AD_____

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TITLE:	Dermal Coverage of Traumatic War Wounds
PRINCIPAL INVESTIGATOR:	Dr. Leon Nesti
CONTRACTING ORGANIZATION:	The Geneva Foundation Tacoma, WA 98402
REPORT DATE:	November 2015
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PREPARED FOR:	U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012

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The Geneva Foundation
917 Pacific Ave, Suite 600
Tacoma, WA 98402

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The proposed study is a prospective, randomized within-patient controlled feasibility study to evaluate the safety and effectiveness of the ReCell Device for re-epithelialization of full thickness wounds treated with INTEGRA MBWM. The ReCell Device is a stand-alone, battery operated cell separation device that enables preparation of a cell suspension from a small, thin, split-thickness skin biopsy. The autologous epidermal cell suspension is available for immediate delivery onto a prepared skin surface. This process has the potential to enhance skin regeneration while minimizing donor site morbidity. The performance of ReCell over INTEGRA MBWM in combination with 1:6 meshed split-thickness skin graft (STSG) will be compared to standard practice control (i.e., 1:1.5 meshed STSG over Integra MBWM). We expect all ReCell-treated and control areas of the wounds to heal adequately. However, we predict areas treated with ReCell will re-epithelialize more quickly than control areas, which has the potential to reduce the risk of infection and scarring in ReCell-treated areas compared to control areas.

15. SUBJECT TERMS Spray skin, Bioartificial dermis, Soft tissue coverage, Traumatic wounds, Regenerative medicine

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Table of Contents

INTRODUCTION:

Objectives/Specific Aims/Hypotheses:

Our hypothesis is that subject areas that receive ReCell treatment over a widened mesh STSG over Integra will have healing equivalent to areas treated with a lower STSG ratio over Integra.

The goal of the study described herein is to determine the effectiveness of the use of the ReCell device over a widened STSG mesh will improve upon the current standard of care. The potential for ReCell's promotion of healing in the interstices of the STSG mesh may close gaps that are potential points of failure during later physical activity. Within the current study, each patient will serve as his or her own control, allowing for comparison of ReCell-treated (experimental) and non-ReCell-treated (control) regions of the wound. The specific aims of this pilot clinical study are delineated below.

Specific Aim 1: Evaluate safety of ReCell treatment of full-thickness wounds treated with INTEGRA™ MBWM compared to control site. The safety and tolerability of ReCell treatment relative to standard of care (the control site) will be evaluated during the first 12 weeks after treatment, when the wound is most vulnerable. Safety-related issues will continue to be monitored through 24 weeks after treatment. Patients will be assessed for the following safety issues at each visit:

- Delayed healing/non-healing of wound and donor site
- Graft loss
- Heterotrophic ossification
- Infection
- Scar contracture
- Durability (i.e. abrasions/injuries at graft site due to graft fragility)
- Allergic response to trypsin
- Subject Complaint (pain and itching)
- Vital Signs
- Blood chemistries and hematology
- Other Treatment-related adverse events requiring surgical intervention prior to 12 weeks post-treatment and serious adverse event (SAE) occurrences.

We predict no difference in safety measures between ReCell-treated areas and control areas of the wound.

Specific Aim 2: Assess the **preliminary effectiveness** of ReCell treatment of full-thickness wounds treated with INTEGRA MBWM compared to a control site. Preliminary effectiveness will be assessed during an acute healing phase (Weeks 1–6) and will focus on healing of both wound and donor sites.

Acute Healing Evaluations:
1. Wound epithelialization
2. Histology
3. Patient pain rating

We predict that, at each point in time, more ReCell-treated areas will be healed as effective as the control areas of the wound.

Specific Aim 3: Assess the **long-term effectiveness** of ReCell treatment of full-thickness wounds treated with INTEGRA MBWM compared to a control site. Long-term effectiveness will be assessed up to 24 weeks post-ReCell treatment and evaluations will focus on the integrity and durability of regenerated tissue as well as physical characteristics such as pliability and cosmesis. Patient satisfaction will also be evaluated. Evaluations to be performed include:

1. Scar assessment scale using the Patient and Observer Scar Assessment Scale (POSAS 2)
2. Vancouver Scar Scale
2. Functional outcome rating
3. Patient satisfaction
4. Histology

We predict that scar/functional outcomes and patient satisfaction will be superior for ReCell-treated areas.

The proposed study is a **prospective, randomized within-patient controlled feasibility study** to evaluate the safety and effectiveness of the ReCell Device for re-epithelialization of full-thickness wounds treated with INTEGRA MBWM. The ReCell Device is a stand-alone, battery operated cell separation device that enables preparation of a cell suspension from a small, thin, split-thickness skin biopsy. The autologous epidermal cell suspension is available for immediate delivery onto a prepared skin surface. This process has the potential to enhance skin regeneration while minimizing donor site morbidity. The performance of ReCell over INTEGRA MBWM in combination with 1:6 meshed split-thickness skin graft (STSG) will be compared to standard practice control (i.e., 1:1.5 meshed STSG over Integra MBWM).

We expect all ReCell-treated and control areas of the wounds to heal adequately. However, we predict areas treated with ReCell will re-epithelialize more quickly than control areas, which has the potential to reduce the risk of infection and scarring in ReCell-treated areas compared to control areas.

Timeline:
Patients will be studied for 24 weeks after ReCell treatment. The first 6 weeks comprise of an acute phase focusing on healing and safety assessments. Follow-up visits at 12

and 24 weeks post treatment focus on long-term effectiveness in terms of aesthetic and functional outcomes, as well as patient satisfaction.

BODY:

Task 1: Receive award; Build research team (Q1-Q2, Nov 2012-Apr 2013)

1a. Hire Program Manager

1b. Hire Clinical Research Coordinator

A Program Manager and a Clinical Research Coordinator were previously hired in Year 1, Quarter 2. The team identified and received competitive quotes for the following resources originally assigned to Avita in Year 1, Quarter 2. These external resources can support the study for less than $110,000. This amount is within the awarded budget:

- Regulatory consulting – Kim Strohkirch, Memphis Regulatory Consultants
- Monitoring – IMARC Research Inc.
- Biostatistics – Dale Glaser, Consultant

Dale Glaser of Glaser Consulting was identified to perform biostatistical analysis for the study in Year 1, Quarter 4. Biostatistics consultant, Dale Glaser, performed additional tasks in Year 2, Quarter 2, including discussing the power and design for the ReCell device study, conducting power analysis, summarizing results, writing up proposed analysis, and also adding comments to the revised protocol.

Task 2: IDE preparation and submission (Q1-Q5, Nov 2012-Jan 2014)

2a. Identify IDE sponsor

J. Peter Rubin, MD at the University of Pittsburgh was previously identified as the IDE Sponsor in Year 1, Quarter 3. A robust clinical monitoring plan has been completed that will ensure real time oversight by Dr. Rubin.

2b. Preparation of IDE

The IDE was previously drafted by the regulatory consultant Kim Strohkirch of Memphis Regulatory Consultants in Year 1, Quarter 2. The IDE was drafted based on cross-referencing of the Avita Medical IDE for the multicenter partial thickness burn pivotal IDE study (http://clinicaltrials.gov/ct2/show/NCT01138917). WRNMMC and UPitt had a conference call with Kim Strohkirch of Memphis Regulatory Consultants on 29MAY2014 to address outstanding questions and finalize aspects of the IDE. The investigators at WRNMMC and UPitt had a subsequent conference call on 24JUN2014 to review IDE text. The IDE was finalized and submitted to the University of Pittsburgh Office for Investigator-Sponsored IND and IDE Support (O3IS) IND/IDE Committee and the FDA for approval on 31JUL2014.

2c. Request for 12 month no-cost extension (NCE)

The request for a 12 month no-cost extension with a revised Statement of Work (SOW) was submitted to the Sponsoring agency in Year 1, Quarter 4 and received approval on 27MAR2014.

2d. Contracting and approval by UPMC

A subaward agreement with the University of Pittsburgh has been executed.

2e. IDE review and approval by University of Pittsburgh Office for Investigator-Sponsored IND and IDE Support (O3IS) IND/IDE Committee

The revised Statement of Work was approved by the sponsor. The IDE was finalized and submitted to University of Pittsburgh Office for Investigator-Sponsored IND and IDE Support (O3IS) IND/IDE Committee and the FDA for approval on 31JUL2014.

2f. Submission of IDE

- **FDA will respond in 30 days**
- **Response to FDA questions within 2 weeks**
- **FDA will have another 30 days to respond**

Kim Strohkirch of Memphis Regulatory Consultants assisted in finalizing the IDE application. The IDE was finalized and submitted to University of Pittsburgh Office for Investigator-Sponsored IND and IDE Support (O3IS) IND/IDE Committee and the FDA for approval on 31JUL2014. Conditional IDE approval from FDA received 29AUG2014. IDE approval received from FDA on 13NOV2014.

2g. IDE received for feasibility study

Final FDA approval of the IDE received 21JAN2015

Task 3: IRB, CRADA and facility approvals (Q3-Q7, May 2013-July 2014)

3a. CRADA

The CRADA between Geneva and Walter Reed National Military Medical Center was fully executed on 23FEB2015.

3b. WRNMMC IRB Coordinating and Site Protocols Preparation & Submission following FDA IDE Approval

Protocol submitted to Kim Strohkirch of Memphis Regulatory Consultants for development of IDE application and the University of Pittsburgh for their development of a site-specific protocol on 17APR2014. Scientific review was successfully completed at WRNMMC on 08MAY2014 with minimal concerns or revisions. Administrative review was completed in 22OCT2014. Protocol was submitted to the WRNMMC IRB 28OCT2014 and reviewed by the IRB on 20NOV2014. Protocol received WRNMMC IRB approval on 09DEC2014.

3c. WRNMMC IRB Coordinating and Site Protocols Approval

IRB approved 09DEC14

IRB approval of Amendment #1 28JAN2015

IRB approval of Amendment #2 07OCT2015 including change of PI from Dr. Fleming to Dr. Nesti

3d. HRPO WRNMMC Coordinating and Site Approval

HRPO approved 4FEB2015

HRPO approval of Amendment with change of PI 16OCT2015.

3e. UPITT IRB External Site Protocol Submission

UPITT IRB external site protocol submitted as of 31OCT2015.

3f. UPITT IRB External Site Approval

UPITT IRB external site approval not received as of 31OCT2015.

3g. HRPO External Site Approval

HRPO external site approval not received as of 31OCT2015.

Task 4: Patient Enrollment (Q8-Q18, Aug 2014-Apr 2017)

#Clinical Patients: 20

Patient Enrollment has started with 1st patient enrolled on 20OCT2015 and receiving treatment on 21OCT2015.

Task 5: Patient Follow-up (Q9-Q20, Nov 2014-Oct 2017)

#Clinical Patients: 20

Patient Follow-up has started subsequent to the 1st enrolled patient who received treatment on 21OCT2015.

Task 6: Histology/Pathology (Q8-Q20, Aug 2014-Oct 2017)

#Tissue Samples: Up to 110

Histology/Pathology of tissue samples has started as of 21OCT2015 for 1st enrolled patient.

Task 7: Final Report (Q20, Nov 2017-Jan 2018)

7a. Review of data and generation of final report

Review of data and generation of final report has not yet begun as of 31OCT2015.

KEY RESEARCH ACCOMPLISHMENTS:

- Staff Recruitment:
  - Hired a Program Director/Manager and a Clinical Research Coordinator.

- Executed a consulting agreement with James Holmes II, MD of Wake Forest University who has provided feedback on protocol.

- Executed a vendor agreement with Annapath who is performing histology services for the study.

- The master CRADA between WRNMMC and Geneva remains in effect. A subaward agreement with the University of Pittsburgh has been executed.

- IDE preparation and submission:

  - Conditional IDE approval from FDA received 29AUG2014. Final IDE approval received from FDA after report date on 13NOV2014. Final FDA approval of the IDE received 21JAN2015

- IRB package preparation and finalization:

  - Administrative review was completed in 22OCT2014
  - Protocol was submitted to the WRNMMC IRB 28OCT2014 and reviewed by the IRB on 20NOV2014
  - IRB approved 09DEC14
  - IRB approval of Amendment #1 28JAN2015
  - IRB approval of Amendment #2 07OCT2015 including change of PI from Dr. Fleming to Dr. Nesti

- HRPO WRNMMC Coordinating and Site Approval:
  - HRPO approved 4FEB2015
  - HRPO approval of Amendment with change of PI 16OCT2015.

- UPITT IRB external site protocol submitted as of 31JUL2015.

- Investigators, Drs. Nesti and Martin, received training on the use of the ReCell spray-on skin device prior to its use for 1st enrolled patient on 20OCT2015. Andrew Quick, the Vice President of Research and Technology at Avita Medical, the manufacturer of the ReCell device, provided the investigators' training in person.

- Patient Enrollment has started with 1st patient enrolled on 20OCT2015 and receiving treatment on 21OCT2015.

- Patient Follow-up has started subsequent to the 1st enrolled patient who received treatment on 21OCT2015.

- Histology/Pathology of tissue samples has started as of 21OCT2015 for 1st enrolled patient.

- ReCell spray skin device utilized in a second compassionate care case:

  - Investigators, Drs. Fleming, Valerio, and Latham, received training on the use of the ReCell spray-on skin device prior to its use for a second compassionate care case on 04DEC2014. Andrew Quick, the Vice President of Research and Technology at Avita Medical, the manufacturer of the ReCell device, provided the investigators' training in person.
  - Although not part of the clinical trial, utilizing their study schema, the investigators demonstrated the feasibility of the usefulness of the ReCell spray-on skin device combined with dermal regenerative matrices in the management of full-thickness traumatic wounds with its use for a second compassionate care case performed on 05DEC2014.
  - The first compassionate care case was presented as a podium presentation at the AMSUS (Association of Military Surgeons of the United States) Annual Meeting in Washington, DC in December 2014.
  - The first compassionate care case was presented at the TERMIS (Tissue Engineering & Regenerative Medicine International Society) Annual Meeting in Washington, DC in December 2014 and at the ASRM (American Society for Reconstructive Microsurgery) Annual Meeting in the Bahamas in January 2015.
  - The first compassionate care case was presented by Dr. Fleming at a research competition at Walter Reed National Military Medical Center on13MAY2015 and received the first place award.
  - The compassionate care case comparisons were presented at MHSRS (Military Health System Research Symposium) in Ft. Lauderdale, FL in August 2015, the TERMIS (Tissue Engineering & Regenerative Medicine International Society) Annual Meeting in Boston, MA in September 2015, and the ASPS (American Society of Plastic Surgeons) Annual Meeting in Boston, MA in October 2015.
  - The compassionate care case comparisons are being written as a manuscript in preparation for journal submission.

REPORTABLE OUTCOMES:

- Although not part of the clinical trial, utilizing their study schema, the investigators demonstrated the feasibility of the usefulness of the ReCell spray-on skin device combined with dermal regenerative matrices in the management of full-thickness traumatic wounds with its use for a second compassionate care case performed on 05DEC2014.

- Investigators, Drs. Fleming, Valerio, and Latham, received training on the use of the ReCell spray-on skin device prior to its use for a second compassionate care case on 04DEC2014. Andrew Quick, the Vice President of Research and Technology at Avita Medical, the manufacturer of the ReCell device, provided the investigators' training in person.

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- The compassionate care case comparisons are being written as a manuscript in preparation for journal submission.

CONCLUSION:

The proposed **prospective, non-randomized, within-patient controlled feasibility study** will enroll 20 active duty wounded warriors to evaluate the safety and effectiveness of the ReCell Device for re-epithelialization of full-thickness wounds treated with INTEGRA MBWM. Given the complex and massive soft tissue injuries that blast injuries cause in a number of our wounded warriors, improved availability of skin regenerative techniques and methods to not only expand autologous skin donor sources but also to aid in lessening donor site morbidity is of great interest and importance. The ReCell Device is a regenerative skin cell separation device that enables preparation of a cell suspension from a small, thin, split-thickness skin biopsy site, thus, providing for great expansion of a limited autologous skin donor site. Additionally, because the autologous epidermal cell suspension is available for immediate delivery onto a prepared skin surface at the time of skin donor harvest, the need for further cell expansion within the laboratory setting is avoided. The performance of ReCell over INTEGRA MBWM in combination with 1:6 meshed split-thickness skin graft (STSG) will be compared to standard practice control (i.e., 1:1.5 meshed STSG over Integra MBWM), with the ultimate potential benefit of earlier re- epithelialization, acceptable durability, and reduction in the risk of infection and scarring for those wounds treated with ReCell.

Based on preclinical and early clinical results, the short-term benefits of this study will include potential viable and readily available regeneration of necessary autologous skin to place on a dermal regenerate in massive soft tissue injuries. This clinical model would be the first to potentially show the benefit of such treatments in traumatic wounds, outside of burn patients. It would also have immense benefits - both for those wounded warriors suffering from soft tissue injuries as well as traumatic civilian injuries that likewise pose significant issues with available autologous skin coverage (e.g. necrotizing fasciitis, motor vehicle accidents or other trauma with associated soft tissue avulsion injuries, etc.). Important data on the mechanism of action, refinements of technique, expansion of the device and technique to future applications, and most importantly, technology transfer throughout WRNMMC, associated MTFs, and civilian or academic centers is of great interest.

Data collected in the completion of the proposed study will support or refute the hypothesis that the use of the ReCell device over a widened STSG mesh in combination with INTEGRA will improve upon the current standard of care for treating full thickness wounds within the wounded warrior. We believe that ReCell will promote improved healing within the interstices finely meshed STSG, thus improving durability among STSG gaps that are potential points of failure during later physical activity. Furthermore, ReCell will reduce the burden on donor skin graft sites by decreasing the amount of autologous skin grafting harvest necessary to cover massive soft tissue. In effect, we propose by using the existing standard for dermal regenerate in INTEGRA, full thickness wounds will be converted into partial thickness wounds, which can then be covered with finely meshed STSG and ReCell regenerative skin expansion system to provide more durable stable skin coverage while also reducing donor site morbidity. Leveraging from our prior

experiences and successes of using ReCell within burn patients, this model will be the first to explore and allow for treating massive soft tissue injuries in a true traumatic setting.

As a result of the delays involved in approvals and the winding down of the war efforts in Afghanistan, an anticipated problem is a lower volume of war trauma patients and therefore possible lower recruitment. However, the investigators will continue to ensure that all relevant providers in general surgery, orthopedic surgery, plastic surgery and trauma services are informed of the study and willing to refer any eligible patients.

Study personnel changes, including transition of PI, program manager and study coordinator, have created some transitional obstacles. However, additional personnel have been identified and the current study staff is working to get up to date and address any areas that need to be improved or resolved.

Although not part of the clinical trial, utilizing their study schema, the investigators demonstrated the feasibility of the usefulness of the ReCell spray-on skin device combined with dermal regenerative matrices in the management of full-thickness traumatic wounds with its use for a second compassionate care case performed on 05DEC2014. Investigators, Drs. Fleming, Valerio, and Latham, received training on the use of the ReCell spray-on skin device prior to its use for a second compassionate care case on 04DEC2014. Andrew Quick, the Vice President of Research and Technology at Avita Medical, the manufacturer of the ReCell device, provided the investigators' training in person.

The first compassionate care case was presented as a podium presentation at the AMSUS (Association of Military Surgeons of the United States) Annual Meeting in Washington, DC in December 2014. Additionally, the first compassionate care case was presented at the TERMIS (Tissue Engineering & Regenerative Medicine International Society) Annual Meeting in Washington, DC in December 2014 and at the ASRM (American Society for Reconstructive Microsurgery) Annual Meeting in the Bahamas in January 2015. Moreover, the first compassionate care case was presented by Dr. Fleming at a research competition at Walter Reed National Military Medical Center on13MAY2015 and received the first place award.

The compassionate care case comparisons were presented at MHSRS (Military Health System Research Symposium) in Ft. Lauderdale, FL in August 2015, the TERMIS (Tissue Engineering & Regenerative Medicine International Society) Annual Meeting in Boston, MA in September 2015, and the ASPS (American Society of Plastic Surgeons) Annual Meeting in Boston, MA in October 2015. In addition, the compassionate care case comparisons are being written as a manuscript in preparation for journal submission.

The results of the study will be presented at national meetings geared toward audiences that provide care to similarly injured patients.

REFERENCES:

PubMed ReCell search performed Nov 26, 2013 yielded the following reports that have been published since the submission of the proposal

Lim J, Liew S, Chan H, Jackson T, Burrows S, Edgar D, Wood F. “Is the length of time in acute burn surgery associated with poorer outcomes?” Burns (2013), http://dx.doi.org/10.1016/j.burns.2013.06.005

Park J, Heggie K, Edgar D, Bulsara M, Wood F. “Does the type of skin replacement surgery influence the rate of infection in acute burn injured patients?” Burns (2013) 39(7):1386-1390, http://dx.doi.org/10.1016/j.burns.2013.03.015

O’Neill T, Rawlins J, Rea S, Wood F. (2012) “Complex chemical burns following a mass casualty plant incident: How optimal planning and organisation can make a difference.” Burns 38: 713-718.

Wood FM, Giles N, Stevenson A, Rea S, Fear M. “Characterisation of the cell suspension harvested from the dermal epidermal junction using a ReCell® kit.” Burns (2012), 38(1):44-51.

Campanella SD, Rapley P, Ramelet AS. “A randomised controlled pilot study comparing Mepitel(®) and SurfaSoft(®) on paediatric donor sites treated with Recell(®).” Burns (2011) Dec;37(8):1334-42.

Anderson JR, Fear MW, Phillips JK, Dawson LF, Wallace H, Wood FM, Rea SM. “A preliminary investigation of the reinnervation and return of sensory function in burn patients treated with INTEGRA®.” Burns (2011) Nov;37(7):1101-8.

Gravante G, Di Fede MC, Araco A, Grimaldi M, De Angelis B, Arpino A, Cervelli V, Montone A. “A randomized trial comparing ReCell system of epidermal cells delivery versus classic skin grafts for the treatment of deep partial thickness burns.” Burns (2007) Dec;33(8):966-72.

APPENDICES:

- FDA IDE Final Approval
- HRPO Amendment Approval

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

OFFICE OF CELLULAR, TISSUES AND GENE THERAPIES

REGULATORY MANAGEMENT STAFF

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FAX TO: J. Peter Rubin, M.D.

Voice Telephone No.: (412) 383-8080 **Facsimile Telephone No.:** (412) 864-2673

FROM: Ron Chamrin

Voice Telephone No.: (240) 402-8269 **Facsimile Telephone No.:** (301) 595-1303

DATE: 1/21/2015 **TIME:** 1535

MESSAGE: IDE 16104

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

J. Peter Rubin, M.D.
Associate Professor of Plastic Surgery
University of Pittsburgh, McGowan Institute of Regenerative Medicine
3500 Fifth Avenue, Hieber Building, Suite 303
Pittsburgh, Pennsylvania 15213

January 21, 2015

Re: IDE 16104
Trade/Device Name: ReCell Autologous Cell Harvesting Device
Dated: December 18, 2014
Received: December 22, 2014
CMS Category: B
Annual Report Due: August 29, 2015

Dear Dr. Rubin:

The Food and Drug Administration (FDA) has reviewed the supplement to your Investigational Device Exemption (IDE) application regarding your traditional feasibility study for a significant risk device proposing revisions to the exclusion criteria and revising the enrollment procedures. FDA has determined you have provided sufficient data to support continuation of your human clinical study; this means that there are no subject protection concerns that preclude continuation of the investigation. Your supplement is therefore approved, and you may implement that change in your study. Your investigation is limited to 1 US institution and 20 US subjects.

We would like to point out that approval of an IDE application does not ensure that the results of this investigation will provide a reasonable assurance of the safety and effectiveness of your device or assure a determination of clearance/approval for your premarket submission.

Since FDA believes this change affects the rights, safety or welfare of the subjects, you must also obtain institutional review board (IRB) approval before implementing this change in your investigation (21 CFR 812.35(a)).

For clarification regarding FDA decisions and recommendations for IDEs, please refer to the FDA guidance "FDA Decisions for Investigational Device Exemption Clinical Investigations: Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff," available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf.

FDA encourages sponsors to collect clinical trial data in accordance with the Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126396.pdf) and to

enroll patients that would reflect the demographics of the affected population with regard to age, sex, race and ethnicity. Reference is made to 21 CFR 812.25(c) regarding description of patient population and to 21 CFR 814.15(d)(1) with regard to the need for data, including foreign data, to be applicable to the U.S. population and U.S. medical practice. We recommend that you include a background discussion of prevalence, diagnosis and treatment patterns for the type of disease for which your device is intended. This should include sex- and race-specific prevalence, identification of proportions of women and minorities included in past trials for the target indication, and a discussion of your plan to address any factors identified or suggested, which may explain potential for under-representation of women and minorities, if applicable. We recommend that you include a summary of this information in your protocol and investigator training materials. Consideration should be given to enrollment of investigational sites where recruitment of needed populations for study can be more easily facilitated.

Future correspondence concerning this application should be identified as an IDE supplement referencing the IDE number above, and must be submitted in duplicate to:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71, G112
Silver Spring, MD 20993-0002

The Federal Food, Drug, and Cosmetic Act (the Act), as amended by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA), authorizes FDA to require an electronic copy (eCopy) for certain types of submissions. An eCopy is an exact duplicate of a paper submission, created and submitted on a CD, DVD, or other electronic media, accompanied by a signed cover letter and the complete original paper submission. This authorization applies to the original, amendments, supplements, and reports, as applicable, for your submission type.

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If you have any minor clarification questions concerning the contents of the letter, please contact Ron Chamrin at 240-402-8269 or Ronald.Chamrin@fda.hhs.gov.

Sincerely yours,

Celia M. Witten, Ph.D., M.D.
Director
Office of Cellular, Tissue and Gene Therapies
Center for Biologics Evaluation and Research

-----Original Message-----
From: Evans, Sharon A CIV USARMY MEDCOM USAMRMC (US) [mailto:sharon.a.evans17.civ@mail.mil]
Sent: Friday, October 16, 2015 12:31 PM
To: Nesti, Leon J LTC USARMY MEDCOM NRMC (US) <leon.j.nesti.mil@mail.mil>
Cc: Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US) <jodi.h.bennett.civ@mail.mil>; Brosch, Laura R CIV USARMY MEDCOM USAMRMC (US) <laura.r.brosch.civ@mail.mil>; Evans, Sharon A CIV USARMY MEDCOM USAMRMC (US) <sharon.a.evans17.civ@mail.mil>; Englar, Nancy E CTR USARMY USAMC (US) <nancy.e.englar.ctr@mail.mil>; Sachtleben, Amanda K CIV USARMY MEDCOM USAMRMC (US) <amanda.k.sachtleben.civ@mail.mil>; 'kelly.a.hummer.ctr@health.mil' <kelly.a.hummer.ctr@health.mil>; Marjorie Osmer <mosmer@genevausa.org>; Rosario, Sandra CIV USARMY MEDCOM USAMRAA (US) <sandra.rosario2.civ@mail.mil>; Woody, Mary Alice (Mary Alice) CIV USARMY MEDCOM USAMMDA (US) <mary.a.woody6.civ@mail.mil>; USARMY Ft Detrick MEDCOM USAMRMC Other CIRO <usarmy.detrick.medcom-usamrmc.other.ciro@mail.mil>
Subject: A-18313, Amendment Approval Memorandum (Proposal Log Number Proposal Log Number DM120195, Award Number W81XWH-13-2-0004) (UNCLASSIFIED)

Classification: UNCLASSIFIED
Caveats: NONE

SUBJECT: Amendment for the Protocol, "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," Submitted by LTC Leon Nesti, MC, USA, Walter Reed National Military Medical Center, Bethesda, Maryland, in Support of the Proposal, "Dermal Coverage of Traumatic War Wounds," Awardee: The Geneva Foundation, Tacoma, Washington, Proposal Log Number DM120195, Award Number W81XWH-13-2-0004, HRPO Log Number A-18313

1. The subject protocol received initial approval by the US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) on 2 February 2015.

2. An amendment to this greater than minimal risk protocol was received by the HRPO on 16 October 2015. The Walter Reed National Military Medical Center (WRNMMC) IRB approved the amendment on 7 October 2015.

3. The amendment allows for change in Principal Investigator from CDR Mark E. Fleming, MC to LTC Leon Nesti, MC, USA.

4. The change proposed in the amendment has been reviewed by the HRPO and found to be acceptable. The protocol amendment is approved (protocol version 4/dated 4 September 2015).

5. Please note the following reporting obligations. Failure to comply could result in suspension of funding.

a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change in the IRB of record,

change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.

b. The following events must be promptly reported by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(1) All unanticipated problems involving risks to subjects or others (UPIRTSOs).

(2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

(3) Change in subject status when a previously enrolled human subject becomes a prisoner must be promptly reported to the USAMRMC ORP HRPO. The report must include actions taken by the institution and the IRB.

c. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

d. The final study report submitted to the WRNMMC IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

e. The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this research; the issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any regulatory agencies including legal or medical actions; and any instances of serious or continuing noncompliance with the regulations or requirements must be reported immediately to the HRPO.

6. Please note: The USAMRMC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

7. Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds. It is recommended that you contact the appropriate contract specialist or contracting officer regarding the expenditure of funds for your project.

8. The HRPO point of contact for this action is Nancy Englar, MHL, BSN, RN, Human Subject Protections Scientist, 301-619-2242, nancy.e.englar.ctr@mail.mil.

SHARON A. EVANS, PhD, CIP
Deputy Director, Human Research Protection Office Office of Research Protections US Army Medical Research and Materiel Command

Note: The official copy of this approval memo is housed with the protocol file at the Office of Research Protections, Human Research Protections Office, 810 Schreider Street, Fort Detrick, MD 21702-5000. Signed copies will be provided upon request.

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Caveats: NONE