categorically as follows:

- Healed – skin re-epithelialization without drainage or dressing requirements for healing
- Not healed – presence of drainage and/or dressings required for healing

7.8.1.2 Percent Re-epithelialization of the Index Burn via Photographic Planimetry

At all follow-up visits the Index Burn will be photographically documented using standardized digital imaging. From these images, a third-party vendor (Quantificare Inc.) will independently document percent re-epithelialization of the Index Burn via photographic planimetry. Planimetry will only be performed on photographs taken using standardized photography equipment.

A random selection of de-identified digital tracings from the third-party vendor (Quantificare Inc.) will be reviewed by an IMM to confirm the percent re-epithelialization reported.

Assessment of healing via digital imaging and quantitative photogrammetry has been established to be a reliable method for wound area assessment in the acute pediatric burn setting and offers benefits over paper tracings as it is

rapid (does not require the child to remain still during manual mapping of the wound) and is non-contacting and therefore avoids the potential for disturbing or contaminating the wound.[8,9]

7.8.1.3 Centralized Review for Requirement for Conventional Autografting

De-identified photographic images of the Index Burn will be reviewed by an IMM to corroborate the requirement for autografting. The IMM will be blinded to treatment allocation, timing photo was taken related to treatment, and the investigator's decision to autograft or not. Acute follow-up images of Index Burns, including images taken the day the investigator made the decision to autograft will be presented, out of time sequence, to the independent burn specialist to review. Each image will be scored as "no autograft required" or "autograft required". For each image, the original burn injury area will be referenced so that the IMM has a reference for the original burn geometry during the review.

7.8.2 Pain Assessments at Index Burn

7.8.2.1 Subject (or Parent/Guardian) Pain Prior to and During Dressing Changes at Index Burn

Pain scoring at the Index Burn will be documented prior to and during each dressing change until dressings are no longer required for the Index Burn. Index Burn dressing changes are to be performed *prior to* any other dressing changes.

The pain score acquired prior to the dressing change is intended to characterize baseline pain associated with the Index Burn and to the extent practical is to be acquired prior to analgesia administration for the dressing change. Immediately after the Index Burn dressing change, the subject (or parent/guardian) will be asked to rate maximum pain felt during that dressing change and is intended to characterize pain associated with the dressing change.

Pain will be assessed using either the Faces Pain Scale-Revised (FPS-R) or the Numeric Rated Pain Scale (NRPS). The FPS-R scale may be used with children ≥5 years of age (at the time of consent), the NRPS may be used for children >7 years of age (at the time of consent) or by a parent/guardian when a child of any age is unable to self-report. The pain scale initially used by the child or parent/guardian should continue to be used through the duration of the study.

The FPS-R and Numeric Rated Pain Scales, both well accepted and validated measurement tools for pain assessment are provided in Appendix A. The FPS-R is recommended for use with younger children in parallel with numerical self-rating scales (0-to-10) for older children. [10]

7.8.2.2 Health Care Provider Pain During Dressing Changes at Index Burn

Pain scores during dressing changes will be assessed by the health care provider performing dressing changes until dressings are no longer required for the Index Burn. This assessment will be documented using the Face, Legs, Activity, Cry, Consolability (FLACC) scale.[11] This scale has been demonstrated to be a reliable and valid tool for assessing pain in critically ill patients and specifically pediatric patients. Immediately after the Index Burn dressing change, the health care provider will document the maximum pain during that dressing change. Categorical and total score should be reported.

7.8.3 Index Burn Itch Assessments

Itching severity at the Index Burn will be documented using the Itch Man Scale. The Itch Man Scale was developed by the Shriners Hospital for Children and has been demonstrated to be a reliable and valid tool to assess itching in pediatric burn patients[12] and should be transferrable to other injuries requiring autografting. The Itch Man Scale is provided in Appendix A.

---

[8]Stockton KA, McMillan CM, Storey KJ, David MC, Kimble RM. 3D photography is as accurate as digital planimetry tracing in determining burn wound area. Burns 2015; 41:80-4.

[9]Gee Kee EL, Kimble RM, Stockton KA. 3D photography is a reliable burn wound area assessment tool compared to digital planimetry in very young children. Burns 2015; 4:1286-90.

[10] Hicks, Carrie L., et al. The Faces Pain Scale–Revised: toward a common metric in pediatric pain measurement. Pain 2001; 93:173-183.

[11] Voepel-Lewis, Terri, et al. "Reliability and validity of the face, legs, activity, cry, consolability behavioral tool in assessing acute pain in critically ill patients." *American Journal of Critical Care* 19.1 (2010): 55-61.

[12] Morris, Vershanna, et al. "Itch assessment scale for the pediatric burn survivor." *J Burn Care Res* 33.3 (2012): 419-424.

Assessments will be performed until dressings are no longer required for the Index Burn. Itch assessments are to be performed prior to the Index Burn dressing change. The Itch Man Scale provides a 5-point Likert scale rating of the intensity of itching with 0 representing no itching and 4 demonstrating an immense amount of itching and distractibility. Subjects will be asked to describe the severity of their itch; children younger than 8 years will be assessed via parental/guardian response.

7.8.4 Burn Outcome Questionnaire

Disease-specific health-related quality of life will be investigated via application of the American Burn Association's Children's Burn Outcome Questionnaire (BOQ). The Children's BOQ is the only burn-specific patient-reported outcome measure validated for the pediatric patient population.

For the purposes of this study, the BOQ will be presented in 3 versions, administered based on the age of the subject at the time of consent (Questionnaires presented in Appendix A):

- BOQ_{0-4} to be administered to the parent/guardian for subjects up to 5 years of age
- BOQ_{5-18}: to be administered to the parent/guardian for subject ages 5 through 16
- BOQ_{11-18}: to be completed by the subject themselves for subject ages 11 through 16.

The BOQs may be read to the subject or parent/legal guardian by the investigator, be self-administered or completed by the parent or legal guardian of the subject. Completion time is approximately 20 minutes for each. These questionnaires are reliable and valid assessment tools with internal consistency reliability of the domains ranging from 0.74 to 0.94 across all questionnaires.[13,14,15,16] The questionnaires have shown sensitivity to change over time in burn outcomes.

The domains measured by the BOQ are outlined in Table 2. Each domain is standardized so that the mean (standard deviation) is 50 (10) for the non-burned control population. The English and Spanish versions have demonstrated credible psychometric properties.[11,21]

Table 2. BOQ Domains

BOQ 0-4	**BOQ 5-18, BOQ 11-18**
Play	Upper extremity function
Language	Physical function and sports
Fine motor	Transfers and mobility
Gross motor	Pain
Behavior	Itch
Family	Appearance
Pain	Compliance
Appearance	Satisfaction with current state
Satisfaction	Emotional health
Worry	Family disruption
	Parental concern
	School reentry

[13] Kazis LE, Liang MH, Lee A, Ren XS, Phillips CB, Hinson M, et al. The development, validation, and testing of a health outcomes burn questionnaire for infants and children 5 years of age and younger: American Burn Association/ Shriners Hospitals for Children. J Burn Care Rehabil 2002; 23:196–207.
[14] Daltroy LH, Liang MH, Phillips CB, Daugherty MB, Hinson M, Jenkins M, et al. American Burn Association/Shriners Hospitals for Children burn outcomes questionnaire: construction and psychometric properties. J Burn Care Rehabil 2000;21(1 Pt 1):29–39.
[15] Meyer 3rd WJ, Lee AF, Kazis LE, Li NC, Sheridan RL, Herndon DN, et al. Adolescent survivors of burn injuries and their parents' perceptions of recovery outcomes: do they agree or disagree? J Trauma Acute Care Surg 2012;73(3 (Suppl 2)): S213–20.
[16] Ryan, CM. The burn outcome questionnaires: Patient and family reported outcome metrics for children of all ages. Burns 2016:42:1144 – 1145.

7.8.5 Scar Assessment

The standard and comprehensive[17] Patient and Observer Scar Assessment Scale (POSAS)[18] will be employed in this study, as a standard tool for capturing both a burn healthcare professional and patient assessment of the scar post-treatment.[19] Because burn injury survivors wear the evidence of their injury every day, it has been asserted that meaningful assessment of burn scars should include patient ratings.'[20]

The POSAS consists of two multi-item numeric rating scales, an observer scale and a patient scale. The Observer Scale is devised with items based on literature review and the developers' clinical experience: 'vascularization', 'pigmentation', 'thickness', 'relief', and 'pliability', rated on a 10-point numeric scale, with 'normal skin' and 'worst scar' used as end-anchor labels. The items on the Patient scale directly correspond to these except with regard to scar color. Individual items for both scales are summed with higher scores representing poorer scars and lower scores representing scars more closely resembling normal skin. Both scales have demonstrated acceptable internal consistency (Cronbach's alpha 0.76 (patient) and 0.69 (observer scale)), suggesting that individual items for each scale can be reliably summed to generate a total score. Inter-observer reliability for the Observer scale has been demonstrated to be slightly superior to another commonly employed scar assessment tool (i.e., the Vancouver Scar Scale or VSS) when a single observer rated the scar (ICC 0.73 for Observer scale vs. ICC 0.69 for the VSS). Evidence of validity of this scar assessment tool was provided by demonstrating concurrent validity of the Observer scale with the VSS ($r=0.89$, $p < 0.001$).[21]

The POSAS is presented in **APPENDIX A**. The observer component of the POSAS will be performed by a Blinded Evaluator; i.e., blinded to treatment assignment.

7.8.6 Investigator Treatment Preference

Investigator(s) at each institution will be requested to respond to the following question based on the subjects they treated and followed throughout the study. Their response will be collected after each treating investigator's last subject last visit is performed.

- In consideration of your overall experience and subject outcomes with each treatment modality, which treatment did you prefer, RECELL or the standardized wound dressing?

7.9 HEALTH ECONOMICS

UB-04/CMS-1500 forms and/or hospital and physician claim forms used for billing purposes will be obtained from the clinical sites and processed by the staff of IQVIA, a consulting firm specializing in health economic outcomes. Data will be extracted from billing codes and/or procedure codes for all hospital care from the time of initial hospital admission through discharge. When available, costs resulting from readmissions during the follow-up period will also be collected, along with number of readmissions. These data may be supplemented via medical resource utilization data collected within the main clinical database of the study. All information will be kept confidential and will be used exclusively for the study purpose. All records will be de-identified with each individual's records labeled only with the assigned subject study identification number.

Publications will not include any confidential or personal identifying data.

[17] Vercelli S, Ferriero G, Sartorio F, Stissi V and Franchignoni F. (2009) How to assess postsurgical scars: A review of outcome measures. *Disability Rehab*, 31(25), 2055-2063.

[18] Draaijers LJ, Tempelman FRH, Botman YAM, Tuinebreijer WE, Middelkoop E, Kreis RW and van Zuijlen PPM. (2004) The Patient and Observer Scar Assessment Scale: a reliable and feasible tool for scar evaluation. *Plas Reconstr Surg*, 113(7), 1960-1965.

[19] Idriss N, Maibach HI. (2009). Scar assessment scales: a dermatologic overview. *Skin Res Technol*, 15(1), 1-5.

[20] Martin D, Umraw N, Gomez M, Cartotto R. (2003). Changes in subjective vs objective burn scar assessment over time: does the patient agree with what we think? *J Burn Care Rehabil*, 24: 239-244.

[21] Durani P, McGrouther DA, Ferguson MWJ. (2009). Current scales for assessing human scarring: a review. J Plast Reconstr Aesthet Surg, 2009;62:713-720.

7.10 UNSCHEDULED VISITS

Unscheduled visits may be performed at any time for evaluation for possible treatment-related or serious adverse events or to address any questions or concerns expressed by the subject or parent/guardian that cannot be adequately managed by telephone or e-mail communication. These visits are to be documented on the eCRFs as Unscheduled Visits.

8.0 RISK ANALYSIS

8.1 ANTICIPATED RISKS

Potential risks to the subject from participation in this study include the following risks associated with grafting procedures and burn treatment. These risks are generally associated with burn treatment and may not be specific to the study treatments.

- Systemic anesthetic complications and/or general procedural complications (including but not limited to: allergic reactions to anesthetic medications; cardiovascular complications such as hypotension or hypertension; pulmonary complications; gastrointestinal complications such as constipation, nausea and vomiting; embolism, or complications associated with urinary catheterization)
- Excessive bleeding at graft or donor areas that may result in anemia or require transfusion
- Infection at donor site or treatment area which may manifest as fever and chills
- Graft rejection/graft loss
- Pruritus
- Hypertrophic scar
- Hyperpigmented scar
- Scar contracture
- Folliculitis
- Granulation tissue
- New injury or shearing to graft or donor areas
- Blisters on graft or donor areas
- Hematoma, seroma or edema at graft or donor areas
- Neuralgia (nerve pain) at graft or donor areas
- Pain at graft or donor areas
- Additional surgical and/or medical intervention to achieve treatment area closure

In addition to the above noted risks, risks associated with exposure to the RECELL Device include:

- Hypersensitivity to trypsin or compound sodium lactate for irrigation
- Viral transfer from animal-derived trypsin enzyme
- Infection/Inflammation
- Pruritus
- Rejection/Graft loss
- Blistering
- No or minimal epithelialization due to improper processing, cell suspension application, inadequate cell suspension volume resulting in delayed or inadequate healing
- Worsened scar (hypertrophic or hyperpigmented scar)
- Granulation
- Inability to prepare cell suspension requiring additional donor skin for processing
- Additional surgical and/or medical intervention to achieve treatment area closure

Furthermore, precautions associated with the use of Mepilex® Ag Wound Dressing (Mölnlycke Health Care) include:

- Sensitivity to silver

The risks described above will be minimized via the selection of physicians that have experience performing skin grafting procedures as part of acute burn management and have been appropriately trained in the use of the RECELL Device and application of RES. Subjects will be adequately screened to ensure that those with conditions and/or

comorbidities that put them at a higher risk for procedural complications are excluded. Subject treatment and follow-up will be performed consistent with current medical best practices. Furthermore, risks will be minimized by requiring subjects to report for routine clinic visits allowing for prospective diagnosis of potential procedure related complications. Subjects will be given instructions on whom to contact if they have questions regarding their medical care or experience health-related problems.

Appropriate therapeutic intervention following medical best practices will be used in the event of medical complications.

8.2 ADVERSE EVENTS

8.2.1 Adverse Events Reporting and Evaluation

All treatment-related and serious adverse events occurring during the course of the clinical study whether related to the investigational device or otherwise, will be recorded on the AE eCRF. Collection of adverse events will commence post-randomization. SAEs will be followed until resolved or until they have stabilized in the event of study closure. Non-serious AEs will be followed until the subject completes the study. For all AEs, the investigator must provide an assessment of the event, treatment resolution, and relationship to the investigational device.

8.2.2 Identification of Adverse Events (AEs), Adverse Device Effects (ADEs)

An adverse event is defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it is considered related to the investigational device by the investigator.

8.2.3 Treatment-Related Adverse Event

A treatment-related adverse event is an adverse event that is judged to be related to the investigational device, study therapy or study-related procedures. Treatment-related AEs will be captured at both Index and Non-Index Burns.

8.2.4 Anticipated (Expected) Adverse Device Events

Potential adverse events that a subject may experience following use of the RECELL Autologous Cell Harvesting Device are discussed in Section 8.1.

8.2.5 Definitions of Specific Treatment-Related Adverse Events

8.2.5.1 Infection

The presence of infection at study treatment areas/or donor sites will be evaluated at each postoperative visit. Infection will be evaluated in accordance with the Center for Disease Control (CDC) guidelines for nosocomial infections using standard clinical measures such as visual examination of the treatment sites for delayed healing, redness, inflammation and surrounding cellulitis. Specifically, infection will be categorized as follows:

- Uninfected: Wound lacking purulence or any manifestations of inflammation
  - Mild: Presence of ≥2 manifestations of inflammation (purulence, or erythema, pain, tenderness, warmth, or induration), but any cellulitis/erythema present extends ≤2cm around the wound, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness
  - Moderate: Infection (as above) in a subject who is systemically well and metabolically stable but who has ≥1 of the following characteristics: cellulitis extending >2cm around the wound, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, or involvement of muscle, tendon, joint or bone
  - Severe: Infection in a subject with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)

In the presence of signs of infection (i.e., purulent exudate, changes in wound appearance such as hyperemia, and erythema in the uninjured skin surrounding the wound), it is preferred that infection be confirmed using microbiological testing procedures and reported within the eCRF. Treatment is to be initiated according to the institutions' infection management protocols, which will be recorded on the applicable eCRF.

Infection will be managed according to the standard protocols of the clinical site. For example, treatment of infection may involve the daily cleaning and dressing of wound sites until such time that the infection is clear. Treatment with broad-spectrum antibiotics until microbiology sensitivities return from the testing laboratory is recommended. Upon return of sensitivities, antibiotic therapy may either continue as is, or be changed at the discretion of the investigator. All treatment regimens applied in the management of infection will be recorded on the eCRF.

8.2.5.2 Allergic Response to Trypsin

The allergic response to trypsin (the enzyme used in the RECELL Device for disaggregation of the skin sample) will be evaluated preoperatively and at every postoperative visit. An allergic response to trypsin is most likely to present as contact dermatitis (defined as an altered state of skin reaction induced by exposure to an external agent)[22]. Substances that produce this condition after single or multiple exposures may be irritating or allergenic in nature and induce an inflammatory response. The most common clinical expression of this induced inflammation is dermatitis (eczema).

Assessment for known or prior allergic response will be performed preoperatively by the investigator and is considered an exclusion criterion. Postoperatively, allergic reaction will be evaluated by assessing for eczema (dermatitis). In the event eczema is observed by the Investigator the subject will be required to answer more questions regarding assessment of eczema onset, progression, remissions, work situation, other possible exposure mediums, as well as a family and medical history. A physical examination will be performed, and a diagnostic skin patch test will be conducted. The standard skin patch test will be used where trypsin will be applied under controlled conditions and the skin will be evaluated over time for allergic response. Outcomes of the testing will be documented on the Adverse Event eCRF and study report.

The incidence of adverse response to trypsin is expected to be low.

8.2.5.3 Scars Requiring Subsequent Surgical Intervention

Scars requiring surgical revision will be considered a treatment-related adverse event and should be reported as serious if the event meets the criteria outlined in Section 7.2.8. Rate and severity of scars requiring surgical intervention will be compared for RECELL versus Control for the purposes of evaluating safety. Scar procedures for functional issues will be counted separately from scar procedures solely for cosmesis.

The incidence of scars requiring subsequent surgical intervention is expected to be low.

8.2.6 Relationship of Adverse Events to the RECELL Investigational Device

The investigator should assess the relationship of the adverse event to the investigational device. The relationship should be assessed using the following categories:

- **Not Related**: The adverse event is definitely not associated with the investigational device/treatment.
- **Unlikely Related:** A direct cause and effect relationship between the investigational device/treatment and the adverse event is improbable, but not impossible.
- **Possibly Related:** A direct cause and effect relationship between the investigational device/treatment and the adverse event has not clearly been demonstrated but is possible or very possible.
- **Related:** A direct cause and effect relationship between the investigational device/treatment and the adverse event exists.

[22] Drake, Lynn A., et al. Guidelines of care for contact dermatitis. Journal of the American Academy of Dermatology 1995; 2:109-113.

8.2.7 Unanticipated Adverse Device Effects (UADEs)

An unanticipated adverse device effect is defined as "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 supplementary application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

If an unanticipated adverse device effect occurs, the investigator must promptly notify AVITA Medical of such an event within 24 hours of first learning of the event. The investigator must promptly notify its reviewing IRB of such an event as soon as possible, but no later than ten (10) working days after first learning of the event. AVITA Medical will conduct an evaluation of the unanticipated adverse device effect and will report the results to FDA and to all reviewing IRBs and participating investigators within 10 working days after AVITA Medical first receives notice of the effect.

8.2.8 Serious Adverse Events (SAEs)

Each adverse event should be assessed for its seriousness using the criteria outlined below. The term serious adverse event is not synonymous with a "severe" adverse event, which may be used to describe the intensity of an event experienced by the subject.

An adverse event should be classified as an SAE if it meets any of the following criteria:

- Results in, or contributes to, a death
- Life-threatening (i.e., the subject was, in the opinion of the investigator, at risk of death at the time of the event, but it does not include an event that, had it occurred in a more severe form, might have caused death)
- Results in permanent disability or incapacity (i.e., permanent impairment of a body function or permanent damage to a body structure)
- Requires subject hospitalization or prolongs hospitalization
- Necessitates medical or surgical intervention to preclude a permanent disability or incapacity
- Results in a congenital anomaly or birth defect

Non-serious adverse events are all events that do not meet the criteria for a "serious" adverse event. Unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and all subject deaths must be promptly reported (preferably within 24 hours but in no event later than 48 hours) to AVITA Medical.

8.2.9 Severity

Each treatment-related adverse event should be assessed for its severity, or the intensity of an event experienced by the subject, using the following.

Mild: Discomfort noticed, but no disruption to daily activity.

Moderate: Discomfort sufficient to reduce or affect normal daily activity.

Severe: Inability to work or perform normal daily activity.

8.2.10 Deaths

The investigator must notify AVITA Medical as soon as possible, preferably within 24 hours but in no event later than 48 hours, of learning of a subject's death, regardless of whether the death is related or unrelated to the investigational device. The investigator should attempt to determine, as conclusively as possible, whether the death is related to the device.

8.2.11 Pre-existing conditions

Pre-existing conditions should not be reported as adverse events unless there has been a substantial increase in the severity or frequency of the problem which has not been attributed to natural history.

8.2.12 Eliciting and Reporting Adverse Events

The investigator will assess subjects for the occurrence of treatment-related adverse events (AEs) at each study visit. To avoid bias subjects should be asked the following non-leading question: "How have you felt since your last visit?" All treatment-related adverse events (serious and non-serious) and all serious adverse events reported by the subject through the 52-week follow-up must be recorded on the source documentation and eCRFs.

9.0 STATISTICAL CONSIDERATIONS

9.1 GENERAL

Data collected in this study will be reported using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, quartiles, standard deviation [SD], minimum, and maximum). Categorical variables will be summarized using frequencies and percentages of subjects in each category. All results will be presented by treatment and appropriate subject populations. All statistical tests will be performed as a one-sided 0.025 level of significance unless otherwise specified below. SAS software version 9.4 or higher will be used for the statistical analysis.

Data listings will be presented sorted by subject number and treatment. All data will be included in the data listings.

Study days will be calculated relative to the date of initial study treatment (i.e., Day 0 is the date of receipt of study treatment).

9.2 ANALYSIS SETS

9.2.1 Safety Analysis Set

The safety analysis population includes all randomized, treated subjects. This is the primary analysis set for safety. Subjects will be analyzed for safety based on the treatment received.

9.2.2 Populations for Analysis

Intent to Treat (ITT) Population: The ITT population will consist of all enrolled subjects who are randomized, with data analyzed according to randomized treatment assignment.

Modified Intent to Treat (mITT) Population: The mITT population will consist of all enrolled subjects who are randomized and treated, with data analyzed according to randomized treatment assignment. This population will be utilized as a primary analysis population for the primary and secondary effectiveness endpoints.

Per Protocol (PP) Population: The PP population will consist of mITT 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 and secondary effectiveness endpoints.

The following are considered major protocol deviations and will exclude a subject from the PP population:

- No endpoint data
- Conventional autografting prior to 10 days post burn
- Inclusionary/exclusionary deviations
- Missing Index Burn healing closure confirmation
- Other significant protocol non-compliance that may confound evaluation of healing (e.g., use of prohibited medications/treatments, inappropriate primary dressing, etc.). Subjects with such non-compliance will be determined prior to database lock and unblinding.

9.3 PRIMARY EFFECTIVENESS VARIABLE AND STATISTICAL HYPOTHESES

The primary effectiveness endpoint is incidence of Index Burns with Day 10 healing, evaluated by an observer blinded to treatment allocation, with confirmation at Day 28. If the Index Burn undergoes a secondary surgical treatment for closure (including conventional autografting) prior to the Day 28 visit, this will be considered an endpoint failure.

The hypothesis to be evaluated is whether the incidence of Day 10 healing post-treatment (confirmed at Day 28 post-treatment) is greater (superior) with RECELL treatment vs. Control treatment. The null and alternative hypotheses to be tested at a one-sided 0.02496 level of significance are:

$$H0: PR \leq PC \text{ vs. } H1: PR > PC$$

where P_R and P_C are the primary endpoint rates for RECELL and control, respectively. The null hypothesis will be tested using a one-sided z-test of proportions at a one-sided 0.02496 level of significance. Additionally, two-sided 95.008% confidence intervals will be presented for the difference between treatments.

9.4 IMPUTATION METHODS

All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. Since effectiveness endpoints are assessed acutely 10- and 28-days following treatment, it is anticipated that there will be minimal missing data. In the case of missing data for a scheduled visit, if there is an unscheduled visit within the respective scheduled visit range, the data from the unscheduled visit will be used for analysis. Note: Data from an unscheduled visit will not replace data that is provided for the scheduled visit.

The primary effectiveness endpoint analysis will be on the mITT population, with secondary analysis on the PP population. In the mITT population, subjects may have missing information on healing, primarily due to premature withdrawal from the study. The analyses performed on the mITT population with available data will be considered primary. However, as sensitivity analyses, the primary endpoint analysis will be repeated on the entire mITT population, where missing data for the components of the primary endpoint will be imputed as outlined directly below; there will be no imputation for other endpoints in the study.

Subjects who are missing healing status will be considered as "missing data subjects". Missing healing status will be imputed using a logistic regression multiple imputation approach for dichotomous outcome data. In this approach, missing healing status will be imputed from logistic regression models with independent variables of age, gender, and other variables to be specified in the formal statistical analysis plan. This will be performed 50 times in order to generate 50 "complete" datasets. The one-sided z-test of proportions assessing treatment difference will be carried out on each of the 50 complete datasets, with the results being combined across the 50 complete datasets using standard multiple imputation theory to obtain one overall p-value comparing the two treatments on the primary endpoint after accounting for missing data.

9.5 SECONDARY EFFECTIVENESS VARIABLES AND STATISTICAL HYPOTHESES

Specific secondary endpoints to be investigated for potential labeling claims include the following:

1. Incidence of Index Burn Day 21 healing (confirmed on Day 28). This variable will be tested in the same manner as the primary effectiveness variable as described in Section 8.3.

2. Percent area of Index Burn requiring autografting. The hypothesis being evaluated is that the percent area of the Index Burn requiring autografting will be less in the RECELL treatment group. The null and alternative hypotheses of interest are:

   $$H_0: \mu_R \geq \mu_C \text{ vs. } H_0: \mu_R < \mu_C$$

   where μ_R and μ_C are the mean percent area of the Index Burn requiring autografting for RECELL and control, respectively. The null hypothesis will be tested using a Wilcoxon Rank Sum test at a one-sided 0.025 level of

significance, due to the anticipated skewness of the data resulting from most patients not requiring autografting.

3. Incidence of conventional autografting to achieve Index Burn healing: The null and alternative hypotheses to be tested at a one-sided 0.025 level of significance are:

$$H_0: AG_R \geq AG_C \text{ vs. } H_1: AG_R \leq AG_C$$

where AG_R and AG_C are the autograft rates for RECELL and control, respectively. The null hypothesis will be tested using the one-sided z-test for proportions at a one-sided 0.025 level of significance.

The three endpoints listed above will be tested one at a time in a fixed hierarchical method in the order given above. The first endpoint will be compared between treatments at a one-sided 0.025 level of significance. If the null hypothesis is rejected, then RECELL will be considered statistically superior to control on incidence of healing at Day 21 and treatment comparison analysis will proceed to the 2nd secondary hypothesis. This process will continue to the 3rd secondary hypothesis as long as the prior hypothesis is rejected at a one-sided 0.025 level of significance. These secondary endpoints/hypotheses will only be evaluated if the null hypothesis for the primary endpoint is rejected.

Analyses will be carried out for the mITT (primary) and PP (secondary) populations. There will be no imputation of missing data for these secondary endpoints.

9.6 TERTIARY ENDPOINTS

Other exploratory endpoints/data collection (not for labeling):

1. Absolute area (cm^2) of Index Burn requiring autografting
2. Index Burn Pain scores at dressing changes assessed by the health care provider performing the dressing change using the Face, Legs, Activity, Cry, Consolability (FLACC) scale.
3. Subject reported Index Burn pain scores at dressing changes.
4. Percent epithelialization of the Index burn per digital planimetry.
5. Index Burn POSAS Scar Ratings
6. BOQ Outcomes (raw scores and recovery curves for all domains), with baseline at Day 10.
7. Investigator treatment preference
8. Health economics/medical resource utilization
9. Index Burn Itch Man Scale ratings.

The percent epithelialization of the Index burn per digital planimetry will be compared between treatments using a Cochran-Armitage test for trend.

For autografted Index Burns, the total area requiring autografting will be compared between treatments using an independent two-sample t test.

Mean Index Burn pain scores at dressing changes as assessed by the health care provider and by the subject will be compared between treatments over time. For the analysis, subjects will contribute pain scores collected from time of treatment through healing, i.e., subjects will contribute multiple observations per subject. Treatment groups will be compared on average pain scores over time using a generalized estimating equation (GEE) analysis of variance. The study day in which the pain score was assessed will be included in the model as a continuous covariate. The within-subject correlation matrix on pain scores will be assumed to be unstructured; if there are issues with convergence, then it will be assumed to be exchangeable. Mean POSAS, BOQ and Itch Man Scale rating outcomes will also be compared between treatment in a similar manner.

All statistical tests comparing treatments will use a one-sided 0.025 level of significance (there will be no adjustment for multiple comparisons due to the tertiary nature of the analysis). There will be no imputation of missing data. These tertiary analyses will be carried out on the mITT and PP populations.

For health economics, the number and cost of resources (e.g., procedures, etc.) will be summarized by treatment group for the primary admission, and for any hospital readmissions if relevant. Additional details for analysis of health economics will be addressed in the Health Economics Statistical Analysis Plan.

9.7 DETERMINATION OF SAMPLE SIZE

Based on medical input, the estimated proportion of subjects with confirmed day 10 healing is anticipated to be approximately 75% for the Control group. It is estimated that the proportion of RECELL subjects with confirmed day 10 healing will be 92.5%. Assuming power of 80%, using a one-sided z-test of proportions and one-sided alpha of 0.025 requires 69 subjects per group (138 subjects total). The total sample size has been increased by 12% to 160 subjects to adjust for missing data.

9.8 INTERIM ANALYSIS / SAMPLE SIZE RE-ESTIMATION

A formal unblinded interim analysis comparing treatments on the primary endpoint will be conducted once 50% of total enrollment has completed the primary effectiveness endpoint follow-up (i.e., 80 subjects have been randomized and reached the Day 28 healing confirmatory visit or would have reached the Day 28 visit had they not prematurely withdrawn). An independent biostatistician who is unrelated to the day-to-day conduct of the study will conduct this unblinded interim analysis and report results to the Data Monitoring Committee (DMC).

The unblinded interim analysis will be based on O'Brien-Fleming stopping rules. At the interim look, the one-sided p-value will need to be less than or equal to 0.00153 with results favoring RECELL in order to stop the study for reasons of overwhelming effectiveness of RECELL; the one-sided p-value will need to exceed 0.45604 to stop the study for futility. The one-sided p-value at the final analysis needs to be less than or equal to 0.02496, rather than the usual 0.025 required for a study without an interim analysis. This interim analysis will be based on patients with available primary endpoint data; there will be with no imputation of missing data at this interim analysis.

If the criterion for early stopping is not met, a conditional power calculation and 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 (to a maximum of 300 randomized subjects) 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%).

Specifically, at the DMC meeting to review the interim effectiveness analysis, the following will take place:

- DMC will inspect the p-values calculated for stopping the trial for overwhelming effectiveness or futility and make a formal recommendation to continue or discontinue the trial as appropriate.

- If the criterion for early stopping is not met, DMC will inspect the conditional power for achieving a successful trial for the current protocol-specified sample size under the assumption that the observed interim treatment effect size is the true treatment effect size.

- If the conditional power for a beneficial RECELL effect under the protocol-specified sample size is between 38% and 80% (the promising zone), the DMC may recommend an increase of the sample size to maintain conditional power of 80%. As discussed in Mehta and Pocock (2011)[23] such a sample size increase will not require a penalty to the final significance level. The maximum sample size increase will be to increase the randomized sample size of 160 subjects to 300 subjects.

- If the conditional power under the protocol-specified sample size is <38% or if it is greater than 80%, then the final sample size will remain as is specified in the protocol.

[23] Mehta CR and Pocock SJ. Adaptive Increase in Sample Size when Interim Results are Promising: A Practical Guide with Examples. Statistics in Medicine 2011; 30:3267-3284.

This analysis will be performed on the mITT population with imputation for missing data first being carried out using the multiple imputation method described in Section 8.4 above (the multiple imputed z-statistic will be used in the calculation of conditional power). The results of the sample size re-estimation, regardless of outcome, will be summarized and reported to the FDA.

9.9 COVARIATES

The potential effects of covariates on the primary effectiveness endpoint will be evaluated using multivariate logistic regression. Covariates will include, but not necessarily limited to: randomized treatment group, anatomical location of burn, % TBSA, % BSA of Index Burn, % BSA of full-thickness burns, age, gender, race, ethnicity, Fitzpatrick skin type, diabetes, smoking, nutritional status, time from initial injury to initiation of study treatment in days, time from initial injury to presentation for definitive burn care in days, and inclusion of joint within Index Burn.

9.10 POOLABILITY ANALYSIS

A poolability analysis will be performed to assess homogeneity of treatment difference on the primary endpoint across investigative sites. If there are less than 8 subjects in the population from an investigative site, the data from that site will be pooled with data from other investigative sites closest to it geographically. Pooling will be determined before the treatment blind is broken and prior to inspecting the outcome data.

The following will be carried out on the mITT and PP populations (available data): Assessment of homogeneity of treatment difference on the primary endpoint will be carried out using logistic regression with treatment, investigative site, and treatment-by-investigative site interaction as the independent variables. Of interest is the significance of the treatment-by-investigative site interaction.

If the treatment-by-investigative site interaction effect is significant at a 0.10 level of significance, then analyses within investigative site will be further inspected. If the interaction is not significant or if it is significant but the direction of the effect is the same in all investigative sites, then investigative sites will be pooled for the final analysis. Otherwise, demographics within site will be inspected to assess if differences in site demographics may be causing the interaction.

There will be no imputation of missing primary outcome data for the poolability analysis.

9.11 SUBGROUP ANALYSES

The analyses comparing treatments on the primary endpoint will be carried out within the following subgroups for the mITT (imputed and available data) and PP populations: anatomical location of burn, % TBSA (below median vs. above median), % BSA of study burn area (below median vs. above median), age (by subgroups; i.e., infants: age 1 to <2 years; children: (≥ 2 years to < 12 years) and adolescent: ≥ 12 years to ≤ 16 years, gender, race, ethnicity, Fitzpatrick skin type, diabetes, smoking, nutritional status, time from initial injury to initiation of study treatment in days (below median vs. above median), time from initial injury to presentation for definitive burn care in days (below median vs. above median), requirement for conventional autografting (yes/no). The purpose of within-subgroup analyses is not to show significant treatment difference within a subgroup, but to assess homogeneity of treatment difference across subgroups. Homogeneity across groupings will be assessed in a similar manner as the assessment of homogeneity across investigative site discussed above.

9.12 OTHER ANALYSES

9.12.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age, sex, weight, height, race, ethnicity, and Fitzpatrick skin type will be summarized for the mITT population by descriptive statistics by treatment group including the mean, median, standard deviation, quartiles, minimum, and maximum for continuous variables and frequencies and percentages for categorical variables.

In addition, relevant and other past/current medical history will be summarized by treatment group for the mITT study cohort.

9.12.2 Surgical Procedure Characteristics

Data concerning area of donor skin used for processing in the RECELL Device, graft size, thickness and location, treatment area, and RES application details (e.g., volume and details for application) will be documented on the eCRFs. Data will be summarized using appropriate descriptive statistics by treatment group for the mITT population.

For subjects undergoing conventional autografting, the amount of surface area autografted (expressed as a percent of the original burn area) will be compared between treatment groups using a two-sided two-sample t-test for the mITT population.

9.13 SAFETY ANALYSES

Safety data will be analyzed using all observed data from the safety population.

A treatment emergent adverse event (TEAE) is an event that began or worsened in severity after the randomized treatment is started. For each treatment group, the number and percentage of subjects with a TEAE will be presented by MedDRA preferred term, including but not limited to the preferred terms indicating infection, allergic reaction, pain, and scars requiring intervention. This analysis will be repeated for treatment and donor site specific serious TEAEs and for treatment and donor site specific TEAES leading to premature discontinuation from the study.

For TEAEs which cannot be attributed to the study treatment or donor site (e.g., headache), the number and percentage of patients with TEAEs, serious TEAEs, and TEAEs leading to premature discontinuation from the study will be presented by MedDRA system organ class and preferred term.

10.0 STUDY OVERSIGHT

10.1 INDEPENDENT MEDICAL MONITOR (IMM)

AVITA Medical will utilize an Independent Medical Monitor (IMM) who will have the responsibility for adjudication and review of the decision for autografting, a random selection of digital tracings, and minimally all serious adverse events. The IMM will be a board-certified burn surgeon. At any time during the course of the study, the IMM may offer opinions or make formal recommendations concerning aspects of the study impacting subject safety (e.g., safety related protocol modifications or input regarding complication rates associated with protocol treatments). An IMM charter will be established and outline the review and adjudication procedures.

10.2 DATA MONITORING COMMITTEE (DMC)

A Data Monitoring Committee (DMC) will be appointed by AVITA Medical. Members of the DMC will be independent of the study investigators and will include a statistician and at least 2 physicians with background and experience with caring for pediatric burn patients. The DMC will be responsible for interim review of adverse events observed in each study arm and will review data related to the conduct and quality of the study. The DMC may make formal recommendations for protocol changes to mitigate risk of adverse events. The DMC will also be responsible for reviewing data from sample size re-estimation analysis.

A DMC charter will be prepared prior to the initiation of the study.

10.2.1 Independent Statistician

An independent statistician will be appointed to interface between the study statistician responsible for routine study activities and the DMC. The independent statistician will be responsible for producing reports/analyses that inform the DMC.

11.0 MONITORING PROCEDURES

All investigators and investigational sites will be monitored on a continuing basis through the course of the clinical trial to oversee compliance with the regulatory and clinical aspects of the study. The clinical monitors (CMs) will maintain current personal knowledge of the study through observation, review of study records and source

documentation, and discussion of the study with the investigators and their staff. Regular reporting of monitoring activities will be provided to AVITA Medical by the CMs. CMs will be appropriately trained and qualified before undertaking any monitoring duties.

The AVITA Medical representative responsible for the monitoring of this study is:

Elizabeth Kirshner, VP, Clinical Research
AVITA Medical Americas, LLC
28159 Avenue Stanford, Suite 220
Valencia, CA 91355
Telephone Number: 661-877-6869
Email: ekirshner@avitamedical.com

12.0 INVESTIGATOR AGREEMENT

An investigator agreement will be signed by each site's principal investigator and a copy will be provided to AVITA Medical. A current *curriculum vita* for the principal investigator and key study personnel at each clinical site will also be provided to AVITA Medical.

13.0 SUBJECT DISCONTINUATION

All treated subjects will be followed for a minimum of 52 weeks (± 28 days) post-treatment. Acceptable reasons for not evaluating a subject through the follow-up period include:

a) Subject Lost to Follow-Up: Unable to locate subject despite documented attempts to notify the subject via three telephone calls and one registered letter. A subject will not be considered lost to follow up until the time of the last scheduled follow-up visit.
b) Subject (or Parent/Legal Guardian) Request to Withdraw: The subject (or parent/guardian) requests to terminate his/her involvement in the study. To the extent possible an exit interview should be conducted with the subject to assess the subject's specific reason(s) for study withdrawal. The treatment area healing status at the time of withdrawal is to be documented.
c) Subject Death: Every attempt should be made to document the cause of death. An autopsy report should be obtained if available.

14.0 REPORTS

Investigators are required to prepare and submit the following complete, accurate and timely reports. Reporting guidelines are outlined in **Table 3** Guidelines for Preparing and Submitting Reports.

Table 3. Guidelines for Preparing and Submitting Reports

Type of Report	Prepared by Investigator & Submitted to	Method	Time of Reporting
Serious Adverse Event (device-related or not)	Sponsor	Submit SAE CRF or email notification	Preferably within 24 hours of knowledge but in not later than 48 hours
	IRB	As required	As required
Death (device-related or not)	Sponsor	Submit SAE CRF or email notification	Preferably within 24 hours of knowledge but in no event later than 48 hours
	IRB	As required	As required
Unanticipated Adverse Device Effects **OR** Unanticipated problems involving risk to subjects **OR** others, serious adverse events related to participation in the study	Sponsor	Verbally and SAE CRF	Within 24 hours of knowledge (Mandatory) **(Sponsor to report to FDA within 10 working days from becoming aware of the event).**
	IRB	As required	As soon as possible but not later than 10 working days of knowledge (Mandatory)
Device Malfunction	Sponsor	Verbally or email notification	Within 24 hours of knowledge
Withdrawal of IRB approval	Sponsor	Verbally/ Written	Within 24 hours (verbally) of knowledge with written notification within 48 hours (Mandatory)
Informed consent not obtained from the participant	Sponsor	Written	Within 5 working days of occurrence. For any use of the device without informed consent, provide written explanation from PI and sub-I (Mandatory)
	IRB	Written	Within 5 working days of occurrence (Mandatory)
Annual Progress report*	Sponsor, IRB and per funding source requirements	Written	Submitted annually or as required by IRB (Mandatory)
Other information upon the request of the Sponsor, IRB, or FDA.	As appropriate	As required	As requested

*A copy of the progress report used for continuing IRB renewal, approved by the IRB, should be submitted to the Sponsor and will satisfy the requirement of the Annual Progress report.

15.0 RECORD RETENTION

Investigators' files containing all records and reports of the investigation should be retained for period of two (2) years after the latter of the completion or termination of the investigational study, or the date that the records are no longer required for the purpose of supporting a submission to the FDA for approval of the device, or as required by local regulations.

The files may be discarded only upon notification from the Sponsor. To avoid error, the investigator should contact the Sponsor before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

In addition, in accordance with the Clinical Investigation Agreement, the Sponsor should be contacted if the site's investigator plans to leave the Investigational Site so that appropriate arrangements can be made to replace him/her.

16.0 INVESTIGATIONAL DEVICES

The investigational devices may only be used for subjects enrolled into this study under the supervision of the investigator and under the terms of the clinical protocol and Investigator's Agreement. The investigator may not provide the device to any person not authorized to use it. The investigator will also ensure that the device components are maintained under secure storage.

The Sponsor will supply the investigator with an adequate number of investigational devices for completion of the study. The Sponsor will also maintain records for each site of the number of devices delivered, used and returned. At the end of the study, all remaining devices will be returned to the Sponsor. The investigational devices may not be reused or re-sterilized after completion of the study.

17.0 DEVIATIONS FROM PROTOCOL AND MEDICAL EMERGENCIES

The investigator will not deviate from the protocol without the prior written approval of the Sponsor except in medical emergencies. In medical emergencies, prior approval for protocol deviations will not be required, but Sponsor personnel must be notified within 24 hours of occurrence. The IRB must also be notified as soon as possible but no later than 5 working days.

18.0 INVESTIGATIONAL SITE TERMINATION

The Sponsor reserves the right to terminate an investigational site at any time for any reason including:

- Repeated failure to complete case report forms
- Failure to obtain Informed Consent
- Failure to report Serious Adverse Events within 48 hours of knowledge
- Loss of or unaccounted investigational devices
- Repeat protocol deviations
- Failure to enroll adequate number of participants in a timely manner

Written notice of the study termination will be submitted to the investigator in advance of such termination.

19.0 REGULATORY CONSIDERATIONS

All aspects of this study are governed by the FDA regulations pertaining to responsibilities of sponsors and investigators (21 CFR 812, Subparts C and E), Protection of Human Subjects (21 CFR 50 and Title 45 CFR Part 46), Institutional Review Boards (21 CFR 56 and 45 CFR 46) and Financial Disclosure (21 CFR 54), as applicable. The Principal Investigator at each clinical site is ultimately responsible for the conduct of the study, and validity and accuracy of the data supplied on the eCRFs. Authorization for completion of study-related procedures may be delegated to appropriately qualified individuals, but responsibility may not be delegated.

20.0 APPENDICES

20.1 APPENDIX A: STUDY QUESTIONNAIRES

20.1.1 Pain Scales

Pain will be assessed using either the Faces Pain Scale-Revised (FPS-R) or the Numeric Rated Pain Scale (NRPS). The FPS-R scale may be used with children ≥5 years of age (at the time of consent), the NRPS may be used for children >7 years of age (at the time of consent) or by a parent/guardian when a child of any age is unable to self-report. The pain scale initially used by the child or parent/guardian should continue to be used through the duration of the study.

20.1.1.1 Faces Pain Scale – Revised (FPS-R)

Pain scoring will be done until the Index Burn no longer requires dressing. The pain score acquired prior to the dressing change is intended to characterize baseline pain associated with the Index Burn and to the extent practical is to be acquired prior to analgesia administration for the dressing change. Immediately after the Index Burn dressing change, the subject (or parent/guardian) will be asked to rate maximum pain felt during that dressing change and is intended to characterize pain associated with the dressing change.

- **Faces Pain Scale – Revised (FPS-R)**

In the following instructions, say "hurt" or "pain", whichever seems right for a particular child.
"These faces show how much something can hurt. This face *[point to face on far left]* **shows no pain. The faces show more and more pain** *[point to each from left to right]* **up to this one** *[point to face on far right]* **- it shows very much pain.**

Point to the face that shows how much you hurt [right now]."

*Score the chosen face **0**, **2**, **4**, **6**, **8**, or **10**, counting left to right, so "0" = "no pain" and "10" = "very much pain". Do not use words like "happy" or "sad". This scale is intended to measure how children feel inside, not how their face looks.*

Sources. Hicks CL, von Baeyer CL, Spafford P, van Korlaar I, Goodenough B. The Faces Pain Scale – Revised: Toward a common metric in pediatric pain measurement. Pain 2001;93:173-183. Bieri D, Reeve R, Champion GD, Addicoat L, Ziegler J. The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: Development, initial validation and preliminary investigation

20.1.1.2 Numeric Rated Pain Scale (NRPS)

Pain Numeric Rating Scale

1. On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your pain RIGHT NOW.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

20.1.1.3 FLACC Scale

Pain scores during dressing changes will be assessed by the health care provider performing dressing changes until the Index Burn no longer requires dressings. Immediately after the Index Burn dressing change, the health care provider will document the maximum pain during that dressing change. Categorical and total score should be reported.

FLACC Behavioral Scale

Categories	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractable	Difficult to console or comfort
Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten.			

20.1.2 Itch Man Scale

The score is intended to capture the maximal itching experienced at the Index Burn since the prior assessment. Prior to the dressing change, ask the subject (or parent/guardian as appropriate) to rate the maximal itching they have experienced since the last assessment.

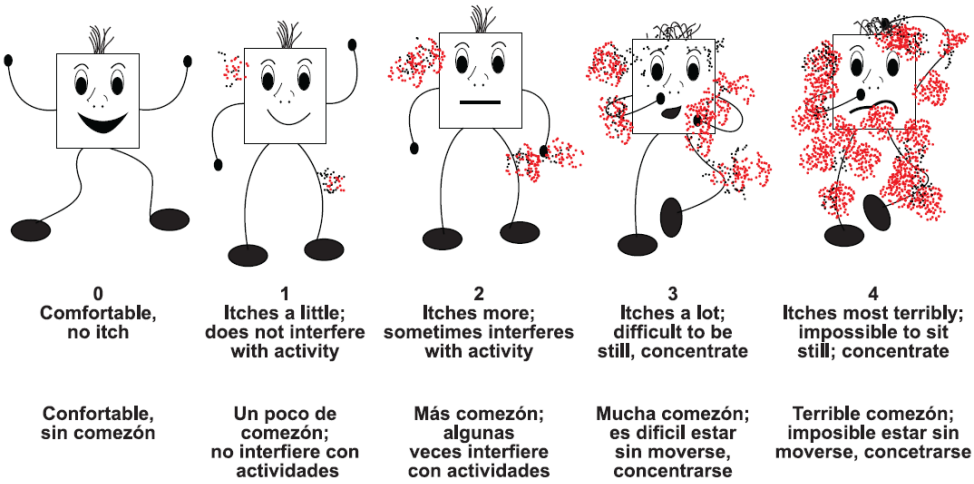


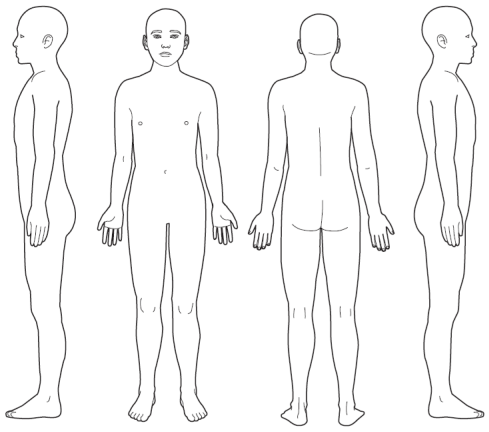
Figure 1. Itch Man Scale (©2000, Blakeney and Marvin).[13]

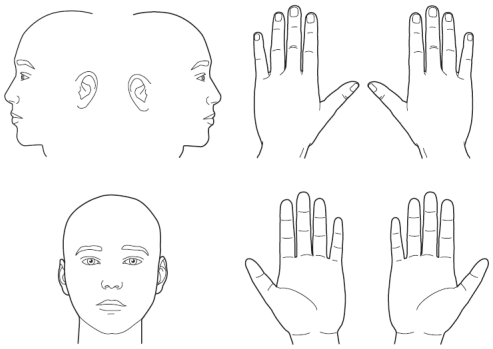
20.1.3 POSAS Scar Assessment Tool

POSAS Observer scale

The Patient and Observer Scar Assessment Scale v2.0 / EN

Date of examination:	**Name of patient:**
Observer:	
Location:	**Date of birth:**
Research / study:	**Identification number:**





	1 = normal skin								worst scar imaginable = 10		
PARAMETER	1	2	3	4	5	6	7	8	9	10	**CATEGORY**
VASCULARITY	○	○	○	○	○	○	○	○	○	○	PALE | PINK | RED | PURPLE | MIX
PIGMENTATION	○	○	○	○	○	○	○	○	○	○	HYPO | HYPER | MIX
THICKNESS	○	○	○	○	○	○	○	○	○	○	THICKER | THINNER
RELIEF	○	○	○	○	○	○	○	○	○	○	MORE | LESS | MIX
PLIABILITY	○	○	○	○	○	○	○	○	○	○	SUPPLE | STIFF | MIX
SURFACE AREA	○	○	○	○	○	○	○	○	○	○	EXPANSION | CONTRACTION | MIX
OVERALL OPINION	○	○	○	○	○	○	○	○	○	○	

Explanation

The observer scale of the POSAS consists of six items (vascularity, pigmentation, thickness, relief, pliability and surface area).
All items are scored on a scale ranging from 1 ('like normal skin') to 10 ('worst scar imaginable').
The sum of the six items results in a total score of the POSAS observer scale. Categories boxes are added for each item. Furthermore, an overall opinion is scored on a scale ranging from 1 to 10.
All parameters should preferably be compared to normal skin on a comparable anatomic location.

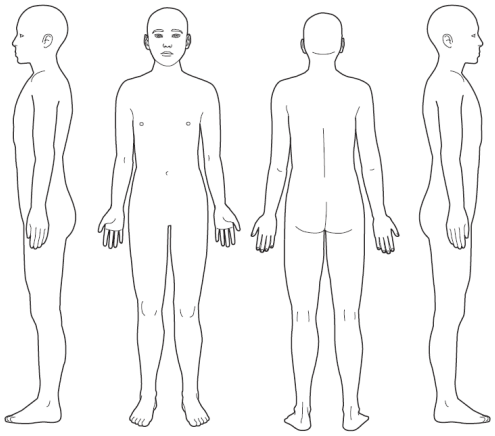
Explanatory notes on the items:

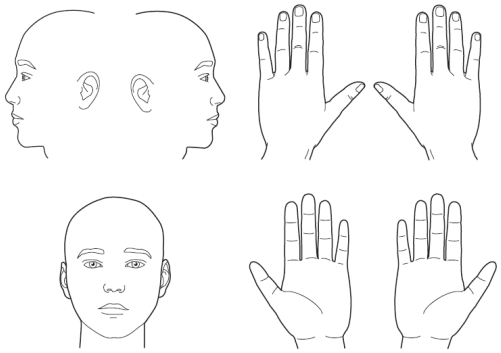
- **VASCULARITY** Presence of vessels in scar tissue assessed by the amount of redness, tested by the amount of blood return after blanching with a piece of Plexiglas
- **PIGMENTATION** Brownish coloration of the scar by pigment (melanin); apply Plexiglas to the skin with moderate pressure to eliminate the effect of vascularity
- **THICKNESS** Average distance between the subcutical-dermal border and the epidermal surface of the scar
- **RELIEF** The extent to which surface irregularities are present (preferably compared with adjacent normal skin)
- **PLIABILITY** Suppleness of the scar tested by wrinkling the scar between the thumb and index finger
- **SURFACE AREA** Surface area of the scar in relation to the original wound area

POSAS Patient scale

The Patient and Observer Scar Assessment Scale v2.0 / EN

Date of examination:	**Name of patient:**
Observer:	
Location:	**Date of birth:**
Research / study:	**Identification number:**





	1 = no, not at all									yes, very much = 10
	1	2	3	4	5	6	7	8	9	10
HAS THE SCAR BEEN PAINFUL THE PAST FEW WEEKS?	○	○	○	○	○	○	○	○	○	○
HAS THE SCAR BEEN ITCHING THE PAST FEW WEEKS?	○	○	○	○	○	○	○	○	○	○

	1 = no, as normal skin									yes, very different = 10
	1	2	3	4	5	6	7	8	9	10
IS THE SCAR COLOR DIFFERENT FROM THE COLOR OF YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○
IS THE STIFFNESS OF THE SCAR DIFFERENT FROM YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○
IS THE THICKNESS OF THE SCAR DIFFERENT FROM YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○
IS THE SCAR MORE IRREGULAR THAN YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○

	1 = as normal skin									very different = 10
	1	2	3	4	5	6	7	8	9	10
WHAT IS YOUR OVERALL OPINION OF THE SCAR COMPARED TO NORMAL SKIN?	○	○	○	○	○	○	○	○	○	○

20.1.4 Burn Outcome Questionnaires

20.1.4.1 $BOQ_{0\text{-}4}$

Burn Outcomes Questionnaire

AGES 0 to 4

AMERICAN BURN ASSOCIATION/SHRINERS HOSPITALS FOR CHILDREN

Today's Date

___ / ___ / ___

1. **In general, would you say this child's health is excellent, very good, good, fair, or poor?** *(Darken one circle)*

① Excellent
② Very good
③ Good
④ Fair
⑤ Poor

Marking Instructions

Use a No. 2 pencil only.

Do not use ink, ballpoint, or felt tip pens.

Make solid marks that fill the circle completely.

Erase cleanly any marks you wish to change.

Make no stray marks on this form.

Do not fold, tear, or mutilate this form.

Correct Mark

Incorrect Marks ✓ ✗ ● •

FOR OFFICE USE ONLY

Today's Date

MONTH	DAY	YEAR
○ Jan		
○ Feb		
○ Mar	0 0	0 0 0
○ Apr	1 1	1 1 1
○ May	2 2	2 2 2 2
○ June	3 3	3 3 3
○ July	4	4 4 4
○ Aug	5	5 5 5
○ Sept	6	6 6 6
○ Oct	7	7 7 7
○ Nov	8	8 8 8
○ Dec	9	9 9 9

The following are descriptions of children. Please fill in the circle that best describes this child *in the past month because of the burn injury.* Please answer every item as best you can. Fill in one circle on each line.

		Very limited or unable	Somewhat limited	Not limited, or able to perform in most situations
2.	Shows awareness and interest in others	①	②	③
3.	Initiates a familiar play routine	①	②	③
4.	Takes turns in simple play	①	②	③
5.	Attempts to imitate adults' previous action during a play activity	①	②	③
6.	During play, child may suggest new things or responds to adult suggestion with another idea	①	②	③

For each item, please fill in the circle that best describes your child *in the past month because of the burn injury.*		Very limited or unable	Somewhat limited	Not limited, or able to perform in most situations
7.	Uses single word with meaning	①	②	③
8.	Finger feeds	①	②	③
9.	Scoops with a spoon and brings to mouth	①	②	③
10.	Holds bottle or spout cup	①	②	③
11.	Lifts open cup securely with 2 hands	①	②	③
12.	Assists such as pushing arms through shirt	①	②	③
13.	Rolls, scoots, crawls or creeps on floor	①	②	③
14.	Walks up entire flight with no difficulty	①	②	③

11767

PLEASE DO NOT WRITE IN THIS AREA

For each item, please fill in the circle that best describes this child *in the past month because of the burn injury.*

		Very limited or unable	Somewhat limited	Not limited, or able to perform in most situations
15.	Walks holding onto people or furniture	①	②	③
16.	Walks without support	①	②	③
17.	Carries objects that can be held in one hand	①	②	③
18.	Pull to stand	①	②	③
19.	Climb onto an adult chair	①	②	③

If this child is under two years of age, skip to question 25. If this child is two years or older, please fill in the circle that best describes your child *in the past month because of the burn injury.*

		Very limited or unable	Somewhat limited	Not limited, or able to perform in most situations
20.	Uses two words together with meaning	①	②	③
21.	Uses 4–5 word sentences	①	②	③
22.	Connects two or more thoughts to tell a simple story	①	②	③
23.	Puts on T-shirt	①	②	③
24.	Puts on and removes front opening shirt including fasteners	①	②	③

The following are descriptions of children's mood states. Please fill in the circle that best describes this child's mood in the past month because of the burn injury.

		Not true	Sometimes true	Very true
25.	Angry moods	①	②	③
26.	Temper tantrums or hot temper	①	②	③
27.	Destroys own things	①	②	③
28.	Unhappy, sad or depressed	①	②	③
29.	Seems unresponsive to affection	①	②	③
30.	Withdrawn, doesn't get involved with others	①	②	③
31.	Stubborn, sullen or irritable	①	②	③
32.	Too fearful or anxious	①	②	③
33.	Nightmares and other sleep disruption	①	②	③

For each item, please fill in the circle that best describes this child *in the past month because of the burn injury.*

Over the past month, how often has this child's health or behavior...	**Never**	**Rarely**	**Sometimes**	**Very often**	**Always**
34. interrupted family meals	①	②	③	④	⑤
35. limited parents' ability to have time for themselves or time with friends	①	②	③	④	⑤
36. made shopping or household chores more difficult or stressful	①	②	③	④	⑤
37. limited parents' ability to work	①	②	③	④	⑤
38. limited family's ability to spend time with others	①	②	③	④	⑤

During the past month, how often has this child...	**None of the time**	**Some of the time**	**About half the time**	**Most of the time**	**All of the time**
39. had pain from the burn injury	①	②	③	④	⑤
40. had itching from the burn injury	①	②	③	④	⑤

During the past month, how much of the time has this child...	**None of the time**	**Some of the time**	**About half the time**	**Most of the time**	**All of the time**
41. been scratching	①	②	③	④	⑤
42. required medicine for pain/itch	①	②	③	④	⑤
43. awakened because of itching	①	②	③	④	⑤

During the past month, how severe has this child's	**Not severe**	**Mildly severe**	**Moderately severe**	**Very severe**
44. pain from the burn injury been?	①	②	③	④
45. itching from the burn injury been?	①	②	③	④

For each item, please fill in the circle that best describes this child *in the past month because of the burn injury.*

Do you agree or disagree with the following statements?

Because of this child's burn injury. . .	**Strongly disagree**	**Moderately disagree**	**Neither agree nor disagree**	**Moderately agree**	**Strongly agree**
46. your child is unattractive to others	①	②	③	④	⑤
47. changes in this child's appearance have interfered with his/her relationships	①	②	③	④	⑤
48. you are uncomfortable taking your child in public because of his/her appearance	①	②	③	④	⑤

Since the burn injury, how satisfied are you now with this child's. . .	**Very dissatisfied**	**Somewhat dissatisfied**	**Not sure**	**Somewhat satisfied**	**Very satisfied**
49. symptom relief (pain and itch)	①	②	③	④	⑤
50. appearance	①	②	③	④	⑤
51. sleep	①	②	③	④	⑤
52. function (ability to play and have fun)	①	②	③	④	⑤
53. overall medical care	①	②	③	④	⑤

Comments:

Over the past month, how much worry or concern have you had about. . .	**None at all**	**Not very much**	**Some**	**A fair amount**	**A great deal**
54. child's recovery from the effects of the burn injury	①	②	③	④	⑤
55. child's amount of pain and suffering	①	②	③	④	⑤
56. child's future health	①	②	③	④	⑤

57. The burn team answered my questions about possible future surgery. . .

① Extremely well
② Very well
③ Moderately well
④ Somewhat well
⑤ Not at all well
⑥ Does not apply

58. Compared to before the burn, how would you rate this child's current overall health?

① Much better
② Better
③ About the same
④ Worse
⑤ Much worse

59. **Before the burn injury, did a doctor, nurse, or other health professional say that this child has any of the following conditions? If yes, please tell us if this child gets treatment from a doctor and if this child's activities are limited by the condition.**

		Has had it	Gets treatment for it	Activities are limited
a.	Asthma	①	②	③
b.	Attention or behavioral problem	①	②	③
c.	Chronic allergies or sinus trouble	①	②	③
d.	Developmental delay	①	②	③
e.	Mental retardation	①	②	③
f.	Diabetes	①	②	③
g.	Epilepsy (seizures)	①	②	③
h.	Hearing problem	①	②	③
i.	Heart problem	①	②	③
j.	Learning problem	①	②	③
k.	Sleep problem	①	②	③
l.	Speech problem	①	②	③
m.	Vision problem	①	②	③
n.	Depression	①	②	③
o.	Other chronic medical problem (specify)	①	②	③

60. **Has this child had surgery for the burn injury in the past 6 months?**

① No ② Yes → Number of operations:

61. **Has this child begun any new treatments for the burn injury in the past 6 months? (indicate no or yes for each item)**

		No	Yes
a.	Wearing splints	①	②
b.	Wearing jobst garment	①	②
c.	Using distractor devices	①	②
d.	Physical therapy	①	②
e.	Occupational therapy	①	②
f.	No new treatments in the past 6 months	①	②

62. What is the child's date of birth?

___ / ___ / ___

63. **Is this child male or female?**

- ○ Male
- ○ Female

64. **What is this child's race?**

- ○ White, non-Hispanic
- ○ Black, non-Hispanic
- ○ Hispanic/Latino
- ○ Pacific Islander
- ○ Asian
- ○ Native American
- ○ Other_____

FOR OFFICE USE ONLY

Child's Birth Date

MONTH	DAY	YEAR
○ Jan		
○ Feb		
○ Mar	0 0	0 0 0
○ Apr	1 1	1 1 1
○ May	2 2	2 2 2
○ June	3 3	3 3 3
○ July	4	4 4 4
○ Aug	5	5 5 5
○ Sept	6	6 6 6
○ Oct	7	7 7 7
○ Nov	8	8 8 8
○ Dec	9	9 9 9

65. **What is the highest level of education achieved by this child's *mother* (or *stepmother*, if that is with whom he/she is living)?**

- ○ 8th grade or less
- ○ Some high school
- ○ Graduated from high school
- ○ Technical school or associate degree
- ○ Some college
- ○ Graduated from college
- ○ Graduate school or professional degree
- ○ Don't know

Burn Outcomes Questionnaire

AMERICAN BURN ASSOCIATION/SHRINERS HOSPITALS FOR CHILDREN

PLEASE DO NOT WRITE IN THIS AREA

11767

66. **What is the highest level of education achieved by this child's *father* (or *stepfather,* if that is with whom he/she is living)?**

- ○ 8th grade or less
- ○ Some high school
- ○ Graduated from high school
- ○ Technical school or associate degree
- ○ Some college
- ○ Graduated from college
- ○ Graduate school or professional degree
- ○ Don't know

67. **Is this child's *mother* (or *stepmother,* if that is with whom he/she is living) employed?**

- ○ No
- ○ Yes, Occupation: _____

68. **Is this child's *father* (or *stepfather,* if that is with whom he/she is living) employed?**

- ○ No
- ○ Yes, Occupation: _____

69. **Who does this child live with now?** *(Darken all circles that apply)*

- ○ Mother/stepmother
- ○ Father/stepfather
- ○ Grandparent (How many?)_____
- ○ Brother or sister (How many?)_____
- ○ Aunt or uncle (How many?)_____
- ○ Other_____

70. **Is there a change in this child's living situation because of the burn?**

- ○ There is a change, and it is mostly due to the burn.
- ○ There is a change, and it is partly due to the burn.
- ○ There is a change, but it is not related to the burn.
- ○ No change in this child's living situation.

71. **Who is filling out this questionnaire?** *(Darken all circles that apply)*

1. Mother or stepmother
2. Father or stepfather
3. Guardian
4. Office staff
5. Other

Thank you for taking the time to complete this survey.

FOR OFFICE USE ONLY

STUDY ID

DO NOT WRITE IN THIS AREA

Instance

- Admission
- 1st clinic visit
- 3 months
- 6 months
- 12 months
- 18 months
- 24 months

Language

- English
- Spanish

Mode of Administration

- by mail
- by telephone
- done in clinic

Mark Reflex® by NCS EM-238584-1:854321 Printed in U.S.A.

Burn Outcomes Questionnaire
AMERICAN BURN ASSOCIATION/SHRINERS HOSPITALS FOR CHILDREN

PLEASE DO NOT WRITE IN THIS AREA

11767

Burn Outcomes Questionnaire

AMERICAN BURN ASSOCIATION/SHRINERS HOSPITALS FOR CHILDREN

AGES 5 to 18

Marking Instructions

Use a No. 2 pencil only.

Do not use ink, ballpoint, or felt tip pens.

Make solid marks that fill the circle completely.

Erase cleanly any marks you wish to change.

Make no stray marks on this form.

Do not fold, tear, or mutilate this form.

Correct Mark ●

Incorrect Marks ✓ ✗ ◒ ⊙

Today's Date

MONTH	DAY	YEAR
○ Jan		
○ Feb		
○ Mar	0 0	0 0 0
○ Apr	1 1	1 1 1
○ May	2 2	2 2 2 2
○ June	3 3	3 3 3
○ July	4	4 4 4
○ Aug	5	5 5 5
○ Sept	6	6 6 6
○ Oct	7	7 7 7
○ Nov	8	8 8 8
○ Dec	9	9 9 9

1 **In general, would you say your child's health is excellent, very good, good, fair, or poor?**
(Darken one circle)

○ Excellent ○ Fair
○ Very good ○ Poor
○ Good

1A **Compared to before the burn, how would you rate this child's current overall health?**

○ Much better ○ Worse
○ Better ○ Much worse
○ About the same

2 **Before the burn injury, did a doctor, nurse, or other health professional say that this child had any of the following conditions? Fill in the "Yes" or "No" circle. If "Yes," please tell us if this child gets treatment from a doctor and if this child's activities are limited by the condition.**

	Has this child ever had it?	Does this child get treatment?	Are this child's activities limited?
Asthma	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Attention or behavioral problems	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Chronic allergies or sinus trouble	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Developmental delay	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Mental retardation	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Diabetes	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Epilepsy (seizure disorder)	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Hearing problem	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Heart problem	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Learning problem	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Sleep problem	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Speech problems	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Vision problems	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Depression	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Drug problem	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Alcohol problem	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Other medical problem _____	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No

○ ◀ *Darken the circle if this child has none of the above conditions.*

3652

PLEASE DO NOT WRITE IN THIS AREA

3 **During the past week, how *often* has this child had *pain* from the burn injury?**

○ None of the time ○ Some of the time ○ About half the time ○ Most of the time ○ All of the time

4 **During the past week, how *bad* has this child's *pain* from the burn injury been?**
(Darken the circle of the number to indicate the severity of the burn pain)

No pain		Mild pain		Moderate pain			Bad pain			Very severe pain
⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩

5 **During the past week, how *often* has this child had *itching* from the burn injury?**

○ None of the time ○ Some of the time ○ About half the time ○ Most of the time ○ All of the time

6 **During the past week, how *bad* has this child's *itching* from the burn injury been?**
(Darken the circle of the number to indicate the severity of the itching from the burn injury)

No itching		Mild itching		Moderate itching			Bad itching			Very severe itching
⓪	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩

7 **Can this child take part in recreational activities with other kids the same age (for example, dancing, bicycling, skating, hiking, jogging)?**

○ Yes, easily ○ Yes, but a little hard ○ Yes, but very hard ○ No

8 **If recreational activities are hard or this child can't do them at all, is he/she limited by . . .**
(Darken the circle of all that apply)

○ Pain ○ Doctor or parent instruction ○ Dislike of recreational activity ○ Too young
○ General health ○ Fear the other kids won't like him/her ○ Activity not in season

2 PAGE TWO

Burn Outcomes Questionnaire
AMERICAN BURN ASSOCIATION/SHRINERS HOSPITALS FOR CHILDREN

9 **During the last week, has it been easy or hard for this child to:**

	Easy	A little hard	Very hard	Can't do	Too young
Bicycle?	○	○	○	○	○
Climb three flights of stairs?	○	○	○	○	○
Climb one flight of stairs?	○	○	○	○	○
Run short distances?	○	○	○	○	○
Walk three blocks?	○	○	○	○	○
Get on or off a bus?	○	○	○	○	○

10 **How often does this child need help from another person for walking and climbing?**

○ Never ○ Sometimes ○ About half of the time ○ Often ○ All of the time

11 **During the last week, has it been easy or hard for this child to:**

	Easy	A little hard	Very hard	Can't do	Too young
Pour a half gallon of milk?	○	○	○	○	○
Use fork or spoon?	○	○	○	○	○
Comb his/her hair?	○	○	○	○	○
Button buttons?	○	○	○	○	○
Pull on a shirt or sweater over his/her head?	○	○	○	○	○
Turn his/her neck to look back over his/her shoulder?	○	○	○	○	○
Get on and off toilet or chair?	○	○	○	○	○
Get in and out of bed?	○	○	○	○	○
Turn door knobs?	○	○	○	○	○
Bend over from a standing position and pick up something off the floor?	○	○	○	○	○

PLEASE DO NOT WRITE IN THIS AREA

3652

People often have problems following all their doctor's recommendations.

12 How often has this child been able to follow the burn team instructions in . . .	Almost always	Most of the time	Half the time	Some of the time	Almost never	N/A
Doing exercises?	○	○	○	○	○	○
Doing wound care?	○	○	○	○	○	○
Wearing dressings?	○	○	○	○	○	○
Wearing garments?	○	○	○	○	○	○
Keeping appointments?	○	○	○	○	○	○

The following questions ask about this child's appearance.

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
13 This child feels that the burn is unattractive to others.	○	○	○	○	○
14 This child thinks people would not want to touch him/her.	○	○	○	○	○
15 This child feels unsure of himself/herself among strangers.	○	○	○	○	○
16 Changes in this child's appearance have interfered with his/her relationships.	○	○	○	○	○

17 During the last month, how often has this child's health or behavior . . .	Always	Very often	Sometimes	Rarely	Never
Limited his/her parents' ability to have time for themselves or time with friends?	○	○	○	○	○
Interrupted simple family activities like meals?	○	○	○	○	○
Made shopping or household chores more difficult or stressful?	○	○	○	○	○
Limited his/her parents' ability to work?	○	○	○	○	○
Limited his/her family's ability to spend time with other families?	○	○	○	○	○

18 Over the past month, how much worry or concern have you had about . . .	A lot	A fair amount	Some	Not very much	None at all
This child's full recovery from the effects of the burn injury?	○	○	○	○	○
This child's level of pain and suffering?	○	○	○	○	○
This child's future health?	○	○	○	○	○

19 How well does each of the following statements describe this child?	None of the time	Some of the time	About half of the time	Most of the time	All of the time
This child has more nightmares.	○	○	○	○	○
This child feels angry.	○	○	○	○	○
This child feels depressed and talks about death.	○	○	○	○	○
This child feels upset.	○	○	○	○	○

These next questions are about school.

20 Compared to before the burn, are this child's grades:

○ Much better now
○ Somewhat better now
○ About the same now
○ Somewhat worse now
○ Much worse now
○ Does not apply; this child was not in school at time of the burn.

21 Was this child in a special class before the burn injury?

○ No
○ Yes (What kind?) _____

22 Is this child in a special class or special school now?

○ No
○ Yes (What kind?) _____

23 Following this child's return to school after the burn injury, how would you rate his/her:	Much better now	Somewhat better now	Same	Somewhat worse now	Much worse now
Acceptance by classmates?	○	○	○	○	○
Acceptance by teachers?	○	○	○	○	○
Ability to perform school work?	○	○	○	○	○

The next questions ask about this child's level of satisfaction.

24 **How satisfied is this child now with his/her:**

	Very satisfied	Somewhat satisfied	Not sure	Somewhat dissatisfied	Very dissatisfied
Pain relief?	○	○	○	○	○
Itch relief?	○	○	○	○	○
Amount and quality of sleep?	○	○	○	○	○
Ability to do chores?	○	○	○	○	○
Ability to do school work?	○	○	○	○	○
Ability to play and have fun?	○	○	○	○	○
Overall medical care?	○	○	○	○	○

25 **Was this child satisfied with school re-entry services received?**

○ Extremely satisfied ○ Slightly satisfied ○ Quite dissatisfied ○ Didn't get services/none offered
○ Quite satisfied ○ Slightly dissatisfied ○ Extremely dissatisfied

26 **How well were this child's questions about future surgery answered?**

○ Extremely well ○ Very well ○ Moderately well ○ Somewhat well ○ Not at all well

27 **What is this child's date of birth?**

Child's Birth Date

MONTH	DAY	YEAR
○ Jan		
○ Feb		
○ Mar	0 0	0 0 0 0
○ Apr	1 1	1 1 1 1
○ May	2 2	2 2 2 2
○ June	3 3	3 3 3
○ July	4	4 4 4
○ Aug	5	5 5 5
○ Sept	6	6 6 6
○ Oct	7	7 7 7
○ Nov	8	8 8 8
○ Dec	9	9 9 9

28 **Is this child male or female?**

○ Male
○ Female

29 **What is this child's race?**

○ White, non-Hispanic
○ Black, non-Hispanic
○ Hispanic/Latino
○ Pacific Islander
○ Asian
○ Native American
○ Other _____

30 **If this child is not in school, what is the reason?** *(Darken all circles that apply)*

○ Too young ○ Burn injury ○ Other (Describe) _____

31 **What is the highest grade in school *this child* has completed?**

○ Nursery

○ K ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 ○ 11 ○ 12

32 **What is the highest level of education achieved by this child's *mother* (or *stepmother,* if that is who he/she is living with)?**

○ 8th grade or less
○ Some high school
○ Graduated from high school
○ Technical school or associate degree
○ Some college
○ Graduated from college
○ Graduate school or professional degree
○ Don't know

33 **What is the highest level of education achieved by this child's *father* (or *stepfather,* if that is who he/she is living with)?**

○ 8th grade or less
○ Some high school
○ Graduated from high school
○ Technical school or associate degree
○ Some college
○ Graduated from college
○ Graduate school or professional degree
○ Don't know

34 **Is this child's *mother* employed (or *stepmother,* if that is who he/she is living with)?**

○ No
○ Yes, she is a _____

35 **Is this child's *father* employed (or *stepfather,* if that is who he/she is living with)?**

○ No
○ Yes, he is a _____

36 **Before the burn injury, who did this child live with?** *(Darken all circles that apply)*

- ○ Mother/stepmother
- ○ Father/stepfather
- ○ Grandparent (How many?)_____
- ○ Brother or sister (How many?)_____
- ○ Aunt or uncle (How many?)_____
- ○ Other _____

37 **Who does this child live with now?** *(Darken all circles that apply)*

- ○ Mother/stepmother
- ○ Father/stepfather
- ○ Grandparent (How many?)_____
- ○ Brother or sister (How many?)_____
- ○ Aunt or uncle (How many?)_____
- ○ Other _____

38 **If there is a change in this child's living situation, was it because of the burn?**

- ○ There is a change, and it is mostly due to the burn.
- ○ There is a change, and it is partly due to the burn.
- ○ There is a change, but it is not related to the burn.
- ○ No change in this child's living situation.

39 **Please let us know who is completing this questionnaire.** *(Darken all circles that apply)*

- ○ Mother
- ○ Father
- ○ Guardian
- ○ Office staff
- ○ Someone else (Relationship to child) _____

Thank you for taking the time to complete this survey.

STUDY ID

DO NOT WRITE IN THIS AREA

Mark Reflex® by NCS EM-233197-1:654321 Printed in U.S.A.

Burn Outcomes Questionnaire

AMERICAN BURN ASSOCIATION/SHRINERS HOSPITALS FOR CHILDREN

PLEASE DO NOT WRITE IN THIS AREA

3652

Burn Outcomes Questionnaire

AMERICAN BURN ASSOCIATION/SHRINERS HOSPITALS FOR CHILDREN

AGES 11 to 18

Marking Instructions

Use a No. 2 pencil only.

Do not use ink, ballpoint, or felt tip pens.

Make solid marks that fill the circle completely.

Erase cleanly any marks you wish to change.

Make no stray marks on this form.

Do not fold, tear, or mutilate this form.

Correct Mark ●

Incorrect Marks ✓ ✗ ⬬ •

Today's Date

MONTH	DAY	YEAR
○ Jan		
○ Feb		
○ Mar	0 0	0 0 0
○ Apr	1 1	1 1 1
○ May	2 2	2 2 2
○ June	3 3	3 3 3
○ July	4	4 4 4
○ Aug	5	5 5 5
○ Sept	6	6 6 6
○ Oct	7	7 7 7
○ Nov	8	8 8 8
○ Dec	9	9 9 9

1 **In general, would you say your health is excellent, very good, good, fair, or poor?** *(Darken one circle)*

○ Excellent ○ Very good ○ Good ○ Fair ○ Poor

1A **Compared to before the burn, how would you rate your current overall health?**

○ Much better ○ Better ○ About the same ○ Worse ○ Much worse

2 **Before the burn injury, did a doctor, nurse, or other health professional say that you had any of the following conditions? Fill in the "Yes" or "No" circle. If "Yes," please tell us if you get treatment from a doctor and if your activities are limited by the condition.**

	Have you ever had it?	Do you get treatment?	Are your activities limited?
Asthma	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Attention or behavioral problems	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Chronic allergies or sinus trouble	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Developmental delay	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Mental retardation	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Diabetes	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Epilepsy (seizure disorder)	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Hearing problem	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Heart problem	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Learning problem	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Sleep problem	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Speech problems	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Vision problems	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Depression	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Drug problem	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Alcohol problem	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Other medical problem _____	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No

○ ◀ *Darken the circle if you have none of the above conditions.*

4334

PLEASE DO NOT WRITE IN THIS AREA

3 **During the past week, how *often* have you had *pain* from the burn injury?**

○ None of the time ○ Some of the time ○ About half the time ○ Most of the time ○ All of the time

4 **During the past week, how *bad* has your *pain* from the burn injury been?**
(Darken the circle of the number to indicate the severity of the burn pain)

No pain		Mild pain		Moderate pain		Bad pain		Very severe pain
⓪	① ② ③	④	⑤ ⑥ ⑦	⑧	⑨ ⑩			

5 **During the past week, how *often* have you had *itching* from the burn injury?**

○ None of the time ○ Some of the time ○ About half the time ○ Most of the time ○ All of the time

6 **During the past week, how *bad* has your *itching* from the burn injury been?**
(Darken the circle of the number to indicate the severity of the itching from the burn injury)

No itching		Mild itching		Moderate itching		Bad itching		Very severe itching
⓪	① ② ③	④	⑤ ⑥ ⑦	⑧	⑨ ⑩			

7 **Can you take part in recreational activities with other kids the same age (for example, dancing, bicycling, skating, hiking, jogging)?**

○ Yes, easily ○ Yes, but a little hard ○ Yes, but very hard ○ No

8 **If recreational activities are hard or you can't do them at all, are you limited by . . .**
(Darken the circle of all that apply)

○ Pain ○ Doctor or parent instruction ○ Dislike of recreational activity ○ Too young
○ General health ○ Fear the other kids won't like me ○ Activity not in season

2 PAGE TWO

9 **During the last week, has it been easy or hard for you to:**

	Easy	A little hard	Very hard	Can't do	Too young
Bicycle?	○	○	○	○	○
Climb three flights of stairs?	○	○	○	○	○
Climb one flight of stairs?	○	○	○	○	○
Run short distances?	○	○	○	○	○
Walk three blocks?	○	○	○	○	○
Get on or off a bus?	○	○	○	○	○

10 **How often do you need help from another person for walking and climbing?**

○ Never ○ Sometimes ○ About half of the time ○ Often ○ All of the time

11 **During the last week, has it been easy or hard for you to:**

	Easy	A little hard	Very hard	Can't do	Too young
Pour a half gallon of milk?	○	○	○	○	○
Use fork or spoon?	○	○	○	○	○
Comb your hair?	○	○	○	○	○
Button buttons?	○	○	○	○	○
Pull on a shirt or sweater over your head?	○	○	○	○	○
Turn your neck to look back over your shoulder?	○	○	○	○	○
Get on and off toilet or chair?	○	○	○	○	○
Get in and out of bed?	○	○	○	○	○
Turn door knobs?	○	○	○	○	○
Bend over from a standing position and pick up something off the floor?	○	○	○	○	○

4334

PLEASE DO NOT WRITE IN THIS AREA

People often have problems following all their doctor's recommendations.

12 How often have you been able to follow the burn team instructions in . . .	Almost always	Most of the time	Half the time	Some of the time	Almost never	N/A
Doing exercises?	○	○	○	○	○	○
Doing wound care?	○	○	○	○	○	○
Wearing dressings?	○	○	○	○	○	○
Wearing garments?	○	○	○	○	○	○
Keeping appointments?	○	○	○	○	○	○

The following questions ask about your appearance.

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
13 I feel that the burn is unattractive to others.	○	○	○	○	○
14 I think people would not want to touch me.	○	○	○	○	○
15 I feel unsure of myself among strangers.	○	○	○	○	○
16 Changes in my appearance have interfered with my relationships.	○	○	○	○	○

17 During the last month, how often has your health or behavior . . .	Always	Very often	Sometimes	Rarely	Never
Limited your parents' ability to have time for themselves or time with friends?	○	○	○	○	○
Interrupted simple family activities like meals?	○	○	○	○	○
Made shopping or household chores more difficult or stressful?	○	○	○	○	○
Limited your parents' ability to work?	○	○	○	○	○
Limited your family's ability to spend time with other families?	○	○	○	○	○

18 Over the past month, how much worry or concern have your parents had about . . .	A lot	A fair amount	Some	Not very much	None at all
Your full recovery from the effects of the burn injury?	○	○	○	○	○
Your level of pain and suffering?	○	○	○	○	○
Your future health?	○	○	○	○	○

19 How well does each of the following statements describe you?	None of the time	Some of the time	About half of the time	Most of the time	All of the time
I have more nightmares.	○	○	○	○	○
I feel angry.	○	○	○	○	○
I feel depressed and talk about death.	○	○	○	○	○
I feel upset.	○	○	○	○	○

These next questions are about school.

20 Compared to before the burn, are your grades:

○ Much better now ○ About the same now ○ Much worse now
○ Somewhat better now ○ Somewhat worse now ○ Does not apply; I was not in school at time of the burn.

21 Were you in a special class before the burn injury?

○ No
○ Yes (What kind?) _____

22 Are you in a special class or special school now?

○ No
○ Yes (What kind?) _____

23 Following your return to school after the burn injury, how would you rate your:	Much better now	Somewhat better now	Same	Somewhat worse now	Much worse now
Acceptance by classmates?	○	○	○	○	○
Acceptance by teachers?	○	○	○	○	○
Ability to perform school work?	○	○	○	○	○

PAGE FIVE 5

The next questions ask about your level of satisfaction.

24 How satisfied are you now with your:	Very satisfied	Somewhat satisfied	Not sure	Somewhat dissatisfied	Very dissatisfied
Pain relief?	○	○	○	○	○
Itch relief?	○	○	○	○	○
Amount and quality of sleep?	○	○	○	○	○
Ability to do chores?	○	○	○	○	○
Ability to do school work?	○	○	○	○	○
Ability to play and have fun?	○	○	○	○	○
Overall medical care?	○	○	○	○	○

25 **Were you satisfied with the type of school re-entry services you received?**

○ Extremely satisfied ○ Slightly satisfied ○ Quite dissatisfied ○ Didn't get services/none offered
○ Quite satisfied ○ Slightly dissatisfied ○ Extremely dissatisfied

26 **How well were your questions about future surgery answered?**

○ Extremely well ○ Very well ○ Moderately well ○ Somewhat well ○ Not at all well

27 **What is your date of birth?**

Your Birth Date

MONTH	DAY	YEAR
○ Jan		
○ Feb		
○ Mar	0 0	0 1 6
○ Apr	1 1	1 1 1
○ May	2 2	2 2 2
○ June	3 3	3 3 3
○ July	4	4 4 4
○ Aug	5	5 5 5
○ Sept	6	6 6 6
○ Oct	7	7 7 7
○ Nov	8	8 8 8
○ Dec	9	9 9 9

28 **Are you male or female?**

○ Male
○ Female

29 **What is your race?**

○ White, non-Hispanic
○ Black, non-Hispanic
○ Hispanic/Latino
○ Pacific Islander
○ Asian
○ Native American
○ Other _____

6 PAGE SIX

Burn Outcomes Questionnaire

AMERICAN BURN ASSOCIATION/SHRINERS HOSPITALS FOR CHILDREN

4334

PLEASE DO NOT WRITE IN THIS AREA

30 **If you are not in school, what is the reason?**

- Burn injury
- Other (Describe) _____

31 **What is the highest grade in school you have completed?**

- Nursery
- K 1 2 3 4 5 6 7 8 9 10 11 12

32 **What is the highest level of education achieved by your *mother* (or *stepmother,* if that is who you are living with)?**

- 8th grade or less
- Some high school
- Graduated from high school
- Technical school or associate degree
- Some college
- Graduated from college
- Graduate school or professional degree
- Don't know

33 **What is the highest level of education achieved by your *father* (or *stepfather,* if that is who you are living with)?**

- 8th grade or less
- Some high school
- Graduated from high school
- Technical school or associate degree
- Some college
- Graduated from college
- Graduate school or professional degree
- Don't know

34 **Is your *mother* employed (or *stepmother,* if that is who you are living with)?**

- No
- Yes, she is a _____

35 **Is your *father* employed (or *stepfather,* if that is who you are living with)?**

- No
- Yes, he is a _____

36 **Before the burn injury, who did you live with?** *(Darken all circles that apply)*

- ○ Mother/stepmother
- ○ Father/stepfather
- ○ Grandparent (How many?)_____
- ○ Brother or sister (How many?)_____
- ○ Aunt or uncle (How many?)_____
- ○ Other _____

37 **Who do you live with now?** *(Darken all circles that apply)*

- ○ Mother/stepmother
- ○ Father/stepfather
- ○ Grandparent (How many?)_____
- ○ Brother or sister (How many?)_____
- ○ Aunt or uncle (How many?)_____
- ○ Other _____

38 **If there is a change in your living situation, was it because of the burn?**

- ○ There is a change, and it is mostly due to the burn.
- ○ There is a change, and it is partly due to the burn.
- ○ There is a change, but it is not related to the burn.
- ○ No change in my living situation.

Thank you for taking the time to complete this survey.

STUDY ID

DO NOT WRITE IN THIS AREA

Burn Outcomes Questionnaire

AMERICAN BURN ASSOCIATION/SHRINERS HOSPITALS FOR CHILDREN

PLEASE DO NOT WRITE IN THIS AREA

4334

20.2 APPENDIX B: SAMPLE INFORMED CONSENT FORM

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

TITLE OF PROTOCOL:	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 Standard of Care Dressings for Treatment of Partial-thickness Burns in Infants, Children and Adolescents (Aged 1-16 Years)
PROTOCOL #:	CTP006-2
STUDY SPONSOR:	AVITA Medical Americas, LLC
PRINCIPAL INVESTIGATOR:	
STUDY SITE FACILITY(IES):	
EMERGENCY CONTACT:	

Your consent is requested for:

☐ Your child

☐ Someone for whom you are the legal representative.

In this consent form, "you" refers to the subject, the person participating in the study. If you are a parent, guardian, or legal representative, please remember that "you" refers to the study subject.

INTRODUCTION

You are being asked to participate in a research study. The research study is being funded through a contract with Biomedical Advanced Research and Development Authority (BARDA) by AVITA Medical, a medical device company committed to developing new medical treatments for treatment of skin injuries. Your study doctor is being paid by AVITA Medical to conduct this study.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law (NCT03626701). This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

PURPOSE OF THE STUDY

The RECELL® Autologous Cell Harvesting device (RECELL® Device) is a device used to prepare a suspension of healthy skin cells from a small sample of your own skin that can be sprayed over skin defects such as burns to help healing. The RECELL® device has been approved by the Food and Drug Administration (FDA) for the treatment of second- and third-degree burns. This study is testing the device to treat second-degree burns (referred to as "partial-thickness" burns) in patients 1-16 years of age. Partial-thickness burns are those that involve the top layer of the skin (called the "epidermis") and part of the layer of skin located beneath the top layer (called the "dermis"). These burns typically appear red, blistered, and often very painful.

This study follows two other clinical studies that AVITA Medical has completed that evaluated the use of the RECELL Device on 131 patients. These prior studies were performed to evaluate the safety and effectiveness of the RECELL Device when used alone or over skin grafts to treat burns.

You are being asked to participate in this study because you have a partial-thickness burn injury.

DESCRIPTION OF THE STUDY
The standard procedure for treatment of partial-thickness burns is to clean the wound thoroughly, remove any dead tissue and to use a standard wound dressing to protect the wound while it heals. Partial-thickness burns typically heal within 10-14 days, if they do not heal within this timeframe, they are likely to require a skin graft to achieve wound closure. Skin grafts may take another 10-14 days or longer to heal. It has been estimated that skin grafting is required in approximately 20% to 30% of children who experience partial-thickness burns.

The overall time it takes a burn to heal is very important as the longer the wound remains unhealed it will continue to be a source of significant pain, there is the potential for infection and other complications, and the wound is more likely to scar if healing is delayed beyond 3 weeks. Therefore, treatments that can reduce the time to healing or decrease the requirement for skin grafting would be beneficial to burn patients and in particular to children with burns.

The purpose of the study you are being asked to participate in is to see if use of the RECELL Device will help heal your partial-thickness burn faster and decrease the need for skin grafting compared with a standardized wound dressing. The data collected in this current study will provide additional information about the safety and effectiveness of the RECELL® device for treatment of partial-thickness burns.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
This study may enroll 160 people with a maximum of 300 people at up to 25 study sites.

HOW LONG WILL I BE IN THIS STUDY?
If you agree and qualify to participate in this study, the length of your participation will be 12 months. You can stop participating at any time without losing any of your rights for your current or future medical care at this hospital. If you decide to stop participating in the study, we encourage you to talk to the investigators or study staff first to be sure you know about any potential health or safety consequences.

WHAT WILL HAPPEN TO ME?
At the hospital, your study doctor will look at your burn to see if you are a possible candidate for this study. The study doctor will give you a complete explanation of the study and the expected results, plus possible side effects. You will have some time to think about participating in this study and discuss it with family or friends, then you will be asked to sign this consent form if you agree to participate. To be treated in this study, your burn wound must be at least 160cm^2 (for example a 5-inch by 5-inch wound) and the time between when your burn injury occurred and when the study treatment is provided must be less than 72 hours.

If you agree to participate in the study, you will have a physical examination and be asked information about your burn, prior treatments, medical history, as well as any medications you have taken over the previous 7 days.

If it appears that your burn injury meets the requirements of the study, you will be assigned to receive either standard of care wound dressings or to undergo treatment with the RECELL Device. The treatment assigned is based on chance, like a flip of the coin. Neither you nor your doctor chooses your assigned group. You will have an equal chance of being in either group. If it is determined that your burn injury does not meet the study requirements, you will not be treated as part of the study. Your doctor will treat your burn as if you were never in the study. If you were assigned a study treatment but your burn ended up not being treated in the study, you will be followed for 28 days. Also, if you have some areas of deeper burns, the deeper burns will be treated consistent with your doctor's standard practices. You will receive training and take-home Aftercare Instructions on how to appropriately care for your burn wounds.

If you are assigned to Standard of Care Wound Dressings
After your burns are cleaned and any dead tissue is removed, standardized wound dressings will be applied to all your partial-thickness burns.

If you are assigned to Treatment with RECELL
You may go to the operating room where you will be given anesthesia. This means you will be asleep while your burn is cleaned and treated. If it appears that your burn injury continues to meet the requirements of the study, your burn will be treated with a liquid skin cell suspension prepared using the RECELL Device. To prepare the skin cell suspension, a thin piece of skin will be removed from an unburned area(s) on your body, called donor site(s). The donor skin is removed with a dermatome device or a special knife that shaves a thin layer of skin. The donor site can be any

unburned area of your body. Most times, it is an area that is hidden by clothes, such as the buttock or inner thigh. The skin cell suspension made from the RECELL Device will be sprayed over all your partial-thickness burns and then a wound dressing will be applied over your burns. Your doctor may also choose to apply the skin cell suspension to your donor site(s).

For both treatments, during and after the procedure, you will have photographs taken of your burns and donor site(s). You must follow your doctor's post-operative care instructions carefully. You must continue to protect the treated areas at least 2 weeks after the treated areas have healed, using a dressing that your doctor recommends. **Do not break any blisters that form.**

HEALING ASSESSMENTS

Your wounds will be evaluated for healing on or before 10- and 28-days post-treatment to determine if your burn is healed or if the treatment area requires skin grafting. Based on the healing of your burn, your study doctor may also look at your burn three weeks after your treatment (Day 21). You will need to visit your study doctor for these visits if you are not hospitalized. At each visit your burn and donor site(s) will be photographed, evaluated for healing and complications like infection, and you will be asked questions concerning pain and itching at the burn area. Approximately 1 week and again at 4 weeks after the procedure you will be asked to complete a burn quality of life questionnaire. It will take approximately 10 to 20 minutes to complete the questionnaire.

WHAT HAPPENS IF MY STUDY BURN REQUIRES SKIN GRAFTING?

Your study doctor evaluating your burn wound will decide whether the wound requires skin grafting. This decision is based mostly on whether there is a high likelihood that the burn wound will not heal sufficiently within 3 weeks. Only those areas that have not healed will be skin grafted.

In skin grafting, skin is taken from a non-injured area of the body and applied over the burn wound (referred to as "donor" skin). The donor skin is removed with a dermatome device or a special knife that shaves a thin layer of skin. The amount of skin that will be removed from the donor site(s) for the skin grafting will be the same or slightly smaller in size than the size of the burn wound to be covered. The skin may then be put through a skin meshing device. The skin meshing device allows the skin to be expanded by making small holes in the skin so that it can be stretched to cover a larger area (called a "meshed graft"). Once the skin graft is applied to your burn wound, it may be held down with staples or a surgical glue and then covered with a wound dressing. The grafted area and donor site(s) will be photographed.

Following the skin grafting procedure, you will continue to see your doctor until the grafted area has healed. At each visit your burn and donor site(s) will be photographed, evaluated for healing and/or complications like infection, and you will be asked questions concerning pain and itching at the treatment area. Once your burn area is determined to be healed you will need to return for study follow-up visits with your doctor based on the date of your initial study treatment (as described below).

STUDY FOLLOW-UP VISITS

After you complete the initial healing assessment period (through 28 days after your treatment or following your skin grafting procedure), you will need to see your study doctor 8, 16, 24, 36 and 52 weeks after your initial study treatment. These visits will occur in-person or may be conducted remotely (e.g., via telemedicine) if necessary. Your last study visit (Week 52) will be conducted in-person. Each visit should take no longer than 1 hour to complete. Between visits the study doctor or study staff may contact you by phone or email to remind you of your next visit and/or to check whether you are having any problems or concerns. It is very important that you complete each visit.

When your study burn is checked for healing the study doctor or staff may do any or all the following:

- Perform a physical assessment, which may include measurement of all or some of the following: temperature, blood pressure, respiration rate, heart rate and weight
- Review your wound(s) including looking at the rate of healing
- Check for any infection or other complications
- Dress your burns as necessary
- Take photographs of your healing burns and/or scars
- Ask simple questions regarding pain and itching

- Ask about medications or supplements you may have taken since your last visit
- Ask about procedures or therapies you may have had since your last visit
- Ask about dressing changes you may have performed at home on your study burns
- Review any adverse events you may have experienced
- Provide you with or read to you a study questionnaire for you to complete

HEALTH ECONOMICS

This study contains a health economics review that will be done to look at reasonable medical expenses, which occur as a direct result of your participation in this clinical trial. Representatives of the Sponsor of this trial will collect data from the Patient Accounting Department at this hospital and any other hospital to which you are admitted from the time of enrollment in this study through the study follow-up period. This is being done to collect data associated with treatment costs. Your name and other information that can identify you will be removed from the billing records so that your privacy is maintained. This is explained in more detail later in this document.

CAN ANYTHING BAD HAPPEN TO ME?

Risks of the study procedures

The risks of the initial burn wound cleaning, the RECELL procedure or graft surgery (if required) include those associated with any surgical procedure or those that may involve general anesthesia.

They may include:

- Reactions to the anesthesia
- Reactions to the medications
- Nausea and vomiting
- Problems breathing
- Excessive bleeding at the burn or donor site
- Changes in blood pressure and heart function
- Changes in lung function
- Constipation
- Blood clot
- Problems with urinary catheterization
- Fever and chills

Complications that may occur at the study treatment area, RECELL skin sample donor site, skin graft donor site or skin graft site include:

- Rejection or loss of the skin graft
- Delayed healing at the study treatment area or skin donor sites
- Pain
- Infection
- Skin irritation
- Itching
- Redness
- Scarring
- Skin discoloration and/or uneven skin surface
- Granulation tissue (a buildup of new connective tissue and tiny blood vessels that may form on a wound)
- New injury to treatment area, graft or donor areas
- Blisters on treatment area, graft or donor areas
- Hematoma (collection of blood), seroma (collection of serum) or swelling at the treatment area, graft or donor areas
- Neuralgia (nerve pain) at the treatment area, graft or donor areas

In addition to the above noted risks, possible risks from using the skin cell suspension prepared from the RECELL Device include an allergic reaction to trypsin (an enzyme used in the RECELL Device) or sodium lactate solution used to prepare the RECELL skin cell suspension. There is also the possibility that there could be an allergic reaction to the dressings used to protect the treatment areas, graft or donor sites.

Risks during the healing period

If a wound becomes infected, does not get enough oxygen, or the skin graft/sprayed-on cells do not work as expected there may be increased scarring and delayed healing or loss of healing. This may result in the need for further surgical treatment. Surgical treatment could include surgical removal of dead or infected tissue in the wound, placement of a skin substitute, or re-grafting the wounded area.

Your study doctor will look at the wounds very closely and he/she will try to take care of any complications as fast as they can. The treatment of side effects and complications will be the same that would be expected for the treatment of side effects and complications for any burn wound or skin grafting procedure performed at the hospital.

OTHER RISKS

Because use of the RECELL Device may have unknown risks to a pregnant mother and her fetus or to a nursing infant you may not participate in this study if you are pregnant or nursing. If you suspect that you have become pregnant, you must notify the study doctor immediately.

There is a risk of equipment malfunction that could result in the need to harvest additional donor skin.

Side effects can also occur after you leave the hospital, so it is important that you attend all the scheduled follow-up appointments. You should also tell your doctor if you suspect any side effects, such as prolonged redness of the area, irritation, infection, or worsening pain.

There is a low risk of loss of confidentiality of your personal information; however, steps have been taken to help ensure this will not happen. You will read more about the protection of your information later in this form.

There may be risks or side effects that are unknown at this time.

WILL I BENEFIT FROM THIS RESEARCH?

There may or may not be direct benefits from being in this study. A published study has shown that use of the cell suspension prepared using the RECELL Device on skin graft donor sites which are a type of partial-thickness skin injury resulted in faster healing. When the cell suspension is applied alone onto second-degree injuries or used in combination with skin grafting to more severe wounds, application of the cell suspension resulted in healing comparable to that of typical skin grafts but used less donor skin. It is also possible, however, that you will receive no benefit. The information collected in this study may also lead to an improved understanding of the resources required to manage your condition, and the associated costs. The findings from this study may provide healthcare providers and hospital decision makers with important information for treating partial-thickness burns in the future.

WILL I GET PAID?

You will receive a $50.00 gift card for each follow-up visit completed to cover fair and reasonable travel expenses to the clinical site. If you withdraw for any reason from the study before completing your follow up visits or fail to show up for a follow up visit, you will not receive payment for those visits.

The findings from this research may result in the future development of products that are of commercial value. You will not receive financial compensation or share in any profits if this should occur.

WILL IT COST ANYTHING TO BE IN THE STUDY?

You will not be charged any additional costs for participating in the study. The only costs you will have are those expected from having your burn treated by conventional means alone.

WHAT OTHER TREATMENT CHOICES ARE THERE?

There are other methods that are used to treat partial-thickness burns that could be offered to you. Your burns could be treated with wound dressings alone, or whatever treatment your doctor and the hospital usually use.

If you choose not to participate in this study, your care will in no way be affected. Your doctor will ensure that you receive appropriate treatment for your burn wounds. Your decision not to participate will not be recorded in your medical records.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?
Taking part in this study is voluntary. You may decide not to participate, or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits you are entitled to. If you decide to stop participating in the study, we encourage you to talk to your study doctor or study staff first to be sure you understand any potential health or safety consequences.

Your study doctor, your local institution and the sponsor of this study, have the right to stop your participation in the study, or cancel the study, without your consent at any time for any of the following reasons:

- if it is in your best interest;
- you do not consent to continue in the study after being told of changes in the research that may affect you;
- or for any other reason.

NEW FINDINGS
You will be given any new information we become aware of that would affect your willingness to continue to participate in the study. In some cases, a new consent form will be given to you to sign, if you wish to remain in the study.

WHAT HAPPENS IF I GET HURT IN THE STUDY?
If you experience an illness, adverse event, or injury that is the result of a device, intervention, procedure, or test required for this study, the sponsor of the study, AVITA Medical, maintains product liability insurance coverage and recognizes its responsibility for design and manufacturing defects in products that it designs, manufactures and markets. You should notify the study doctor as soon as you believe you have experienced any study related illness, adverse event, or injury.

The study doctor and the sponsor will determine if the event or injury was a result of your participation in this study. The sponsor is not responsible for expenses that are due to pre-existing medical conditions, underlying disease, your negligence or willful misconduct, or the negligence or willful misconduct of third parties. You do not give up any legal rights as a research participant by signing this consent form.

For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call the hospital's Institutional Review Board (IRB) chairperson _____ at _____.

WILL THE HOSPITAL, STUDY DOCTOR, OR AVITA MEDICAL BENEFIT FROM THIS STUDY?
The sponsor is providing money and other support to help with this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WHAT ABOUT THE USE, DISCLOSURE AND CONFIDENTIALITY OF HEALTH INFORMATION?
By taking part in this study, your personal health information, as well as information that directly identifies you may be used and disclosed by the study doctor, sponsor and agents of the sponsor. Information that identifies you includes, but is not limited to, such things as your name, address, telephone number, and date of birth. Your personal health information includes all information about you that is collected or created during the study for research purposes. It also includes your personal health information that is related to this study and that is maintained in your medical records or billing records at this institution and at other places such as other hospitals and clinics where you may have received medical care. Examples of your personal health information include your health history, your family health history, how you respond to study activities or procedures, laboratory and other test results, medical images (including photographs), and information from study visits, phone calls, surveys, and physical examinations.

Your personal health information and information that identifies you may be given to others during and after the study. This is might happen if it is necessary in order to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor, AVITA Medical; representatives of the Sponsor; investigators at other sites who are assisting with the research; reading or analysis centers; Department of Health and Human Services (DHHS) agencies; Governmental agencies in other

countries, Governmental agencies to whom certain diseases (reportable diseases) must be reported; the Institutional Review Board; representatives of _____ Hospital who are eligible to review research records, in addition to the Food and Drug Administration (FDA).

As noted previously, this study contains a health economics review that will be done to assess medical expenses which occur as a direct result of your treatment within this clinical trial. Representatives of the Sponsor of this trial will collect hospital and physician billing data from the Patient Accounting Department at this hospital from the time of enrollment in this study through the study follow-up period.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study.

This research study involves the treatment or diagnosis of a medical condition and information collected or created as part of the study may be placed in your medical record and discussed with individuals caring for you who are not part of the study. This will help provide you with appropriate medical care. In addition, all or part of your research related health information might be used or disclosed for treatment, payment, or healthcare operations related to providing you with medical care.

When you sign this consent and authorization form you authorize or give permission for the use of your health information as described in the consent form. You can cancel your authorization to use and disclose your health information at any time by sending a written notice to the investigator in charge of the study at the following address:

_____ (Principal Investigator)

_____ (Facility)

_____ (Mailing Address)

If you do not authorize this use or withdraw your authorization you will not be able to be in this study. If you withdraw your authorization, no new health information that identifies you will be gathered after that date. Your health information that has already been gathered may still be used and disclosed to others. This would be done if it were necessary for the research to be reliable. You will not have access to your health information that is included in the research study records until the end of the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions or complaints about the study or in the event of a research-related injury, contact the study investigator, _____ at _____.

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, you should contact the Chairperson of the IRB at _____.

The IRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact the IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Your signature below will show that you acknowledge and agree that:

- You (your child) understand this consent form
- You (your child) will freely take part in this research study,
- You have had a chance to ask questions and all your questions have been answered,
- You authorize the release of medical and research records for the purpose of this study and
- You have understood the information above

By signing this consent form, you have not given up any of your legal rights.

You will be given a signed copy of this consent form.

SIGNATURES
I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have had those questions answered and voluntarily consent to participate in this study. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

CONSENT SIGNATURE:

All children are required to assent, unless the investigator determines that the capability of the child is so limited that the child cannot reasonably be consulted.

If assent is obtained, have the person obtaining assent document this on the consent form.

_____
Name of Participant (minor child)

_____ _____
Signature of Participant (minor child) Date

OR

_____ _____
Signature of Parent or Legal Guardian Date

_____
Relationship to Participant (Parent, Legal Guardian, etc.)

STATEMENT OF PERSON CONDUCTING INFORMED CONSENT DISCUSSION

Using language that is understandable and appropriate, I have discussed this study and the items listed above with the participant and/or their authorized representative. I have asked whether or not any questions have arisen regarding the investigational procedure and have answered those questions to the best of my ability.

_____ _____
Signature of the person who conducted the informed consent/assent discussion Date

_____ _____
Print Name Study Role

20.3 APPENDIX C: SUBJECT/PARENT/GUARDIAN AFTERCARE INSTRUCTIONS