Protocol Title: Epidermal Coverage of Traumatic Wound Injuries via Use of Autologous Skin Cell Harvesting Device in Combination with Widened Meshed Autograft Applied Over Bilayered Wound Matrix

NCT02469168

Informed Consent

Approved 11-14-14

WALTER REED NATIONAL MILITARY MEDICAL CENTER
BETHESDA, MD

This consent form is valid only if it contains the IRB stamped date

Consent for Voluntary Participation in a Research Study Entitled: Epidermal Coverage of Traumatic Wound Injuries via Use of Autologous Skin Cell Harvesting Device in Combination with Widened Meshed Autograft Applied Over Bilayered Wound Matrix

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Study site(s): _X_WRNMMC, __ FBCH, __USUHS, ___WRAIR, ___NMRC, ___JPC, _ _ OTHER
Study sites:

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.

1. INTRODUCTION OF THE STUDY

You are being invited to participate in this research study because you are being treated for a full-thickness or deep partial-thickness traumatic wound injury at Walter Reed National Military Medical Center (WRNMMC). This study involves research to investigate a new skin graft spray device, called ReCell that may allow us to harvest less skin to cover your traumatic wound.

Taking part in this study is voluntary. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your benefits to which you are otherwise entitled. Leaving the study will not affect your medical care. Please read the information below, and ask questions about anything you do not understand, before deciding whether to take part in the study.

If significant new findings develop during the course of this study that may relate to your decision to continue participation, you will be informed.

2. PURPOSE OF THE STUDY

The purpose of this study is to learn how effective the Autologous Cell Harvesting Device kit "ReCell" is when used with widened split-thickness skin graft (STSG) mesh to assist in closing traumatic wound injuries. Because of the size of your wound, you may require a significant amount of skin to be harvest (remove tissue for transplantation) in order to close your wound. With the use of ReCell, we can potentially harvest (remove tissue for transplantation) a significantly less amount of skin to close your wound. This technique has been tested in other

countries, but not in the United States. The ReCell device has not been approved by the Food and Drug Administration (FDA) therefore, it is considered experimental. However, the FDA has allowed its use to study its safety and effectiveness under an Investigational Device Exemption (IDE) application #16104. To date, there is no preliminary data applicable for this indication (use in traumatic wounds). However, ReCell is currently being evaluated in the United States as a primary treatment of partial-thickness burns compared with standard split thickness meshed skin grafts.

The specific goals of this research study is to evaluate the safety, tolerability and preliminary as well as long–term effectiveness of the ReCell device for healing full-thickness wounds that have already been treated with an advanced wound care dressing called Integra Meshed Bilayer Wound Matrix (Integra™ MBWM).

3. PROCEDURES TO BE FOLLOWED

If you agree to participate in this research study, and all of your questions have been answered to your satisfaction, you will be asked to sign and date this consent form showing that you understand the purpose and treatment of this study.

After signing the consent form, you will be assigned a unique 3-digit study ID number that will be used throughout the study to "de-identify" all of your protected health information we will be collecting.

Due to the nature of the study, only patients whose wounds have been treated with Integra™ MBWM as part of their standard of care will qualify for participation. Therefore, before starting treatment with the investigational product, the targeted study wound area will be treated with Integra™ MBWM. The wound will then be allowed to heal for approximately two to four weeks, at which time a viable granulation layer (new, healthy tissue that forms on the surface of the wound) is produced suitable for the next stage of skin grafting. Skin grafting is a surgical procedure in which a piece of skin is taken from one part of the body and put on another (transplanted).

There are 3 main phases of this research study: A Screening/Pre-Treatment phase which is the time period from consenting/enrollment into the study to just prior to receiving treatment with the investigational product (ReCell device) in the operating room; an Acute Healing Phase (Week 1-6 post-treatment) and a Long-term Effectiveness Phase (Week 12 and 24).

The following screening/pre-treatment procedures will be performed to determine if you are an appropriate candidate for participation in this research study. Some of these procedures may be done as part of your routine care. A table listing all of the study related test and procedures is presented on the last page of this informed consent document. The screening pre-treatment evaluations may be performed up to 30 days prior to receiving treatment with the investigational product, the ReCell device.

You will be asked questions about your medical history including medications you are currently using, any allergies you may have and demographic information such as your date of birth, gender and race/ethnicity.

A physical examination will be performed on you including obtainment of your height and weight. You will also have your vital signs (heart rate, breathing rate, blood pressure) and temperature taken.

An evaluation of the wound area treated with Integra™ MBWM will be made. Members of the study team will review your medical record to obtain the surgical report for this procedure. The investigator will inspect the wound area treated with Integra™ MBWM to determine if all areas are fully engrafted as indicated by the formation of a viable granulation (new, healthy tissue) layer as this will allow for grafting (transplanted) with the investigational ReCell device.

A baseline assessment for the presence or absence of a condition called heterotopic ossification will be made. Heterotopic ossification refers to the presence of bone in tissue where bone normally does not exist (non-skeletal tissue) and is commonly seen in individuals who have sustained a military blast trauma injury. This baseline assessment will be accomplished by obtainment of radiographic imaging (x-rays) of your traumatic wound area. If your medical record contains an x-ray taken of your traumatic wound injury within 30 days prior to your enrollment into this study, we will use these x-rays for this baseline assessment for the presence/absence of heterotopic ossification.

A baseline assessment for pain and itching at your wound site will be obtained for comparison after receiving study treatment with ReCell. You will be asked to rate your pain using a 0-10 point verbal numerical rating scale where "0" equals no pain and "10" equals worst pain possible. Additionally, you will be questioned if experiencing itching at the wound site. If so, you will be asked to rate the intensity using the following options: mild, moderate and severe.

As part of a study requirement and per standard of care pre-operatively, you will have a blood sample obtained. One tablespoon of blood will be drawn for baseline safety assessments for the study and for evaluation to make sure you are suitable to have surgery. This sample will be obtained at the time your pre-operative evaluation is being conducted. If in-patient, the hospital phlebotomy (blood drawing) team will perform and if an out-patient, you will be instructed to report to the WRNMMC out-patient laboratory setting.

If female, and are pregnant or nursing, you will be excluded from participation in this study. Additionally, if of childbearing potential, you must agree not to become pregnant while participating in this study. The risk to the fetus or to women who are pregnant is not fully known at this time. Therefore, you cannot take part in this study if you are pregnant or become pregnant.

If you meet all of the eligibility criteria, you will be scheduled for the surgical procedure.

The pre-operative and anesthesia procedures utilized will be those consistent with standard of care meaning they will be the same ones followed even if you were not in the study. Per WRNMMC procedures and guidelines for pre-operative patients, individuals will undergo the following activities prior to surgery: obtainment of a medical history including current medication use, a physical examination, weight, vital signs (heart rate, breathing rate, and blood pressure), temperature, laboratory work and possibly, a standard chest x-ray and electrocardiogram (EKG), if deemed necessary. All females will be required to provide a urine

sample for the purpose of pregnancy testing. You will be instructed not to have anything to eat or drink after midnight the morning of surgery. You will receive general anesthesia for the entire surgical procedure. Therefore, you will be unconscious (asleep) during surgery and will not remember or feel anything that happens. You will be given a separate consent form to sign that is routinely obtained prior to receiving general anesthesia and giving permission for the surgical procedure. Both the anesthesiologist (doctor who administers anesthesia) and the surgeon will go over the risks associated with this type surgery with you.

It is anticipated that the surgical procedure will take up to 3 hours to complete. Once asleep, the surgical wound area will be prepped according to hospital standard procedures.

Next, the INTEGRA™ MBWM treated wound area will be divided into two similarly sized study regions within itself. One side (1/2 of the wound) will then be labeled as "A Region" and the other side (1/2 of the wound) will be labeled as "B Region" with a surgical pen by the surgeon.

For this study, we will be comparing two different split-thickness skin graft (STSG) treatment methods. The first method will involve a standard skin grafting which will be identified as the "Control". The second method will involve a skin grafting with significantly less skin and supplemented with the experimental spray skin graft (ReCell).

You will receive both of these treatment methods. One treatment method will be applied to the "A Region" of the the INTEGRA™ MBWM treated wound and the other treatment method will be applied to the "B Region" of the INTEGRA™ MBWM treated wound.

Each study participant will be treated with meshed STSG over both the Control and ReCell regions of the Integra-treated wound. The control area will have standard practice 1:1.5 meshing (only) STSG, and the experimental area will have 1:5 meshing STSG plus application of ReCell (ReCell will be applied over the 1:5 meshed STSG). To create a meshed graft, a "mashing" apparatus is used to put open spaces (small splits or cuts) in the STSG in an organized fashion. This expands the graft so it can cover a larger surface area. The difference in ratio determines the expansion of the skin graft. For example, the 1:1.5 ratio has open spaces that are one and a half as large as the skin and the 1:5 ratio has open spaces that are five times as large as the skin. The larger the meshing ratio, the larger the surface area is that can be covered by the graft.

Treatment Summary Table:

ReCell Region (experimental)	**Control Region (standard of care)**
ReCell + 1:5 Meshed STSG	1:1.5 Meshed STSG (no ReCell)
INTEGRA™ MBWM	INTEGRA™ MBWM
Wound Bed	Wound Bed

Assignment of treatment methods (ReCell versus Control) to the INTEGRA™ MBWM treated wound regions will done by randomization. This means that whichever study treatment you receive to "A Region" and "B Region" will be determined purely by chance, like flipping a coin. You will not be told which study treatment (ReCell or Control) was applied to each side of your wound until the end of the study (Week 24 post-treatment) because you will be asked later on

throughout the study to complete short evaluation questionnaires pertaining to you wound site after treatment.

Selection of donor sites is of importance and consideration will be given for promotion of the same functional and cosmetic characteristics as the area to be grafted and treated with the ReCell; i.e., a donor site is chosen with similar pigment and texture to the treatment site. Oftentimes, skin is selected from the thigh area. However, this may not be an optimal area of choice for you. The investigator will discuss selection of donor site options with you ahead of time.

STSG Meshing:

Donor tissue for the control STSG will be meshed at 1:1.5 with a meshing system and the ReCell treatment area will have a 1:5 meshed STSG using the same meshing system as the control area, followed by ReCell treatment. The meshing system allows for expanding the size of skin obtained by putting small slits or cuts into it.

Donor tissue for the STSG for the ReCell treatment area may be harvested (removal of tissue) from the same area as for the control STSG or from a separate area.

Pre-Treatment Photography:

A digital photograph will be taken of the control and ReCell site ("A" region and "B" region) before and after treatment while in the operating room. Additionally, photographs will be taken of donor sites prior to and following tissue removal.

Pre-Treatment Punch Biopsy:

A 3 mm diameter (approximately 1/8 ínch) tissue sample will be obtained from the INTEGRA™ MBWM wound area. **In addition**, a punch biopsy will be taken of normal adjacent skin. Your doctor will discuss the procedure with you in detail prior to surgery and you will be asked to sign a separate consent form accordingly to WRNMMC policies for this type of procedure. You will not feel this procedure as you will be "asleep" for your surgical procedure. This biopsy will be analyzed to determine skin composition relative to normal skin.

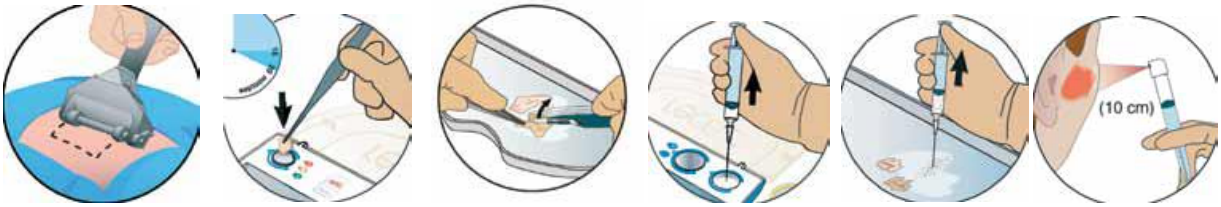
Control Surgical Methods:

The Control assigned area will be treated as per standard of care surgical practices utilizing the prepared STSG meshed at 1:1.5.

ReCell Surgical Methods:

Below is a picture of the investigational product, the Autologous Cell Harvesting Device kit (ReCell):

Step-By-Step ReCell Procedure:



1 2 3 4 5 6

1. A thin, split thickness shave biopsy, 0.15 - 0.2 mm (0.006 inch to 0.008 inch) in depth, is taken of site matched skin
2. Skin sample is incubated in the ReCell enzyme solution (trypsin) for approximately 15 minutes
3. Skin sample is removed from incubator, mechanically agitated to separate cells
4. Cells are then rinsed and collected using ReCell buffer solution
5. Cells are filtered and suspension is drawn up
6. ReCell suspension is then sprayed or dripped on wound followed by covering with recommended dressing

ReCell Donor Site will be approximately 2x2 cm in area (size of a postage stamp).

This procedure should allow complete wound coverage. If there is insufficient cell suspension to cover the wound bed, another biopsy will be taken and the cell suspension preparation process will be repeated to create another cell suspension.

There is a maximum amount of surface area the ReCell device can cover. Therefore, any wound area outside the study regions will be treated according to standard of care.

Upon completion of surgery, the treatment areas will be dressed (covered) with very specific guidelines to promote graft take and healing. The primary dressing (dressing that is in direct contact with the wound surface) will be of a non-adherent wound dressing called Telfa™ Clear. Post-treatment photographs will be taken after placement of the primary dressing. After placement of the primary dressing, a secondary dressing, Xeroform™ Petrolatum ("vaseline") Gauze will be applied to keep the treated wound areas moist followed by wrapping the surgical area with a bulk dressing (e.g. gauze) to protect the wound surface.

It is very important that care is taken not to manipulate nor disturb these dressing (e.g. remove, bump, get wet or soiled) until the first post-operative visit unless medically necessary as doing so

could compromise the treated wound area in terms of graft take and healing.

The primary dressing (dressing that is in direct contact with the wound surface) at the donor area sites will be Xeroform™ Petrolatum ("Vaseline") Gauze. After placement of the primary dressing the donor sites will then be wrapped with bulk dressing (e.g. gauze) plus or minus a compressive wrap (ace-wrap) based on the area of harvest (extremity vs torso). The donor area dressing will be removed in 48 hours (2 days). The primary dressing (Xeroform™ Petrolatum Gauze) will remain in place and will be gradually peeled off over several days.

Post-Operative Care:

Following surgery, you will be transferred to the Post Anesthesia Care Unit (PACU) and then to the In-Patient ward. Post-Operative recovery in terms of hospitalization and length of stay will be as per standard of care for this type of procedure.

Acute Healing Phase (Week 1-6 post-treatment): Preliminary effectiveness will be assessed during this period of the study and will focus on healing of both wound and donor sites. During this time, it is important care is taken not to cause trauma to these areas. You will be asked to follow the recommended guidelines for care post-treatment with the ReCell device:

- Prevent the treated area from getting wet while the wound is still open
- Refrain from strenuous activity
- Protect the healed area; don't bump, wear loose clothing over treated area
- Once the area has healed, massage and keep area moisturized (using a gentle moisturizer) at least twice a day
- Avoid direct sun exposure at least 4 weeks following treatment and use sunscreen

Long-term Effectiveness Phase (Week 12 and 24): Long-term effectiveness will be assessed at Weeks 12 and 24 during this period of the study and will focus on the integrity, durability and physical characteristics such as scarring. Additionally, we would like to evaluate your satisfaction after receiving treatment with the investigational ReCell device.

Throughout the study at specific time points, study evaluations will be made (please refer to study procedure schedule located on last page of this document)

Post-Treatment Study Visits

You will be re-evaluated by the Orthopaedic Surgery Service, General Surgery Service and/or Plastic Surgery Service clinic at WRNMMC or on the in-patient wards. At all post-treatment study visits (Week 1 ± 3 days, Weeks 2, 3, 4, 6 ± 2 days, Weeks 12 and 24 ± 14 days post-treatment), a member of the study team will perform the following assessments:

- Healing progress at the wound and donor sites
- Infection
- Vital Signs and Temperature
- Digital Photography to document the healing process at the ReCell donor site and at the treated and control wound sites
- Medication Use (up until Week 12)

- Any problems or concerns you may have experiences since your last visit

At each of these visits, we would also like to further evaluate the treated areas (ReCell and Control) by identifying if you are experience any scar pain or scar itching. This will be accomplished by asking you to complete the "patient" portion on the Patient Observer Scar Assessment Scale (POSAS) that, on a 10-point scale, allows you to rate if you are experiencing scar pain and scar itching at both of the treated wound areas from "no, not at all" to "yes, very much".

In additional to above assessments, additional "visit specific" assessments will be made as outlined below:

At Week 1 post–treatment:

- Bloodwork: A blood sample of one tablespoon will be drawn for safety evaluation post-operatively, which is consistent with standard of care practices, meaning even if you were not in the study, you would have this done.

At Week 2, 4 and 12 post–treatment:

- **Punch Biopsies:** A 3mm (approximately 1/8 inch) tissue sample of the treated wound site will be obtained by a surgeon investigator. You will be asked to sign a consent form prior to the procedure. The area to be biopsied will be prepped (cleaned), draped then injected with lidocaine to numb the wound site first in attempts to minimize any pain or discomfort you may feel with this procedure. A sample collection of 3mm diameter will be taken from both the control and ReCell treated sites from a centralized area of each wound region. The biopsies will be obtained for histologic analysis (study of tissues under a microscope) to determine skin composition relative to normal skin. The Study Coordinator will call you within 72 hours after the biopsy procedure to inquire about any problems or concerns you may be experiencing.

At Week 12 and 24 post-treatment:

- **Scar assessment scales:** Scar appearance at the treated wound will be evaluated by you and by two independent observers (WRNMMC dermatologist subject matter experts) using the entire POSAS (both patient and observer scales) assessment tool. Like you, the two independent observers will not know which region of the wound received control or ReCell treatment. Therefore, your will be asked to evaluate the treated "A" Region and treated "B" Region of your wound. Each scar (control and ReCell-treated sites denoted as "A'Region and "B" Region) will be evaluated once by each of you and all 3 evaluations made will be "unknown" to each other.

- In addition, an evaluation of scar appearance at the treated wound will be made by the two WRNMMC dermatologists unaware of which wound region received control or ReCell treatment. This will be accomplished utilizing the Vancouver Scar Scale (VSS). This assessment tool uses word descriptions from four categories to score the appearance

of a scar. Each scar (control and ReCell-treated sites denoted as "A" Region and "B" Region) will be evaluated once by each of the WRNMMC dermatologists and evaluations made will be "unknown" to each other.

- **Functional Outcome Rating Questionnaire**: This questionnaire consists of a 10-point scale to evaluate scar pain. You will be asked to evaluate if the scar is painful at the control and ReCell-treated sites denoted as "A" Region and "B" Region on the form since you will not know which study treatment (Control or ReCell) was applied to each side of your wound.

- **Patient Satisfaction**: A 2-question patient satisfaction questionnaire pertaining to the treatment you received for your wound.

At Week 24 post-treatment:

- Radiographic imaging (x-rays) of your treated wound area to determine the presence or absence of heterotopic ossification (the presence of bone in tissue where bone normally does not exist (non-skeletal tissue).

The total duration of participant time commitment for each of the post-treatment study visits is approximately 1 hour.

Additional Information Pertaining to Punch Biopsies:
All punch biopsy samples will be coded and labeled with your unique 3-digit study ID number (not your name) at the time they are obtained. The tissue samples will be cut in half by a study team member. One half of the sample will be processed then delivered via courier to a local laboratory facility located outside of WRNMMC for processing. As part of the processing procedures, your tissue sample will be embedded (placed in paraffin blocks) and prepared (stained) slides will be prepared by someone at the outside laboratory facility. Within a few days, the prepared (stained) slides and paraffin blocks will be returned to WRNMMC via courier and stored in a secured area within the Department of Orthopaedics. Results from the prepared (stained) slides will be interpreted (provide meaning of) by a Dermatopathologist (a doctor who specializes in dermatology and pathology) from WRNMMC.

The other half of tissue sample will be frozen then stored in a freezer located within the Department of Orthopaedics Biomechanical Lab, Room 2010. The reason for freezing half of the biopsy sample is to preserve the ability to return to the frozen sample in need be, in the event we do not obtain an adequate staining quality needed for interpretation on the initially prepared (stained) slide, another slide can be made.

At the end of the study, the frozen sample and the paraffin blocks will be destroyed. The slides will be kept indefinitely by the Investigator.

4. ALTERNATIVES TO PARTICIPATION:

If you decide to not participate in this research study, there are alternate treatments or procedures you may wish to consider:

- Getting reconstructive surgery without being in this, or any, study
- Participating in another study
- No additional surgical treatment

5. AMOUNT OF TIME FOR YOU TO COMPLETE THE STUDY

Your participation in this research study will last up to 28 weeks (screening, treatment with study device and follow-up). Your active participation in this study begins when you sign this consent form and ends at the Week 24 post-treatment follow-up visit. During this time you will be re-evaluated 7 times post-ReCell treatment; at Week 1, 2, 3, 4, 6, 12 and 24. Each visit will last approximately 1 hour of your time, dependent upon the assessments and procedures scheduled for that particular visit. These visits will occur at WRNMMC in a private room within the Orthopaedic Surgery, General Surgery and/or Plastic Surgery Service clinic or on the in-patient ward, with the exception of the blood draw at Week 1 post-treatment which will take place within WRNMMC out-patient laboratory setting if you are of an out-patient status.

6. NUMBER OF PEOPLE THAT WILL TAKE PART IN THIS STUDY

A total of 20 participants are expected to take part in this study.

7. POSSIBLE RISKS OR DISCOMFORTS FROM BEING IN THIS STUDY

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the study investigator if you have any questions.

There are no known risks of the ReCell device based on results from over 5,000-treatment procedures conducted worldwide.

Possible risks and discomforts from being in this research study may include the following:

- Risks that are common and the same as those for standard of care therapy for split-thickness to include: lack of take of the skin graft (< 10% total graft loss; ≥ 10% partial graft loss), heterotophic ossification (the presence of bone in soft tissue where bone normally does not exist) (≥ 10%), delayed healing/non-healing of wound and donor sites or rejection of the skin graft, scar contractures that impact limb function (< 10%), durability (i.e. abrasions/injuries at graft site due to graft fragility), infection at wound or donor sites, bleeding, keloid formation, reduced or loss of skin sensation or increased sensitivity, scarring, skin discoloration, uneven skin surface (< 5%).

- The punch biopsy procedure conducted as part of this research has potential risks associated with them. The biopsy has a risk of bleeding, bruising, redness, swelling, and pain; less common are scarring and infection. The application of lidocaine to numb the skin during the biopsy very rarely affects heart rate.

- The use of the ReCell device may lead to complications such as an adverse reaction to the enzyme Trypsin that is used to prepare the spray skin cell suspension or Compound Sodium Lactate (Hartmann's Solution) used for irrigation (rare occurrences)

- The blood draws performed as part of this study (and as part of your standard medical care) include risks. The risks include pain and/or mild discomfort and bruising. Less

common risks include a small blood clot, infection or bleeding at the puncture site, feeling lightheaded, multiple punctures to locate veins and on rare occasions fainting during the procedure.

- Minimal radiation exposure for radiographic imaging (x-rays) for the assessment of heterotopic ossification (the presence of bone in soft tissue where bone normally does not exist) performed as part of the study and/or part of your standard medical care.

- General anesthesia involves some risk, but major side effects and complications from anesthesia are uncommon. Your specific risks depend on your health, the type of anesthesia used, and your response to anesthesia, and will be discussed with you by the anesthesiologist and/or surgeon. Awareness or the concern of "waking up" during general anesthesia is very rare because anesthesia specialists devote careful attention and use many methods to prevent this. Most side effects of general anesthesia are minor and can be easily managed.

- Your participation in this research study does potentially involve a risk of a breach of confidentiality of the medical record information and associated privacy. The study investigators will take steps to reduce these risks by: 1) removing direct participant identifiers (i.e., names, social security numbers, medical record numbers) from information stored in the study records; 2) securing, in a separate location, and limiting access to information linking codes assigned to the study record information with direct participant identifiers; and 3) limiting access to information contained within the study records to study investigators only.

As with any research or clinical procedure, there may be side effects that are currently unknown and certain of these unknown risks could be permanent, severe or life threatening, or even cause death. You will be watched carefully for any side effects. You should inform your study doctor about any side effects you experience while taking part in the study.

If we learn of any new information about study risks, you will be informed promptly of any new significant findings relative to the ReCell device which may affect your willingness to continue your participation in this study.

8. POSSIBLE BENEFITS FROM BEING IN THIS STUDY

We cannot guarantee or promise you will receive benefits from participating in the study; the treatment provided may or may not directly benefit you.

The potential benefits to you may include:

- Decrease in the amount of skin required to be harvested (removal of tissue)
- Reduction of donor site morbidity (complications at the site)
- Reduction in your recovery time
- Reduction or elimination of your disability
- Improved appearance and contour of the healed wound site and self- esteem
- Improved quality of life

There is a possibility the ReCell treatment you receive may prove to be more effective than the standard of care treatment or than other available treatments, although this cannot be guaranteed.

Findings from this study may yield information to help us better understand healing properties to improve upon the current standard of care for individuals with traumatic wounds requiring skin grafting. Additionally, increased knowledge and technological advancement in the field of regenerative medicine may result from the conduct of the research study and potentially help a large number of patients in the future.

9. CONFIDENTIALITY/PRIVACY OF YOUR IDENTITY AND YOUR RESEARCH RECORDS

The principal investigator will keep your research records of your participation in this study. These records may be looked at by staff from the Walter Reed National Military Medical Center (WRNMMC), the Center for Innovation in Restorative Medicine (CIRM) located at University of Pittsburgh School of Medicine (the data coordinating center for this study), the statistician from Glaser Consulting, the study monitors from IMARC, Inc who will review all information obtained to ensure the accuracy of data collected, the Department of Research Programs, the Walter Reed National Military Medical Center Institutional Review Board (IRB), representatives from the U.S. Army Medical Research and Materiel Command (USAMRMC), the Office of Research Protections (ORP), the Human Research Protections Office (HRPO), the U.S. Food and Drug Administration (FDA), and/or other government agencies as part of their duties.

These duties include making sure that the research participants are protected. Confidentiality of your records will be protected to the extent possible under existing regulations and laws but cannot be guaranteed. Complete confidentiality cannot be promised, particularly for military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities. Your research records may be disclosed outside of WRNMMC, but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to authorized research study personnel.

Your name, social security number, medical record number or any other personal information that could identify you as an individual will be removed from all study forms. When you enter the study, you will be assigned a 3-digit study ID number. All information collected for the purpose of this study will be coded and your study ID number will be used on all study forms. The link between your name and your study ID number will be kept confidential to the greatest extent provided by law. The master list linking your 3-digit study ID number and your identifying information will be kept by CAPT Fleming (or his designee) in a locked file cabinet located in the Orthopaedic Surgery clinic at WRNMMC.

Your study records and digital photographs will be maintained in a locked file cabinet in a locked room located in the Orthopaedic Surgery clinic at WRNMMC accessible only to personnel involved with this study. Precautions are in place to ensure all electronic records will be stored in password-protected files. Access to this information will be limited to research team members and to those health care professionals who are providing clinical services as part of this research study. Biopsy samples shipped to Annapath, Inc. located in Bowie, MD, will be sent coded. Study data collected at WRNMMC will be coded then transmitted to CIRM (data

coordinating center) via site-secured computers, uploading data onto a password protected software application called Medrio.

Although we will do everything in our power to protect your privacy and the confidentiality of your records, just as with the use of your medical information for health care purposes, we cannot guarantee the confidentiality of your research records, including information that we obtained from your medical records.

By signing this consent document, you give your permission for information gained from your participation in this study to be published in medical literature, discussed for educational purposes, and used generally to further medical science. You will not be personally identified; all information will be presented as anonymous data. So, your name will not appear in any published paper or presentation related to this study.

This research study meets the confidentiality requirements of the Health Insurance Portability and Accountability Act (HIPAA).

The purpose of this research study is to obtain data or information on the safety and effectiveness of the Autologous Cell Harvesting Device (ReCell); the results will be provided to the sponsor of the study J. Peter Rubin, MD affiliated with the University of Pittsburgh School of Medicine, the FDA and other federal and regulatory agencies as required.

10. CONDITIONS UNDER WHICH YOUR PARTICIPATION IN THIS STUDY MAY BE STOPPED WITHOUT YOUR CONSENT

Your taking part in this study may be stopped without your consent if remaining in the study might be dangerous or harmful to you. Your taking part in this study may also be stopped without your consent if the military mission requires it, or if you lose your right to receive medical care at a military hospital. The decision to stop your participation in this study can be made by the Principal Investigator, the study Research Medical Monitor, the Sponsor of this study or the FDA at any time without your consent.

Your participation in this study may be discontinued by the study investigator without your consent for one or more of the following reasons: failure to follow the instructions of the study staff, if the investigator feels your continuing participation is believed to be harmful to your well-being or in the event there is a need to initiate care contraindicated to study procedures and/or requirements, pregnancy, serious inter-current illness and if the study is cancelled due to other administrative reasons and/or unanticipated circumstances.

If your participation is stopped, the investigator will notify the subject and provide reason for doing so in person, by mail, email and/or telephone.

11. ELIGIBILITY AND PAYMENT FOR BEING IN THIS STUDY

You will not receive any payment for your participation in this research study.

Your participation may lead to new inventions or products. If the investigators are able to develop new products from the research use of your tissue sample, there are currently no plans to share with you any money or other rewards that may result from the development of these new

products.

12. COMPENSATION IF INJURED AND LIMITS TO MEDICAL CARE

You will not receive any compensation (payment) if you are injured as a direct result of being in this study. You should understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the study investigator before you enroll in this study.

Should you be injured as a result of your participation in this study, you will be given medical care for that injury at no cost to you.

Medical care is limited to the care normally allowed for Department of Defense health care beneficiaries (patients eligible for care at military hospitals and clinics). Necessary medical care does not include in home care or nursing home care. If you need to be hospitalized, you may have to pay the normal fees for subsistence (hospital meals), as per standard regulations.

If at any time you believe you have suffered an injury or illness as a result of participating in this research study, you should contact the Human Protections Administrator, Department of Research Programs, at Walter Reed National Military Medical Center at 301-295-8273.

13. COSTS THAT MAY RESULT FROM TAKING PART IN THIS STUDY

A DoD organization is funding this study. There is no charge to you for taking part in this study.

14. IF YOU DECIDE TO STOP TAKING PART IN THIS STUDY AND THE INSTRUCTIONS FOR STOPPING EARLY

Participation in the research study is voluntary. You have the right to decline participation, to withdraw or discontinue participation from this study at any time or for any reason (i.e., you no longer wish to participate or if you have any concerns related to your continued participation). If you agree to participate in this study then later change your mind, in no way will your decision affect the quality of routine care you receive.

If you decide to stop taking part in this study, you should tell the Principal Investigator (CAPT Mark Fleming, at 301) 295-2441) or another member of the research team as soon as possible. You will be asked to complete some of the assessments/procedures required at the Follow-Up (final) Visit in order for you to safely stop taking part in this study. Any information and tissue samples obtained from you up to the time of stopping your study participation will continue to be used by the University of Pittsburgh research team. By leaving this study at any time, you in no way risk losing your right to medical care and there will be not penalty to you and you will not lose your benefits to which you are otherwise entitled.

In the event you are withdrawn from the study before completion of the Week 24 post-treatment assessment, you will be asked to come to the clinic for a final assessment of safety evaluations. You will continue to be treated in accordance with acceptable standards of medical treatment.

15. YOUR RIGHTS IF YOU TAKE PART IN THIS STUDY

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care.

16. AUTHORIZATION FOR RESEARCH USE OF PROTECTED HEALTH INFORMATION

The Federal Health Insurance Portability and Accountability Act (**HIPAA**) includes a Privacy Rule that gives special safeguards to Protected Health Information (**PHI**) that is identifiable, in other words, can be directly linked to you (for example, by your name, Social Security Number, birth date, etc.). We are required to advise you how your PHI will be used. This authorization is effective until this study is closed.

(1) What information will be collected?

For this research study, we will be collecting information about your overall health status, medical history including current medication use, allergies, information related to your traumatic wound injury and treatment with INTEGRA™ MBWM, demographic information (date of birth, gender, race/ethnicity) findings on physical examinations including height and weight, vital signs, results from radiographic imaging (x-rays) used for evaluation of heterotopic ossification (the presence of bone in soft tissue where bone normally does not exist), results from your bloodwork, information pertaining to the pre/post-surgical use and application of the ReCell device kit, information regarding the harvesting of skin used for STSG meshing, wound care dressings and treatments, information regarding the healing process at the wound treatment areas and donor sites, findings from the punch biopsy analysis, digital photographs of the wound treatment and donor sites, pain, itching and scar evaluations using the POSAS and Vancouver assessment tools, your responses to the functional outcome and patient satisfaction questionnaires, medication use during study participation and any device and/or surgical related problems or concerns, if any.

(2) Who may use your PHI within the Military Healthcare System?

The members of the research team will have access to your health information in order to find out if you qualify to participate in this study, to administer research treatments, to monitor your progress, and to analyze the research data. Additionally, your PHI may be made available to health oversight groups within the DoD such as the WRNMMC Department of Research programs, the WRNMMC Institutional Review Board (IRB), an assigned Medical Research Monitor, representatives from the U.S. Army Medical Research and Materiel Command (USAMRMC), the Office of Research Protections (ORP) and the Human Research Protections Office (HRPO). The study monitors from IMARC, Inc who will review all information obtained to ensure the accuracy of data collected in the research records during their on-site visits to WRNMMC will have access to your PHI that is not de-identified, but will keep your information confidential.

(3) What persons outside of the Military Healthcare System who are under the HIPAA requirements will receive your PHI?

Your coded PHI may be shared with the Center for Innovation in Restorative Medicine (CIRM) located at University of Pittsburgh School of Medicine (the data coordinating center for this study) for the purpose of monitoring the overall conduct of the study, the statistician from Glaser Consulting for the purpose of analyzing the collected data and authorized officials from the FDA, and/or other government agencies as part of their duties. The tissue samples obtained from the punch biopsy procedure will be sent to Annapath, Inc. for the purpose of processing for analysis to determine skin composition relative to normal skin. If you experience a complication, we may need to send a copy of your medical record to the study sponsor and FDA. Once your data are shared

outside WRNMMC we cannot guarantee it will remain private, which is why we limit the identifiable data sent out. Confidentiality of your records will be protected to the extent possible under existing regulations and laws but cannot be guaranteed.

(4) What is the purpose for using or disclosing your PHI?

a. The members of the research team need to use your PHI in order to analyze the information to determine if you are eligible to for this study, monitor your recovery progress and safety, and evaluate healing and long term effectiveness.

b. Tissue samples obtained from the punch biopsy procedure will be sent to Annapath, Inc. coded with your 3-digit study ID number, for the purpose of processing sample for analysis to determine skin composition relative to normal skin.

(5) How long will the researchers keep your PHI?
The research team in the Department of Orthopaedics and Rehabilitation will retain your coded PHI and coded photos for up to seven years past completion of the study as requested by the Sponsor of this study. Upon completion of the seven year storage of documents requirement, all documents will be shredded per WRNMMC policy regarding destruction of confidential documents and all digital / electronic files will be erased. The master code which links your name and 3-digit study ID number will be destroyed as soon as all data collection for this study is completed. Maintenance of data, coded biopsy results, coded photographs will be stored indefinitely at the discretion of the Sponsor (Dr. J. Peter Rubin, at the University of Pittsburgh Medical Center) for potential educational purposes as well as review and analysis.

(6) Can you review your own research information?
You may look at your personal research information at any time before your identifiers are permanently removed from the data. As part of this research study, some information that we obtain from you will be placed into your WRNMMC medical records, including the results of pregnancy tests (for women of childbearing potential) and other medical tests. Any information that is entered into your medical records will be available to you, in accordance with the WRNMMC Notice of Privacy Practices.

(7) Can you cancel this Authorization?
Yes. If you cancel this Authorization, however, you will no longer be included in the research study. The study information collected prior to this cancellation will be used by the research team. No further data will be collected.

If you want to cancel your Authorization, please contact the Principal Investigator in writing:
CAPT(S) Mark E. Fleming, MC, USN
Deputy Director for Surgery
Department of Orthopedics,
Walter Reed National Military Medical Center (WRNMMC)
8901 Wisconsin Ave Bethesda, MD 20889
Phone: 301-295-2441
E-mail: Mark.E.Fleming.mil@mail.mil

(8) What will happen if you decide not to grant this Authorization?

If you decide not to grant this Authorization, you will not be able to participate in this research study. Refusal to grant this Authorization will not result in any loss of medical benefits to which you are otherwise entitled.

(9) Can your PHI be disclosed to parties not included in this Authorization who are not under the HIPAA requirements?

There is a potential that your research information will be shared with another party not listed in this Authorization in order to meet legal or regulatory requirements. Examples of persons who may access your PHI include representatives of the DoD Higher Level Review, the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP), and the DHHS Office for Civil Rights. This disclosure is unlikely to occur, but in that case, your health information would no longer be protected by the HIPAA Privacy Rule.

(10) Who should you contact if you have any complaints?

If you believe your privacy rights have been violated, you may file a written complaint with the WRNMMC Privacy Officer, located at 8901 Wisconsin Ave, Bethesda, MD 20889, Telephone: 301-319-4775.

Your signature at the end of this document acknowledges that you authorize WRNMMC personnel to use and disclose your Protected Health Information (PHI) collected about you for research purposes as described above.

16. CONTACTS FOR QUESTIONS ABOUT THE STUDY

If you have questions about the study, or if you think you have a study-related injury you should contact CAPT(S) Mark E. Fleming, at 301) 295-2441. For questions about your rights as a research participant, contact the Human Protections Administrator, Department of Research Programs in Building 17 at 301) 295-8273 or WRNMMC Staff Judge Advocate Office at 301) 295-2215.

A copy of this consent form will be provided to you.

OPTIONAL CONSENT FOR DIGITAL PHOTOGRAPHY OF YOUR WOUND AND DONOR SITES

The research team is requesting permission to digitally photography your wound and donor sites as a means to capture the progression of healing in these areas post ReCell treatment. Photos utilized for study purposes will be coded and marked with your unique identification number. You are not required to give permission and can refuse at any time after giving consent to have digital photographs of your medical evaluation. You understand that you may participate in the study without permitting these photographs. Additionally, you understand digital photography of your wound and donor sites may be obtained and stored in your medical record per WRNMMC

requirements as a part of your standard of care, but will not be used for study related purposes.

BY AGREEING TO THIS OPTIONAL CONSENT FOR DIGITAL PHOTOGRAPHY OF YOUR WOUND AND DONOR SITES:

☐ I **consent** to the digital photography, as described above

☐ I **DO NOT** consent to the digital photography:

Participant's Signature	Date	Time

SIGNATURE OF RESEARCH PARTICIPANT

You have read (or someone has read to you) the information in this consent form. You have been given a chance to ask questions and all of your questions have been answered to your satisfaction.

BY SIGNING THIS CONSENT FORM, YOU FREELY AGREE TO TAKE PART IN THE RESEARCH IT DESCRIBES.

Participant's Signature	Date	Time

Participant's Printed Name

SIGNATURE OF INVESTIGATOR

You have explained the research to the participant and answered all of his/her questions. You believe that the volunteer subject understands the information described in this document and freely consents to participate.

Investigator's Signature	Date (Must be same as participant)	Time

Investigator's Printed Name

Procedure	**Screening/ Pre-Treatment**	**OR**	**Assessments for Safety Tolerability and Preliminary Effectiveness**					**Assessments for Safety, Aesthetic, & Functional Outcomes**	
			Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 12**	**Week 24**
Visit Window Interval	**-30 Days**		**±3 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±14 days**	**±14 days**
Informed Consent/Enrollment	**X**								
Medical History[a]	**X**								
Demographics[b]	**X**								
Physical Examination	**X**								
Vital Signs[c]	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Injury Assessment of area treated with INTEGRA™ MBWM[d]	**X**								
Pain and Pruritus (baseline eval)	**X**								
Hematology/Chemistry[e]	**X**		**X**						
Radiographic Imaging[f]	**X**								**X**
Verification of Eligibility Criteria[g]	**X**								
Randomization[h]		**X**							
Histology[i]		**X**		**X**		**X**		**X**	
Digital Photography[j]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Donor Site Tissue Harvesting[k]		**X**							
Application of Investigational Product (ReCell Procedure)		**X**							
Wound & Donor Site Healing Assessments[l]			**X**	**X**	**X**	**X**	**X**	**X**	
POSAS[m]			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Vancouver Scar Scale (VSS)								**X**	**X**

Functional Outcome Rating								**X**	**X**
Patient Satisfaction								**X**	**X**
Concomitant Medications[n]	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Events[o]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

a) Current medication use and allergies
b) Date of birth, gender, race/ethnicity
c) Oral temperature, heart rate, respiration rate and blood pressure
d) Assessment to determine if traumatic wound is fully engrafted as indicated by formation of a viable granulation layer
e) Complete blood count (CBC) with differential panel, coagulation "clotting ability" tests and comprehensive metabolic panel (CMP)
f) Radiographic imaging (anterior/posterior and lateral films) for assessment of heterotopic ossification (presence/absence) pre-treatment/baseline if not previously obtained within 30 days of study enrollment and at Week 24 post-treatment
g) Verification of eligibility will be performed at Screening and Re-verification of eligibility just prior to picking up investigational device from pharmacy
h) Wound site will be labeled as "A" region and "B" region PRIOR to opening randomization envelope
i) Pre-treatment (baseline) biopsies at Integra area and of adjacent normal skin; then at Weeks 2, 4, 12 post-treatment, biopsies will be taken from the Recell and Control treated sites.
j) Photos will be taken at following time points: PRE-TREATMENT- Control and ReCell sites ("A" region and "B" region); Donor sites (ReCell, 1:1.5 and 1:5 meshing) following tissue removal, at treatment wound area prior to primary dressing placement and of the ReCell donor site, control area and ReCell treated area at each post-treatment visit for assessment of healing process
k) ReCell donor tissue harvested for cell suspension; donor tissue harvested for STSG Control area (meshed at 1:1.5) and donor tissue for the ReCell treatment area (meshed at 1:5 mesh)
l) Assessments made for: Atypical healing and/or delayed healing/non-healing, graft loss, heterotopic ossification, infection scar contracture, durability (i.e. abrasions/injuries at graft site due to fragility), allergic response to trypsin
m) Subject to complete "patient" part of POSAS at all post-treatment study visits. Full POSAS (including patient and two independent observers) completed at Week 12 and 24 post-treatment
n) Concomitant medication use (excluding anesthetic regimen) and all treatment regimens applied in the management of infection during the acute healing phase
o) AEs assessed from time of enrollment through study completion (Week 24) including AEs related to treatment requiring surgical intervention prior to Week 12 post-treatment and all serious adverse event occurrences