CONTINUED ACCESS PROTOCOL: 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

Investigational Plan

Study Number: CTP001-7

Device: ReCell Autologous Cell Harvesting Device

Study Type: IDE Study (IDE 13053)

Date: August 25, 2016

Sponsor: Avita Medical Americas, LLC
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PRINCIPAL INVESTIGATOR'S STATEMENT

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

Signature: _____ Date: _____
Principal Investigator

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APPENDICES

0.0 TABLE OF REVISIONS

Location of Change	*Changed from*	*Changed to*	*Comment*
Throughout	CTP001-6	CTP001-7	Protocol designator updated to have protocol version specific to Continued Access
Throughout	Formal hypothesis statements	Analyses for informational purposes only – All hypothesis statements have been deleted	This protocol is intended to allow for continued access to the ReCell device and as such no formal hypotheses will be investigated.
Section 1.0 Protocol Summary	Enrollment limited to 30 subjects	Enrollment increased to up to 60 subjects	Requesting approval to allow for up to 60 subjects to be treated under CTP001-7. This allows for approval for anticipated subject accrual for the period between protocol approval and anticipated timing for ReCell FDA marketing approval.
Section 1.0 Protocol Summary / Purpose	The objective of this investigation is to evaluate the safety and effectiveness of ReCell when used as an adjunct to meshed skin graft in patients requiring skin grafts for closure of burn injuries.	The overall purpose of this is study to provide continued access to the ReCell device following completion of protocol CTP001-6, and allow for collection of supplementary clinical outcome data for the ReCell device when used as an adjunct to meshed grafts in subjects with acute thermal burn injuries who require skin grafting for closure of burn injuries.	Updated study purpose to reflect continued access.
Section 1.0 Protocol Summary / Analyses	--	Data will be analyzed and summarized in an interim analysis at a time to coincide with the submission of the ReCell marketing application. At that time all available data will be presented. Data will be analyzed consistent with the CTP001-6 protocol; however, there are no formal statistical hypotheses to be investigated.	New section to clarify timing of analysis and overall strategy for analysis.

Location of Change	*Changed from*	*Changed to*	*Comment*
Section 2.1 Introduction	--	Added statement: The purpose of this protocol is to allow Investigators who have participated in CTP001-6 protocol conducted under IDE 13053 to continue to enroll subjects into the clinical investigation while Avita Medical prepares the marketing application for the ReCell device. There are no substantive changes to the CTP001-6 to render this Continued Access protocol (CTP001-7), as the study design and endpoints remain unchanged. All clinical data collected under this Continued Access Protocol that is available at the time Avita Medical submits the ReCell marketing application will be included within the application. Subject follow-up will continue until the last enrolled subject completes the 52-week visit.	Provide clarification for the purpose of the continued access protocol.
Section 2.3 Prior Investigations – Summary of CTP001-5 protocol	As of July 31, 2014, 98 subjects have been enrolled in the pivotal study since subject enrollment was initiated on May 27, 2010. There have been no adverse events indicative of systemic toxicity or poor tolerability associated with the use of ReCell within the CTP001-5 cohort.	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 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	Represents update to -5 protocol.

Location of Change	*Changed from*	*Changed to*	*Comment*
		Office (HRPO) or Human Patients Research Review Board (HSRRB). There have been no adverse events indicative of systemic toxicity or poor tolerability associated with the use of ReCell within the CTP001-5 cohort.	
3.0 Intended Use *and* Appendix A3	The ReCell® Autologous Cell Harvesting Device (ReCell) is intended to be used at point-of-care for the safe and rapid preparation of skin cell suspension from a small sample of a patient's own skin. Under the supervision of a healthcare professional, the cell suspension produced by the ReCell system is suitable for use as an adjunctive treatment of burn wounds requiring grafting.	The ReCell Autologous Cell Harvesting device is an autograft-sparing technology indicated for use at the patient's point-of care for preparation of an autologous epithelial cell suspension to be applied to a prepared wound bed. Under the supervision of a healthcare professional, the suspension is used to achieve epithelial regeneration for definitive closure of burn injuries, particularly in patients having limited availability of donor skin for autografting.	Intended use updated based on current indication agreed to by FDA for Expedited Access Pathway designation
4.2 Study Duration	Thirty (30) subjects will be enrolled and treated within this study. It is anticipated that enrollment will be completed within a 9-month period.	Up to 60 subjects will be enrolled and treated within this study. It is anticipated that enrollment will be completed within an 18-month period. Subject follow-up will continue until the last enrolled subject completes the 52-week visit.	Section updated to reflect anticipated enrollment within the continued access protocol.
6.3 Interim Analyses	No interim analyses for evaluation of the primary effectiveness endpoints are planned. However, it is planned that data from this clinical investigation will be summarized in	Data will be analyzed and summarized in an interim analysis at a time to coincide with the submission of the ReCell marketing application. At that time all available data will be presented. Subject	Section updated to describe anticipated timing for an interim analysis of data collected under this protocol.

Location of Change	*Changed from*	*Changed to*	*Comment*
	a Clinical Study Report (CSR) and presented to the FDA once all subjects have completed their 36 week visit. All available data including 52 week data for subjects who have completed the study at that time will be included in the report. The CSR will be amended once all subjects have completed the study.	follow-up will continue until the last subject treated under this Continued Access Protocol has completed their 52 week visit.	
Section 7.2.8	The Investigator must notify Avita Medical as soon as possible, within 24 hours, of learning of a subject's death, regardless of whether the death is related or unrelated to the investigational device.	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.	Modified to be consistent with Section 7.2.10 and Table 3 (Section 11).

1.0 PROTOCOL SUMMARY

Title: **CONTINUED ACCESS PROTOCOL:** 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

Purpose: The overall purpose of this is study to provide continued access to the ReCell device following completion of protocol CTP001-6, and to allow for collection of supplementary clinical outcome data for the ReCell device when used as an adjunct to meshed grafts in subjects with acute thermal burn injuries requiring skin grafting for closure of burn injuries.

Design: This is a prospective, randomized, multicenter, evaluator blinded, within-subject controlled study. Patients 5 years or older with a total body surface area (TBSA) thermal burn injury between 5 and 50% (inclusive) will be considered for participation in this study. Following burn excision and confirmation of eligibility, a grafting plan will be developed and documented in accordance with investigators' standard of care. Among the excision sites, two comparable contiguous or non-contiguous areas (i.e., similar in burn injury depth, graft plan and size) at least 300 cm^2 in size will be identified and labeled as Area A and Area B. The wound regions will be randomly assigned to receive grafting consistent with the Investigator's pre-identified graft plan (control) or to receive application of the ReCell-generated cell suspension applied over a graft more widely meshed than identified in the pre-specified graft plan (ReCell-treated). For example, if the graft plan called for a 2:1 mesh graft, for the ReCell-treated wounds, the area will be treated with 3:1 mesh graft and over-sprayed with the ReCell-generated cell suspension. The donor area for skin allocated to ReCell and control treatment areas will be measured and documented. The two treatment areas will be compared with respect to healing characteristics and the amount of donor skin harvesting required.

Follow-up visits will be performed at 1, 2, 4, 6, 8, 10, 12, 24, 36 and 52 weeks post treatment. Acute healing and pain outcomes will be evaluated in the early post-operative period (i.e., through 12 weeks). Pain, healing durability and scar outcomes will be evaluated in the longer-term follow-up visits (i.e., 24, 36 and 52 week visits). Treatment-related and serious adverse events will be captured throughout the duration of the study.

Treatment-area closure will be evaluated via direct visualization by the treating investigator and by a qualified clinical investigator blinded to treatment allocation (i.e., Blinded Evaluator). The blinded assessment will serve as the primary healing assessment.

At all visits, all subjects' study treatment areas will be documented photographically using standardized digital photography. 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 patient.

Co-primary Effectiveness Endpoints:

1. Confirmed treatment area closure at (or prior to) the Week 8 visit. Complete wound closure is defined as skin re-epithelialization without drainage, confirmed at two consecutive study visits at least 2 weeks apart by direct visualization by a qualified clinician. Blinded Evaluator assessment of wound closure will be performed at Weeks 4, 6, 8, 10 and 12.

2. The actual expansion ratios (treatment area to donor site area, inclusive of donor skin needed for secondary treatments) will be calculated separately for the ReCell and control treatments.

   Treatment area and donor area will be based on measurements of the treatment and donor site wound bed at the time of the grafting procedure (obtained intra-operatively). Calculation of expansion ratios will include any donor skin required for re-treatments performed to achieve wound closure, if applicable.

Additional Effectiveness Endpoints: The following additional effectiveness endpoints will be investigated: Subject Satisfaction at Week 24 (evaluating whether there is a preference for the ReCell treatment), 24 Week Observer POSAS Overall Opinion Score and 24 Week Patient POSAS Overall Opinion Score.

Safety: Safety will be assessed with evaluation of the following:

1. Delayed healing (all visits)
2. Infection (all visits)
3. Allergic response to trypsin (all visits)
4. Treatment area durability, in terms of any evidence of recurrent wound breakdown following initial complete closure (Week 12, 24, 36 and 52)
5. Scars necessitating surgical intervention
6. Treatment-area pain via numeric rating scale (1-10, where 1 represents no pain and 10 represents worst possible pain) will be evaluated at all visits, and incorporated as a component of the POSAS beginning at Week 12
7. Treatment-related and serious adverse events (all visits)

Other Evaluations:

1. Healing assessment by treating investigator (all visits)
2. POSAS and Subject Satisfaction evaluations at Week 12, 36 and 52
3. Subject and Blinded Evaluator blinding effectiveness

Enrollment: Up to 60 patients enrolled at up to 18 investigational sites in the United States.

Analyses: Data will be analyzed and summarized in an interim analysis at a time to coincide with the submission of the ReCell marketing application. At that time all available data will be

presented. Data will be analyzed consistent with the statistical plan develop for the CTP001-6 protocol; however, there are no formal statistical hypotheses to be investigated.

2.0 BACKGROUND

2.1 INTRODUCTION

In 2009, Avita Medical, with support of the Armed Forces Institute for Regenerative Medicine (AFIRM), initiated a multicenter randomized within-patient controlled study to investigate the use of the ReCell® Autologous Cell Harvesting Device for treatment of specific burn injuries. Data from this study was intended to support a premarket application to the FDA to obtain marketing approval for the device. The ReCell burns study (reference CTP001-5) was designed to evaluate ReCell treatment (alone) versus conventional meshed split-thickness skin grafts (alone) on particular partial-thickness thermal injury (deep, but with confluent dermis). By contrast, the overwhelming clinical use of ReCell is in conjunction with mesh graft on mixed-depth injuries including deep partial-thickness without confluent dermis and including areas of full-thickness injury. ReCell has been a successful part of burn care when used in conjunction with grafting, as evidenced by recent large-scale publications of outcomes concerning infection rates[1] and length of hospital stay[2], and successful patient outcomes from recent US FDA-approved Compassionate Use Cases. With a shift in standard care away from the use of skin grafting for deep partial-thickness injury, completion of recruitment in CTP001-5 seemed an insurmountable hurdle, and in any event the study design is directed toward a research question of less relevance than it had years ago.

Rather than as a replacement for mainstay skin grafting practice in burn care, ReCell has the potential for more clinically relevant use as an adjunct to skin grafting, enabling a reduction in the required area of donor harvesting via use of increased meshing ratios without compromising short- or long-term outcomes (healing, durability, scar). Protocol CTP001-6 was conducted with the purpose of demonstrating that the ReCell system is suitable for use as an adjunctive treatment of burn wounds requiring grafting.

The purpose of this protocol is to allow Investigators who have previously participated in IDE 13053 to continue to enroll subjects into the clinical investigation while Avita Medical prepares the marketing application for the ReCell device. There are no substantive changes to the CTP001-6 to render this Continued Access protocol (CTP001-7), as the study design and endpoints remain unchanged. All clinical data collected under this Continued Access Protocol that is available at the time Avita Medical submits the ReCell marketing application will be included within the application. Subject follow-up will continue until the last enrolled subject completes the 52-week visit.

2.2 RECELL (THE INVESTIGATIONAL DEVICE)/JUSTIFICATION FOR INVESTIGATION

ReCell is designed to provide an environment to enhance skin regeneration, and to facilitate rapid wound healing, providing the potential to eliminate or minimize scar formation and reduce existing scars. By introducing an autologous epidermal cell suspension onto a meshed graft, the ReCell technology takes advantage of, and enhances, the body's natural regenerative response to heal itself.

[1] Park JH, Heggie KM, Edgar DM, Bulsara MK, Wood FM. (2013). Does the type of skin replacement surgery influence the rate of infection in acute burn injured patients? Burns (39) 1386-1390.

[2] Lim J, Liew S, Chan H, Jackson T, Burrows S, Edgar DW, Wood FM. (2014). Is the length of time in acute burn surgery associated with poorer outcomes? Burns (40) 235-240.

ReCell has been demonstrated to deliver viable keratinocytes, melanocytes, fibroblasts and Langerhans cells to the wound surface.[3] Preliminary clinical data demonstrate that wounds treated with ReCell rapidly re-epithelialize with reduction of systemic effects, wound infection or adverse reactions, yield improved scar texture, reduce contracture, heal free of erythema and achieve re-pigmentation at the treatment site.[4, 5,6,7,8]

ReCell is a disposable, stand-alone and fully self-contained, battery powered, autologous cell harvesting and processing device containing enzymatic and carrier solutions, sterile surgical instruments and spray applicators. The device is designed to facilitate rapid harvest of autologous cells from the epidermal dermal junction using a combination of enzymatic and physical disruption and the immediate application of a non-cultured epidermal suspension to the wound area via an aerosol spray syringe. ReCell does not require use of specialized laboratory or staff. The ReCell suspension consists of a mélange of viable keratinocytes, melanocytes, fibroblasts and Langerhans cells suspended within a mixture of growth factors, cytokines, τPA, μPA and receptors. The ReCell suspension essentially resets the wound response from 'inflammatory' and 'damage-control' (inflammation, myofibroblast-mediated contraction, etc.) to "proliferation" and "growth" (production of growth factors, proliferation and migration of cells, etc.), taking advantage of and controlling the body's natural response to heal. Introduction of the cells from an uninjured area programmed for regeneration into the wounds directly influences the rate of epithelialization and the underlying wound bed.

ReCell is based on previous work of Wood & Stoner and the recognition that autologous transplantation of epidermal cells could offer long-term wound closure in a clinically advantageous time-frame while optimizing the patient's outcome.

ReCell is designed to provide a simple, safe technique for the harvesting of epidermal cells for enhancement of epidermal repair. The initial step involves harvesting a small split-thickness skin biopsy (1/80th of the intended treatment area), followed by enzymatic and mechanical processes to allow for separation of the cells and creation of a suspension consisting of a mixed population of live keratinocytes, melanocytes, papillary fibroblasts and undifferentiated cells of the basal junction. The suspension is then applied onto the prepared meshed graft. The cells migrate over the surface of the interstices of the meshed graft providing epidermal reconstruction with normal color and texture. The applied cells are incorporated into the developing epidermis. The speed of epithelialization is crucial as the "sealing" of the skin surface limits the

[3] Stoner ML, Wood FM. (2000). The treatment of hypopigmented lesions with cultured epithelial autograft. *J Burn Care Rehabil*, 21 (1 Pt 1), 50-54.

[4] Cervelli V, De Angelis B, Spallone D, Lucarini L, Arpino A and Balzani A. (2009). Use of a novel autologous cell-harvesting device to promote epithelialization and enhance appropriate pigmentation in scar reconstruction. *Clin Exp Derm*, 35, 776-780.

[5] Gravante G, Di Fede MC, Araco A, Grimaldi M, De Angelis B, Arpino A, Cervelli V and Montone A. (2007). A randomized trial comparing ReCell® system of epidermal cells delivery versus classic skin grafts for the treatment of deep partial thickness burns. *Burns* 33, 966-972.

[6] Goodman GJ. (2008). An automated autologous cell transplantation method for the treatment of hypopigmented scarring. *Dermatol Surg*, 34, 578-581.

[7] 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.

[8] 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.

inflammation that has been implicated as the pivotal factor in hypertrophic scar formation. By providing a source of viable and metabolically responsive epithelial cells into the interstices of a meshed graft, ReCell has the potential to provide wound coverage while minimizing the donor skin requirements and may improve the healing process by improving graft take and minimizing the hypertrophic meshed scar associated with the use of meshed split-thickness grafts.

2.3 PRIOR INVESTIGATIONS AND MARKET EXPERIENCE

The safety of ReCell has been demonstrated with some 5,000 treatment procedures conducted worldwide. ReCell has CE Marking in Europe, TGA clearance in Australia, SFDA clearance in China and Health Canada approval as well as approval in other markets (e.g., Taiwan, Hong Kong, Mexico, Brazil and Venezuela). There have been no reports of adverse events associated with the use of ReCell that have met the requirements for vigilance reporting to regulatory authorities.

Furthermore, the ReCell device has been evaluated in several clinical studies and has been the subject of several literature publications and case studies evaluating the use of the device for treatment of burn wounds, as well as other skin defects. The clinical experience with the ReCell device can be categorized as follows:

- A total of 147 Patients have been treated in three clinical studies conducted in Europe and Australia. In these studies, the ReCell device was evaluated for various types of epidermal reconstruction, including 48 patients treated for burn wounds. These studies included both pediatric and adult patients. Safety was assessed based on adverse events, vital signs and concomitant medication. Percent epithelialization of ReCell-treated recipient sites was assessed through a minimum of 6 weeks. Within these studies, use of the ReCell device in epidermal restructuring was well tolerated. Among all patients treated, there was no association between use of the ReCell device with any alteration in vital signs. Overall the safety profile of ReCell device observed in these studies demonstrated that the ReCell device can be used in patients requiring epidermal restructuring without causing any systemic toxicity. Although the three studies were uncontrolled and evaluated patients with TBSA involvement less than 4%, re-epithelialization of the recipient wound regions proceeded well within the first weeks after treatment, with many of the treated wounds achieving nearly complete closure within the first week, with complete closure achieved for nearly all patients by Week 6. Therefore, application of the ReCell device demonstrated the clinical benefit of coverage of a larger wound defect from a skin cell suspension prepared from a much smaller skin sample compared with traditional methods of skin grafting.

- In a prospective clinical study performed by Gravante et al, the ReCell device was compared to conventional meshed split-thickness skin grafts (STSGs) to treat deep partial-thickness burns.[5] In this study 42 patients were treated with ReCell and 40 patients underwent conventional grafting. Healing was complete in approximately 13 days for the ReCell and 12 days for the classic grafting group ($p > 0.05$). Sixty-nine patients needed only one operative procedure (84.1%), 13 required two steps (16.9%) to complete few remaining areas that did not heal, and no significant differences were observed between groups for patients requiring two procedures (7 in the ReCell group versus 6 in the grafting group). Of the 82 study patients, 27 (33%) developed at least one contracture at hospital discharge after one month from surgery. Of these, 12 were after ReCell and 15 after skin grafting

(chi-square test: not significant between groups). None of the 82 patients reported intraoperative or postoperative adverse effects.

- In small study reported by Zajicek et al, application of ReCell to widely meshed grafts in 14 patients with deep burns resulted in faster re-epithelialization compared with control wounds where ReCell was not applied. Additionally, successful ReCell treatment adjunct to mesh grafting over engrafted Integra Dermal Regeneration Template and ReCell treatment of donor sites was reported by O'Neill et al.[9,10]

- Under BB IDE 13053, protocol CTP001-5, the safety and effectiveness of the ReCell device for coverage of partial thickness burn wounds has been investigated. 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 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). There have been no adverse events indicative of systemic toxicity or poor tolerability associated with the use of ReCell within the CTP001-5 cohort.

3.0 INTENDED USE OF THE INVESTIGATIONAL DEVICE (PROPOSED INDICATION)

The proposed indication for use for the ReCell device is as follows:

The ReCell Autologous Cell Harvesting device is an autograft-sparing technology indicated for use at the patient's point-of care for preparation of an autologous epithelial cell suspension to be applied to a prepared wound bed. Under the supervision of a healthcare professional, the suspension is used to achieve epithelial regeneration for definitive closure of burn injuries, particularly in patients having limited availability of donor skin for autografting.

4.0 STUDY DESIGN, DURATION AND OBJECTIVES

4.1 STUDY DESIGN

This is a prospective, randomized, multicenter, evaluator blinded, within-subject controlled study being performed to allow for continued evaluation of the safety and effectiveness of ReCell when used as an adjunct to meshed grafts in subjects with acute thermal burn injuries requiring skin grafting for closure.

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[9] Zajicek R, Pafcuga I, Suca H, Konigova R, Broz L, Matouskova E. (2012). Healing of widely meshed autografts using freshly isolated autologous epidermal cells and acellular xe-derma xenodermis. Hojeni Ran 6(2).

[10] O'Neill TB, Rawlins J, Rea S, Wood F. (2012). Complex chemical burns following a mass casualty chemical plant incident: how optimal planning and organisation can make a difference. Burns. 38(2012), 713-718.

This study will compare the use of the ReCell-generated cell suspension applied over a graft more widely meshed than a standard comparator. For example if the standard (control) graft plan calls for a 2:1 mesh graft, this will be compared to treatment with a 3:1 meshed graft that is over-sprayed with the ReCell-generated cell suspension. The donor area for harvested skin allocated to the ReCell and control treatment areas will be measured and documented. The two treatment areas will be compared with respect to healing characteristics and donor skin requirements.

Specific co-primary effectiveness endpoints of this study include: (1) Confirmed treatment area closure (healing) prior to or at 8 weeks. (2) Comparison of the actual expansion ratios associated with the two treatment areas at the time of treatment. Data will be analyzed consistent with those from the CTP001-6 protocol; however, there are no formal statistical hypotheses to be investigated.

The following additional effectiveness endpoints will be investigated: Subject Satisfaction at Week 24 (evaluating whether there is a preference for the ReCell treatment), 24 Week Observer POSAS Overall Opinion Score and the 24 Week Patient POSAS Overall Opinion Score.

Safety will be evaluated in terms of long-term durability, scarring necessitating surgical intervention and treatment-related adverse events.

4.2 STUDY DURATION

Each subject will participate in up to 11 total visits (treatment visit and 10 follow-up study visits) over a period of 52 weeks. Up to 60 subjects will be enrolled and treated within this study at up to 18 institutions. It is anticipated that enrollment will be completed within an 18-month period. Subject follow-up will continue until the last enrolled subject completes the 52-week visit.

4.3 STUDY OBJECTIVES

The overall objective of this is study to provide continued access to the ReCell device following completion of protocol CTP001-6, and to allow for collection of supplementary clinical outcome data for the ReCell device when used as an adjunct to meshed grafts in subjects with acute thermal burn injuries who require skin grafting for closure. Effectiveness and safety endpoints are delineated below. See also **Section 6.10** and **Section 6.11** for further details. These endpoints and endpoint assessment remain consistent with Protocol CTP001-6.

4.3.1 Co-Primary Effectiveness Endpoints

4.3.1.1 Confirmed Treatment Area Closure at (or prior to) the Week 8 Visit

Treatment area closure is defined as complete re-epithelialization without drainage, confirmed at 2 consecutive study visits at least 2 weeks apart (e.g., at Week 6 and Week 8, or if a visit is missed, Week 8 and Week 12) by direct observation by a local investigator blinded to treatment assignment (i.e., Blinded Evaluator).

4.3.1.2 Ratio of Actual Expansion Ratios

The actual expansion ratio, computed as the ratio of measured treated area to the measured donor site area, will be calculated for the ReCell-treated and control treatments. Then, the actual expansion

ratio for the ReCell-treated area will be compared to the actual expansion for the control. The actual expansion ratios will be compared as a new ratio (a ratio of ratios), i.e. ReCell-treated area/ReCell-associated donor site area: Control area/Control-associated donor site area.

Treatment area and donor area will be based on measurements of the treatment and donor site wound bed at the time of the grafting procedure (obtained intra-operatively). Calculation of expansion ratio will include any donor skin required for re-treatments performed to achieve wound closure, if applicable.

4.3.2 Additional Effectiveness Endpoints

The following additional effectiveness endpoints will be investigated:

1. Subject Satisfaction at 24 Weeks: Subject satisfaction will be measured by asking the subject to specify which treatment region they are more satisfied with (Area A or Area B).
2. POSAS – 24 Week Observer Overall Opinion Score: The observer component of the POSAS questionnaire requires the Blinded Evaluator to provide an overall opinion of the treatment area compared to normal skin scored from 1 (normal skin) to 10 (worst imaginable scar).
3. POSAS – 24 Week Patient Overall Opinion Score: The patient component of the POSAS questionnaire requires the subject to provide an overall opinion of the treatment area compared to normal skin scored from 1 (normal skin) to 10 (worst imaginable scar).

As noted above, the standard and comprehensive[7] Patient and Observer Scar Assessment Scale (POSAS)[8] will be employed in this study, as a standard tool for capturing both a physician observer and patient assessment of the scar post-treatment.[11] 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.[12]

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 authors' 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 ($r=0.89$, $p < 0.001$).[13]

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

[12] 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.

[13] Durani P, McGrouther DA, Ferguson MWJ. (2009). Current scales for assessing human scarring: a review. *J Plast Reconstr Aesthet Surg*, 62(6), 713-720.

The POSAS is presented in **APPENDIX A2. PROCEDURE FOR SCAR RATING (POSAS)**. The observer component of the POSAS will be performed by the Blinded Evaluator; i.e., a site investigator blinded to treatment assignment. Additionally, as the subject will not be told which study treatment area was treated with the ReCell device (and which was not), the patient assessment will also be blinded.

4.3.3 Safety Endpoints/Assessments

Safety of the ReCell device will be based on the following:

4.3.3.1 Delayed Healing

Treatment areas that do not heal within 8 weeks from the primary study procedure, based on the investigator's assessment, will be considered to have delayed healing.

4.3.3.2 Infection

The presence of infection will be evaluated at each postoperative visit. Infection will be evaluated in accordance with standard clinical measures such as visual examination of the treatment areas for purulence, erythema, pain, tenderness, warmth, induration, and cellulitis or more severe systemic symptoms of infection. Infection assessment will take place for both the ReCell-treated and the control areas that will allow for comparisons to be drawn. Refer to **Section 7.2.5.1** for additional details.

4.3.3.3 Allergic Response to Trypsin

The allergic response to Trypsin[14] will be evaluated preoperatively and at every postoperative visit. The evaluation tools for assessment of the allergic response to Trypsin are identified in **Section 7.2.5.2** and **APPENDIX A4. ASSESSMENT OF HYPERSENSITIVITY TO TRYPSIN**.

4.3.3.4 Treatment Area Durability

Wound durability, in terms of the incidence of recurrent wound breakdown following initial complete closure, will be documented as an adverse event.

4.3.3.5 Scars Necessitating Surgical Intervention

Scars that, in the opinion of the investigator, necessitate surgical intervention will be documented as adverse events. This includes, but is not necessarily limited to: dermabrasion and/or laser resurfacing, contracture release and scar excision and regrafting.

4.3.3.6 Pain

Treatment area pain will be assessed at all follow-up visits using a numeric pain scale of 1-10, where 1 represents no pain and 10 represents worst possible pain. Beginning at Week 12, pain assessments will be made as a component of the POSAS.

[14] Trypsin is the enzyme used in the ReCell Device for disaggregation of the biopsy

4.3.3.7 Treatment-Related and Serious Adverse Events

All treatment-related and serious adverse events occurring during the course of the clinical study (beginning from the initiation of the grafting procedure), whether related to the investigational device or otherwise, will be recorded on the AE Case Report Form. For all treatment-related and serious AEs, the Investigator must provide an assessment of the event, treatment resolution, and relationship to the investigational device. See also **Section 7.2.**

4.3.4 Additional Data Collection

4.3.4.1 Unblinded Healing Assessment

Subjects treated under this protocol will be followed for wound healing by the treating investigator(s), and the assessments will be documented in the CRF. Wound healing will be defined consistent with the definition identified in **Section 4.3.1.1.**

4.3.4.2 Subject Satisfaction and POSAS At Weeks 12, 36 and 52

Subject Satisfaction and POSAS ratings at Weeks 12, 36 and 52 will be documented and reported.

4.3.4.3 Blinding Effectiveness

Blinding effectiveness will be evaluated for both the Blinded Evaluator and the Subject.

At Week 8, the Blinded Evaluator will be asked to indicate which treatment each area received. Potential responses are ReCell, Control or unsure.

At Week 24, the Subjects will be asked to indicate which treatment each area received. Potential responses are ReCell, Control or unsure.

5.0 STUDY PROTOCOL

5.1 SUBJECT ELIGIBILITY

5.1.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for participation in the study:

1. The subject requires skin grafting as a result of an acute thermal burn injury (i.e. injuries caused by exposure of the skin to fire/flames, excessive heat, hot steam or water).
2. The area of total burn injury is 5-50% TBSA inclusive.
3. Two areas requiring skin grafting, each at least 300cm^2 (or 600cm^2 contiguous), excluding hand/face and joints.
4. The subject is at least 5 years of age.
5. The subject (or family, for those under 18 years of age) is willing and able to complete all follow-up evaluations required by the study protocol.

6. The subject is to abstain from any other treatment of the wound(s) for the duration of the study unless medically necessary.
7. The subject agrees to abstain from enrollment in any other interventional clinical trial for the duration of the study.
8. The subject and/or guardian are able to read and understand instructions and give informed, voluntary, written consent.

5.1.2 Exclusion Criteria

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

1. The subject's burn injuries were caused by chemicals, electricity, and/or radioactive substances.
2. The subject is unable to follow the protocol.
3. The subject has other concurrent conditions that in the opinion of the investigator may compromise patient safety or study objectives.
4. The subject has a known hypersensitivity to trypsin or compound sodium lactate for irrigation (Hartmann's) solution.
5. Life expectancy is less than 1year.

5.2 STUDY PROCEDURES

Study procedures are standardized to the extent possible and are explained in detail within this clinical investigation plan.

Study visits and procedures are summarized in **Table 1**.

Table 1: Study Visits/Procedures

Assessments		Follow-Up Visits (Weeks Post-Treatment)									
	Treat-ment	1	2	4	6	8	10	12	24	36	52
Visit Window Interval	NA	±1 day	±3 days	±3 days	±3 days	±5 days	±5 days	±5 days	±14 days	±14 days	±28 days
Size of Donor Site	X (including re-treatment)	-	-	-	-	-	-	-	-	-	-
Photography Treatment Area †Pre-excision, post-excision & post grafting	X†	X	X	X	X	X	X	X	X	X	X
Photography Donor Area (Post-harvest)	X	-	-	-	-	-	-	-	-	-	-
Clinical (non-blinded) Assessment of Treatment Area Closure	-	X	X	X	X	X	X	X	X	X	X
Blinded Assessment of Treatment Area Closure [a]Treatment Area Endpoint	-	-	-	-	X	X	X[a]	X	X	-	-	-
Investigator Blinding Effectiveness Assessment	-	-	-	-	-	-	X	-	-	-	-	-
Subject Blinding Effectiveness Assessment	-	-	-	-	-	-	-	-	-	X	-	-
Subject Assessment of Pain	-	X	X	X	X	X	X	-	-	-	-
POSAS	-	-	-	-	-	-	-	X	X	X	X
Subject Satisfaction	-	-	-	-	-	-	-	X	X	X	X
Dressing Changes/ Concomitant Medications and Therapies	X	X	X	X	X	X	X	X	X	X	X
Treatment-Related and Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X

5.2.1 Investigator Training

Investigators treating study wounds will be board-certified general or plastic surgeons. Support throughout the study for all study procedures and follow-up visits will be provided by a suitably qualified Avita Medical representative. The overall, lead principal investigator for the study may act as the Avita Medical representative in this capacity.

Investigators will be trained in the use of the ReCell device by the 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 left to the investigators to ensure proper education and training of those involved with the follow-up care of their patients. The Avita Medical representative will evaluate the investigator's skill in processing biopsies with the ReCell device. ReCell devices for use with study subjects will not be provided to the site until investigator training is satisfactorily completed. Investigators with prior training and experience with the ReCell device may be waived from this requirement.

An Avita Medical representative, including the overall, lead principal investigator or qualified designee, will attend the first surgery and potentially subsequent surgeries at each clinical site.

5.2.2 Screening and Enrollment

Acute burn cases requiring skin grafting will be considered for entry into the study. Patients (or their legal representative/guardian) will have the nature of the study, the study procedures, and the risks fully explained. Patients who meet all of the eligibility criteria and none of the exclusion criteria will be asked to sign (or their legal representative/guardian) the study-specific Institutional Review Board approved Informed Consent form (Reference **APPENDIX B** for the Sample Informed Consent Form) before any study-specific procedures are conducted.

A patient is considered to be enrolled once written informed consent has been obtained. If a patient is determined to be ineligible following consent but prior to wound randomization, the patient will be considered a screen failure. The reason for the screen failure will be documented. Only subjects that are enrolled and undergo wound randomization will be included in the analysis populations.

The following procedures will be conducted and data documented on the Pre-Treatment Case Report Form:

- Informed Consent
- Evaluation of compliance with inclusion and exclusion criteria
- Demography and medical information
- Relevant medical history
- History of original defect requiring skin grafting and treatments already received for the injury
- Physical Exam
- Assessment of any concomitant medications/therapies

5.2.3 Treatment Visit

5.2.3.1 Pre-Randomization Graft Plan

Digital photographs of the burn injury areas will be taken prior to excision as recommended in **APPENDIX A1. PROCEDURE FOR PHOTOGRAPHY**.

As deemed medically necessary, burn injury areas will be excised to remove non-viable tissue according to standard practice. Use of a conservative, dermal-preserving technique is suggested, where possible. After excision, a grafting plan will be defined to describe the type of skin grafting to be used over the burn injury area(s) requiring grafting. Areas to receive sheet graft, minimally perforated graft, and meshed graft (meshed 1:1, 2:1, 3:1) will be documented in detail on a Lund and Browder chart. It is anticipated that often, only one type of skin graft will be employed; however, this protocol allows the flexibility for use of up to a maximum of 3 different graft types, which may be appropriate particularly for larger burns.

5.2.3.2 Study Treatment Area Selection

A study treatment area is to be identified in accordance with the patient selection criteria.

Note: Study treatment areas should not include facial burns or burn wounds over joints. Patients with a facial burn can be enrolled in the study as long as another appropriate area can be identified as the study treatment area (e.g. abdomen), provided that the facial wound will not compromise the ability of the subject to comply with study procedures, and/or the study area treatment does not interfere with the facial treatment. Similar considerations should be given to joint burns.

The study treatment area is to be comprised either of two separate, but similar areas or two contiguous areas – wherein each of the two areas (Area A and Area B) contain equal representation of the graft types documented in the grafting plan. In other words, if the study treatment area is anterior torso and the grafting plan is 2:1 mesh, then this area can be symmetrically bisected into two areas, A and B. If more than one meshing ratio is planned, then each of the two meshing ratios are to be equally represented across Area A and Area B.

After hemostasis is achieved, the wound will be marked with a surgical pen to unambiguously describe Area A and Area B. The study treatment area (comprised of A and B) will be photographed, multiple times as necessary, including easily-identifiable anatomical reference points in the image, so that during follow-up blinded assessments of healing, the photograph can be referred to by staff preparing the masking drapes needed to ensure blinding of the assessor. Markings for Area A, Area B, and non-study treatment areas should be added to the Lund and Browder chart used to document the grafting plan.

If a subject has consented to study participation but a protocol-compliant study treatment area cannot be identified, the subject will be considered a screening failure and will not be included as part of the intent-to-treat population. Standard care for treatment and follow-up should ensue.

Post-excision, intraoperative identification of Area A and Area B is essential. For a paired comparison to be valid, the treatment areas must be similar in size (within ± 20%), severity of injury and grafting plan.

A description of the anatomical location, treatment area sizes, and the grafting plan will also be documented in the surgical record of the patient to act as a source document for study monitoring purposes.

5.2.4 Randomization

Allocation of treatments to the treatment areas will be done at random, using a pre-determined random assignment of treatments to the two defined wound regions (A and B). Wound regions will initially be labeled A and B by the physician, and then an envelope will be opened, which will indicate which treatment to assign to A and which to B.

5.2.5 Donor Site Preparation/Skin Graft Harvest

Grafting is to proceed according to the grafting plan for the area randomly allocated to Control. The area allocated to ReCell treatment will be grafted at a higher meshing ratio, per **Table 2**.

Table 2. Graduated Mesh Graft Plan Based on Standard of Care Graft Plan

Standard of Care Graft Plan: If the graft plan requires:	**For ReCell Graft Plan Use**
Sheet, minimally perforated or 1:1	2:1 mesh
2:1 mesh	3:1 mesh
3:1 mesh	4:1 mesh

Donor sites are to be identified such that sufficient skin for both the conventional grafting and the skin samples needed for ReCell will be harvested. The skin is to be harvested using standard technique (e.g. powered dermatome), at depths from 0.006 to 0.012" (inclusive). In addition to the skin required for grafting, the amount of skin to be harvested for the ReCell-treated area must include an additional one square centimeter for each 80 cm^2 of area to be ReCell-treated; the skin sample required for creation of cell suspension (1 cm^2 per 80 cm^2 of treatment area) is to be trimmed from this harvested skin.

The total donor site area harvested for grafting of the control area, and the total donor site area harvested for the grafting of and application of cell suspension to the ReCell-treated area is to be measured and documented. Donor sites are to be measured and reported as the area of the rectangle that encompasses the donor site, i.e. the longest dimension is multiplied by the longest perpendicular dimension. Digital photographs of the donor site(s) will be taken.

The prepared graft will be maintained in moistened saline gauze until used for grafting onto the prepared wound. The meshed graft may be fixed to the wound with surgical glue, suturing or stapling at the surgeon's discretion. (Note: use of fibrin sealant is not permitted.)

5.2.6 Surgical Procedure for ReCell Treatment

5.2.6.1 ReCell Processing and Cell Suspension Application

The ReCell-assigned treatment area will be treated as described in the product's Instructions for Use (**APPENDIX A3**). In summary, 1ml of fluid physically covers a treatment area of 80 cm^2. Each milliliter of fluid contains cells harvested from a square centimeter of thin split-thickness skin sample.

The reagents and components of the ReCell kit are used, in a scalable fashion, to facilitate disaggregation of cells from skin samples into filtered cell suspension. Areas to be harvested for skin samples are to be clean and show no evidence of surrounding cellulitis or infection. Treatment area sizes and cell suspension volumes are to be recorded.

Application of the Cell Suspension

Before proceeding with cell application, 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 surface. 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 and introducing the suspension are also described in detail in the Instructions for Use.

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

The size (area) of the skin sample processed with ReCell, and the volume of cell suspension applied to the ReCell-treated wound area will be recorded on the CRF. Treatment areas are to be measured and reported as the area of the rectangle that encompasses the wound area, i.e. the longest dimension of the wound is multiplied by the longest perpendicular dimension.

Digital photographs of the ReCell-treated area will be taken following cell suspension application.

After cell suspension application, treated areas are to be covered with a non-adherent, low-absorbent, small pore dressing (e.g., Telfa™ Clear wound dressing by Covidien,). Secondary dressings of Xeroform™ Occlusive Petrolatum Gauze (Covidien), or similar, are placed over the primary dressing. Additional padding of gauze and a crepe bandage may be used.

The patient **will not** be told which treatment area was treated with the ReCell device.

5.2.7 Surgical Procedure for Control Treatment Areas

Treatment areas are to be measured and reported as the area of the rectangle that encompasses the wound area, i.e. the longest dimension of the wound is multiplied by the longest perpendicular dimension.

Digital photographs of the treatment area will be taken following application of the graft.

The treatment area will be covered with a non-adherent, low-absorbent, small pore dressing (e.g., Telfa™ Clear wound dressing by Covidien, or Conformant™ 2 by Smith & Nephew). Secondary dressings of Xeroform™ Occlusive Petrolatum Gauze (Covidien) or similar are placed over the primary dressing. Additional padding of gauze and a crepe bandage may be used.

The patient **will not** be told which graft area was treated with the control graft.

5.2.8 Post-operative Care

The primary dressing should remain in place for a minimum of 6-8 days and is not to be manipulated until the first study visit, unless medically necessary.

Beginning at 48-hours post-treatment, secondary dressings are to be changed every other day for review of the treated areas, and can be replaced as appropriate. 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. Use of silver sulfadiazine is prohibited. Silver-impregnated dressings are not be used pro-actively or prophylactically, as the silver may inhibit the cell suspension.

Once closure of the wounds is achieved, the primary dressing will usually have come away of its own accord. It is essential that any dressing not easily removed be soaked in aqueous or oil-based solutions to prevent trauma upon removal.

Important Note: The treated areas are to be protected for a minimum of two weeks subsequent to closures, using light hydrophobic compression garments/sleeves or dry gauze and elastic bandaging (e.g. - ACE™). 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.

Thereafter, post-operative care should be consistent with the standard of care for the clinical site. All therapies will be documented on the CRF.

Subjects and caregivers 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 Xeroform dressings with daily changes (to prevent the dressing from drying and adhering) should be used until the treatment area has approximately 2 weeks to mature. Please note that if punctate

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.

5.2.9 Retreatment

Due to the nature of the burn injuries included in this study, re-treatment/re-grafting may be necessary and should be performed at the discretion of the investigator. If clinically acceptable, it is preferred that retreatment be performed in accordance with the originally assigned treatment.

5.2.10 Follow-Up Visits

Follow-up assessments will be carried out within the following time periods throughout the study (see also Table 1. Study Visits and Procedures):

- Week 1 ± 1 day
- Week 2 ± 3 days
- Week 4 ± 3 days
- Week 6 ± 3 days
- Week 8 ± 5 days
- Week 10 ± 5 days
- Week 12 ± 5 days
- Week 24 ± 14 days
- Week 36 ± 14 days
- Week 52 ± 28 days

Subjects should be instructed to immediately contact the clinical site with any dressing issues, questions, or concerns prior to the Week 1 visit.

Subjects returning outside of the visit window for their scheduled visit will have their information collected according to the protocol and recorded on the CRF. These visits will be documented as protocol deviations, and taken into consideration during the data analysis. Subjects may choose to return at visits other than the study schedule above, and these will be recorded as unscheduled visits, with the minimum documentation of any treatment-related or serious adverse events occurring since the last visit.

At all follow-up visits, the subject will be asked to list any medications and/or concomitant procedures pertaining to wound healing (i.e. antibiotics, steroids, topical wound treatments, etc.) taken since the last visit. The Investigator or other designated study personnel will ascertain whether the subject has experienced any treatment-related or serious adverse events since the last visit. All treatment-related and serious adverse events will be documented regardless of their relationship to the device.

Photography and completion of the POSAS will be as shown in Table 1.

5.2.10.1 Unscheduled Visits

Unscheduled visits may be performed at any time for evaluation for possible treatment-related or serious adverse event or to address any questions or concerns expressed by the subject that cannot be adequately

managed by telephone or e-mail communication. These visits are to be documented on the Follow-Up Visits Case Report Form as an Unscheduled Visit.

5.2.11 Assessment of Treatment Area Closure

Healing status will be evaluated in person by the treating investigator(s) at all visits and by a qualified individual blinded to treatment assignment (i.e., Blinded Evaluator) at the Week 4 - Week 12 visits. Blinded Evaluators will have a minimum of 2 years clinical experience in assessing and treating acute burn wounds.

For the blinded assessment, healing of the 2 treatment areas will be assessed one at a time (per subject) via direct visualization by the Blinded Evaluator who will be blinded to the treatment regimens of the wound areas. Prior to the healing assessment, subjects must be draped such that all grafted areas, with the exception of the wound area to be evaluated, are hidden from view. At no time are the 2 treatments areas to be viewed simultaneously by the Blinded Evaluator.

Closure must be confirmed at two consecutive study visits (e.g., at Week 6 and Week 8, or if a visit is missed, Week 8 and Week 12).

Blinded assessments will begin at Week 4 and will continue through Week 12. At the Week 8 assessment, the Blinded Evaluator will be asked to identify which treatment group they believe the wound was assigned. Potential answers are: treatment (ReCell), control (standard comparator) or "unsure".

6.0 STATISTICAL CONSIDERATIONS

6.1 GENERAL

The statistical analysis of the data obtained from this study will be performed using SAS® Version 9.1 or higher. Data collected in this study will be presented separate from the CTP001-6 cohort but will analyzed, as applicable, in a similar manner. Data will be presented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages. All results will be presented by treatment. For the co-primary effectiveness endpoint for confirmed treatment area closure, the hypothesis test of non-inferiority will be one-sided with a 5% significance level; for the endpoint of relative reduction in donor site area, the hypothesis test of superiority will be one-sided with a 2.5% significance level, all other statistical tests will be two-sided at the 5% significance level, unless otherwise noted.

The following provides a summary overview of analyses to be performed.

6.2 HANDLING OF DROPOUTS AND MISSING DATA

Every attempt will be made to contact subjects who are non-compliant or lost to follow-up, and such attempts will be documented in the subject's study record. All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. For evaluation of the co-primary effectiveness endpoints, it is anticipated that there will be minimal missing data. However, multiple imputation and sensitivity analyses (e.g., pattern mixture models) will be performed if appropriate to account for missing data.

6.3 INTERIM ANALYSES

Data will be analyzed and summarized in an interim analysis at a time to coincide with the submission of the ReCell marketing application. At that time all available data will be presented. Subject follow-up will continue until the last subject treated under this Continued Access Protocol has completed their 52 week visit.

6.4 MULTIPLE COMPARISONS / MULTIPLICITY

No adjustments for multiple comparisons will be necessary. The data collected under this protocol will be considered supplementary to the primary CTP001-6 cohort. P values, when presented, will be for informational purposes only.

6.5 ANALYSIS SETS

6.5.1 Safety Analysis Set

The safety analysis population will include all enrolled subjects who received treatment with ReCell. Data will be analyzed based on treatment received.

6.5.2 Primary Effectiveness Analysis Sets

Primary effectiveness will be assessed on the following two analysis sets:

- Intent to treat population (ITT) – All those enrolled into the study who are randomized. Data will be analyzed based on the treatment assigned to an area, regardless of the actual treatment of the area. The ITT population will be the primary analysis population for evaluation of the superiority hypothesis for the co-primary effectiveness endpoint of donor area harvest requirements.
- Per protocol population (PP) – ITT subjects who receive both study treatments and have no major protocol deviations. Data will be analyzed based on the actual treatment of an area. The PP population will be the primary analysis population for the test of non-inferiority for the co-primary effectiveness endpoint of confirmed treatment area closure at or before 8 week post-treatment.

The following will be considered major protocol deviations that will exclude a subject from the PP population:

- Major inclusionary/exclusionary deviations
- Missing primary wound healing endpoint visit
- Other significant protocol non-compliance that may confound evaluation of healing (e.g., use of prohibited medications/treatments, inappropriate primary dressing, etc.).
- Treatment of an area differs from the assigned treatment of the area

The determination of whether a deviation meets the definition of a major protocol deviation will be done in a blinded fashion without knowledge of outcomes for the subject/treatment area in question.

6.6 SAMPLE SIZE JUSTIFICATION

It is anticipated that up to 60 subjects may be accrued in the period between the time the protocol is approved and receipt of FDA marketing approval for the ReCell device.

6.7 SUBJECT DISPOSITION

The number and percent of randomized subjects (ITT Population) in the Per Protocol and Safety Populations and completing the study will be summarized. The number and percent of randomized subjects who do not complete the study will be presented, along with the reason for discontinuation. The number of subjects signing the informed consent and the number of screening failures (consented but not randomized subjects) will be presented. The reason(s) for non-randomization will be summarized using counts and percentages for screening failures.

The number of consented subjects, the number of randomized subjects and the number of treated subjects will be presented for each investigative site.

Subject accounting will be summarized in the following manner. For each visit, the number and percentage of subjects who withdraw consent, who are eligible, who have the visit, who do not have the visit, and who are lost-to-follow-up will be presented.

6.8 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The demographics, prior medical history, physical exam and characteristics of the total burn injury and treatment areas will be summarized overall and by treatment (if applicable) for the ITT and PP Populations. Continuous variables will be summarized using the mean, standard deviation, median, minimum and maximum; categorical variables will be summarized using counts and percentages of subjects in each category.

6.9 SURGICAL PROCEDURE CHARACTERISTICS

Data concerning area of donor skin used for ReCell processing, graft thickness, treatment area, and ReCell cell suspension application details (e.g., volume and details for application) will be documented on the CRF. Data will be summarized using descriptive statistics by descriptive statistics for continuous variables.

6.10 EFFECTIVENESS ANALYSES

The analyses of effectiveness will be performed based on both the ITT and PP Populations. The analysis based on the PP Population will be considered the primary analysis for co-primary effectiveness endpoint of confirmed treatment area closure. The analysis based on the ITT Population will be considered the primary analysis for the co-primary endpoint of the ratio of ratios of donor skin area harvested/graft area. Where indicated, nominal P values (unadjusted), will be presented for informational purposes only.

6.10.1 Co-Primary Effectiveness Endpoints

6.10.1.1 Co-Primary Effectiveness Endpoint - Confirmed Treatment Area Closure

The 97.5% one-sided confidence interval for the difference of the proportions between the ReCell and control treatment areas will be computed using the normal approximation taking correlation into account.

6.10.1.2 Co-Primary Effectiveness Endpoint - Ratio of Ratios of Donor Skin Area Harvested/Graft Area

The ratio of the area of donor skin harvested (inclusive of any secondary treatments) to study graft area for the ReCell-treated and control wounds will be calculated. From these values a "ratio of ratios" [R] will be calculated as follows:

- ReCell treatment area/corresponding donor area) / (control treatment area/corresponding donor area)

Donor skin measurements will generally be based on measurements obtained intra-operatively at the time of the primary procedure but will also include any donor skin required for re-treatments performed to obtain wound closure if applicable. A one sample t-test with a one-sided significance level of 0.025 will be performed.

6.10.2 Additional Effectiveness Endpoints

1. **Subject Satisfaction at 24 Weeks:**

   A one-sided binomial test at a significance level of 0.0250 will be performed to compare outcomes for subject satisfaction for the ReCell and Control treatment regions.

2. **POSAS – 24 Week Observer Overall Opinion Score:**

   A one-sided paired t-test at a significance level of 0.0250 will be performed to compare outcomes for 24 Week POSAS Observer Overall Opinion Score for the ReCell and Control treatment regions.

3. **POSAS – 24 Week Patient Overall Opinion Score: Hypothesis to be tested is that the overall opinion score for the Patient component of POSAS is lower for ReCell than for Control (a lower score represents a better outcome)**

   A one-sided paired t-test at a significance level of 0.0250 will be performed to compare outcomes for 24 Week POSAS Patient Overall Opinion Score for the ReCell and Control treatment regions.

6.11 SAFETY ANALYSES

The Safety population will be used for all safety analyses.

The number of treatment-related adverse events (AEs), serious AEs, procedure related AEs and device related AEs will be presented, as well as the number and percentage of subjects (or treatment areas as applicable) experiencing any AEs, any serious AEs, any procedure related AEs and any device related AEs.

For AE's specific to treatment areas, the proportions of treatment areas with each type of AE will be compared between using McNemar's Test.

Documented adverse events will be coded using the Medical Dictionary for Regulatory Activity (MedDRA) terminology for data summaries. Each adverse event will be coded with 2 levels including Preferred Tem (PT) and System Organ Class (SOC). Documented adverse events will be summarized overall and for each treatment (if applicable) by system organ class and preferred term. Docunented adverse events will also be tabulated by severity and relationship to study treatment. Where applicable, McNemar's Test will be used to test for a difference between treatments in the true proportions experiencing at least one AE in each SOC.

The following dichotomous safety outcomes will be summarized by treatment using counts and percentages, and two-sided 95% confidence intervals for the true proportions (across all follow-up time points) will be presented by treatment. Also, for each safety outcome, a 95% confidence interval for the difference in the true proportions between treatments will be presented. The presence of the listed outcomes (observed at any post-treatment time point) will each be analyzed using McNemar's Test to test for a difference in overall proportions between treatments.

- Delayed Healing
- Infection
- Allergic response to trypsin
- Wound durability, in terms of recurrent wound breakdown following initial complete closure
- Scars necessitating surgical intervention

6.11.1 Additional Safety Analyses

6.11.1.1 Subject Assessment of Pain at Treatment Area

Treatment area pain will be assessed using the Pain Score from the Patient Assessment scale of the POSAS which is a numeric rating scale where 1 represents no pain and 10 represents worse possible pain. Pain scores will be summarized by treatment descriptively (mean, median, standard deviation, range) at 2, 4, 6, 8, 10 and12 weeks. Paired t-tests will be used to test the difference between the two treatments by study visit. A nominal P value (unadjusted) will be presented. Only observed data will be used in the analysis.

6.12 OTHER ANALYSES

6.12.1 Treatment Area Closure Assessment by Investigators

The ReCell and control treatment areas will be assessed for closure (i.e., healing) by the Investigators at all study visits (un-blinded assessment). The proportion of treatment areas that have achieved wound healing at each follow-up visit, based on the Investigator's assessment, will be summarized between the two treatments. The 95% confidence intervals for the correlated proportions will be calculated and the difference of the proportions between the ReCell and control treatments presented. This analysis will be performed for both the ITT and PP Populations.

6.12.2 Long-term Wound Appearance – POSAS Scores

Individual components of both the Observer and Patient Assessment of the POSAS, and Total POSAS scores, and the POSAS overall opinion ratings will be summarized descriptively (mean, median, standard deviation, range) by visit and treatment. Two-sided 95% confidence intervals will be presented for the means for each treatment. A paired t-test will be used for comparison between the two treatments. Nominal P value (unadjusted) will be presented. Only observed data will be used in the analysis.

6.12.3 Blinding Effectiveness

Blinded Evaluator and Subject blinding effectiveness assessments data will be summarized by treatment using counts and percentages.

7.0 RISK ANALYSIS

7.1 ANTICIPATED RISKS

The potential risks to the subject arising from participation in this study include:

Risks associated with grafting procedures and burn treatment include:

- 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
- Pruritis
- 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 at 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 risk, 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
- Additional surgical and/or medical intervention to achieve treatment area closure

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 application of the ReCell device. Subjects will be adequately screened to ensure that patients with conditions and/or comorbidities that put them at a higher risk for procedural complications are excluded. Patient 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. Participants will be given instructions on whom to contact in the event that 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.

7.2 ADVERSE EVENTS

7.2.1 Adverse Events Reporting and Evaluation

All treatment-related and serious adverse events (AE) occurring during the course of the clinical study (beginning from the initiation of the grafting procedure), whether related to the investigational device or otherwise, will be recorded on the AE Case Report Form. For all AEs, the Investigator must provide an assessment of the event, treatment resolution, and relationship to the investigational device.

7.2.2 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.

7.2.3 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.

7.2.4 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 7.1**.

7.2.5 Definitions of Specific Major Treatment-Related Adverse Events

7.2.5.1 Infection

The presence of infection for the ReCell-treated areas and control site 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 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 patient who is systemically well and metabolically stable but who has ≥1 of the following characteristics: cellulitis extending >2cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, or involvement of muscle, tendon, joint or bone
- Severe: Infection in a patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)

In the presence of symptoms (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. Treatment is to be initiated according to the institutions' infection management protocols, which will be recorded on the CRF and Adverse Event form.

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 CRF.

7.2.5.2 Allergic Response to Trypsin

The allergic response to trypsin will be evaluated pre- and post-operatively. The allergic response to trypsin[15] 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)[16]. Substances that produce this condition after single or

[15] Trypsin is the enzyme used in the ReCell Device for disaggregation of the biopsy

[16] Drake LA, Dorner W, Goltz RW, Graham GF, Lewis CW, Pariser DM, Salasche SJ, Skouge JW, Chanco Turner ML and Lowery BJ. (1995). Guidelines for Contact Dermatitis, *J Am Acad Derm*, 32(1):109-113.

multiple exposures may be irritating or allergic in nature and induce an inflammatory response. The most common clinical expression of this induced inflammation is dermatitis (eczema).

The evaluation tools for assessment of the allergic response to Trypsin have been developed in accordance with guidelines published in the Journal of the American Academy of Dermatology[16]. 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 CRF and study report. Please see **APPENDIX A4. ASSESSMENT OF HYPERSENSITIVITY TO TRYPSIN** for assessment procedures for an allergic response to Trypsin.

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

7.2.5.3 Scars Requiring Subsequent Surgical Intervention

Any treatment area undergoing a subsequent surgical intervention for scar revision will also be considered a major treatment-related adverse event.

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

7.2.6 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:

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

7.2.7 Unanticipated Adverse Device Effects (AEs)

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.

7.2.8 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 in-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. Further reporting requirements will be aligned with the stipulations of any specific funding source.

7.2.9 Severity

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

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

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

3 = Severe: Inability to work or perform normal daily activity.

7.2.10 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. The cause of death and the Investigator's discussion regarding whether or not the death was device-related should be described in a written report.

7.2.11 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.

7.2.12 Eliciting and Reporting Adverse Events

The Investigator will assess subjects for the occurrence of adverse events (AEs) at each study visit. In order 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 study CRFs provided by Avita Medical.

8.0 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:

Andrew Quick, Sr Vice President, Clinical Development
Avita Medical Americas, LLC
9221 Corbin Ave, Suite 220
Northridge, CA 91324
Telephone Number: 818-698-8345
Email: aquick@avitamedical.com

9.0 INVESTIGATOR AGREEMENT

An investigator agreement will be signed by each 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.

10.0 SUBJECT DISCONTINUATION

All subjects will be followed for a minimum of 52 weeks (± 28 days). 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 Request to Terminate: The subject requests to terminate his/her involvement in the study. To the extent possible an exit interview should be conducted with the subject in order to assess the subject's specific reason(s) for study withdrawal.

c) Subject Death: Every attempt should be made to document the cause of death. An autopsy report should be obtained if available.

11.0 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**. Reporting in compliance with Department of Defense standards will only be conducted where Department of Defense funding is used in support of the study.

Table 3. Guidelines for Preparing and Submitting Reports

Type of Report	Prepared by Investigator and Submitted to:	Method	Time of Reporting:
Serious Adverse Event (device-related or not)	Sponsor	Submit SAE CRF or fax notification	Preferably within 24 hours of knowledge but in no event later than 48 hours
	IRB	As required	As required
Death (device-related or not)	Sponsor	Submit SAE CRF or fax 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	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, BSI, IRB, USAMRMC 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.

12.0 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.

13.0 DEVICE ACCOUNTABILITY AND LABELING

The study 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 and that device accountability records are maintained.

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. Throughout the study, device accountability records will be reviewed by the Sponsor's appointed monitor. The investigator is responsible for ensuring that the device accountability records are complete and up to date at all times. At the end of the study, all remaining devices will be documented and returned to the Sponsor as instructed in the Study Procedure Manual. The study device may not be reused or re-sterilized after completion of the study.

All investigational devices will be labeled with the statement "CAUTION - Investigational Device. Limited by Federal (U.S.) Law to Investigational Use".

14.0 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.

15.0 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.

16.0 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 CRFs. Authorization for completion of study-related procedures may be delegated to appropriately qualified individuals, but responsibility may not be delegated.

Appendix A1

PROCEDURE FOR PHOTOGRAPHY

ONE-TIME PHOTOGRAPHIC DOCUMENTATION OF STUDY DONOR SITES
SERIAL PHOTOGRAPHIC DOCUMENTATION OF STUDY TREATMENT AREAS

Equipment:

Camera: Nikon D90 D-SLR 12MP Body (or equivalent)

Procedures:

In these clinical photographs the only variable allowed to change is the skin condition itself. Therefore, anything extraneous to the condition (clothing, surgical dressings, etc.) should be eliminated from the photographic field at the Treatment through the Follow Up assessment visits. The necessity of reproducible serial photos should be stressed to the patients to ensure their cooperation. Lighting, framing, exposure, and reproduction ratios must be held constant. In the end, the images should read like a time-lapse movie. ***In order to accomplish this, you must review the baseline photo at each follow-up visit so that you can frame follow-up photos in the same way.***

1. The supplied equipment is to be used exclusively for this study. No modification, adjustments or repairs of the camera equipment is to be undertaken without the expressed instruction of Avita Medical.

2. Magnification: A standardized reproduction ratio/magnification is utilized for the photography. The auto focus feature of the lens is disabled. The lens is preset and rubber coated to prevent tampering or readjustment. Accurate focal distance is achieved by moving the camera/lens toward or away from the target area until critical focus is achieved.

3. F/Stop: The aperture of the lens will be preset and locked.

4. ***Each view should be photographed twice.***

5. This step is optional. Photographs of the Subject ID/Visit Information Card can be used to differentiate between photographic sessions for each visit.
   The Information Card may contain the following information:
   a. Protocol No. (CTP001-6)
   b. Date
   c. Visit Week
   d. Site Number & Subject ID Number
   e. Patient's Initials *(optional)*
   f. Date of Birth
   g. Photographer's Initials

6. Pre-excision, the full extent of the burn injury is to be documented photographically.

7. At the treatment visit, and any other time during the study when skin is harvested for re-treatment of study treatment areas, the donor sites should be labeled as skin harvested either for Control Area or ReCell Treatment Area.
    a. As many or as few photographs may be taken in order to document the extent (all boundaries) of the donor sites, including anatomical reference points to orient the viewer.
    b. Each view should be photographed twice.
    c. Donor sites for Control and ReCell treated areas may be included in the same view, or may each be photographed separately. In either case, any shared border must be unambiguously delineated with a surgical marker.
    d. Donor site photography should also be conducted in conjunction with adverse event reports involving donor sites, with the exception of anticipated pain and pruritis. Again, be sure to mark Control Area, ReCell Area, or non-study Donor, as appropriate.

8. The study treatment areas are to be documented photographically:
    (1) Post-excision (after hemostasis, prior to randomization and grafting)
    (2) After grafting (prior to application of ReCell or primary dressing)
    (3) At each follow-up visit, including unscheduled visits
    (4) If there is an Adverse Event (other than pain or pruritus)

    a. Prior to photography, the study treatment areas are to be labeled Area A and Area B, with unambiguous delineation of any common boundary.
    b. Area A and Area B may be included in the same view, or may each be photographed separately. In either case, any shared border must be unambiguously delineated with a surgical marker.
    c. Non-study treatment areas may be photographed in conjunction with associated adverse event reports.

9. All images will be monitored for compliance to the photographic procedures.

10. All supplied photographic equipment and photographic originals remain the property of the Sponsor.

Appendix A2

POSAS SCAR RATING, SUBJECT SATISFACTION, AND BLINDING ASSESSMENT

POSAS Assessment - Completed at Weeks 12, 24, 36 and 52.

Ideally, scars should be evaluated clinically under the same conditions such as room temperature and humidity. At the time of measurement the skin and scar tissue of the patient should be adapted to this situation. Especially pigmentation may change because of seasonal variation.

(www.posas.org)

The POSAS consists of two parts: a Patient Scale and an Observer Scale. Both scales contain six items that are scored numerically and make up a 'Total Score' of the Patient and Observer Scale. The sum altogether will give the 'Total Score' of the POSAS. Besides the 10-step scale, category boxes are available to score nominal parameters (e.g. type of colour). Moreover, the patient and observer also score their 'Overall Opinion'.

The six items and Total Score of the Patient and Observer Scale POSASv2.0
Each item of both scales has a 10-point score, with 10 indicating the worst imaginable scar or sensation. The lowest score is '1', and corresponds to the situation of normal skin (normal pigmentation, no itching etc), and goes up to the worst imaginable. The Total Score of both scales can be simply calculated by summing up the scores of each of the six items. The Total Score will therefore range from 6 to 60. One may argue if the results of the separate items should be weighted to come to a more accurate Total Score. To date no convincing evidence is available that indicates that weighting improves the accuracy of the Total Score. Currently, the significance of weighting parameters is under investigation. Besides the six items the 'Overall Opinion' of the scar quality is scored separately of both patients and observers.

Categories (Observer Scale POSASv2.0)
Category boxes are provided to score the items not only quantitatively on a ten step scale but also qualitatively. In this way not only the severity but also the direction of the disorder (e.g., hypopigmentation or hyperpigmentation) is addressed. The categories are not included in calculating the Total Score of the POSAS. However, they are considered clinically relevant for complete documentation.

Overall Opinion (Patient and Observer Scale POSASv2.0)
Both the patient and the observer are asked to give their Overall Opinion on the appearance of the scar. Again, a 10-point scale is used in which 10 corresponds to the worst imaginable scar. The 'Overall Opinion' is not part of the Total Score of the Observer and Patient Scale of the POSAS.

Patient Scale: To minimize bias, the Patient Scale of the POSAS should be completed PRIOR to the Observer Assessment. Provide the patient plenty of time, preferably in a quiet area, to complete the questionnaire. Instruct the patient to only select one of the scored boxes (i.e., no "half" scores). Assessed for both "Area A" and "Area B".

****SUBJECT TO COMPLETE SEPARATELY FOR AREAS A AND B****

Please Check (✓ or X) <u>One</u> Box Only for <u>Each</u> Question

	1=no, not at all → yes, very much = 10									
1. Has the scar been painful the past few weeks?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
2. Has the scar been itching the past few weeks?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

	1 = no, as normal skin → yes, very different = 10									
3. Is the scar color different from the color of your normal skin at present?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
4. Is the stiffness of the scar different from your normal skin at present?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
5. Is the thickness of the scar different from your normal skin at present?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
6. Is the scar more irregular than your normal skin at present?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

	1 = as normal skin → very different = 10									
7. What is your overall opinion of the scar compared to normal skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

POSAS Observer Scale: Should be performed by the same Blinded Evaluator for each assessment. Only select one of the scored boxes (i.e., no "half" scores). Assessed for both "Area A" and "Area B".

	1= normal skin → worst scar imaginable = 10									
1. Vascularity	☐ **1**	☐ **2**	☐ **3**	☐ **4**	☐ **5**	☐ **6**	☐ **7**	☐ **8**	☐ **9**	☐ **10**
	☐ **Pale**		☐ **Pink**		☐ **Red**		☐ **Purple**		☐ **Mix**	
2. Pigmentation	☐ **1**	☐ **2**	☐ **3**	☐ **4**	☐ **5**	☐ **6**	☐ **7**	☐ **8**	☐ **9**	☐ **10**
			☐ **Hypo**		☐ **Mix**		☐ **Hyper**			
3. Thickness	☐ **1**	☐ **2**	☐ **3**	☐ **4**	☐ **5**	☐ **6**	☐ **7**	☐ **8**	☐ **9**	☐ **10**
			☐ **Thicker**		☐ **Thinner**					
4. Relief	☐ **1**	☐ **2**	☐ **3**	☐ **4**	☐ **5**	☐ **6**	☐ **7**	☐ **8**	☐ **9**	☐ **10**
			☐ **More**		☐ **Less**		☐ **Mix**			
5. Pliability	☐ **1**	☐ **2**	☐ **3**	☐ **4**	☐ **5**	☐ **6**	☐ **7**	☐ **8**	☐ **9**	☐ **10**
			☐ **Supple**		☐ **Stiff**		☐ **Mix**			
6. Surface Area	☐ **1**	☐ **2**	☐ **3**	☐ **4**	☐ **5**	☐ **6**	☐ **7**	☐ **8**	☐ **9**	☐ **10**
			☐ **Expansion**		☐ **Contraction**			☐ **Mix**		
7. Overall Opinion	☐ **1**	☐ **2**	☐ **3**	☐ **4**	☐ **5**	☐ **6**	☐ **7**	☐ **8**	☐ **9**	☐ **10**

Explanatory notes on the items: (provided to Blinded Evaluator)

- **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

Subject Satisfaction - Completed at Week 12 and Week 24

****SUBJECT TO COMPLETE**** **Please Check (✓ or X) <u>One</u> Box Only for <u>Each</u> Question**

1. Are you more satisfied with Area A or Area B? ☐ Area A ☐ Area B

Comments:

Blinding Assessment - Completed at Week 8 (Blinded Evaluator) and Week 24 (Subject)

TREATMENT AREA A			
Which treatment do you think this area received?	☐ ReCell	☐ Control	☐ Unsure

TREATMENT AREA B			
Which treatment do you think this area received?	☐ ReCell	☐ Control	☐ Unsure

Appendix A3

INSTRUCTIONS FOR USE

INSTRUCTIONS FOR USE

ReCell® Autologous Cell Harvesting Device

CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use.

Table of Contents

A BACKGROUND

A1 DESCRIPTION

ReCell® is a single-use, stand-alone, battery-operated, autologous cell harvesting device containing enzymatic and delivery solutions, sterile surgical instruments, and actuators. The ReCell device enables a thin split-thickness skin sample to be processed to produce a cell suspension for immediate delivery onto a prepared wound surface.

The cell suspension contains a mixed population of cells obtained from the disaggregation of the skin sample including primarily keratinocytes and fibroblasts, but also melanocytes, Langerhans cells, and epidermal basal cells. The preservation of melanocytes is important for restoring natural pigmentation to the recipient area.

The Enzyme used to process the cells is a biological agent and as such may have slight variations in colour and texture.

A2 INTENDED USE / INDICATIONS

The ReCell Autologous Cell Harvesting device is an autograft-sparing technology indicated for use at the patient's point-of care for preparation of an autologous epithelial cell suspension to be applied to a prepared wound bed. Under the supervision of a healthcare professional, the suspension is used to achieve epithelial regeneration for definitive closure of burn injuries, particularly in patients having limited availability of donor skin for autografting.

A3 CONTRAINDICATIONS

- ReCell is contraindicated for patients with wounds that are clinically infected or necrotic.
- ReCell should not be used to prepare cell suspensions for application to patients with a known hypersensitivity to trypsin or compound sodium lactate solution.
- The skin sample collection procedure specified for use of ReCell should not be used with patients having a known hypersensitivity to anaesthetics, adrenaline/epinephrine, povidine-iodine, or chlorhexidine solutions.

A4 WARNINGS

- Cell suspension produced with ReCell should only be applied to the patient from whom the original skin sample was taken (autologous use only).
- ReCell is provided to the healthcare professional sterile and is intended for single use. Do not reuse, freeze or re-sterilise device components.
- Do not use ReCell or device components if packaging is damaged or there are signs of tampering.
- Do not use ReCell or device components if the date of use is beyond the stated expiration date on the packaging.
- ReCell components should be handled using aseptic technique.

- If a skin sample is harvested and processed according to these instructions, it should only require between 15 and 30 minutes of contact with the Enzyme. Contact in excess of 60 minutes is not recommended.
- Contaminated materials and waste must be disposed of using appropriate biohazard waste receptacles.
- The separation Enzyme is derived from animal tissue and, although strict controls have been implemented in the manufacturing process to minimize the risk of pathogen contamination, a small risk of contamination exists and absolute freedom from infectious agents cannot be guaranteed.
- ReCell is internally powered by four non-replaceable AA batteries. The device should not be used in the presence of flammable materials and must not be incinerated on disposal.

A5 PRECAUTIONS

- Protective eyewear and other protective clothing should be worn.
- For optimum cell viability, the skin sample should be processed immediately after harvesting.
- The ReCell device is for single use only. Do not reuse, freeze or re-sterilise any items within the device.
- Do not use the device if there is evidence of container tampering or damage.

A6 ADVERSE REACTIONS

Any adverse reaction or suspected adverse reaction related to ReCell should immediately be reported to Avita Medical.

A7 MEANING OF SYMBOLS

The packaging system is labelled with various symbols. These symbols are internationally harmonised and define certain characteristics of the product and the manufacturing process:

This symbol states that the product is for single use only

This symbol states that the temperature adjacent specifies the storage temperature range

This symbol states that the user should refer to the accompanying instructions for use

This symbol states that the temperature adjacent specifies the upper limit of storage temperature

This symbol states that the date adjacent is the date of manufacture

This symbol states that the product or components within have been sterilised using ethylene oxide

This symbol states that the date adjacent is the expiry date of the product

This symbol states that the product or components within have been sterilised using gamma irradiation

This symbol states the manufacturer of the product

This symbol states that the product or components within have been sterilised using steam

A8 COMPONENT STERILISATION AND TESTING

- The Processing Unit and needles have been sterilised by ethylene oxide.
- The Enzyme has undergone filtration and terminal sterilisation by gamma irradiation.
- The scalpel and spray nozzles have been sterilised by gamma irradiation.
- The syringes have been sterilised by either ethylene oxide or gamma irradiation.
- The Buffer and sterile water have been sterilised using steam.

A9 STORAGE

Upon receiving ReCell, examine the packaging for external signs of damage. If the external kit packaging or the packaging for any of the individual components appears damaged, contact your local sales representative immediately. Do not use any components of the device if the packaging appears damaged. If returning ReCell, ensure all original packaging and components are returned with the device.

ONCE THE CONTENTS OF THE KIT HAVE BEEN INSPECTED REMOVE THE ENZYME FROM THE KIT AND IMMEDIATELY REFRIGERATE AT 2-8°C. THE REST OF THE DEVICE SHOULD REMAIN INTACT WITHIN ITS ORIGINAL PACKAGING.
All other components are to be stored at room temperature.

Do not open or use ReCell outside of the expiration date listed on the packaging.

A10 DISPOSAL

- ReCell and all individual components are intended for single use. ReCell components are not reusable and should be discarded after single use. Reuse may lead to infection or disease transmission.
- Follow local regulations for proper disposal.
- Contaminated materials and waste must be disposed of using appropriate biohazard receptacles.
- ReCell contains batteries and electrical components – DO NOT INCINERATE
- A procedure for removal of Processing Unit Battery/Electronics is as follows:
    - Take proper Biohazard precautions when handling the used Processing Unit.
    - Remove the Processing Unit top cover. Set top cover aside.
    - Remove Processing Unit inner tray and set aside.
    - Open inner main tray by pressing both sides of the outer housing simultaneously.
    - Verify that the parts are separated (inner main tray and outer housing). If the parts of the inner tray and outer housing are not separated, a small, flat-blade screwdriver may be used to assist in releasing the inner and outer parts.
    - Lift the battery inner tray to expose battery compartment.
    - Remove the batteries and the electronics and dispose of them in the appropriate waste streams.
    - Dispose of the remaining components in accordance with the appropriate methods.

B RECELL TREATMENT

B1 MATERIALS

The following materials and instruments will be needed during the ReCell procedure.

- Surgical gloves and a suitable sterile drape
- Protective eyewear and garments
- Skin preparation solution
- Local anaesthetic with adrenaline where not contraindicated
- Appropriate wound dressings. See "Aftercare" below for details
- 1 or 2 x fine-point (long nosed) forceps of choice
- Skin harvesting instrument of choice, e.g., Zimmer® Dermatome (Zimmer Orthopedic Surgical Products, Inc., USA), Silver's knife, Humby knife, Dermablade® (Personna® American Safety Razor Co, USA)
- Wound bed preparation tool of choice
- Clock or timer to monitor incubation time

B2 RECELL KIT SET UP

Perform the following set up steps in the order shown to avoid setup errors. A separate ReCell Setup Card is included with the device for reference during a procedure.

The ReCell kit contains both sterile and non-sterile components. Select and prepare sterile and non-sterile work areas. Using standard aseptic technique set up a sterile surgical field.

- Ensure that the batch number of the Enzyme used matches the Enzyme batch number listed on the ReCell kit outer packaging and is within the expiration date. Using aseptic technique, remove the Processing Unit from the sterile packaging and transfer it to the sterile field.
- Open the Processing Unit and note the removable inner white plastic insert. This insert acts as a sterile tray for use in preparing and scraping the skin sample.

PERFORM SELF-TEST

Perform the self-test to verify the device is functioning correctly.

- Test the device to ensure functionality by pressing the button marked (?). All lights should illuminate during the self-test. When the unit has completed the self-test (this takes approximately 30 seconds), it will beep once and the green 'ready' light (✓) will illuminate to indicate that the Processing Unit is functioning correctly. If lights do not illuminate, or the red light (!) illuminates, do not use the device. The unit will automatically turn off after 1 minute if Enzyme heating is not initiated.
- If the device turns off after self-test, additional self-tests may be run.
- Do not press the run button (⏵) at this time.

A – PREPARE ENZYME (COMPONENT SET A)

- In the non-sterile work area, remove the cover from the vial marked Enzyme to expose the injection diaphragm. Wipe the diaphragm with a sterile alcohol wipe and allow to dry (optional).
- Connect a sharp, sterile needle to a sterile 10-ml syringe and draw up the entire volume of sterile water.
- Inject the entire volume of sterile water into the Enzyme vial. DO NOT USE Buffer at this stage as this may inhibit the Enzyme action.
- Mix gently until dissolved. Do not shake and use care to avoid foaming. Draw the Enzyme back into the syringe.
- Using aseptic technique, dispense the entire volume of Enzyme into the left-hand well of the Processing Unit (Well A+E). Discard syringe and needle.

B – PREPARE BUFFER SOLUTION (COMPONENT SET B)

Introduce the following items into the sterile field.

- 2 x 10-ml syringes
- 1 x 19ga sharp needle
- 1 x sheet sterile syringe labels
- 1 x cell strainer
- 2 x disposable surgical scalpel

The four (4) Buffer vials are to remain outside the sterile field

- Apply the “BUFFER” label to one of the new 10-ml syringes. The “BUFFER” syringe will be used several times to draw Buffer from the vials. Set aside within the sterile field.
- Apply the “UNFILTERED SUSPENSION” label to the other 10-ml syringe. The “UNFILTERED SUSPENSION” syringe will be used several times to collect ReCell cell suspension from the tray and dispense into the cell strainer. Set aside within the sterile field.
- It is important that these syringes are used only for their intended, labelled purpose and that they remain sterile.
- Remove the cover from a vial marked Buffer. Wipe the diaphragm of the vial with a sterile alcohol wipe and allow it to dry (optional).
- Attach the sharp, sterile needle to “BUFFER” syringe and draw up the entire volume of Buffer (approximately 10 ml) from the vial.
- Dispense the entire volume of Buffer into the empty centre well of the Processing Unit (Well B). The entire 10 ml of Buffer will be used to rinse skin samples.
- Set the “BUFFER” syringe and needle aside within the sterile field for later use.

C – PREPARE DELIVERY ITEMS (COMPONENT SET C)

Introduce all items into the sterile field.

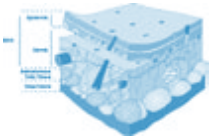
- 4 x 10-ml syringes
- 4 x blunt drawing-up needles
- 4 x spray nozzles

B3 WOUND BED PREPARATION

- Clean, vascularized wound bed – To optimise the treatment, the cell suspension should only be applied to a clean, vascularised wound bed with no remaining necrotic tissue. This can be achieved with either dermabrasion using a rotating diamond-head burr, laser ablation, sharp dissection or other alternative techniques depending on the nature of the wound.
- Infection free – The cell suspension must not be used in the presence of any contamination or infection, as initial re-epithelialisation and long term viability are highly dependent on the absence of infection. Prophylactic antibiotics may be prescribed if the patient is at risk of contamination or infection. Wound swabs for up-to-date microbiology are recommended 48 hours prior to the planned surgery.
- Pinpoint bleeding – The wound bed should be prepared so that dermis is exposed and pinpoint bleeding is observed. Accurate debridement to the level of viable tissue is essential; all necrotic tissue must be removed.

B4 STEP-BY-STEP INSTRUCTIONS FOR PREPARING THE RECELL CELL SUSPENSION

1. Take Skin Sample



Skin Sample Type

It is essential that the skin sample harvested is a thin, split-thickness biopsy that penetrates to the dermis and leaves pinpoint bleeding at the donor site. The use of a dermatome, Silver's knife, Humby knife or DermaBlade® is recommended.

Size of Skin Sample

Choose the appropriate skin sample size for the application. Each square centimetre of skin sample can create up to 1 ml of cell suspension for treatment of an area of up to 80 cm². Choice of Donor Site

It is essential the donor site is clean, of appropriate depth, and shows no evidence of surrounding cellulitis or infection.

Harvesting the skin sample

Using the preferred instrument such as a dermatome, Silver's knife, or Humby knife, take a split-thickness shave biopsy of the donor. The skin sample may be trimmed from skin harvested for split-thickness skin grafting. Use the table above to estimate the skin sample size needed, or calculate by taking 1/80 of the total

treatment area.

Clean the donor site with antiseptic solution such as povidine-iodine or chlorhexidine. Allow the antiseptic to dry before removing with sterile saline (antiseptic solutions may be cytotoxic and as such, may affect cell viability if left on the skin sample site).

If desired, infiltrate the subcutaneous tissue with a tumescent solution of choice, to provide a firmer surface and anaesthesia for taking the skin sample. Ensure that anaesthetic is not injected intradermally.

The donor site area may be lubricated, for instance with sterile mineral oil, to ease travel of the dermatome.

2. Heat Enzyme

Verify that the Enzyme has been transferred to Well A+E. The Processing Unit will quickly overheat if the run button (⏵) is pressed before the Enzyme has been placed in the well. Any malfunctioning of the unit, including overheating, will be indicated by the red light (!) illuminating. Should this occur, use another ReCell kit and contact your local representative to arrange the return or replacement of the unit.

Press the run button (⏵) to heat the Enzyme in Well A+E. If the device is ready (✓) then heating will commence. If more than one minute has passed since the last self-test, a self-test will automatically run, followed immediately by heating of the Well A+E. The orange light will illuminate when warming begins and the Enzyme will be heated and maintained at the approximately 37 °C.

3. Incubate the Skin Samples

When the orange warming light turns off and the green (✓) illuminates the Enzyme has reached its target temperature. This will take approximately 3 minutes. The orange light will flash from time to time, indicating that the heating element has been activated to maintain temperature

Place a skin sample into the heated Enzyme for 15 to 20 minutes to allow extra-cellular matrix breakdown. Keep other skin samples moist in sterile gauze moistened with sterile saline. If the skin samples are thick, they may require longer incubation.

4. Draw up Buffer

This step may be performed whilst the skin sample is incubating.

Remove the cover from the second vial marked Buffer. Wipe the diaphragm of the vial with a sterile alcohol wipe and allow it to dry (optional). Using aseptic technique and the “BUFFER” syringe with sharp needle, draw up the required volume of Buffer from the Buffer vial. Use one millilitre of Buffer per square centimetre of the first skin sample and add 0.5 ml Buffer to allow for loss during processing. The following table provides example surface areas

to be treated, skin sample sizes needed, volumes of Buffer to use, and approximate resultant suspension volumes. Place the syringe with Buffer in the sterile field for use in steps 7 and 8, below.

Surface Area to be Treated per Syringe	Skin Sample Size Needed	Starting Volume of Buffer	Approximate Resultant Suspension Volume
Up to 80 cm^2	1 cm^2 (1 cm x 1 cm)	1.5 ml	1.0 ml
Up to 160 cm^2	2 cm^2 (1 cm x 2 cm)	2.5 ml	2.0 ml
Up to 320 cm^2	4 cm^2 (2 cm x 2 cm)	4.5 ml	4.0 ml

Each 1 ml of suspension may be used to treat of up to 80 square centimetres.

5. Test Scrape for Cell Disaggregation

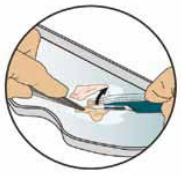
After 15 to 20 minutes, remove the skin sample from the heated Enzyme with sterile forceps and place the skin sample dermal side down on the sterile tray. Gently scrape the epidermis with the scalpel to test if cells disaggregate, i.e., epidermal cells easily come off. If the cells do not come off freely, return the skin sample(s) to the heated Enzyme for a further 5 to 10 minutes and then repeat the test scrape. When the cells scrape off freely, proceed to the next step.

After approximately 60 minutes, an alarm will sound and will sound each minute for 15 minutes. At 75 minutes, the Processing Unit will turn off and stop heating the enzyme. Incubation of a skin sample for more than 60 minutes is not recommended.

6. Rinse Skin Samples

Upon a successful test scrape, briefly rinse the skin sample in the middle well (Well B) containing the Buffer to rinse off and deactivate the residual Enzyme. Return the skin sample to the sterile tray.

7. Scrape Cells from the Skin sample



With the skin sample dermal side down on the sterile tray, apply a few drops of Buffer from the previously filled "BUFFER" syringe onto the skin sample. Using the forceps to anchor the skin sample, gently scrape the epidermal surface with the blade of the scalpel. Once the epidermis has been scraped away into suspension, scrape the remaining dermis more rigorously. Continue scraping until the dermis has nearly disintegrated.

8. Rinse and Aspirate; Draw up cell suspension

Use the remaining Buffer in the "BUFFER" syringe to rinse the scalpel and tray, collecting the cells into one corner of the tray. Tilt the tray as necessary. Set the "BUFFER" syringe aside for later use. Using the "UNFILTERED SUSPENSION"

syringe, collect and draw up the cell suspension. Using the drawn-up suspension, rinse the tray. Draw up and rinse several times to maximize cell collection. Finally, draw up the cell suspension into the syringe.

9. Filter Cells

Dispense the cell suspension into the cell strainer in Well C. Set the "UNFILTERED SUSPENSION" syringe aside, within the sterile field, for use with subsequent suspensions from the remaining skin samples.

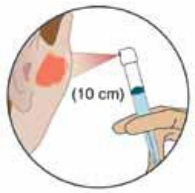
10. Draw up Cell Suspension

Attach a blunt needle to a new 10-ml syringe. Carefully remove the cell strainer, tapping the cell strainer over the well to release any drops of cell suspension. Draw up the filtered cell suspension from Well C. There is a conical point in the centre of the bottom of Well C to aid in drawing up all of the cell suspension. Return the cell strainer to Well C.

11. Dressings

Prior to applying the cell suspension, ensure the dressings are cut and prepared for immediate application. The primary dressing should be fixed or held at the lower aspect of the wound prior to applying the cell suspension. Section C, Aftercare, provides information on dressing selection and use.

12. Apply ReCell Suspension to Wound Bed



The cell suspension can be sprayed using the spray nozzles provided, dripped onto the wound or introduced under the primary dressing using a blunt drawing-up needle.

The minimum volume of cell suspension required for spray application is approximately 2 ml.

Spray Application

Remove the needle from the syringe containing the cell suspension. Attach the spray nozzle supplied to the syringe using firm pressure. Invert the syringe several times prior to the application to ensure an even suspension. Check that the aperture of the attached spray nozzle faces the wound. Hold the spray applicator approximately 10 cm from the most elevated point of the wound and in a position such that the first drop of suspension falls onto the wound surface. 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. A fine mist of cell suspension should be delivered to the wound surface. To cover a larger area, carefully move the spray applicator in one continuous motion from one side of the wound to the other as you spray.

Drip Application

Do not remove the blunt needle from the syringe containing the cell suspension. Invert the syringe several times prior to application to ensure an even suspension. Starting at the most elevated point of the wound, carefully drip the cells onto the wound surface.

Application under Primary Dressing

If introducing the cell suspension under a dressing do not remove the blunt needle from the syringe containing the cell suspension. Invert the syringe several times prior to application to ensure an even suspension. Place the cut dressing over the wound and gently introduce the needle under the dressing and introduce the cell suspension. Larger wounds may require introducing the needle and suspension at several points to ensure complete coverage.

Note: The fibrin in the prepared wound bed provides an ideal environment to cell adhesion. Many, but not all, of the delivered cells will adhere to the wound. It is normal for some of the cell suspension to run off the wound with Buffer. A well-prepared suspension has enough cells to treat the wound, allowing for run off.

C AFTERCARE

The following information, precautions, and notes provide guidelines for care after ReCell. Discuss appropriate aftercare with your Avita representative and provide patient with the "After ReCell" guidance brochure.

C1 INITIAL DRESSING

Cover the ReCell-treated wound with a non-adherent, non-absorbent, small pore dressing such as Telfa™ Clear (Covidien, USA) wound dressing. Always follow the instructions as set by the dressing manufacturer. Dry dressings such as Telfa™ Clear wound dressing may be applied moist at the direction of the healthcare professional by lightly soaking the dressing in sterile saline before dressing the wound. The dressing may be fixed to the wound with surgical glue (other than fibrin sealant), sutures, or staples, as necessary.

Place a secondary dressing (moderately absorbent, minimal adherence, low shear, readily removable) over the primary dressing. An example is Xeroform™ Occlusive Petrolatum Gauze (Covidien), or similar, placed over the primary dressing with a moist saline or Povidine-Iodine compress, and followed by Webril™ (Covidien, USA) and a crepe bandage.

C2 SUBSEQUENT DRESSINGS

Dressings may be debulked after 48 hours to facilitate review of the wound. The primary dressing should remain in place for 6-8 days, or as clinically indicated. IT IS ESSENTIAL THAT PRIMARY DRESSING REMOVAL IS ATRAUMATIC. ANY DRESSING NOT EASILY REMOVED SHOULD BE SOAKED WITH AN AQUEOUS OR OIL-BASED SOLUTION PRIOR TO REMOVAL TO PREVENT TRAUMA. Once the primary dressing has been removed, an appropriate protective dressing such as Jelonet® (Smith & Nephew, UK) or Mepitel® (Mölnlycke, Sweden) should be applied to protect the wound surface.

Do not use dry dressings as protection over an area of punctate blistering, as dried exudate could cause newly regenerated skin to adhere to the dressing, leading to potential injury upon dressing removal. Instead use (for instance) a greasy or paraffin gauze dressing until any blistering or open areas resolve.

Any signs or symptoms of infection or impaired healing at this stage should be recorded and addressed.

C3 AFTERCARE PRECAUTIONS

- Patients should take necessary precautions to prevent the treated area from getting wet while the wound is still open.
- Do not disrupt the primary dressing for a minimum of 5 days. Ensure that primary dressing removal is atraumatic - Do not forcibly remove the primary dressing.
- Up to two additional weeks may be needed after initial closure of the treated area for the newly regenerated skin to mature and become robust. During this time protective dressings must be worn, particularly on extremities.

- Use of known cytotoxic medication (for instance, silver sulfadiazine) is contraindicated for areas treated using ReCell.
- Patients and caregivers should be provided with adequate information and materials for appropriate protection against re-injury during healing and maturation of the treated area.
- Patients should be advised to refrain from strenuous activity.
- Patients should avoid direct sun exposure for at least four weeks following treatment.

C4 SCAR MANAGEMENT

When the wound has healed, the patient should be advised to continue to protect the area from any surface trauma and to avoid direct sun for at least four weeks. Regular use of sun block and twice-daily massage with a non-oily skin moisturizer is recommended.

The patient should be advised that the wound area will change over the subsequent weeks and months. The pigmentation and skin texture will continue to mature and improve during this time and the final result may take up to 12 months to be achieved.

Follow-up procedures should follow standard protocols for the specific injury and treatment given.

D TROUBLESHOOTING

Enzyme powder does not dissolve completely

Make sure that the Enzyme is mixed well with the sterile water by inverting the vial several times. Often a small amount of particulate matter remains undissolved in the reconstituted solution. This does not reduce the activity of the Enzyme.

Do not use Buffer to dissolve the Enzyme as it may interfere with the Enzyme action.

Skin sample is too large, too thick or too thin

Take particular care when harvesting the skin sample. It should be a thin (0.15 to 0.20 mm) split-thickness shave biopsy with just a very thin section of dermis (see previous instructions for dermatome settings). The skin sample of the appropriate thickness will ensure successful disaggregation of cells. The maximum size of skin sample recommended for use with the ReCell device is 3 cm by 2 cm.

If the skin sample is too large (greater that the maximum recommended), cut it into a smaller size and discard the excess.

If the skin sample is too thick, cut the skin sample into 1 cm by 1 cm pieces before placing in the heated Enzyme. If the cells cannot be disaggregated, repeatedly return the skin sample to the heated Enzyme for a further 5 to 10 minutes, up to a maximum of 60 minutes of total time. If the cells still do not scrape off freely it may be necessary to take another thin, split-thickness skin sample from a DIFFERENT donor site and repeat the process using a new ReCell device.

If the skin sample is too thin, you should take another skin sample from a DIFFERENT donor site and repeat the process.

Buffer added to Enzyme vial

If Buffer is mistakenly added to the Enzyme vial, instead of sterile water, the Enzyme activity may be inhibited. If Buffer is mixed with the Enzyme powder, the Enzyme should be discarded and a new ReCell device used.

Difficult Cell Disaggregation

Ensure that the heating element is switched on. The green light (✓) will illuminate when the ReCell device is switched on and ready for use. The orange light will illuminate when the device is warming. Disaggregation of the cells will take longer if the skin sample is too large or thick. See above for advice.

Nozzle blocked

If the cell suspension is not easily sprayed or does not come out at all, the nozzle attached to the syringe may be blocked. Use one of the other nozzles provided or consider dripping the suspension on to the wound.

Insufficient treatment area coverage

If cell suspension is lost in the application process and sufficient coverage of the treatment area was not achieved, take another skin sample and repeat the process with a new ReCell device to create additional cell suspension and complete the treatment.

For further information regarding ReCell Autologous Cell Harvesting Device, contact:

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Tel: +1 818 356 9400
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Appendix A4

PROCEDURE FOR ASSESSMENT OF HYPERSENSITIVITY TO TRYPSIN

Hypersensitivity to trypsin will be documented as an adverse event within the patient's medical notes and on the Case Report Form. All information obtained from the investigation will be provided as part of the adverse event documentation.

Accurate diagnosis is key to the management, and understanding of causes of contact dermatitis. For the purposes of this clinical study, confirmation that trypsin is the causative agent for immunologic hypersensitivity will be provided by an assessment of the patient's history, and the if necessary, a diagnostic patch test in accordance with the guidelines established by The American Academy of Dermatology.[16]

The patient history will be clinically focused. The investigator will assess the general medical status of the patient as the first assessment. The investigation will then move to the onset of the reaction where the location of the dermatitis, description and symptoms will be evaluated and recorded. The progression of the hypersensitivity will be determined by assessing for relationship of exposure time to the reaction and assessing if there have been further reactions following exposure to the ReCell® device (trypsin enzyme). If further reactions have been noted by the patient, these should be investigated in regard to their relationship to stress/anxiety, response to any therapy's the patient has initiated to treat the reaction, presence on weekends or vacations, and the results of exposing the reaction area to water. The will help rule our trypsin as a causative agent but possibly lead to further investigations being required as the patient's environment could be stimulating hypersensitivity reactions.

It is possible that trypsin may not be the causative agent and if this is considered a possibility, further investigating into the patients work situation (nature of work, duration in present job/activity, other colleagues effect with dermatitis, changes in procedures, chemical exposure, protective measure, other symptoms, cleaning agents, hand washing frequency and agents. Material safety data sheets in relation to the patient's job), other exposure possibilities (hobbies, knitting, sewing, macramé, paint, ceramics, jewelry, cooking, sports, animals, cosmetics and personal care products, household activities), family history and medical history.

Following an assessment of history, a physical examination will be performed and will include assessment of dermatitis location (symmetry, involved versus uninvolved skin) and lesion type being acute (eczema, vesicular/bullous, urticarial, excoriations, crusts) or chronic (lichenification, pigment change, atrophy, scarring, loss of hair), and other applicable observations.

Following the above assessment, the patient will be subjected to a skin patch diagnostic test according to the guidelines established at the investigative site. Positive results will be investigated further according to the expert judgment of a dermatologist and the investigator.

[16] Drake LA, Dorner W, Goltz RW, Graham GF, Lewis CW, Pariser DM, Salasche SJ, Skouge JW, Chanco Turner ML, Lowery JJ. (1995). Guidelines for Contact Dermatitis. *J Am Acad Derm*, 32(1):109-113.

Appendix B

SAMPLE ICF

CONSENT TO BE IN A RESEARCH STUDY

TITLE OF PROTOCOL:	Continued Access Protocol: 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
PROTOCOL #:	CTP001-7
STUDY SPONSOR:	Avita Medical
PRINCIPAL INVESTIGATOR:	
STUDY SITE FACILITY(IES):	
EMERGENCY CONTACT:	

INTRODUCTION

You are being asked to be in a research study. The research study is being sponsored and funded by Avita Medical, a medical device company committed to developing new medical treatments for burn repair. 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. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

PURPOSE OF THE STUDY

The ReCell® Autologous Cell Harvesting device (ReCell® device) is a device used to prepare a spray solution of healthy skin cells from a small sample of your own skin that can be applied over skin grafts to treat burn injuries (the word "autologous" means structures or cells derived from your body). The ReCell® device is an investigational device meaning that it has not yet received approval from the Food and Drug Administration (FDA) for commercial distribution and can only be used within a clinical study.

Avita Medical has completed patient enrollment into a clinical study that was designed to evaluate the safety and effectiveness of the ReCell device when used with skin grafts (this study is identified with protocol number CTP001-6). Data from the CTP001-6 study will be included within a premarket approval (PMA) application which will be submitted to FDA to obtain approval for the ReCell device. The purpose of this current study is to allow the burn physicians who participated in the CTP001-6 study to have continued access to the ReCell device for treatment of burn injuries while Avita Medical prepares and the FDA reviews the PMA application. The data collected in this current study will be submitted with the PMA application to provide additional information concerning the safety and effectiveness of the ReCell® device.

You are being asked to participate in this study because you have a burn that will require skin grafting. A skin graft will be required for your injury whether or not you choose to participate in this research study.

A skin graft is the transplanting of skin to another location on the body.

DESCRIPTION OF THE STUDY

The standard procedure for skin grafting is using skin from a non-injured area of the body, called a "donor site" and placing it over the wound. The skin is removed with a dermatome device or a special knife. It shaves a thin layer of skin which may then 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 cover a larger area.

The ReCell® Autologous Cell Harvesting Device is an investigational device. This means it has not been approved by the U.S. Food and Drug Administration (FDA) and can only be used in research. Devices that do not have approval by the FDA cannot be sold or prescribed by your physician. It is being tested for use with burn injuries requiring skin grafting. With the ReCell® device, a small, thin piece of skin, about the size of a postage stamp is harvested (approximately 1 inch x 1 inch). It is then processed to separate out the cells which can then be put in a suspension (liquid) for delivery. These cells, which came from your skin, are then sprayed onto the prepared burn wound.

These cells are a mixture of mostly epidermal cells (the outer layer of your skin), but also includes other cells normally present in skin.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 60 people at up to 8 study sites will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

If you qualify to participate in this study, the length of your participation will be 1 year. You can stop participating at any time you wish 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 learn about any potential health or safety consequences.

WHAT WILL HAPPEN TO ME?

At the hospital, your doctor will look at your burn and see if you are a possible candidate for this study. A complete explanation of the study and the expected results, plus possible side effects will be told to you by the study doctor. Following some time to consider your participation, you will be asked to read and sign this consent form.

The first step in the study is a review of your past medical history. Your burn will also be assessed to make sure that you have a minimum of 5% and a maximum of 50% of your body injured from the burn. Your burn must be serious enough to be classified as a burn injury requiring skin grafting. You must have received your burn by exposure to fire, excessive heat, direct flames, flash explosions, hot steam, or water.

You will eventually go to the operating room where you will be given anesthesia and your burn injury will be prepared for treatment. Your burn will be re-evaluated to confirm that you still meet the requirements of the study. If not, you will be taken out of the study and no further information will be collected about you. Your doctor will treat your burn as if you were never in the study.

If you can still be in the study, your burn injury will then be divided into two treatment areas. Each area will be randomly assigned a treatment. One area will receive the standard skin graft. The other area will be grafted and sprayed with the cell suspension (liquid) prepared using the ReCell device. You will not be told until the end of the study which area was sprayed with the cell suspension. We will be comparing how each of the two treatment areas heal. Any areas of your injury that are not part of the study may be treated with skin grafts or some other standard treatment which will be recommended by your study doctor. The treatment combination that will give you the best result will be chosen by your doctor.

During the skin grafting procedure, you will have photographs taken of your treatment and donor site areas. Following this review, the treatment will proceed according to the doctor and his / her team. You will have pieces of skin removed from unburned area(s) (donor) for your skin grafts and for use in the ReCell device. The amount of skin that will be taken and used from the donor site(s) for the skin graft will be the same or slightly smaller in size than the size of the burn area to be covered. Once the skin has been prepared it will be applied to your burn wound.

Some small amount of the skin that will be taken from the donor site will be used in the ReCell device. Once the skin has been processed, the skin cells will be applied onto your burn wound in the areas assigned to receive the ReCell treatment.

Additional photographs will be taken after all the treatments have been applied. All of your study wounds will be dressed with Telfa™ Clear wound dressing. You will then be taken to the recovery room. When you are awake and ready, you will be taken to your hospital room for your post-operative care.

Most of your dressings will remain in place for 6-8 days. You should follow your doctor's post-operative care instructions carefully and you should continue to protect the treated areas through at least 2 weeks after the graft areas have healed, using a suitable dressing that your doctor recommends.

Follow-Up Visits

You will need to visit your study doctor 1, 2, 4, 6, 8, 10, 12, 24, 36, and 52 weeks after your surgery. Each visit should take no longer than 1 hour to perform. In between visits the investigator or study staff may contact you by phone or post card to remind you of your next visit and/or to check whether you are having any problems or have any concerns. It is very important that you return for each and every visit.

When you come in for your study follow-up visits, the study doctor or staff may do any or all of the following:

- Review your wounds including looking at the rate of healing of all study wound sites
- Check for any infection or other complications

- Dress your wounds as necessary
- Take photographs of your healing wounds and/or scar
- Ask simple questions regarding pain and your impression of the appearance for all wound sites
- Ask about medications, supplements, procedures or therapies
- Ask about dressing changes you may have performed at home on your study wounds
- Review any adverse events you may have experienced
- Ask about your satisfaction with the treatment

CAN ANYTHING BAD HAPPEN TO ME?

Risks of graft surgery

The risks of skin grafting include those associated with any surgical procedure that involves general anesthesia and may include:

- Reactions to the anesthesia
- Reactions to the medications
- Nausea and vomiting
- Pain
- Problems breathing
- Excessive bleeding
- Infection
- Changes in blood pressure and heart function
- Changes in lung function
- Constipation
- Blood Clot
- Problems with urinary catheterization
- Fever and chills
- Lack of take of the skin graft (rejection or loss of graft)
- Skin Irritation
- Itching
- Redness
- Scarring
- Skin discoloration and/or uneven skin surface
- 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 at donor areas

In addition to the above noted risks, possible risks from using the ReCell spray skin device include sensitivity to trypsin (an enzyme used in the ReCell device) or compound sodium lactate solution.

Risks during the healing period

If a wound becomes infected, does not get enough oxygen, or the skin graft/sprayed-on cells don't take there may be increased scarring, or loss of skin graft. This may result in the need for further surgical treatment. Surgical treatment could include debridement of the wounded area (surgical removal of dead or infected tissue in the wound), placement of a skin substitute, or re-grafting of the wounded area.

Because your study doctor looks at the wounds very closely, he/she will try and 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 skin grafting procedure performed at the hospital.

OTHER RISKS

You may not participate in this study if you are pregnant as use of the ReCell device may involve unknown risks to you or your fetus if you are pregnant. If you suspect that you have become pregnant, you must notify the study doctor immediately.

There is the risk of equipment malfunction that could result in the possibility of a need for harvesting additional donor skin.

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

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. Use of cell suspensions prepared using the ReCell device for grafting may improve healing of your injury and may result in less scarring. Although only part of your wound sites will be treated with the ReCell-derived skin cell suspension, these areas may look better in the long-term. It is also possible, however, that you will receive no benefit. Information learned from this study may help burn patients in the future.

WILL I GET PAID?

You will receive $100.00 at each follow-up visit to cover fair and reasonable travel expenses to the clinical site. If there are extenuating circumstances that make it difficult for you to return for your follow-up visit the sponsor of the trial, Avita Medical, may be able to provide additional assistance to assure that you return for each follow-up visit. 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. There are no plans to provide you with financial compensation or for you to 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 injury treated by conventional means alone.

WHAT OTHER TREATMENT CHOICES ARE THERE?

There are other methods that are used to treat burn injuries that could be offered to you. Your burn could be treated with a skin graft alone, or whatever standard of care treatment your doctor and the hospital use.

If you choose not to participate in this study, your care will in no way be affected. Your doctor will still do his/her best to ensure that you receive all of the standard care that he/she provides for skin graft patients. 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 to which you are entitled. If you decide to stop participating in the study we encourage you to talk to your study doctor or study staff first to learn about any potential health or safety consequences.

However, 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.

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 or other support to _____ 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. 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 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, and information from study visits, phone calls, surveys, and physical examinations.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as 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; the Institutional Review Board; representatives of _____ Hospital are eligible to review research records, in addition to the Food and Drug Administration (FDA).

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.

If this research study involves the treatment or diagnosis of a medical condition, then 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 in providing you with appropriate medical care. In addition, all or part of your research related health information may be used or disclosed for treatment, payment, or healthcare operations purposes 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 revoke or take away your authorization to use and disclose your health information at any time. You do this by sending a written notice to the investigator in charge of the study at the following address:

_____ (Principal Investigator)

_____ (Facility)

_____ (Mailing Address)

If you 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 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 _____.

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 those questions answered. 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.

Printed Name of Subject _____

Signature of Subject _____ **Date** _____

STATEMENT OF PERSON CONDUCTING INFORMED CONSENT DISCUSSION

I have fully explained the procedures involved in this study, identifying those that are investigational, and have explained their purpose. 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.

_____
Printed Name of Person Conducting Informed Consent Discussion

_____ _____
Signature of Person Conducting Informed Consent Discussion Date

The following should be included if you are recruiting subjects with diminished mental capacity or individuals who cannot otherwise provide informed consent:

Legally Authorized Representative Name (Print) _____

The above named Legally Authorized Representative has legal authority to act for the research subject based upon (specify health care power of attorney, spouse, parent, etc.)

Legally Authorized Representative Signature_____ **Date** _____