

Study Protocol and Statistical Analysis Plan

NCT 02076022

November 08, 2018



[reviewer notes~]

## Triage Section

Provide a short title for this study (200 characters or less):

AMP 30: Autologous Fat Grafting, Amputation Sites Pain: Randomized

T1.0 Select the type of application: New Research Study

T2.0 Is the proposed research study limited to the inclusion of deceased individuals? \* No

The review and approval of proposed innovative practices are not subject to IRB review and approval. The introduction of innovative procedures or therapies into clinical practice (i.e., independent of a research activity approved by the IRB) should be reviewed with the applicable department chairperson and the UPMC Technology Assessment Committee/Innovative Practices Sub-Committee prior to their implementation. The contact person is Mary Gardner at 412-647-6883.

T2.1 Are any research activities being conducted at the VA Pittsburgh Healthcare System or with VA funds? \* No

Respond to the following questions to determine the IRB-of-record:

Research is conducted using only VA records and/or subjects recruited thru the VA:

University or UPMC facilities are not engaged in research:

University or UPMC funds are not expended in direct support of research:

If all true, then the VA is the IRB-of-record and UPitt IRB review is not required. If all false, only UPitt IRB review is required. Otherwise, dual review from both the VA and UPitt IRB is required.

Please select the external IRB of record:

Provide the name of the Central IRB:

Quality assurance projects are not subject to IRB review and approval. UPMC has adopted an oversight process that requires the submission of all quality assurance projects for review. At UPMC, submissions are reviewed by the Quality Improvement Review Committee (QRC). You can contact the QRC at askqrc@upmc.edu.

Research studies that are limited to the inclusion of deceased individuals are not subject to IRB review and approval. Research performed on individuals who have been declared legally dead and/or research involving the collection of tissues from deceased individuals is not subject prior review and approval by the University of Pittsburgh IRB.

There are, however, ethical issues associated with research conducted on or involving deceased individuals. To address these ethical issues, all University faculty who desire to perform research on or involving deceased individuals must submit a project application for review and approval by the Committee for Oversight of Research and Clinical Training Involving the Dead Research Involving the Dead (CORID). Note that, as per UPMC policies, research involving the medical records of deceased individuals is subject to obtaining the written consent of the decedents' next-of-kin or the executors of the decedents' estates.

For studies that include BOTH living and deceased subjects, IRB review and approval is required.

Emergency Use is the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval [21 CFR312.310]. Detailed information on the submission process is available on the IRB website under the A-Z Guidance, Emergency Use.

All of the following conditions must exist to justify the emergency use of an unapproved investigational drug, biologic, or device. Check all the boxes that apply:

Selections

There are no items to display

[reviewer notes~]

Triage Section

T3.0 What is the anticipated risk to the research participants?

Greater Than Minimal Risk

T3.1 Why do you feel that all aspects of this research study, including screening and follow-up, involve no more than minimal risk to the research subjects?

T4.0 Does the proposed study qualify for 'exempt' IRB review or for a determination of either 'not research' or 'no human subject' involvement?

\*

T5.0 Does the proposed research study qualify for 'expedited' IRB review status?

\*

[reviewer notes~]

Cover Sheet Section

CS1.0 What is the reason for this submission?

New Research Protocol Submission

CS1.1 Has this research study been approved previously by the University of Pittsburgh IRB?

\* No

If the study expired, you are required to upload the completed Renewal Report Form and a Data and Safety Monitoring Report.

Upload the Renewal Report Form and Data and Safety Monitoring Report:

Name	Modified Date
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Previous IRB #:

CS1.1.1 Has this research study (or a substantially similar research study) been previously disapproved by the University of Pittsburgh IRB or, to your knowledge, by any other IRB?

\* Yes

If Yes, identify the IRB, IRB number if Pitt IRB disapproved, and the primary reasons for disapproval:

PRO11090266The board's major concern is that no portion of this procedure (either stem cell augmented or not) is currently used in amputees. Amputees who lack soft tissue coverage have extensively scarred, fibrotic limbs, and these are not easily amenable to injection techniques. Further, while prior protocols have discussed this procedure in the face, none has been used for lower extremity, weight bearing reconstruction. Data from the use of this technique from non-weight bearing areas are scant. No comment from the DOD scientific review were included, nor were relevant references. As such, the board had substantial concern that this protocol will expose human subjects to risks of an experimental surgery whose feasibility and potential benefits can not be adequately assessed at this time. Because of this, the board voted that the protocol be disapproved until information is obtained concerning 1) animals studies of similar nature, 2) data from other sources such as the smaller pilot protocol (PRO11090215) regarding this exact procedure so that the "augmented" grafts can be used as controls, or 3) satisfactory demonstration of long term benefits to this procedure in the face, from which POTENTIAL applicability in a weight bearing surface can be inferred. Other lesser concerns include: 1) lack of blinding of investigators doing the outcome assessments, 2) information regarding when randomization will occur and how it will be done are lacking, 3) what will occur at each visit (functional assessment), 4) a clear description of the risks associated with functional assessment, and 5) potential issues regarding reimbursement/compensation for PT visits are not clear

[reviewer notes~]

Cover Sheet Section

CS2.0 Title of Research Study:

Adipose Stromal Cell Enriched Autologous Fat Grafting for Treating Pain at Amputation Sites: A Single Center Site, Prospective, Randomized, Pilot Outcomes Trial

CS2.0.1 Requested approval letter wording: Protocol Informed Consent

CS2.1 Research Protocol Abstract: During the current conflicts, over 1050 military personnel have sustained combat-related amputations. The ability of a wounded warrior to achieve maximal function after amputation is dependent upon successful fitting of and adaptation to a prosthesis. However, many patients with amputations suffer from pain when wearing a prosthesis related to thin soft tissue coverage and inadequate padding over bony structures and nerve trunks. This inadequate soft tissue coverage also contributes to poor socket interface, secondary skin breakdown, and further limitation of function. A clinical solution that allows for the minimally invasive generation of new soft tissue padding at an amputation site without the need for further limb shortening, lengthy scars, a prolonged recovery, and significant donor site morbidity would have the potential to significantly help our wounded warriors and change clinical practice. Autologous fat grafting is a potential solution. Grafting of autologous fat tissue is a minimally invasive surgical technique that starts with the harvest of fat tissue from the abdomen or thighs using liposuction through incisions less than 5mm in length. The lipoaspirate is then processed to concentrate the adipose fraction and reinjected into the donor site. This surgical procedure involves the immediate transplantation of a patient's own tissue in a single operative procedure. It has the advantages of: • Minimal access incisions • Ability to transfer significant amounts of tissue (hundreds of grams of tissue) • Can be used in setting of previous surgical procedures and presence of hardware • Usually performed as outpatient procedure • Minimal donor site morbidity at graft harvest site • Low risk compared with more invasive surgical procedures • Can be repeated multiple times, if necessary, even using the same donor sites Fat transfer is considered globally as a treatment option in which a patient's own fat tissue may be used to increase the volume of fat in the subcutaneous tissues of the body. The origin of fat injections reportedly started in 1893 when German physician Franz Neuber used a small piece of upper arm fat to build up the face of a patient whose cheek had a large pit caused by a tubercular inflammation of the bone. [Fettransplantation. Chir Kongr Verhandl Dtsch Ges Chir 1893:22; 66] With increasing acceptance as a safe and efficacious procedure over the decades, fat grafting has been widely used in reconstructive and cosmetic arenas to replace soft tissue defects and deficiencies. This has included areas of the face and hand as well as larger soft tissue volume deficits in craniofacial areas and breast reconstruction cases in cancer patients. The clinical success of fat grafts has been universal in terms of body sites reported to date at the best of our knowledge. This includes both non-weight bearing areas of the hands, breasts and face as well as weight-bearing areas such as the legs and buttocks. In another clinical trial, fat pads in the weight bearing foot were replaced or supplemented with fat grafts in fifty (50) subjects and the procedure was shown to be safe, efficacious and beneficial in the long term (Chairman, 1994). In an OVID database search of fat grafting articles, over 9000 articles have referenced the use

of fat grafts in a wide arena of clinical situations. Specifically to this application over 100 references were directly pertinent to fat grafting knowledge required for this proposal. We propose a prospective, randomized clinical study to assess the efficacy of minimally invasive autologous fat transfer addressing pain and poor prosthetic fit at amputation sites. Objective: The objective of this study is to assess the efficacy of minimally invasive autologous fat transfer at the amputation sites and the modulation of pain at the respective sites. We hypothesize that autologous fat grafting can provide a minimally invasive therapy facilitated by enabling technology of specialized instrumentation to effectively mitigate pain syndromes at amputation sites, by introducing volume stable subcutaneous tissue over bony prominences and peripheral nerve trunks, thereby avoiding surgical revisions and preserving limb length. We further hypothesize that enriching the fat graft with autologous adipose stromal cells utilizing the Tissue Gensis Cell Isolation System (CIS), a regenerative medicine approach, will lead to improved retention of the fat graft over time and result in a more favorable outcome. Specific Aims: 1) Treat painful amputation sites in 30 patients with fat grafting to provide additional subcutaneous tissue padding over bony structures and nerve trunks. Limb anatomy and healing of the graft over time, along with stability/persistence of the new tissue, will be assessed by high resolution CT scanning with 3D reconstruction. Patients will be followed for 24 months after treatment to define long term outcomes. The primary outcome measures will be pain at the amputation site and improved ability to tolerate a prosthesis. Patients will be randomized to receive either standard fat grafting (15 patients) or cell enriched fat grafting (15 patients). Patients will be enrolled who have pain at an amputation site that limits function and/or interferes with the ability to use a prosthesis. 2) Assess biologic properties of the cells within the fat graft and correlate with clinical outcomes. This will include adipose stem cell yield per volume of fat tissue, cell proliferation, capacity for adipogenic differentiation, lipolysis, and cell sub-population analysis by multiparameter flow cytometry. Results of these assays will be correlated with graft volume retention to search for predictors of good clinical outcome that are related to variation on adipose biology between subjects. 3) Measure quality of life in patients before and after autologous fat grafting using validated psychosocial measures. This will include, among other tools, SF 36, the Beck inventory, and instruments designed for assessing limb function. Study Design: Single center site, prospective, randomized, pilot outcomes study with treatment performed at the University of Pittsburgh. The primary outcome measurements will be: 1) fat graft retention at the amputation site; and 2) improved ability to tolerate a prosthetic device. This study will examine if fat grafting with cell enrichment using the Tissue Gensis Cell Isolation System, (CIS) will demonstrate increased fat retention and decreased pain compared to standard fat grafting alone. Clinical Impact: This study will significantly impact military trauma care by validating a minimally invasive cell based technique for alleviating pain at amputation sites and improving function with a prosthesis. Importantly, the goal will be reached without invasive surgery, increased risk, and a prolonged recovery. Given the high amputation rate in the current conflicts, this work is highly relevant to the care of the wounded warrior. A major

goal of this study will be to transfer the techniques and knowledge gained to physicians throughout the Department of Defense healthcare system.

CS2.2 Select the category that best describes your research: Biomedical research

[reviewer notes--]

#### Cover Sheet Section

CS3.0 Name of the Principal Investigator:

J. Peter Rubin

Note: Adjunct faculty of the University, including lecturers and instructors, are not permitted to serve as a PI or Faculty Mentor but may serve as co-investigators. Refer to Chapter 4 on the HRPO website for more information.

CS3.1 Affiliation of Principal Investigator:

UPitt faculty member

If your answer was Other, fill in the Principal Investigator's affiliation:

If you chose any of the Pitt options, please indicate the specific campus: Main Campus - Pittsburgh

If you chose the UPitt faculty member option, provide the PI's University Faculty Title: UPMC Endowed Professor and Chair of Plastic Surgery, Professor of Bioengineering

CS3.1.1 Indicate below the name of the qualified University faculty member or UPP or UPMC staff member who will serve as a mentor and provide supervision or guidance regarding the conduct of this research study.

CS3.2 Address of Principal Investigator: UPMC Center for Innovation in Restorative Medicine  
Department of Plastic Surgery University of Pittsburgh  
6B Scaife Hall, Room 690  
3550 Terrace Street Pittsburgh, Pa. 15213

CS3.3 Recorded Primary Affiliation of the Principal Investigator:

U of Pgh | School of Medicine | Plastic Surgery



CS3.4 Identify the School, Department, Division or Center which is responsible for oversight of this research study:

U of Pgh | School of Medicine | Plastic Surgery

CS3.5 Telephone Number of Principal Investigator:

412-383-8080

CS3.6 Recorded Current E-mail Address of Principal Investigator to which all notifications will be sent: rubinjp@upmc.edu

CS3.7 Fax Number:

412-383-9053

CS3.8 Does this study include any personnel from Carnegie Mellon University, and/or use any CMU resources or facilities (e.g., Scientific Imaging and Brain Research Center (SIBR)?

\* No

CS3.9 Is this your first submission, as PI, to the Pitt IRB?

\* No

[reviewer notes~]

Cover Sheet Section

CS4.0 List of Co-Investigators:

Last	First	Organization
Chen	Wendy	U of Pgh   School of Medicine   Plastic Surgery
Coleman	Sydney	U of Pgh   School of Medicine   Plastic Surgery
Cooper	Rory	U of Pgh   School of Health and Rehabilitation Sciences   Rehabilitation Science and Technology

Crytzer	Theresa	U of Pgh   School of Health and Rehabilitation Sciences   Rehabilitation Science and Technology
Donnenberg	Albert	U of Pgh   School of Medicine   Medicine
Donnenberg	Vera	U of Pgh   School of Medicine   Cardiothoracic Surgery
Dreifuss	Stephanie	Physician Services Division (UPP and CMI)
Egro	Francesco	U of Pgh   School of Medicine   Plastic Surgery
Foley	Karen	U of Pgh   School of Medicine   Plastic Surgery
Gusenoff	Jeffrey	U of Pgh   School of Medicine   Plastic Surgery
Haas	Gretchen	U of Pgh   School of Medicine   Psychiatry
James	Isaac	U of Pgh   School of Medicine   Surgery   Plastic Surgery
Marra	Kacey	U of Pgh   School of Medicine   Plastic Surgery
Mermon	Diana	U of Pgh
Minteer	Danielle	U of Pgh   School of Medicine   Plastic Surgery
Ng-Glazier	Joanna	U of Pgh   School of Medicine   Plastic Surgery
Peterson	Sara	U of Pgh   School of Health and Rehabilitation Sciences   Rehabilitation Science and Technology
Radomsky	Elizabeth	UPMC   Hospital Divisions
Schusterman	Mark	U of Pgh   School of Medicine   Plastic Surgery
Simon	Patsy	U of Pgh   School of Medicine   Plastic Surgery
Turer	David	U of Pgh   School of Medicine   Plastic Surgery

There are no items to display

[reviewer notes~]

Cover Sheet Section

CS5.0 Name of Primary Research Coordinator:Karen Foley

CS5.1 Address of Primary Research Coordinator:

UPMC Center for Innovation in Restorative Medicine  
Department of Plastic Surgery  
University of Pittsburgh  
Sally Building 3380 Blvd. of the Allies, Suite 158  
Pittsburgh, Pa. 15213

CS5.2 Telephone Number of Primary Research Coordinator:

412-641-3726

CS6.0 Name of Secondary Research Coordinator:

CS6.1 Address of Secondary Research Coordinator:

CS6.2 Telephone Number of Secondary Research Coordinator:

CS6.3 Key Personnel/Support Staff (Only list those individuals who require access to OSIRIS):

Last	First	Organization
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Simon	Patsy	U of Pgh   School of Medicine   Plastic Surgery
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There are no items to display

[reviewer notes~]

Cover Sheet Section

CS7.0 Will this research study use any Clinical and Translational Research Center (CTRC) resources?

No

CS7.1 Please select the sites you intend to use:

There are no items to display

[reviewer notes~]

#### Cover Sheet Section

CS8.0 Select the entity responsible for scientific review.

Department Review - (a dean, department chair, division chief, or center head) Note:  
DoD funded studies require departmental review

CS8.1 Select the school, department or division which is responsible for scientific review of this submission.

U of Pgh | School of Medicine | Plastic Surgery

CS8.1 Select the CTRC which is responsible for scientific review of this submission

[reviewer notes~]

#### Cover Sheet Section

CS9.0 Does this research study involve the administration of an investigational drug or an FDA-approved drug that will be used for research purposes?

\* No

CS9.1 Do you plan to utilize the Investigational Drug Service (IDS) to dispense the drug?

\*

CS10.0 Is this research study being conducted under a University of Pittsburgh-based, sponsor-investigator IND or IDE application?

\* Yes If YES, you are required to submit the IND or IDE application and all subsequent FDA correspondence through the Office for Investigator-Sponsored IND and IDE Support (O3IS). Refer to applicable University policies posted on the O3IS website ([www.O3IS.pitt.edu](http://www.O3IS.pitt.edu)).

## CS10.1 Append to this application:

(1) Copy of the current version of the clinical protocol submitted with the IND or IDE application which corresponds to this IRB submission:

Name	Modified Date
IDE 15444 application version 6.0	9/14/2015 9/18/2015 1:48 PM

(2) Copy of the FDA's letter which acknowledges receipt of the application and assignment of the IND or IDE number:

Name	Modified Date
FDA approval IDE 15444 AMP 30 9.20.13.pdf	10/10/2013 2:51 PM

[reviewer notes~]

## Cover Sheet Section

CS11.0 Use the 'Add' button to upload one or more of the following:  
the sponsor protocol (including investigator initiated studies) and/or other brochures  
the multi-center protocol and consent form template, if applicable

Name	Modified Date
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Is this research study supported in whole or in part by industry? This includes the provision of products (drugs or devices). \* No

Is this a multi-centered study?\* No

[reviewer notes~]

## Cover Sheet Section

CS12.0 Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation?\* Yes

HUSC GUIDANCE REQUIREMENTS FOR THE REVIEW OF HUMAN SUBJECT RESEARCH PROTOCOLS BY THE HUMAN USE SUBCOMMITTEE (HUSC), RADIATION SAFETY COMMITTEE (effective 7/1/2018)

For Research Protocols Involving the Use or Evaluation of Diagnostic or Therapeutic Procedures that Emit Ionizing Radiation: • Formal HUSC review/approval is required if the:

research protocol involves the use or the evaluation (i.e., for safety and/or effectiveness) of a radioactive agent or a device that is not currently FDA-approved for commercial marketing; including radioactive drugs or devices that are the subject of a FDA-accepted IND or IDE application or approved for clinical investigations under the FDA's Radioactive Drug Research Committee (RDRC) process. 1

research protocol addresses (i.e., in the objectives or specific aims) the evaluation (i.e., for safety and/or effectiveness) or involves the use of a FDA-approved radiopharmaceutical or device-associated procedure for an "experimental" indication or using "experimental" procedures (i.e., an indication or procedures that are not consistent with standard clinical practice or the current FDA-approved product labeling). 1

Note: HUSC review/approval is not required for research protocols that involve the use of diagnostic procedures being performed, in a manner and frequency that are consistent with standard clinical practice, for subject screening or to evaluate the outcome of a treatment regimen. This would include diagnostic procedures for off-label uses that are routinely performed in clinical practice. 1,2,3

Note: HUSC review/approval is not required for research protocols that involve the use of therapeutic procedures being performed in a manner and frequency that is consistent with standard clinical practice. 1,2,3

research protocol involves the enrollment of individuals (e.g., healthy volunteers) who will not be undergoing the procedure in association with the diagnosis or treatment of a disease or condition. 1

For Humanitarian Use Devices: • Formal HUSC review/approval is required for all Humanitarian Use Devices that emit ionizing radiation.

For any questions related to these requirements or their application, contact the Chair of the HUSC (412-647-0736) or the University's Radiation Safety Officer (412-624-2728).

1 All research protocols wherein the parameters (e.g., dose, dosing frequency) for performing the procedure(s) that emit ionizing radiation are defined in the protocol must include an Authorized User (i.e., a physician or dentist who has expertise and who is credentialed in the respective medical specialty) as a listed co-investigator; i.e., so as to ensure adequate notification and respective compliance with the protocol. 2 The risks of radiation exposure associated with the diagnostic or therapeutic procedure must continue to be addressed in the protocol and consent form using the standard, HUSC-accepted

wording. (For diagnostic procedures refer to the University Human Research Protection Office website – [www.hrpo.pitt.edu](http://www.hrpo.pitt.edu): A-Z Guidance/Radiation Guidance. For therapeutic procedures, address the specific risks currently known to be associated with the respective procedure.<sup>3</sup> The University of Pittsburgh IRB, at its discretion, may request formal HUSC review of the research protocol.

- CS12.1 After reviewing the HUSC guidance above, does your research protocol require HUSC review? (Note: University of Pittsburgh's Radiation Safety Committee oversight is limited UPMC Presbyterian-Shadyside, Magee Women's Hospital of UPMC, Children's Hospital of Pittsburgh-UPMC, and Hillman Cancer Center. If other sites, you will be required to obtain approval from your radiation safety officer. Please contact [askirb@pitt.edu](mailto:askirb@pitt.edu) for more information.)

Yes

Upload Radiation Forms:

Name	Modified Date
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- CS13.0 Does this research study involve the deliberate transfer of recombinant or synthetic nucleic acid molecules into human subjects?

\* No

Upload Appendix M of NIH Guidelines:

Name	Modified Date
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- CS14.0 Are you using UPMC facilities and/or UPMC patients during the conduct of your research study?

\* Yes If Yes, upload completed Research Fiscal Review Form:

Name	Modified Date
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7/24/2015 10:51 AM

[reviewer notes~]

## Cover Sheet Section

CS15.0 Indicate the sites where research activities will be performed and/or private information will be obtained.

Choose all sites that apply and/or use Other to include sites not listed:

Sites:

University of Pittsburgh

UPMC

There are no items to display

University of Pittsburgh

Campus:

Main Campus - Pittsburgh

There are no items to display

List university owned off-campus research sites if applicable:

UPMC

Sites:

UPMC Presbyterian

UPMC Magee Women's Hospital

UPMC Montefiore

UPMC Shadyside

Other UPMC Site- Specify below:

There are no items to display

UPMC Montefiore HospitalUPMC Anesthetic Plastic Surgery Center 3380  
Blvd. of the AlliesSuite 158Pittsburgh, PA 15213UPMC Hematopoietic



Stem Cell Lab Hillman CenterUPMC InSitu Lab MUHOrthotics and  
Prosthetics Rehabilitation Center, Bakery Square

UPMC Cancer Network Sites:

Site

There are no items to display

If you selected School, International or Other, list the sites:

\*For research being conducted at non Pitt or UPMC sites, upload a site permission letter granting the researcher permission to conduct their research at each external site:

Name Modified Date

CS15.1 Have you, J. Peter Rubin , verified that all members of the research team have the appropriate expertise, credentials, and if applicable, hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB protocol?

\* Yes

CS15.2 Describe the availability of resources and the adequacy of the facilities to conduct this study:

\* The PI over this clinical trial has sufficient time to oversee the study conduct. With the placement of experienced leadership and staff resources to assist with the implementation of direction and follow through of the day to day research process and procedures. The PI's has ultimate oversight of all conduct in relationship to this clinical trial inclusive of all research staff, who have been trained in research conduct and compliance and possess GCP demonstrated in their extensive experience in clinical trial process. This DOD contractual agreement has provided adequate funding to complete the study goals, and we have access to protected servers for data security and information protection whenever data is generated, collected, or stored. We have addressed in this protocol resources for medical and psychological assessments should

they be needed above the research procedures outlined in the study design for this study. The PI has adequate resources to manage the storage and distribution of data/biologic samples for this clinical trial. The PI has adequate space to conduct the research activities, allowing for space appropriate for the disclosure of private information (e.g., interview or exam room). We have adequate safeguards for the research staff and participants within the facilities and ability to handle emergency situations should they arise. We have adequate space for storing data to maintain the confidentiality for the participants of this study and we do not anticipate any issues with the availability of resources and the adequacy of the facilities to meet the needs for this clinical trial.

[reviewer notes~]

#### Cover Sheet Section

CS16.0 Special Research Subject Populations:

#### Categories

None

There are no items to display

[reviewer notes~]

#### Cover Sheet Section

CS17.0 Does your research involve the experimental use of any type of human stem cell?\* No

[reviewer notes~]

#### NIH Definition of a Clinical Trial

A research study<sup>1</sup> in which one or more human subjects<sup>2</sup> are prospectively assigned<sup>3</sup> to one or more interventions<sup>4</sup> (which may include placebo or other control) to evaluate the effects of those interventions on health related biomedical or behavioral outcomes.<sup>5</sup>

1 See Common Rule definition of research at 45 CFR 46.102(d) .

2 See Common Rule definition of human subject at 45 CFR 46.102(f) .

3 The term “prospectively assigned” refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

4 An intervention is defined as a manipulation of the subject or subject’s environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

5 Health-related biomedical or behavioral outcome is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects’ biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

CS18.0 \* Based on the above information, does this study meet the NIH definition of a clinical trial? ☒ ☒ Yes ☐ ☐ No

If Yes, click Save and then [Click Here For Study Team's CITI Training Records](#) . Please ensure all personnel's training is up to date

[reviewer notes~]

## Section 1 - Study Objective, Specific Aims, Background and Significance

- 1.1 Objective: What is the overall purpose of this research study? (Limit response to 1-2 sentences.)The objective of this study is to assess the efficacy of minimally invasive autologous fat transfer at the amputation sites and the modulation of pain at the respective sites. We hypothesize that autologous fat grafting can provide a minimally invasive therapy facilitated by enabling technology of specialized instrumentation to effectively mitigate pain syndromes at amputation sites, by introducing volume stable

subcutaneous tissue over bony prominences and peripheral nerve trunks, thereby avoiding surgical revisions and preserving limb length. The premise of this study is that we will compare two minimally invasive techniques as an alternative to invasive operations, with the understanding that this therapy does not preclude more invasive procedures in the future. We further hypothesize that enriching the fat graft with autologous adipose stromal cells utilizing the Tissue Genesis Cell Isolation System (CIS), a regenerative medicine approach, will lead to improved retention of the fat graft over time and result in a more favorable outcome.

- 1.2 Specific Aims: List the goals of the proposed study (e.g., describe the relevant hypotheses or the specific problems or issues that will be addressed by the study). 1) Treat painful amputation sites in 30 patients with fat grafting to provide additional subcutaneous tissue padding over bony structures and nerve trunks. Limb anatomy and healing of the graft over time, along with stability/persistence of the new tissue, will be assessed by high resolution CT scanning with 3D reconstruction. Patients will be followed for 24 months after treatment to define long term outcomes. The primary outcome measures will be pain at the amputation site and improved ability to tolerate a prosthesis. Patients will be randomized to receive either standard fat grafting (15 patients) or cell enriched fat grafting (15 patients) utilizing the Tissue Genesis Cell Isolation System (CIS). Patients will be enrolled who have pain at an amputation site that limits function and/or interferes with the ability to use a prosthesis. 2) Assess biologic properties of the cells within the fat graft and correlate with clinical outcomes. This will include adipose stem cell yield per volume of fat tissue, cell proliferation, capacity for adipogenic differentiation, lipolysis, and cell sub-population analysis by multiparameter flow cytometry. Results of these assays will be correlated with graft volume retention to search for predictors of good clinical outcome that are related to variation on adipose biology between subjects. 3) Measure quality of life in patients before and after autologous fat grafting using validated psychosocial measures. This will include, among other tools, SF 36, the Beck inventory, and instruments designed for assessing limb function.

- 1.3 Background: Briefly describe previous findings or observations that provide the background leading to this proposal. Traumatic amputations are prevalent and pose many challenges for our wounded warriors. A recent publication reported that during the current conflicts, over 950 military personnel have sustained combat-related amputations, with 15% of them occurring more than 12 weeks after initial injury (1). Updated statistics place this number of amputees at over 1050 (personal communication, COL Paul Pasquina, Chief of the Integrated Department of Orthopaedics and Rehabilitation, Walter Reed National Military Medical Center-WRNMMC). The ability of a wounded warrior to gain optimal function after an amputation most often depends on his or her ability to successfully fit and adapt to a prosthesis. Once out of the acute phase, many patients with amputations suffer from pain when wearing a prosthesis, either from thin soft tissue

cover over bony structures or peripheral nerves not well padded with soft tissue. Extrinsic residual limb pain is usually mechanical in origin related to the prosthetic socket or other prosthetic components. It is often the result of a mismatch between residual limb tissue tolerance and the prosthetic loads on the soft tissues. This sensitivity is often accentuated by superficial nerve trunks or neuromas at severed nerves that are exposed to excessive external mechanical loading (2). Poor socket interface, secondary skin breakdown, and/or pain may severely limit function. This presents a very difficult clinical problem. The standard of care treatment, when even possible, would involve surgical revision of the amputation site and often encompasses shortening of the bone, lengthy scars, and prolonged healing. If a below knee amputation has to be converted to an above knee level, then there are serious functional implications. For local tissues at the amputation site that are of poor quality (e.g. scarred or covered with a skin graft), a distant muscle flap may be required (3,4). These flaps may require transfer to the amputation site using microvascular anastomosis of the blood vessels. The procedure is highly invasive and can add the morbidity of decreased function, deformity, and risk of wound healing problems at the muscle donor site. Failure rates in lower limb flaps can be as high as 18.5% (5,6). Flap ulceration rates tend to be higher in these weight-bearing flaps, both skin and muscle free flaps frequently need secondary debulking procedures to improve function, and painful neuromas are not uncommon (6,7). A clinical solution that allows for the minimally invasive generation of new soft tissue padding at an amputation site without the need for further limb shortening, lengthy scars, a prolonged recovery, and significant donor site morbidity would have the potential to significantly help our wounded warriors and change clinical practice. Autologous fat grafting is a potential solution. Grafting of autologous fat tissue is a minimally invasive surgical technique that starts with the harvest of fat tissue from the abdomen or thighs using liposuction through incisions less than 5mm in length. The lipoaspirate is then processed to concentrate the adipose fraction and reinjected into the donor site. This surgical procedure involves the immediate transplantation of a patient's own tissue in a single operative procedure. It has the advantages of:

- Minimal access incisions
- Ability to transfer significant amounts of tissue (hundreds of grams of tissue)
- Can be used in setting of previous surgical procedures and presence of hardware
- Usually performed as outpatient procedure
- Minimal donor site morbidity at graft harvest site
- Low risk compared with more invasive surgical procedures
- Can be repeated multiple times, if necessary, even using the same donor sites

The transfer of autologous fat tissue is not a new concept but just another method as we have seen with many types of flaps using various combinations of muscle, fat and skin have been well documented. Tissue flaps come from many different locations, and are used in many different ways to accomplish the desired results. Flaps have their own blood supply, they are more resilient than skin grafts, and usually produce much better results from a cosmetic standpoint because they can provide a better match for skin tone and texture. Skin flaps are also a better choice when tissue "bulk" is needed to fill contour defects. The obvious advantage is to use autologous fat tissue versus xenografts and allografts; each having known risks of rejection and adverse events. Today, fat transfer is considered globally the standard of

care for many clinical indications that uses the patient's own fat tissue to increase the volume of fat in the subcutaneous tissues of the body. The origins of fat injections reportedly started in 1893 when German physician Franz Neuber used a small piece of upper arm fat to build up the face of a patient whose cheek had large pit caused by a tubercular inflammation of the bone. [Fettransplantation. Chir Kongr Verhandl Dtsch Ges Chir 1893:22; 66] In 1895, another German doctor, Dr. Karl Czerny, did the very first documented breast augmentation when he transplanted a fatty tumor from the patient's lumbar region, or lower back, to a breast defect [Plastischer Ersatz der Brustdruse durch ein Lipom. Zentralbl. Chir. 27: 72, 1895]. From this time and especially after the advent of liposuction procedures, the number of fat transfer cases are in the thousands if not in the tens of thousands. With increasing acceptance as a safe and efficacious procedure in reconstructive and cosmetic arenas to replace soft tissue defects and deficiencies in the face and hand, larger soft tissue volume deficits were being treated with increasing amounts of fat in the entire craniofacial areas and this is especially true with breast reconstruction in cancer patients. With increasing clinical success, the use of fat injections have been employed to smooth and repair aged hands; fill wrinkled, creased faces; reshape buttocks; enlarge breasts; as well as repair of inverted nipples and repair of other clinical indications. It should be noted that the clinically efficaciousness of fat grafts has been universal in terms of body sites reported to date at the best of our knowledge. This includes both non-weight bearing areas of the hands, breasts and face as well as weight-bearing areas such as the buttocks. Fat grafting is a procedure that is common standard of care and practice for many plastic and reconstructive surgeons and the American Society of Plastic Surgeons reported 57,643 fat graft procedures were performed in the U.S. in 2010 (an increase of 14% from 2009). Indeed, the equipment required for fat transfers is present in most operative room suites and surgical centers around the world. Specifically, fat grafting is considered an acceptable option in the reconstruction of the breast (8-10) and facial atrophy associated with HIV treatment (11-22). There is emerging interest in research of this technique and a search of [clinicaltrials.gov](http://clinicaltrials.gov) reveals thirteen trials studying use of fat grafting for innovative clinical applications. These trials demonstrate successful fat transfer to challenging tissue beds such as post-traumatic craniofacial defects (NCT01345591) and non-healing lower extremity wounds (NCT00815217). Large animal studies support the use of adipose derived stem cells have been used extensively in the veterinarian practices. One major company, Vet-stem has treated over 3000 horses with horses treated with isolated adipose vascular cells for tendon injuries and had a 77% return to prior level of performance and 94% of them were sound one year or more after treatment.[23,24] In addition, a 92% and 72% return to prior level of performance in horses with acute and chronic suspensory ligament injuries, respectively.[25] And in weight bearing joint injuries, treated horses demonstrated a 57% return to prior level of performance.[26] In 2007, adipose vascular cells were then used on dogs for joint and spine regeneration. In summary, the adipose vascular cells have proven clinically effective in a variety of anatomical sites that have different weight bearing load; especially in horse joints. The literature has unequivocally demonstrated that clinical fat grafting in buttocks

(a similar weight-bearing anatomic region) can be performed safely and effectively with retention rates approximating 75% up to 2 years and beyond (27-29). In an OVID database search of fat grafting articles, over 9000 articles have referenced the use of fat grafts in a wide arena of clinical situations. Specifically to this application over 100 references were relevant to this proposal and provided below.(30-136)Clinically, atrophied fat pads in the weight bearing foot were replaced or supplemented with fat grafts. [Chairman EL. Restoration of the plantar fat pad with autolipotransplantation; J Foot Ankle Surg. 1994 Jul-Aug;33(4):373-9] This procedure was shown to be safe, efficacious and had long term benefits. We propose a clinical trial to assess the efficacy of minimally invasive autologous fat transfer to address pain and poor prosthetic fit at amputation sites. We plan to randomize 15 subjects to the standard fat grafting surgical procedure which involves the immediate transplantation of a subject's own tissue and does not require FDA oversight. Additionally, we will use our knowledge and expertise working with adipose stromal cells to compare a regenerative medicine cell therapy modification of the fat grafting procedure with more traditional fat graft preparations. We plan to randomize 15 subjects to the enriched adipose stromal cells using the Tissue Gensis Cell Isolation System (CIS) IDE # (pending) to process the cells for the modification of the fat grafting procedure. The PI not only has experience with fat grafting in his clinical practice, but also serves as principal investigator in a clinical trial assessing the impact of facial fat grafting for wounded military personnel. The Biomedical Translational Initiative (BTI) (Structural fat Grafting for Craniofacial Trauma, W911QY-09-R-0030) from the Office of the Assistant Secretary of Defense involves the treatment of 20 wounded warriors with facial injuries using minimally invasive fat grafting techniques. This study has established significant infrastructure to evaluate soft tissue reconstruction after facial trauma, and demonstrates the ability of the PI to assemble and manage the team for an interdisciplinary clinical trial. This study, still in progress, has treated 15 subjects out of a targeted enrollment of 20 subjects with no serious adverse events and improved outcomes in all subjects. Another phase of this trial, currently funded through the Armed Forces Institute of Regenerative Medicine (AFIRM) clinical trials program and starting to recruit subjects, assesses the efficacy of a regenerative medicine approach of enriching the fat graft with autologous adipose stromal cells. That same intervention will be trialed in this study, as well. The biggest problem associated with fat grafting is unpredictable rates of fat graft resorption. This is likely related to the ability of the regenerating adipose tissue to rapidly develop a new blood supply. This study will examine if fat grafting with cell enrichment will demonstrate increased fat retention and decreased pain compared to standard fat grafting alone. A modified preparation of the fat graft involves concentrating the endogenous stromal cells in the graft material in an effort to increase graft retention over time. The aspirated fat material used for fat grafting consists of mature adipocytes, a small amount of fibrous tissue, and immature adipose stromal vascular fraction cells (SVFs). These adipose stromal cells are a mixed population of non-lipid laden cells that serve to turn over mature adipocytes and vascular elements. One cell type, "Preadipocytes," or adipose derived stem cells (ASC's), as well as endothelial precursor cells and multilineage

progenitor cells, were identified. Of note, ASCs have been shown to stimulate angiogenesis when stressed under hypoxic conditions and these cells may be instrumental in healing and volume retention of fat grafts. Yoshimura, et. al. (137) found that fat aspirated with a liposuction cannula (i.e. the method of fat harvest for fat grafting) is deficient in ASCs compared to whole fat. This is due to the fact that a major portion of ASCs are located around larger blood vessels that are left intact in the donor site after liposuction with a blunt cannula. The relative lack of ASCs in lipoaspirate may explain problems with fat graft reabsorption over time. Enriching lipoaspirate with ASCs should increase angiogenesis and, therefore, fat graft retention. This cell therapy approach takes advantage of the innate ability of ASC's to both secrete angiogenic factors and also differentiate into mature adipocytes. The improved blood vessel ingrowth can result in improved graft volume retention and superior reconstructive outcomes. Yoshimura was among the first to concentrate ASCs in fat grafts. Numerous animal model studies have demonstrated that fat graft enrichment with a higher concentration of ASCs can improve long-term graft survival and retention. In one of the earliest rodent studies, Matsuda et al. (138) transplanted omental tissue with or without preadipocytes isolated from epididymal adipose tissues under the dorsal skin of Wistar rats. After 12 weeks, high levels of triacylglycerol content, capillary density, and VEGF production were observed. More importantly, grafts with a higher ASC concentration significantly enhanced adipose tissue formation. More recently, two additional animal studies have shown improved fat graft survival, including increased neovascularization, with a higher ASC concentration. In a 6-month animal study, Lu and coworkers (139) reported that fat grafts with a higher ASC concentration displayed: 1) significantly increased transplant survival versus non-ASC controls, and 2) significantly greater capillary density in comparison to fat not enriched with ASC. Histological analyses revealed that human ASC-derived endothelial cells accounted for the increased microvasculature. Furthermore, in a murine fat-transplantation model, Zhu et al. (140) were able to demonstrate that at both 6 and 9 months after transplantation, fat grafts with a higher concentration of ASCs increased graft retention by 2-fold and improved the capillary density compared to control grafts. The technique of concentrating autologous ASCs with fat grafts has been utilized clinically safely and with good clinical results. Yoshimura et. al. (141) performed standard autologous lipoinjection or ASC concentrated fat grafts on six patients with facial lipoatrophy. This is a similar scenario to the study we propose here, as the fat grafts are used for addressing pain at amputation sites in abnormal tissue beds with a deficiency in subcutaneous volume. Standard fat grafting has already been demonstrated as a safe and minimally invasive technique over decades of widespread practice in plastic surgery. Concentrating already present ASCs within the graft to create greater healing potential is not expected to cause any increased risk above the fat grafting procedure. Because endogenous adipose stromal cells within the graft are highly bioactive and secrete angiogenic factors, we will assess functional properties of these cells as predictors of graft success. Our group at the University of Pittsburgh has developed clinically useful and scalable GMP methods for the concentration of SVF extraction under an NIH funded



program, led by Dr. Rubin (Co-Director of the Adipose Stem Cell Center) in collaboration with Dr. Albert Donnenberg, director of the clinical laboratories for cell processing. We are currently starting a fully funded project with the Armed Forces of Regenerative Medicine (AFIRM). We are utilizing our extraction techniques to perform SVF enriched fat grafting for facial trauma reconstruction and this has received IRB approval at our institution. This process is regulated under human cells, tissues and cellular and tissue-based products (HCT/P) guidelines under section 361 of the CFR (21CFR1271.10). HCT/P therapies are exempt from the requirement for the submission of an Investigational New Drug (IND) application. For this project proposal, we have expanded the team to encompass expertise in reconstructive fat grafting, lower extremity reconstruction, physical medicine and rehabilitation, prosthetic design, nutritional support, and evaluation of psychosocial outcomes. Given the initial success with autologous fat grafting for facial reconstruction after trauma (analysis ongoing), even without enrichment of the graft with adipose stromal cells, we believe this therapy can be effectively applied for the treatment of limb pain. This procedure can be performed on an outpatient basis with no significant incisions on the limb, only small port sites measuring less than 5 mm. It is noted that this is a completely new, experimental application of a conventional treatment.

- 1.4 Significance: Why is it important that this research be conducted? What gaps in existing information or knowledge is this research intended to fill? This study will significantly impact military trauma care by validating a minimally invasive cell based technique for alleviating pain at amputation sites and improving function with a prosthesis. Importantly, the goal will be reached without invasive surgery, increased risk, and a prolonged recovery. Given the high amputation rate in the current conflicts, this work is highly relevant to the care of the wounded warrior. A major goal of this study will be to transfer the techniques and knowledge gained to physicians throughout the Department of Defense healthcare system, as well as the general US healthcare team who treats amputees from non-military trauma and illness.

[reviewer notes~]

## Section 2 - Research and Design Methods

- 2.1 Does this research study involve the use or evaluation of a drug, biological, or nutritional (e.g., herbal or dietary) supplement?

\* No

2.1.1 Does this research study involve an evaluation of the safety and/or effectiveness of one or more marketed nutritional (e.g., herbal or dietary) supplements for the diagnosis, prevention, mitigation or treatment of a specific disease or condition or symptoms characteristic of a specific disease or condition?

\*

2.1.1.1 List each of the marketed nutritional supplements being evaluated in this research study. Specify for each supplement the corresponding IND number or attach FDA correspondence specifying that an IND is not required.

Marketed nutritional supplement	IND number
There are no items to display	

Upload FDA correspondence specifying that an IND is not required, if applicable:

Name	Modified	Date	Version
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[reviewer notes~]

## Section 2 - Research Design and Methods

2.2 Will this research use or evaluate the safety and/or effectiveness of one or more devices?

\* Yes

2.2.1 Does this research study involve an evaluation of the safety and/or effectiveness of one or more devices not currently approved by the FDA for general marketing?\* Yes

If YES, describe your plan to prevent unauthorized use of the investigational device: The Investigator will permit trial-related monitoring, audits, IEC review, and regulatory inspection(s), providing direct access to source data/documents, permitting authorized inspectors to inspect all facilities and records relating to the study and aid the inspector to perform the audit in a timely fashion. Transportation of cellular products between the operating room and the Hematopoietic Stem Cell Laboratory (HSC Lab) will be performed according to Foundation for the Accreditation of Cellular Therapies standards and will be only permitted through the use of trained personnel, whether they are lab personnel, medical staff or couriers. The lipoaspirates and SVF suspensions (device output) will be

given respective accession numbers according to SOP 2010-05-R0 Procedure for Accessioning in the Hematopoietic Stem Cell Laboratory (HSC Lab) [Attachment 33] and labeled according to SOP 1997-13-R16 Procedure for Labeling Specimens and Products [Attachment 34]. For transport, the product labeled lipoaspirates and SVF suspension (device output) will be placed into transportation containers, such as an Igloo cooler, that has been specifically validated to maintain the storage conditions for a specified amount of time. In addition, a secondary container such as a biohazard bag will be used according to SOP 1997-08-R14 Procedure for Shipping Samples and Products [Attachment 35]. At the time of receipt of the lipoaspirate to the HSC Lab, the product will be received as per SOP 1995-18-R12 Procedure for Receipt of Human Hematopoietic Progenitor Cells [Attachment 36] and 1995-20-R15 [Attachment 37], with the arrival date and time documented in the Sample Log Book. At no time is the product left unattended. Cell products will be assigned an expiration time as per SOP 2005-22-R1 Policy for Product Storage Conditions and Expiration [Attachment 38], however, stability testing of the SVF has not been completed for this cell type. Chain of custody documentation will occur at the time of delivery to the HSC Lab or its personnel and again at the release of the products.

- 2.2.1.1 List each of the unapproved devices being evaluated in this research study. Specify for each listed device the corresponding Investigational Device Exemption (IDE) number or provide a justification for why you feel that this device and its use, as proposed in this research study constitute a non-significant risk (i.e., to include potential failure of the device) to the research subjects:

Unapproved device	IDE #	Non-significant risk justification
View Tissue Genesis Cell Isolation System (CIS)	IDE 15444	

There are no items to display

[reviewer notes~]

## Section 2 - Research Design and Methods

- 2.2.2 Does this research study involve the use or evaluation of the safety and/or effectiveness of one or more devices approved by the FDA for general marketing?\* Yes
- 2.2.2.1 Does this research study involve an evaluation of one or more FDA-approved devices for a clinical indication, subject population, and/or operational parameter that is not specified

in the current FDA-approved product labeling for that device (i.e., for an “off-label” indication)?

\* No

- 2.2.2.1.1 List each of the devices being evaluated for an “off-label” indication. Specify for each listed device the corresponding Investigational Device Exemption (IDE) number for this device/research study; or provide a justification for why you feel that this device and its “off-label” use, as proposed in this research study (i.e., to include potential failure of the device) constitute a non-significant risk to the involved research subjects.

\*

Device	IDE #	Non-significant risk justification
There are no items to display		

[reviewer notes~]

## Section 2 - Research Design and Methods

- 2.3 Summarize the general classification (e.g., descriptive, experimental) and methodological design (e.g., observational, cross-sectional, longitudinal, randomized, open-label single-blind, double-blind, placebo-controlled, active treatment controlled, parallel arm, cross-over arm) of the proposed research study, as applicable.

Prospective, Randomized, Non-blinded, Surgical outcomes, Pilot study assessing clinical outcomes following fat grafting for pain at amputation sites(with and without adipose stem cell enrichment) .

- 2.3.1 Does this research study involve a placebo-controlled arm?

\* No

[reviewer notes~]

## Section 2 - Research Design and Methods

- 2.4 Will any research subjects be withdrawn from known effective therapy for the purpose of participating in this research study?

\* No

2.4.1 Provide a justification for discontinuing subjects from known effective therapy for the purpose of study participation.

2.4.2 Describe the risks to subjects associated with discontinuing them from known effective therapy for the purpose of study participation.

[reviewer notes-]

## Section 2 - Research Design and Methods

2.5 Will screening procedures (i.e., procedures to determine research subject eligibility) be performed specifically for the purpose of this research study?

\* Yes

2.5.1 List the screening procedures that will be performed for the purpose of this research study. Do NOT include the inclusion/exclusion criteria in this section as they will be addressed in section 3; questions 3.13 and 3.14.

This is a prospective randomized single site study in which 30 patients with amputation stump pain will be enrolled. Each subject will undergo an assessment to evaluate: 1.) the 3 dimensional structure of the amputation site; 2) personal occupational therapy; and 3.) nutritional evaluations. Initial screening through the TRIALSPARK platform(described more in section 4.2) will involve completing an online screening questionnaire through a web-based study landing page. This online questionnaire will take approximately 5-10 minutes to complete and will include questions related to the injury, physical and medical conditions associated/surrounding the injury as related to pre-screen approach similar to the telephone screening script; and does not confirm eligibility as there are additional screening measures associated with this study. Study staff will be able to review responses via TRIALSPARKS'S backend management platform. If the participant seems eligible, study staff will contact the prospective participant to continue the screening process. (for reference, the online prescreen questionnaire is attached in "other attachment" section of the protocol). Screening Visit: All screening procedures will be performed at the UPMC Aesthetic Plastic Surgery Center in a private room, the UPMC laboratory located on the 5th floor at Montefiore University Hospital (MUH) and Orthotics and Prosthetics Rehabilitation Center located at Bakery Square for O&P evaluation. The total time of participant commitment for these screening procedures will take approximately 3.5-4 hours and may

occur on different dates. The following research procedures will be completed prior to the PI's determination of subject's study eligibility:

1. Obtain Informed Consent, assignment of subject unique identifier
2. Performance of history and physical exam inclusive of participant's limb with evaluation for heterotopic ossification (HO); exam completed by PI and / or a co-investigator.
3. The investigator will rate the appearance of the graft site using a limb volume and appearance grading scale
4. Collection of subject's vital signs (Temperature, heart rate (HR), respiratory rate, blood pressure (BP), medication profile to include prescription and vitamins / supplements, allergies, height, weight, Body mass index (BMI) calculation, collection of demographic information to include date of birth, gender, race, hand dominance, ethnicity, level of education, relationship status, smoking status and employment status.
5. All participants who are women of child bearing potential will receive a urine pregnancy dip test. If the test result is positive the subject will not continue participation in this research study.
6. Structured Clinical Interview for DSM-IV (SCID; DSM is the diagnostic and statistical manual of mental disorders) will be included in the baseline to evaluate the presence/absence of Axis I psychiatric disorders. This evaluation will be completed using a standard psychiatric diagnostic interview that enables determination of DSM-IV-based diagnoses. As part of the clinical interview a demographic history will be completed. The information contained in the SCID will be collected by a member of Dr. Gretchen Haas's clinical team who is experienced in psychosocial interviewing with participants. This SCID will take approximately 45-60 minutes of the subject's time to complete. Individuals who manifest either: 1) evidence of currently active alcohol or psychoactive drug abuse or dependence on the SCID interview, or 2) a GAF score of 40 or lower due to any acute psychiatric symptomatology (e.g. suicidality, psychosis, severe depression or mania) will be reviewed by the Co-I for Psychosocial Assessment with the PI for determination of possible medical instability. Final determination of medically unstable status will be made by the PI on the basis of overall medical status and appropriateness for medical procedures; the patient may be considered ineligible for study participation per the Physician's discretion.
7. Medical and surgical history review: If the subject has been followed at UPMC facilities, the principal investigator, co-investigators and / or study staff will perform a medical history review (pertaining to the trauma event and surrounding surgical and medical procedures). A medical history review will consist of prior procedures to include, but not be limited to blood tests (including but not limited to complete blood count (CBC) with Differential and Platelets, comprehensive chemistry panel, urinalysis, and culture results) operative procedures, physical therapy assessments, consultations, history of Heterotopic Ossification (HO), CT, MRI scans, EKG, Chest X-rays, history and physical exams. If medical records do not accompany the subject or are not available at the time of screening evaluation for investigator review, the investigator in lieu of direct medical record review will accept direct report from the referring physician, prosthetics and/or orthotics referral source and /or subject self report and will document this reported information to research chart. This report will consist of past medical /surgical history pertaining to the affected limb injury and/or events surrounding the limb trauma. The Principal Investigator will base determination of study eligibility on a combination of

evaluation criteria to include physical examination, screening lab values, referral physician direct report, prosthetics and/or orthotics referral direct reports and /or subject self report, study O&P evaluation and psychological (SCID) assessment all pertaining to past injury and current status of the area of interest. 8. Baseline evaluation of amputation stump pain, the study coordinator will provide a Pain Assessment form to the participant to complete. This form will document the nature/character of the discomfort limiting function and or interferes with their ability to use a prosthetic device. The subject will be instructed to document the discomfort to include frequency, location, intensity (1 to 10 scale with 10 as most intense), type of pain (physiological or phantom). It will include subject self-intervention related to pain and use of prosthetic devices. 9. Blood Tests- approximately 30mls (2 tablespoons) will be collected for the following laboratory assessments: Serum CBC with Differential and platelets .Comprehensive Chemistry panel including Calcium, Pre-Albumin, and Albumin. PT/ PTT/ INR On receiving the laboratory results, the Investigator will initial and date the results and assign clinical significance to any out of range values. Subjects with clinically significant results attributed to any disease entity will be evaluated and per MD discretion excluded from the trial. 10. Orthotics and Prosthetics: One of the aims of this study is to evaluate prosthetic fit problems at an amputation site that limits function and / or interferes with the ability to use a prosthesis which is known to have a direct impact on the ability to perform activities of daily living as well as social participation. This aim is important to identify pain and functional issues associated with the use of a prosthesis and/or other assistive technology used in conjunction with a prosthesis or in lieu of. This study will seek to address residual limb problems for individuals with upper and lower limb loss, including individuals with partial hand, partial foot and more proximal injuries. We will utilize this novel procedure to help improve function and tolerability for individual with limb loss. Reasons for “intolerability” may include inappropriate soft tissue padding, soft tissue coverage, or pain that doesn’t allow the consistent wearing of a prosthetic socket. This may be manifested by excessive pain, inability to achieve adequate suspension of the prosthesis on the individual, continual skin breakdown, excessive pressure/shear on skin, soft tissue, nerves, scars, etc. The degree of pain and intolerability associated with the prosthesis can be described as follows; While a generally accepted score of 4 or greater on a visual analogue scale from zero (no pain) to ten (worst possible pain) is considered intolerable, currently, the field of amputee and prosthetic care lacks a validated instrument to measure “intolerability” of socket fit or prosthetic use. Therefore, we will consider individuals for this procedure, who by the patient and rehabilitation teams’ report are unable to successfully progress in prosthetic rehabilitation despite multiple interventions, including surgical and non surgical. These patients will have undergone multiples prosthetic limb and socket adjustments, various external padding attempts and even often interventions such as skin grafts, muscle flaps, neuroma injection or resection, or heterotopic ossification surgical resection. We will only consider patients who have received a minimum of 3 months of unsuccessful prosthetic fitting trials for inclusion in this study. This information pertaining to the history of prosthetic fit attempts may be received from referral physician, prosthetics and/or

orthotics direct report and/or subject self report self-report and /or medical record review. Typical standard care will include providing a customized prosthetic socket by casting the individual's residual limb and utilizing various socket and liner materials to provide optimal residual limb to prosthesis interface. This will also include modifications by reducing excessive pressure points, incorporating additional padding and utilizing a variety of prosthetic components and alignment techniques to best accommodate each individual. In addition, many patients may have already received interventions such as skin grafting, muscle flaps, residual limb reconstructive surgeries, neuroma injections or excision to best achieve a functional and non-painful residual limb. When defining "maximal attempts to refit the prosthesis" we define it as patients who have been unsuccessful in achieving a functional and comfortable prosthetic socket despite a minimum of 3 months of working with a prosthetist. This will include a minimum of at least 5 different socket adjustments. "Changes in the design of the prosthesis", will include re-casting the residual limb, providing pressure relieves within the socket, changing the alignment of the prosthetic components to alter ground reactive forces, and adding padding to pressure sensitive areas. The approximate range of the defect volumes can be small (5-10cc), or as much as 300cc if the defect is a very local soft tissue deficiency over a pressure point. The volume of the defect correlates with moderate or severe intolerability of the prosthesis. The following evaluations will be conducted by or under the supervision of a certified prosthetist and/or occupational or physical therapist. For the Orthotics and Prosthetics evaluation all study participants will be assessed pre and post the procedure to determine the functional changes related to prosthetics ambulation and residual limb health and structure. All participants will be asked to complete the all of or a subset of the following questionnaires and assessments prior to the surgical procedure (Screening) and after the surgical procedure. a. "Prosthetics Evaluation Questionnaire" (PEQ) is a self-report questionnaire containing 54 questions organized into nine functional domains related to prosthesis-related changes in quality of life. The PEQ was developed to fill the need for a comprehensive self-report instrument for individuals with lower limb loss. (143- Legro 1998). Psychometric analysis supported the reliability and validity of the PEQ for evaluating the function of the prosthesis and the major health related quality of life domains. The PEQ is estimated to take 15 minutes or less to complete. b. The 6minute walk test (6MWT) is a reliable measure of functional capacity, involves a moderate degree of exercise intensity, and is related to a moderate degree to postural control abilities in persons with lower-limb amputations. (144 - Lin S-J, Bose NH, 2007). This 6MWT is estimated to take 20 minutes or less to complete, including the baseline rest period, set-up, and 6 minutes of continuous walking. c. The Amputee Mobility Predictor (AMP) is 21 item instrument designed to assess determinants of the lower-limb amputee ability to ambulate. The AMP is estimated to take approximately 15 minutes or less to complete. d. Lower Extremity Functional Scale (LEFS) is a self-reported questionnaire containing 20 questions about a person's ability to perform everyday tasks. The LEFS is anticipated to take approximately 10 minutes or less to complete. e. The Disabilities of the Arm, Shoulder, and Hand (DASH) outcome Measure is a 30-item, self-report questionnaire designed to



measure physical function and symptoms in people with musculoskeletal disorders of the upper limb. The DASH is estimated to take approximately 10 minutes or less.f. Functional Mobility Assessment (FMA) is a self-report questionnaire to assess perceived user function related to assistive technology use. The FMA is expected to take approximately 10 minutes or less.g. Prosthetic Device Use History: Compliance with prosthesis use affects activities of daily living (ADLs) as well as impacting social interaction. The participant's prosthetic devices (both pre and post procedure) will be evaluated and a history will be obtained from the participant to determine average daily use and related issues/concerns.

Permission to contact the participant's prosthetist and/or therapist may be obtained to identify specific prosthetic devices/components previously trialed as part of routine clinical care. This questionnaire is estimated to take approximately 30 minutes to complete.h.

Physical Examination: A physical examination will be conducted to evaluate general UE and LE function and specifically the amputation stump. The stump characteristics will be recorded, including , but not limited to measurements, range of motion, strength, skin integrity/areas of pressure, pain and prosthesis/socket interface. This physical examination is anticipated to take approximately 30 minutes to complete. If upon examination, it is determined that the participant is at increased risk for developing pressure ulcers and/or the participant's current wheelchair and seating is not addressing their needs, they will be referred to the UPMC Center for Assistive Technology for a full assistive technology evaluation per routine clinical care.11. Nutritional Assessment /Education: Nutrition has long been a recognized factor impacting wound healing. Ablina (142) noted delay of the healing process in relation to severe protein and calorie deficiencies. Each subject will recall their dietary intake over the 48 hours prior to the screening visit date to be evaluated for current nutritional habits. Nutritional education will be provided by the research coordinator /co-investigator based on the evaluation of the subject's dietary intake record. This education, if necessary will follow content provided for Recommended Daily Allowances (RDA) and the American Heart Association (AHA) recommendations. Approximate time estimated 20 minutes.

Eligibility Determination: Upon the completion and evaluation of all screening procedures subject eligibility determination for continued study participation will be completed by the Principal Investigator (PI).Randomization - For this study, 70 potential subjects will be enrolled and screened with a goal of 30 subjects to undergo the operative autologous fat grafting procedure. Each subject will be assigned to a specific randomization block based on whether they have an upper or lower extremity amputation. Each randomization block will have six (6) subjects. There will be a computer generated randomization assignment for each subject to receive the surgical intervention that will be either fat grafting alone or fat grafting with stromal vascular fraction cells. A randomization table will be generated using a software program (155) [Research Randomizer, Version 3.0]. This will allow for statistical examination between the two different treatments within each randomization block (3 subjects receive fat graft and 3 subjects receive fat graft with stromal vascular fractions). There will be five (5) randomization blocks for a total of thirty (30) subjects. Therefore based on the prevalence of subjects who have either the upper and lower extremity amputation, there may be a

range from one (1) to five (5) randomization blocks for one of the treatment groups. We expect that there will be a higher number of lower extremity amputees who call-in or are referred for screening. The proposed block randomization scheme will be flexible to handle various numbers of either upper or lower extremity amputations as well preserve the statistical rigor for testing. Due to participant's schedule, travel distance and/or coordination of the screening study visit, procedures may be performed on different days as long as the screening procedures do not exceed a length of 2 weeks for completion. The principal investigators eligibility determination will occur up to 45 days post the date of completion of the last screening visit procedure date.

2.5.2 What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the screening procedures?

Addressed below:

Upon discovery the PI and/or co-investigator will notify the subject of any event that could be of clinical significance needing further evaluation, or of a diagnosis of any unexpected disease or condition that occurred during the conduct of the study's research procedures. The study investigator will at the time of discovering the event contact the referring physician or primary physician for further evaluation of the event. Should the event be of a critical nature needing immediate intervention, the study investigator or co-investigator will proceed with immediate clinical intervention and screening procedures will be concluded. HO is not grounds for exclusion and we wish to be able to study subjects with Heterotopic Ossification (HO). HO is prevalent in extremity amputation wounds in military trauma.ii. If HO is present, we will ascertain that HO remains stable and does continue to increase in volume, as documented by CT imaging of stabilization. iii. Medical management will be instituted with NSAIDS as indicated and appropriate for the patient. iv. We will then determine if the HO is the primary source of pain, or causing erosion of skin on physical exam. Fat grafting over the HO will be performed as part of study provided that: HO is ruled out as primary source of pain through clinical exam, and HO is deeper and not eroding through skin, allowing adequate fat coverage. v. It is anticipated that adding more soft tissue coverage over HO will be beneficial. vi. If elective excision of HO is required, that procedure will be performed in the first stage with 3 month recovery period before fat grafting.

[reviewer notes~]

Section 2 - Research Design and Methods

- 2.6 Provide a detailed description of all research activities (e.g., all drugs or devices; psychosocial interventions or measures) that will be performed for the purpose of this research study. This description of activities should be complete and of sufficient detail to permit an assessment of associated risks. At a minimum the description should include:

all research activities

personnel (by role) performing the procedures

location of procedures

duration of procedures

timeline of study procedures

For the Pre-Graft Study Visit (PGSV) subjects will return to UPMCs Aesthetic Plastic Surgery Center prior to the surgery procedure date. Procedures for pre-graft visit may occur on the same day or due to the coordination of the participant's schedule and travel distance the procedures may be performed on different days as long as the completion of the procedures do not exceed a length of 4 days. This visit will require approximately 3-3.5 hours duration of the participant's time. During this visit the following research procedures will be completed: 1.) Performance of a limited/brief medical history review and physical exam inclusive of amputee limb completed by PI and /or a co-investigator. The investigator will rate the appearance/volume of the graft site using the limb volume and appearance grading scale. 2.) 2D Photographs will be taken of the limb. The pictures will be taken of the amputation stump. The pictures will be taken at the UPMC Aesthetic Plastic Surgery Center in a private room and will take approximately 10 minutes. Digital recording (i.e. photography or video) are being collected from any and all portions of the subject's pre-operative, operative, and post-operative course of treatment. These may include, but not be limited to, videos of personal interviews, functional assessment testing and clinical exams or photos of follow up clinical course, biopsies, etc. and will be de-identified and stored indefinitely in a secure password protected location on the UPMC server. These digital recordings and/or photos may be used for medical education and training, publication, and media reports – and, in any mode of transmission, including and not limited to: print, e-mail, television, internet, etc. While photographs will be de-identified, video recordings will remain identifiable. Regarding the use of these digital recordings for education, training, publication and storage purposes, the subject will not be identified by name, only by a unique code number. The subject's identifiable features in these photographs will be blacked out (i.e., eyes, facial features, etc.). Regarding the use of the subjects digital recordings for media purposes, the subject may be identified by name, but permission from the subject will be obtained in a separate consent document prior to the recordings being obtained (Media consent). The subjects are not required to give this permission and can refuse at any time after giving consent to these digital recordings being obtained and can still participate in this study without permitting these

recordings. 3.) All participants who are women of child bearing potential will receive a urine pregnancy dip test. If the test result is positive the subject will not continue participation in this research study. 4.) Collection and review of new medications to include prescription and vitamins / supplements, allergies and vital signs (Temp, HR, Resp, BP), weight, body mass index (BMI) calculation, and adverse event reporting. 5.) Serial Computed Tomography Imaging or MRI scan will be performed. A high resolution Computed Tomography (CT) Scan of the amputation stump will be performed at Presbyterian Hospital and will take approximately 60 minutes. This scan will be pre-procedural and will serve as a baseline. All CT scans will be performed on a 64-slice scanner (LightSpeed, GE Healthcare), using slice thickness of 1.25 mm and pitch of 1.375. kVp, mA, and FOV will be optimized to the subject and body part to be imaged. Soft tissue and bone kernels will be employed. These images will be volumetrically reformatted into coronal and sagittal planes for confirmation of findings. Additionally, surface-rendered volumetric reformats will be created emphasizing both bony structures and soft tissues. In the event that a CT scan is contraindicated or declined by a study participant, MRI will be performed using a 1.5 T MRI scanner (Signa HDx, GE Healthcare). The MR imaging protocols will include coronal and axial planes using T1- weighted spin echo sequences as well as coronal, axial, and sagittal planes using T2-weighted fast spin echo with fat suppression and/or short tau inversion recovery (STIR) sequences. Again, FOV, TR/TE time, acquisition time and other parameters will be optimized to the subject and body part to be imaged. Intravenous contrast will not be administered for either CT or MR imaging. Images will be reviewed by radiology. Volume measurements of the implanted material will be made on all post-procedural CTs or MRIs. These volumetric measurements are expected to be precise to within 5% of the actual volume of material. Trends in volume of tissue will be analyzed over time across the multiple CT or MRI scans. Both linear and volumetric measurements will be used to quantify implanted material. Subjects must remove compression sleeves prior to CT scans. 6.) To further evaluate pre-surgical amputation stump pain, the study coordinator will provide a Pain Assessment form to the participant to complete. This form will document the nature/character of the discomfort limiting function and or interferes with their ability to use a prosthetic device. The subject will be instructed to document the discomfort to include frequency, location, intensity (1 to 10 scale with 10 as most intense), type of pain (physiological or phantom). It will include self interventions related to pain and use of prosthetic devices. 7.) Psychosocial Assessment: One of the aims of the proposed study is to evaluate pre- and post-operative quality of life and symptoms of psychological distress. This aim will also consider psychosocial factors (pre- and post- surgery) that predict psychological well-being and quality of life outcomes following surgery. The aim is important for identification of psychosocial factors that may play a role in and be critical to enhancing quality of life outcomes from amputation stump surgery. Participants will be asked to complete a psychosocial battery that includes: a) self-report measures of satisfaction with physical appearance, anxiety and depressive symptoms, social functioning and social avoidance and distress and; b) questionnaires that assess significant predictors of quality of life

outcomes from post-trauma limb surgery: perceived social support, self-esteem, coping style and pre-surgical expectations of/post-surgical outcomes. A research technician experienced in psychosocial interviewing with participants will meet with each participant during the baseline evaluation to administer the self-report battery of psychosocial questionnaires. A comprehensive battery of tests for evaluation of quality of life has been assembled for this study. It is important to properly determine the impact of the surgical changes and the investigators have selected psychosocial assessment instruments to evaluate four domains:

- a. Satisfaction with appearance/surgical outcomes – The Satisfaction with Appearance (SWAP) scale (145) is a 14-item questionnaire with good internal consistency and test-retest reliability that measures both subjective and social-behavioral aspects of body image and has been used in populations with significant physical disfigurements or deformities.
- b. Satisfaction with Medical/Health Services - Patient Satisfaction with Health Services – the Client Satisfaction Questionnaire (CSQ-8) is a widely used brief inventory of satisfaction with services (amount of help, kind of help, availability of help) provided by a medical service or program (146).
- c. Social Functioning, Distress, Depression and Avoidance - To evaluate hypothesized pre- versus post-operative changes in quality of life, social functioning, symptomatology and coping, we will include the following measures:
  - Social Distress and Avoidance - Individuals with disfigurements can suffer extreme anxiety and avoidance in interpersonal interactions. The Social Anxiety and Distress (SAD) Scale (147) is a widely used measure of social avoidance and distress that has shown to be sensitive to pre-/post- surgical improvement in recent studies of patients undergoing reconstructive surgery for significant physical deformity.
  - Anxiety and Depressive Symptomatology will be monitored using the Beck Depression Inventory, PHQ brief and the PCL-S (Post trauma checklist- Brief) (148), a self-report questionnaire that taps post traumatic stress disorder (PTSD) symptoms for use among individuals in the military.
  - Self-esteem will be assessed by the Rosenberg Self Esteem Inventory (149), a brief (10-item), a self-report inventory examines how social structural positions relate to self-esteem.
  - Coping Style will be assessed with the Brief COPE inventory (150) an abbreviated version of the situation-specific coping inventory (151) that has been effectively used to characterize psychological coping with physical illness and disability. An extensive body of research on clinical and psychosocial outcomes from surgical and medical interventions has yielded evidence that psychosocial coping style is an important factor that contributes to psychological well-being, physical health and quality of life outcomes.
  - Perceived Social Support will be analyzed by the Perceived Social Support Questionnaires(PSSQ)-Family and Friends (152). This 6-item self-report inventory with satisfactory internal reliability and construct validity that inquires regarding the perceived availability of social support for needs for support, information and feedback. Social support, along with psychosocial coping cognitions and behaviors contributes significantly to psychological well-being, physical health and quality of life outcomes. Each of these may be important covariates that contribute to variance in quality of life outcomes in this study.
- d. Quality of Life and General Functioning Outcomes - Quality of life and general functional status will be evaluated using the SF-36 (153, 154), a self-report inventory

widely used in medical outcome research with self-rated indices of health, quality of life, energy, role limitations due to physical problems or emotional problems, and functionality in everyday physical, emotional, and social function domains.e. A brief (shortened) demographic history form will be completed as part of the psychosocial assessments. This psychosocial evaluation (self-report measure) will take an estimated 1.5-2.0 hours and will take place at the UPMC Plastic Surgery Center in a private room. 8. Pre-Operative Laboratory tests will be obtained via a peripheral blood draw performed by laboratory personnel located on the 5th floor of the UPMC Montefiore Hospital building. Blood tests will not need to be repeated at PGSV if screening blood tests were collected within 30 days of operative procedure date. Blood tests approximately 30mls (2 tablespoons) will be collected for the following laboratory assessments: Serum CBC with Differential and platelets, Comprehensive Chemistry panel, pre-albumin, Albumin and PT/ PTT/ INR. On receiving the pre-op laboratory results, the Investigator will initial and date the results and assign clinical significance to any out of range values. Subjects with clinically significant results attributed to any disease entity will be excluded from the trial. 9. Electrocardiogram (EKG) and or chest x-ray, as indicated by past medical history.10. The study coordinator will provide the participant with a Diary Card and Pain Log with instruction to begin completion of the Diary Card and Pain Log 24 hours after their fat grafting surgery and continue until Post operative Day 3-6. The subject will be instructed to document a self assessment of the following events pertaining to the surgical site: Pain, Bruising, Redness of the skin, Itching, Swelling, Bleeding, Other (any concerns/issues not listed). The subject will be instructed to identify on the Diary Card the location, date and day of each documented event. The subject will be asked to continue completion of logs if an event/issue persists at PO day 3-6 until the next post –op visit (POV1). Per guidance from the FDA, we will plan for a 10-14 day time staggering interval between the administration of the investigational product for each of the first six subjects randomized to the TGI IDE arm of this clinical trial to capture any detrimental or unknown risks associated with the products or procedures, such as anaphylactic reactions to any components of the lipoaspirate or contaminations (during the procedures involving fat harvesting and machine processing of lipoaspirate) which may lead to sepsis. Operative Visit: All surgical procedures will be performed at UPMC Shadyside Hospital located on the 2nd floor, UPMC Magee or Montefiore Hospitals within the operating room suites. These procedures are being conducted as an outpatient admission and all monitoring conducted during the peri-operative care period will be performed per standard practice according to the UPMC policy and procedures for this facility. Prior to the surgical procedure being conducted, the subject will be seen by the research team in the DAS area and at which time PI and co-investigator(s) will mark areas of surgical interest and may document with 2D photographs. Should new areas be identified or included at this time for surgery, photographs will be taken of the areas of interest at this time. The fat graft surgical procedure will be performed at this visit and will take approximately 4-5 hours to complete. The fat grafting is planned as an outpatient procedure which is conducted within the UPMC Shadyside Hospital located on the 2nd floor, UPMC Magee or

Montefiore Hospitals within the operating room suites. In brief, fat tissue to be used for grafting is harvested (usually from abdomen or thighs) with a small liposuction cannula in the operating room. Specific details of the Fat Harvest and Graft Preparation follow: Subjects will receive general anesthesia or a block with sedation. A dilute epinephrine solution (concentration 1:1,000,000) will be injected into the harvest site, which is usually abdominal or thigh subcutaneous tissue. A blunt tip hollow cannula is then used to aspirate through 5mm incisions. Up to 1500cc of lipoaspirate solution mixture will be obtained. This mixture once centrifuged is anticipated to produce an adequate volume of concentrated adipose tissue for injection, cell processing, and research assays. For the 15 subjects randomized to the Autologous Standard fat graft processing we will prepare the fat graft as follows: Once harvested the aspirated fat tissue will be processed as standard graft material. It will be divided into small aliquots and centrifuged in a sterile rotor (3000 rpm for 3 minutes/1200g), and top fluid oil layer from the fat tissue fractions were removed, and transferred into 3mL syringes, each filled with 2.5mL of the lipoaspirate and injected into the amputation stump. This graft preparation will be performed in the operating room. Standard fat graft material will serve as a control treatment and will be injected into limb using specialized injection cannulas as described below ("Fat Graft Placement"). For the 15 subjects randomized to the Autologous Fat Graft enhanced with adipose stromal cell processing we will prepare the cells as follows: Approximately 60-150 cc of lipoaspirate will be collected from the subject to be processed at the HSC lab using the Tissue Genesis Cell Isolation System™ (CIS) to yield approximately 3-8cc of Stromal Vascular Fraction (SVF) suspension. Per the Principal Investigator's clinical evaluation of the area of deficit as it relates to the amount of fat volume necessary to appropriately fill the deficit, the team may employ a second Tissue Genesis Cell Isolation System™ (CIS) concurrently. The aspirated fat processed as standard graft material will be divided into small aliquots and centrifuged in a sterile rotor (3000 rpm for 3 minutes/1200g), and allowed to decant before separating the fluid and oil layers from the fat tissue fractions, and transferred into 60 ml syringes. This graft preparation will be performed in the operating room. a. The lipoaspirate for concentration along with a 5cc aqueous solution syringe for each 60 cc syringe will be transported from the operating room to the Hematopoietic Stem Cell Laboratory (HSC Lab) at the UPMC Hillman Cancer Center, 5117 Centre Ave., Pittsburgh, PA 15213. This facility is directly across the street from the operating room and connected via a connecting bridge. No specimen during transport will be transported outside of a building(s). In brief, this is a state-of-the-art laboratory that was constructed of materials compliant with 21 CFR 211, has a cleanroom that is ISO Class 6, and is GMP compliant with regards to function. This facility is registered with the FDA (FEI# 3004565478), is FACT accredited (since 1999) and is CAP accredited (CAP LAP # 7190853). b. In the Hematopoietic Stem Cell Laboratory (HSC Lab), the stromal vascular fraction (SVF) cell suspension (device output) will be processed using the Tissue Genesis Cell Isolation System™ according to procedures and a cell count will be performed as described in SOP 2008-02-R0. Prior to administration to of the SVF to the subject, rapid endotoxin testing, cell viability, cell count determinations and Gram staining will be

performed as described in SOPs 2005-13-R5 [SOPs are Attached] and 2008-02-R0. The acceptable endpoints are: AO viability  $\geq 50\%$ ; Endotoxin levels  $< 5\text{EU/kg}$  of recipient ideal body weight, cell yields  $\geq 1\text{E}+05$  total SVF cells per mL of adipose stroma and gram stain negative. The determinations will be recorded in triplicate. All handling and procedures with the lipoaspirates and isolation of the SVF are handled in sterile areas and all personnel are appropriately gowned and gloved as well as all laboratory instruments (pipettes, etc.) have been appropriately sterilized/cleaned. c. The released adipose stromal vascular fraction preparation will be transported back to the operating room. The concentrated autologous stromal vascular fraction cells will arrive back in the operating room close to the time that the standard fat graft preparation process is completed. It is anticipated that the time required for preparing the Autologous Stromal cells concentrated fat graft will add no more than 30 minutes to the overall operating time compared to Autologous Standard fat graft processing. d. The Standard graft material and the stromal vascular fraction cells will be mixed and subsequently injected into the amputated stump a target concentration of  $2.0 - 3.0 \times 10^6$  stromal vascular cells/mL of injected fat graft is desired in this study. However, we recognize that there will be significant variation in cell yield between patients, as well as variation in required graft volumes. The actual cell dose for each subject will be collected to the intraoperative source document. The procedure for combining the SVF with the lipoaspirate prepared in the operating room will be performed inside the sterile operating room by Dr. Rubin or a co-investigator who is specifically trained in the techniques of fat graft processing using the Coleman method as well as this cell-enrichment technique of combining SVF with lipoaspirate. i. To manually combine the standard fat graft material and the SVF suspension (device output), each of the syringes will be connected via luer to luer lock. The contents of the lipoaspirate syringe are transferred to the SVF syringe and the cell suspension will be injected slowly back and forth between the two (2) syringes. The final 1 mL SVF-fat graft syringe is now considered cell-enriched and ready for injection into the subject. ii. It should be noted that in the event of fat harvest from both abdomen and thigh, abdominal fat grafts will be combined with abdominal fat SVF and thigh fat grafts will be combined with thigh fat SVF. Fat Graft Placement: The plastic surgeon will use the specially designed hollow injection cannulas (smaller diameter cannulas with varied shapes and tip sizes specifically made to deliver smaller amounts of fat) to fill the desired areas with the designated portion of fat. Incisions for cannula sites average less than 5 mm. The Coleman Cannula System is not experimental and is commercially available in the United States and in compliance with Federal regulations for surgical instruments. A maximum fat graft volume, to include control grafts and SVF-concentrated grafts, of 300mL will be injected. The graft volume necessary to treat the stump site will be determined by the clinical judgment of Drs. Rubin and Coleman. They are plastic surgeons who have significant experience in fat grafting techniques. In addition, previous high-resolution 3D CT scans will be used to help determine the fat volume needed to treat. As is standard of care for fat grafting, the fat will be injected in small 3mL syringes to prevent excessive ischemia that may otherwise be seen with larger graft volumes. If additional SVF



product is required, one of two approaches will be considered. The first approach is the possible acquisition of a second TGI system to isolate and process additional SVF. The second approach will be the use of the available autologous standard fat graft material to fill the remainder of the amputation/stump deficit. Once the surgical procedure has been completed, the subject will be transported to the recovery room where he/she will be monitored until released to go home. Post-Op Care/Monitoring: The UPMC hospital facility specific (UPMC Montefiore, Shadyside and Magee) SOP for post-anesthesia care unit will be followed and all research subjects who will be cared for in the same manner as standard of care patients. The nursing staff will monitor the subjects as applicable per surgical procedure. Given the fat grafting procedure of this retrospective protocol, the nursing staff will focus on extremity clinical exams, including neurovascular exam and color of skin. At discharge, research subjects will receive instructions for self clinical exams at home and will be instructed to make the surgeon aware of any excessive swelling, drainage, redness, fever, severe changes in pain or sensation or any other concerning findings.

**Basic Science Assays of Adipose Tissue** The PI and /or Co-investigator will obtain a total up to 80cc of lipoaspirate as research samples. The research samples will be transported to the University of Pittsburgh's Adipose Stem Cell Center. The research samples will remain under the oversight of Kacey Marra, PhD, Co-Investigator, on the 16th floor of the Biomedical Science Tower, University of Pittsburgh. The samples will be de-identified and will be stored to include assigned code numbers until planned analysis occurs. The information linking these code numbers to the corresponding subjects' identities will be kept in a separate, secure location. Should the subject decide to withdraw or be withdrawn from study participation, these samples will continue to be stored with the destruction of the linkage code to the subject's identity. These samples are only intended to be stored until analysis is performed, not beyond the length of the study term. The following lab process will take place in the University of Pittsburgh's Adipose Stem Cell Center: Approximately 5-25ccs of the lipoaspirate sample will be used to obtain stromal cells. The specimens will be digested in balanced salt solution containing 1 mg/ml collagenase and 3.5% fatty acid free BSA in a 37°C shaking water bath until fragments are no longer visible and digest has a milky appearance. Digests are filtered and centrifuged at 1000 rpm for 10 minutes. Floating adipocytes are removed and the remaining digests are treated with an erythrocyte lysis buffer. Plating media will be changed every two days until confluence (~4 days to reach 90% confluence).  $1 \times 10^6$  Autologous stromal vascular fraction cells /patient will be stored at -80°C. Remaining cells will be utilized in the experiments below. We have been successfully culturing human preadipocytes in our laboratory for the past 9 years.

**Adipose derived stem cells (ASC) yield:** The number of cells isolated per gram of adipose tissue will be determined using a Coulter cell counter technique. Comparison of isolated cells from gentle centrifugation of lipoaspirate at 200 rpm for 3 minutes to adipose-derived stem cells will be determined.

**Adipose derived stem cells (ASC) Viability:** Cell viability will be determined using the Live/Dead assay. The live cells will be stained with fluorescein diacetate (FDA, Green) and dead cell nuclei will be stained with propidium iodide (PI, Red). Adipose

derived stem cells (ASC) Proliferation: Cellular proliferation of preadipocytes will be assessed with the CyQUANT Cell Proliferation Assay Kit (Invitrogen, Carlsbad, CA) at 48 and 96 hours. Media will be changed every 48 hours. Adipose derived stem cells (ASC) Differentiation: To assess the potential of the ASC to differentiate into the adipogenic cell type within the HA gels, cells will be treated plating media containing 0.2 nM dexamethasone, 0.5 uM insulin, 0.2 nM triiodothyronine, antibiotics, and 540 uM IBMX in addition to their current media. To confirm adipogenesis, lipid inclusions cells will be confirmed by staining with Oil Red-O. Additionally, protein expression of PPAR gamma and FABP4 will be determined using western blot analysis, and RNA expression of these adipogenic markers will be determined using PCR. Flow Cytometry Adipose derived stem cells (ASC) characterization: We will characterize ASC from each patient for stem cell surface antigens using flow cytometry. Passage zero preadipocytes isolated (as described above) from the abdominal subcutaneous tissue will be divided into aliquots of  $5 \times 10^5$  cells and stained with selected monoclonal antibodies (mAbs) against progenitor cell surface markers. The antibodies include mAbs against CD34, CD45, CD90, CD133, CD105 and CD166. Rationale for these surface markers includes the following: 1) markers that are routinely examined for bone marrow stem cell markers, and have also been examined as ASC markers and 2) will be able to discern stem cell purity by testing for these markers. The cells will be incubated with mAbs C, and washed in PBS. At least 100,000 viable cells will be incubated for 30 min with 7AAD(-) staining in each sample will be acquired and analyzed using a FACS Aria fluorescence-activated cell sorter (Becton-Dickinson).

#### 2.6.1 Will blood samples be obtained as part of this research study?

\* Yes \*If submitting a protocol for expedited review, it should be clear that the planned blood draws are within the parameters described here:  
<http://www.hhs.gov/ohrp/policy/expedited98.html> (see Expedited Research Category #2)

If Yes, address the frequency, volume per withdrawal, the total volume per visit, and the qualifications of the individual performing the procedure: Lab tests via peripheral blood draw performed by laboratory personnel located on the 5th floor of UPMC MUH building. For blood tests, approximately 30ml (2tbsp) will be collected at the following time points: 1. Screening 2. Preoperative (PGSV)

#### Study Flow Chart:

Name	Modified Date
AMP 30 Schema MOD 5	7/10/2015 10:47 AM

[reviewer notes-]

## Section 2 - Research Design and Methods

- 2.7 Will follow-up procedures be performed specifically for research purposes? Follow-up procedures may include phone calls, interviews, biomedical tests or other monitoring procedures.\* Yes

See study flow chart in question 2.6

Post-operative assessments for clinical outcomes of treatment include amputation stump form and pain assessment, evaluation by prosthetics and occupational therapy, nutritional evaluations (baseline, POV1 and POV3 only) and QOL measures will be performed at 7-21 days, 2, 3, 6, 12 months and at 24 months after treatment. Patients will be followed for approximately 2 years after surgery; the structure of these visits is outlined below. There are no more follow-up procedures planned or anticipated after post-op visit 6.

Post op study visit (Day 3-6): This study visit will occur with the study investigator or research team and will take place approximately in 3-6 days post surgical procedure for the purpose of incision assessment and potential suture removal, if applicable. The entire visit will take approximately 30-45 minutes and will be scheduled with the subject prior to hospital discharge post fat graft procedure.

1. Limited medical history and physical exam with a limb exam completed by the PI and /or the Co-investigator
2. Adverse Event Reporting (Should an adverse medical event occurred prior to the visit and be reported by the subject, the research team will do due diligence to collect information pertaining to the event through subject report and /or medical record review and /or referring physician report)
3. Collection of subject's medication profile to include prescription and vitamins / supplements, allergies, vital signs (Blood Pressure, Heart rate, respirations, temperature) and collection and distribution of Post-operative Diary Card and Pain Log . The subject will be asked to continue logs if an event/issue persists beyond normal post op healing, until the next post-op visit (POV1)

POSV1-6 (Post-Operative Study Visits 1-6) The following study visits will occur with the study investigator or research team and will take place at 7-21 days (POV1), month 2 (POV2), month 3 (POV3), month 6 (POV4), month 12 (POV5) and two years (POV6) (+/- 2 weeks) after the surgical fat grafting procedure. The duration of time for each visit will be approximately 3-4 hours. All visits will be scheduled by the research coordinator and discussed with the subject prior to the fat graft procedure. The following research procedures will be completed at this visit:

1. Collection of subject's medication profile to include prescription and vitamins / supplements, allergies, vital signs (Temp, HR, Resp, BP) and weight and BMI calculation and post operative pain assessment
2. Limited medical history & physical exam including amputation stump completed by the PI and /or the Co-investigator. The investigator will rate the appearance/volume of the graft site using the limb volume and appearance grading scale
3. Adverse Event Reporting (Should an adverse medical event occurred prior to the visit and be reported by the subject, the

research team will do due diligence to collect information pertaining to the event through subject report and /or medical record review and /or referring physician report)4.

Nutritional Evaluation (POV1) and (POV3) only: Each subject will recall their dietary intake over the 48 hours prior to the visit date to be evaluated for current nutritional habits. Nutritional education will be provided by the research coordinator /co-investigator based on the evaluation of the subject's dietary intake record. This education, if necessary will follow Recommended Daily Allowances (RDA) and American Heart Association (AHA) recommendations. Approximate time estimated 20 minutes.5. Prosthetic and Orthotic: At Visit 2 and/or 3 PO only the subject will be evaluated by the Prosthetic /Orthotics/Occupational therapy team (limited physical exam) in conjunction with the PI to determine weight bearing readiness as well as readiness to obtain a standard of care check socket by their primary prosthetist. The participant's prosthetic device (including check socket and or permanent socket) and any other assistive devices used will be fitted as part of their routine standard of care and will only be documented that the visit happened. The subject will be instructed NOT to wear the prosthetic sockets until seen by research team and/or clearance received to utilize any new prosthetic devices which is anticipated to occur at approximately POV3 or POV4. The subject may be asked to attend an interim visit at 4-5 months PO, if the check socket and permanent socket fabrication fall out of the PO visit 2-3 range. At Post op visit 4 (6 months post op), POV5 (month 12) and POV6 (month 24) the prosthetist and therapist will implement the assessments and select the appropriate assessments based on the participant's functional status, amputation site(s), and assistive technology used. The following assessments are dependent upon the location (upper versus lower extremity) and may or may not be completed depending upon the site of interest.

a. Prosthetics Evaluation Questionnaire (PEQ) is a self-report questionnaire containing 54 questions organized into nine functional domains related to prosthesis-related changes in quality of life. The PEQ was developed to fill the need for a comprehensive self-report instrument for individuals with lower limb loss. (Legro 1998). Psychometric analysis supported the reliability and validity of the PEQ for evaluating the function of the prosthesis and the major health related quality of life domains. The PEQ is estimated to take 15 minutes or less to complete.

b. The 6 Minute Walk Test (6MWT) is a reliable measure of functional capacity, involves a moderate degree of exercise intensity, and is related to a moderate degree to postural control abilities in persons with lower-limb amputations. (Lin S-J, Bose NH, 2007). This 6MWT is estimated to take 20 minutes or less to complete, including the baseline rest period, set-up, and 6 minutes of continuous walking. This test will not be conducted if the participant is not able to functionally ambulate with use of prosthetic device.

c. The Amputee Mobility Predictor (AMP) is a 21 item instrument designed to assess determinants of the lower-limb amputee ability to ambulate. The AMP is estimated to take approximately 15 minutes or less to complete.

d. Lower Extremity Functional Scale (LEFS) is a self-reported questionnaire containing 20 questions about a person's ability to perform everyday tasks. The LEFS is anticipated to take approximately 10 minutes or less to complete.

e. The Disabilities of the Arm, Shoulder, and Hand (DASH) outcome Measure is a 30-item, self-report questionnaire designed to

measure physical function and symptoms in people with musculoskeletal disorders of the upper limb. The DASH is estimated to take approximately 10 minutes or less.f. Functional Mobility Assessment (FMA) is a self-report questionnaire to assess perceived user function related to assistive technology use. The FMA is expected to take approximately 10 minutes or less.g. Prosthetic Device Use History: Compliance with prosthesis use affects activities of daily living (ADLs) as well as impacting social interaction. The participant's prosthetic devices (both pre and post procedure) will be evaluated and a history will be obtained from the participant to determine average daily use and related issues/concerns. This questionnaire is estimated to take approximately 30 minutes for the subject to complete.h. Physical Examination: A physical examination will be conducted to evaluate general UE and LE function and specifically the amputation stump. The stump characteristics will be recorded, including measurements, range of motion, strength, skin integrity/areas of pressure, pain and prosthesis/socket interface. This physical examination is anticipated to take approximately 30 minutes to complete. If upon examination, it is determined that the participant is at increased risk for developing pressure ulcers and/or the participant's current wheelchair and seating is not addressing their needs, they will be referred to the UPMC Center for Assistive Technology for a full assistive technology evaluation per routine clinical care.6. CT Scan with 3D renderings or MRI ( Visit 4 PO, Visit 5 PO and Visit 6 PO).7. All participants who are women of child bearing potential will receive a urine pregnancy dip test. If the test result is positive the subject will not continue to the CT or MRI scan. ( Visit 4 PO, Visit 5 PO and Visit 6 PO)8. Psychosocial assessment (Visit 1 PO, Visit 3 PO, Visit 4 PO, Visit 5 PO and Visit 6 PO) will be conducted satisfaction with surgical outcomes, quality of life and functional outcomes and improvement in self-esteem, psychiatric distress, and psychological coping.9. Structured Clinical Interview for DSM-IV (SCID) (Visit 4, 5, and 6 PO only) to evaluate any change in the presence/absence of psychiatric disorders and will be compared to PGSV1 SCID results. This SCID will take approximately 45-60 minutes of the subject's time to complete.10. 2D Photographs will be collected at each of the post op visits 11. Limb Pain Assessment will be collected at each of the post op visits . 12. Core Needle Biopsy of fat grafting site - POV3 and POV5 only -(this will only be done with subjects where it is determined by the PI that the biopsy will not interfere with the desired outcome of the fat grafting). In subjects where the biopsy is considered to be appropriate, core biopsies will be taken from the area treated with standard fat graft or treated with SVF concentrated fat graft. These samples will be histologically analyzed for differences in vascularity and other evidence of in vivo activity. The samples will be processed within the UPMC system. The research coordinator will provide telephone follow up 48 to 72 hours to the subject post biopsy. This contact is to obtain a subject self report assessment of signs and symptoms of an adverse event post biopsy (i.e., excessive bleeding, redness, extreme tenderness, and potential signs of infection) as a post procedure standard of care safety assessment. Procedures for Study post operative visits #1-12 usually occur on the same day; however, due to coordination of participant's schedules and travel distance the procedures may be performed on different days as long as the completion of the procedures do not exceed a length of 4 days total. In

addition, due to the subjects traveling distances who are enrolled into this trial, we have included a (+/-) of 14 days (2 weeks) for the completion of POVisit 1- Visit 6 as a convenience for the coordination of schedules. Upon completion of POSV 6 and pending any adverse event reporting information received, the subject's participation in this study will be concluded. TELEPHONE INTERVIEWS (20-30min; done by coordinator) Telephone Interviews 1 and 2- The phone interviews will consist of a collection of current medications and any concerns or problems experienced after biopsy ((i.e., excessive bleeding, redness, extreme tenderness, and potential signs of infection) as a post procedure standard of care safety assessment. Telephone Interview 3 - (18 months post operative procedure +/-2 weeks) — This phone interview will consist of a collection of current medications, allergies to update the profiles limb pain subject report assessment including any concerns or problems encountered related to use of a prosthesis .

[reviewer notes-]

## Section 2 - Research Design and Methods

2.8 Does this research study involve the use of any questionnaires, interview or survey instruments?\* Yes

Upload a copy of all materials except for the SCID or KSADS which are on file at the IRB. The use of all instruments must be addressed in question 2.6 and/or question 2.7 (except for an exempt submission where they should be addressed on the appropriate uploaded exempt form).

Name	Modified Date
Diary Card	7/24/2012 3:06 PM
BECK	2/17/2015 2:05 PM
Pain Log	7/24/2012 3:07 PM
QOL Demographics_Brief	2/17/2015 2:13 PM
LEF	3/31/2014 11:48 AM
Prosthetics Usage Questionnaire	7/24/2012 3:05 PM
QOL Demographics	2/17/2015 2:13 PM
SF-36	2/17/2015 2:14 PM

SWAP	2/17/2015 2:08 PM
PHQ-Brief	2/17/2015 2:10 PM
ROSENBERG SEI	2/17/2015 2:11 PM
Pain Assessment Tool V 3.0 (10.12.16)	10/17/2016 12:29 PM
PEQ	7/24/2012 3:03 PM
SAD	2/17/2015 2:09 PM
Functional Mobility Assessment	7/24/2012 3:06 PM
Amputee Mobility Assessment	4/2/2014 1:47 PM
AMP	9/27/2012 1:51 PM
COPE	6/17/2016 9:28 AM
CSQ-8	2/17/2015 2:09 PM
PSSQ	2/17/2015 2:12 PM
DASH	11/15/2013 11:55 AM
PCL-S	2/17/2015 2:11 PM

Previously the name and publisher for commercially available materials were listed in the textbox below but effective 9/1/2015, all materials (except for the SCID and KSADS) must be uploaded using the Add button above.

[reviewer notes~]

## Section 2 - Research Design and Methods

- 2.9 If subjects are also patients, will any clinical procedures that are being used for their conventional medical care also be used for research purposes?\* yes

If Yes, describe the clinical procedures (and, if applicable, their frequency) that will be used for research purposes: Medical record information that will be extracted from the medical chart review is limited to only those items pertaining to the subject's history of the trauma and all surgical procedures, consults, medications, lab values, and culture results leading up to the fat grafting procedure. Pre-procedure blood tests, including but not limited to blood clotting, red blood cell count, electrolytes, and cultures,

history/physical exams of the body (especially the affected limb), MRI and CT scans, menstrual status and/or results of pregnancy testing, and any medical information that could adversely impact the outcome of the fat grafting procedure. Permission to contact the participant's prosthetist may be obtained to identify specific prosthetic devices/components previously trialed as part of routine clinical care as well as new prosthetic devices/components received during the course of the subject's participation in this clinical trial.

2.10 The blood sample question was moved to 2.6.1.

[reviewer notes~]

Section 2 - Research Design and Methods

2.11 What is the total duration of the subject's participation in this research study across all visits, including follow-up surveillance?\* 26-28 months

[reviewer notes~]

Section 2 - Research Design and Methods

2.12 Does this research study involve any type of planned deception? If Yes, you are required to request an alteration of the informed consent process (question 4.7)

\* No

2.12.1 Describe the planned deception:

\*

2.12.2 Provide a justification for this planned deception:

\*

2.12.3 Describe when and how subjects will be debriefed:

\*

[reviewer notes~]

Section 2 - Research Design and Methods



2.13 Does this research study involve the use of UPMC/Pitt protected health information that will be de-identified by an IRB approved "honest broker" system?

\* No

2.13.1 Identify the name of the honest broker system:

2.13.2 Specify the IRB-assigned honest broker system number (e.g., HB123456):

2.13.3 Specify the names of the individuals who will provide the honest broker services:

Last	First	Organization
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There are no items to display

Previous inputted information for Question 2.13.3:

2.13.4 Upload the signed honest broker assurance agreement:

Name	Modified Date
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There are no items to display

[reviewer notes-]

## Section 2 - Research Design and Methods

2.14 Will protected health information from a UPMC/Pitt HIPAA covered entity be accessed for research purposes or will research data be placed in the UPMC/Pitt medical record?\* Yes

If you answer Yes, you are required to submit this study to the Research Informatics Office, Health Record Research Request (R3). Per UPMC Policy HS-RS0005, all research projects that access or involve UPMC electronic protected health information (e-PHI) must be submitted to R3, with the exception of clinical trials that are contracted through the UPMC Office of Sponsored Programs and Research Support (OSPARS). Complete the R3 intake form available at <http://rio.pitt.edu/services>. An R3 representative will conduct a review. You will be notified once your R3 review is complete or if anything further is needed.

Describe the medical record information that will be collected from the UPMC/Pitt HIPAA covered entity and/or the research-derived information that will be placed in the medical records. The medical record information that will be extracted from the medical chart review are only those items pertaining to the subject's history of the trauma and all surgical

procedures, consults, medications, lab values, and culture results leading up to and after the fat grafting procedure. Pre-procedure blood tests, including but not limited to blood clotting, red blood cell count, electrolytes, and cultures, history/physical exams of the body (especially the affected limb), MRI and CT scans, menstrual status and/or results of pregnancy testing, and any medical information that could adversely impact the outcome of the fat grafting procedure. This research study will result in identifiable information that will be placed into the subjects medical records held at UPMC. The nature of the identifiable information resulting from the subject's participation in the this research study that will be recorded in their medical record will be derived from the fat grafting procedure as detailed above. Psychiatric interview information will be entered into the medical record only if it is important to ensure the subject's medical or physical safety.

- 2.14.1 Will protected health information from a non-UPMC/Pitt HIPAA covered entity be obtained for research purposes or will research data be placed in the non-UPMC/Pitt medical record? \* Yes

If Yes, describe how the HIPAA requirements will be met: If the subject is coming from an outside entity, other than a UPMC covered entity, and the patient's medical records accompany the potential subject or be voluntarily sent in anticipation of the visit for the Principal Investigator's screening evaluation. We will look at all records that are provided appropriate to the study and may include the following: all information pertaining to the trauma event and surrounding surgical and medical procedures, prior procedure blood tests (including but not limited to complete blood count (CBC) with Differential and Platelets, comprehensive chemistry panel, urinalysis, and culture results) operative notes, physical therapy assessments, consultations, prosthetic/orthotics evaluation/ history, CT, MRI scans, EKG, Chest X-rays, history and physical exams, and any other information pertaining to the affected injury, limb trauma that could directly affect the outcome of the proposed surgical procedure. Research data will not be placed in non-UPMC/Pitt medical records.

I, J. Peter Rubin, certify that any member of my research team accessing, reviewing and/or recording information from medical records have completed the CITI Privacy & Information Security course or, if completed within the past year, the Internet-Based Studies in Education and Research (ISER) HIPAA for Researchers (Formerly RPF Module 6). The HIPAA certificates must be available for review if audited but do not need to be uploaded into this OSIRIS application.

\* Yes

- 2.14.2 Are you requesting a waiver of the requirement to obtain written HIPAA authorization for the collection of the PHI? \* No

[reviewer notes~]

Section 2 - Research Design and Methods

2.15 Does this research study involve the long-term storage (banking) of biological specimens?

\* No

2.15.1 Broadly describe the intended future use of the banked biological specimens:

2.15.2 Indicate the planned length of storage of the banked biological specimens:

\*

2.15.3 Will biological specimens be stored without identifiers or linkage codes? \*

[reviewer notes~]

Section 2 - Research Design and Methods

2.16 Will research participants be asked to provide information about their family members or acquaintances?

\* No

2.16.1 Describe what information about the third party will be obtained from the participant:

2.16.2 If the information about the third party is of a private nature, can the identity of the third party be readily ascertained or associated with this information?

\*

Describe the private information that will be collected and recorded about the third party:

[reviewer notes~]

Section 2 - Research Design and Methods

2.17 What are the main outcome variables that will be evaluated in this study?

Primary outcomes:Improvement of pain at the amputation site, improved ability to tolerate a prosthesis, and generation of a stable volume of adipose tissue at the amputation site (as measured by clinical assessment by rehabilitation sciences and prosthetics team, quality of life measures, and high resolution imaging). This will be compared between the standard fat grafting group (n=15) and the adipose cell enriched fat grafting group (n=15).Secondary outcomes:Local and systemic complications resulting from fat graft procedure (infection, fat necrosis, hematoma, seroma); basic assays of adipose cell behavior to elucidate the functional properties of adipose cells used for grafting, with correlation to outcomes.

2.18 Describe the statistical approaches that will be used to analyze the study data.

\* Addressed below:

Pain and Serial computed tomography imaging will be performed and measured as parametric data sets before fat grafting and afterwards at various time points using a paired t-test model. Repeated measures analysis of variance will be used to evaluate change over time in all outcome measures. Using standard conventions of  $\alpha=0.05$  and  $\beta=0.8$ , an enrollment of thirty patients may provide sufficient power to detect a Cohen's effect size of about 0.9 which is anticipated to be adequate for detecting clinically meaningful differences in the volume of soft tissue. A composite functional score will be constructed from the prosthetics and occupational therapy evaluations and compared between study groups. The details of this analysis, including which evaluations will be included in the score and relative weight, can be best determined as the study progresses and initial data sets are acquired. Additionally, each assessment score from the specific tests will also be considered individually for comparison.

[reviewer notes~]

## Section 2 - Research Design and Methods

2.19 Will this research be conducted in (a) a foreign country and/or (b) at a site (e.g., Navajo Nation) where the cultural background of the subject population differs substantially from that of Pittsburgh and its surrounding communities? \* No

Note that copies of training records, licenses, certificates should be maintained in the study regulatory binder and are subject to audit by the Research Conduct and Compliance Office (RCCO).

In addition, individuals planning to conduct human subject research outside the United States must complete an optional module on the CITI training website: International Studies. Click [here](#) to access the instruction sheet for accessing optional CITI modules.

- 2.19.1 Address the following for each of the foreign/culturally different sites where this research will be conducted: • Name of site • Name of authorized individual (e.g., IRB Chair) from the local IRB or other human subject protections entity that is responsible for the review and approval of the project; upload approval letter with an English translation, if applicable • Name and qualifications of the site collaborator responsible for the conduct of the research (e.g., site PI) • The anticipated number of subjects that will be enrolled at that site • If Federally funded, provide the Federalwide Assurance number (FWA) assigned to the site \*

Site	Date Modified
There are no items to display	

- 2.19.1.1 Provide a description of the context of cultural norms and local laws and highlight differences between U.S. culture in all areas relevant to your study, including, at a minimum:

- Age of majority of participants to be enrolled
- If study includes minors or decisionally impaired subjects, summarize laws on guardianship
- If your study involves any invasive medical procedure (including blood draws), provide assurance that the individuals undertaking those procedures for research purposes are appropriately credentialed.
- If your study involves the administration of a drug, device or biologic for research purposes, describe the process for shipping, labeling, storing and dispensing, and indicate how these are consistent with all relevant local (and US) laws, including those requiring import / export permits.
- If your study involves collection of biological specimens, describe the process for shipping, labeling, storing and using such samples. Identify any special local consent requirements, and any special permits that may be required by local law.

\*

- 2.19.1.2 Describe any aspects of the local cultural, political or economic climate that might increase the risks of harm for either local participants or researchers. Describe the steps you will take to minimize these risks. UPitt Faculty, Staff, and Students must access the Travel Registry page. Go to [my.pitt.edu](http://my.pitt.edu) and the link is displayed under My Resources.

\*

- 2.19.2 Will all individuals being recruited to participate in this research study be able to read and comprehend English\*

If No, describe how consent will be obtained. Explain provisions for culturally appropriate recruitment and consent accommodations such as, translations or involvement of native language speakers, especially if literacy is not widespread in this country.

- 2.19.2.1 If translated documents are used, upload a signed translator certification form and back translations (if applicable):(Translator Certification Form is available under the Resources tab located to right of this item)

Name	Modified Date
There are no items to display	

- 2.19.3 Will all of the research procedures described in this IRB application be conducted at the foreign/culturally different sites?

\* ☐ ☐ Yes ☐ ☐ No

If No, describe the subset of research procedures to be performed at the sites:

- 2.19.4 To what extent do the local site requirements to protect subject confidentiality and privacy differ from US standards. If applicable, explain how those will be addressed by this research team:\*

- 2.19.5 If the researcher is a student, describe how the student will communicate with the advisor during the conduct of the research and how the advisor will oversee the research:

[reviewer notes~]

## Section 2 - Research Design and Methods

- 2.21 Will this research study be conducted within a nursing home located in Pennsylvania?

\* No

- 2.21.1 Does this research involve a medical procedure or an experimental treatment?\*

2.21.2 Does the research study involve the exposure of nursing home residents to pain, injury, invasion of privacy, or ask the resident to surrender autonomy?

\*

If Yes to either question, upload the Pennsylvania Department of Health approval letter. 28 PA Code Section 201.29 (o) specifies that prior to the initiation of research, and in addition to IRB approval, any study that includes experimental research or treatment conducted in a nursing home must be approved by the Pennsylvania Department of Health. A signed consent form from nursing home resident-subject is also required.

Name Modified Date

[reviewer notes~]

### Section 3 - Human Subjects

3.1 What is the age range of the subject population? 18 years of age and older.

3.2 What is their gender? \* Both males and females Provide a justification if single gender selected:

3.3 Will any racial or ethnic subgroups be explicitly excluded from participation? \* No If Yes, identify subgroups and provide a justification:

3.4 For studies conducted in the U.S., do you expect that all subjects will be able to comprehend English?

\* Yes

If No, identify what languages will be understood by subjects and describe your plan to manage communication with non-English speaking subjects during all phases of the study:

3.4.1 If translated documents are used, upload a signed translator certification form and back translations (if applicable):

Name	Modified Date
There are no items to display	

[reviewer notes-]

## Section 3 - Human Subjects

3.5 Participation of Children: Will children less than 18 years of age be studied?\* No

If No, provide a justification for excluding children: Our target population for this study is military and civilian, who are restricted to age 18 years and above. Children will be excluded because any active growth surrounding an amputation site will obscure our ability to detect changes due the surgical procedure over time.

3.5.1 Specify the age range of the children to be studied. (Check all that apply below:)

\*

Choices
There are no items to display

3.5.2 Provide a rationale for the specific age ranges of the children to be studied:

3.5.3 Describe the expertise of the study team for conducting research with children within this age range:

3.5.3.1 Have you obtained the following clearances from all research staff who may have direct contact with children under the age of 18? Direct contact under the law includes face-to-face, and telephonic or electronic, contact with minors. Please see the Child Clearances guidance document for further explanation?

Pennsylvania Department of Public Welfare Child Abuse History Clearance; Pennsylvania State Police Criminal Record Check; and FBI Criminal Background Check

Note: If No, once all clearances are obtained, a modification must be submitted. If you selected N/A, please explain:

It is important to note that "direct contact" refers not only to face-to-face meetings but also extends to communication via phone (including text messaging), social media or internet. Direct contact also includes the care, guidance, supervision or control, or



routine interaction with, minors. Conversely, a participating investigator or support staff member who does not have direct contact, either electronically or in person, with children does not need to obtain clearances (e.g., statistician, non-clinical laboratory personnel, etc.). If your research study provides babysitting services, the babysitters must have the required child clearances. \* Note: It is the responsibility of the principal investigator to ensure that all research staff have these clearances prior to any interaction with children. Contact Human Resources at 412-624-8150 for assistance with this process.

3.5.4 Describe the adequacy of the research facilities to accommodate children within this age range:\*

3.5.5 Permitted Categories of Research: The Federal Policy and FDA regulations governing human subject protections specify that research involving children must fall into one of the following permitted categories.

\*

45 CFR 46.406

The risk represents only a minor increase over minimal risk.

The research procedures present experiences to the subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.

The research procedures are likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for understanding or amelioration of the subjects' disorder or condition.

45 CFR 46.407

The risk is justified by the anticipated benefit to the subjects; and the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

Provide a justification which must address all considerations related to the designated category of research:

[reviewer notes~]

Section 3.0 - Human Subjects

3.6 Does this research study involve prisoners, or is it anticipated that the research study may involve prisoners? \* No

3.6.1 The Federal Policy and FDA regulations specify that research involving prisoners must fall into one of the following permitted categories.

\*

\*Provide a justification for your designation:

General Requirements: The Federal Policy and FDA regulations specify that research involving prisoners must also conform to each of the following general requirements. Describe how your study meets each of the following regulations.

3.6.2 Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities, and opportunity for earnings in the prison are not of such a magnitude that the prisoner's ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired. [45 CFR 46.305 (a)(2)]\*

3.6.3 The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers.[45 CFR 46.305 (a)(3)] \*

3.6.4 The procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners.[45 CFR 46.305 (a)(4)] \*

3.6.5 Information regarding the research is presented to the potential prisoners-subjects in a language which is understandable to them.[45 CFR 46.305 (a)(5)]\*

3.6.6 Adequate assurance exists that the parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.[45 CFR 46.305 (a)(6)] \*

3.6.7 Where there may be a need for follow-up examination or care of the prisoners-subjects after the end of their participation in the research, adequate provision has been made for such examination or care; taking into account the varying lengths of individual prisoners' sentences, and the prisoners have been informed of this fact. [45 CFR 46.305 (a)(7)]. \*

[reviewer notes~]

### Section 3 - Human Subjects

3.7 Will pregnant women be knowingly and purposely included in this research study?

\* No

General Requirements: The Federal Policy [45 CFR 46, Subpart B] specify that research involving pregnant women and/or fetuses must also confirm to each of the following criteria. Describe how your study meets each of the requirements.

3.7.1 Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses. [45 CFR 46.204 (a)] [Include references]\*

3.7.2 The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the women or the fetus; or, if there is no such prospect of direct benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means. [45 CFR 46.204 (b)]

\*

3.7.3 Any risk is the least possible for achieving the objectives of the research. [45 CFR 46.204 (c)]\*

3.7.4 No inducements, monetary or otherwise, will be offered to terminate the pregnancy. [45 CFR 46.204 (h)]

\*

3.7.5 Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy. [45 CFR 46.204 (i)]

\*

3.7.6 Individuals engaged in the research will have no part in determining the viability of a neonate.[45 CFR 46.204 (j)]

\*

[reviewer notes~]

### Section 3 - Human Subjects

3.8 Does this research study involve neonates of uncertain viability or nonviable neonates?

\* No

General Requirements: The Federal regulations [45 CFR 46.205] specify that research involving neonates of uncertain viability and nonviable neonates must conform to each of the general requirements. Describe how each of the following requirements will be met.

3.8.1 Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates (include references). [45 CFR 46.205 (a)(1)] \*

3.8.2 Individuals engaged in the research will have no part in determining the viability of the neonate. [45 CFR 46.205 (a)(3)]\*

3.8.3 Does this research study involve neonates of uncertain viability? [45 CFR 46.205(b)]\*

3.8.3.1 The Federal regulations specify that, until it is ascertained whether or not a neonate is viable, a neonate may not be involved in research unless one of the following conditions is met. \*

\*Provide a justification for your selection:

3.8.4 Does this research study involve nonviable neonates? [45 CFR 46.205(c)]\*

General Requirements: The Federal regulations specify that, after delivery, a nonviable neonate may not be involved in research unless each of the following additional conditions are met [45 CFR 46.205(c)].

3.8.4.1 Vital functions of the neonate will not be artificially maintained. [45 CFR 46.205 (c)(1)]\*

- 3.8.4.2 The research will not terminate the heartbeat or respiration of the neonate. [45 CFR 46.205 (c)(2)]\*
- 3.8.4.3 There will be no added risks to the neonate resulting from the research. [45 CFR 46.205 (c)(3)] \*
- 3.8.4.4 The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means. [45 CFR 46.205 (c)(4)]\*

[reviewer notes~]

### Section 3 - Human Subjects

- 3.9 Fetal Tissues: Does this research involve the use of fetal tissues or organs?\* No

General Requirements: In accordance with the Pennsylvania Abortion Control Act, fetal tissues or organs may only be obtained for use in research subsequent to obtaining the written informed consent of the mother. The Pennsylvania Abortion Control Act specifies that research involving the use of fetal tissue or organs must also conform to each of the following requirements. [Indicate how you will conform to each requirement]

- 3.9.1 Informed consent for the research use of fetal tissue derived from an abortion will be obtained separate from, and after, the decision and consent to abort has been made.  
\*
- 3.9.2 No consideration of any kind (i.e., monetary or otherwise) will be offered to the mother in obtaining her consent for the research use of the fetal tissue or organs.  
\*
- 3.9.3 The mother will not be permitted to designate a recipient of the fetal tissue or organs for use in research.  
\*
- 3.9.4 All persons who participate in the procurement or use of the fetal tissue or organs will be informed as to the source of the tissue (e.g., abortion, miscarriage, stillbirth, ectopic pregnancy).

\*

[reviewer notes~] ---&gt;

## Section 3.0 - Human Subjects

3.10 What is the total number of subjects to be studied at this site, including subjects to be screened for eligibility? Note: The number below is calculated by summing the data entered in question 3.11. Any additions or changes to the values entered in 3.11 will be reflected in 3.10.\* 70

3.11 Identify each of the disease or condition specific subgroups (include healthy volunteers, if applicable) that will be studied.

Click on the "Add" button and specify for each subgroup:

- 1) how many subjects will undergo research related procedures at this site; and
- 2) if applicable, how many subjects will be required to undergo screening procedures (e.g., blood work, EKG, x-rays, etc.) to establish eligibility. Do Not include subjects who will undergo preliminary telephone screening.\*

	Subgroup	Number to undergo research procedures	Number to undergo screening procedures
View	amputees receiving TGI cell enriched processing fat grafting	15	35
View	amputees receiving standard fat grafting	15	35

There are no items to display

3.12 Provide a statistical justification for the total number of subjects to be enrolled into this research study at the multicenter sites or this site.\* Described below: The proposed study is designed as a single center, prospective, randomized pilot outcome study to exam the effect of two (2) fat grafting procedures on either upper or lower extremity amputations. The major endpoint is pain at the amputation site and the ability to wear prosthesis. To the best of our knowledge, there are no clinical reports that describe quantitatively the change in extremity amputation site pain to fat grafting over time. This is especially true in comparing an upper extremity amputation site [low weight bearing

site] compared to a lower extremity amputation site [high weight bearing site]. Therefore we have provided an adequate number of potential subjects to be screened and enrolled to study pain at the amputation site with these different treatments. For this study, 70 potential subjects will be screened and enrolled with a goal of 30 subjects to undergo the operative autologous fat grafting procedure. Each subject will be assigned to a specific randomization block based on whether they have an upper or lower extremity amputation. Each randomization block will have six (6) subjects. There will be a computer generated randomization assignment for each subject to receive the surgical intervention that will be either fat grafting alone or fat grafting with stromal vascular fraction cells. A randomization table will be generated using a software program [Research Randomizer, Version 3.0]. This will allow for statistical examination between the two different treatments within each randomization block (3 subjects receive fat graft and 3 subjects receive fat graft with stromal vascular fractions). There will be five (5) randomization blocks for a total of thirty (30) subjects. Therefore based on the prevalence of subjects who have either the upper and lower extremity amputation, there may be a range from one (1) to five (5) randomization blocks for one of the treatment groups. We expect that there will be a higher number of lower extremity amputees who call-in or are referred for screening. The proposed block randomization scheme will be flexible to handle various numbers of either upper or lower extremity amputations as well preserve the statistical rigor for testing.

[reviewer notes~]

### Section 3.0 - Human Subjects

- 3.13 Inclusion Criteria: List the specific criteria for inclusion of potential subjects.
- 1.) Aged 18 years or older and able to provide informed consent
  - 2.) Has an amputation with pain that limits the fitting and use of a prosthesis, despite maximal attempts to refit the prosthesis and/or change the design of the prosthesis and/or Have an amputation with pain that limits the use of an assistive device(s) despite maximal attempts to change the design of use of the device
  - 3.) Be at least 3 months post-injury or post-surgery (from surgical procedures) so that acute edema is resolved
  - 4.) Soft tissue deficiencies are noted at amputation stump and are covered by intact skin
  - 5.) Willing and able to comply with follow up examinations, including radiographic studies
  - 6.) Subjects who are, in the opinion of the Investigator, able to understand the study, comply with the study design and are willing to return to the clinic for all the research required follow-up visits
  - 7.) Subjects with residual limb problems including upper and lower limb loss, and/or individuals with partial hand, partial foot and more proximal injuries.
  - 8.) Subjects with Intolerability that may include inappropriate soft tissue padding, soft tissue coverage and pain that doesn't allow the consistent wearing of a prosthetic socket. (This may include excessive pain, inability to achieve adequate suspension of prosthesis on the individual, continual skin breakdown, excessive pressure/shear on skin, soft tissue, nerves, scars, etc.) and/or Subjects with

Intolerability that limits use of an assistive device(s) that aid mobility of daily living activities involving the functional use of affected limb.9.) Subjects who are unable to consistently wear a prosthetic socket must have received a minimum of 3 months of unsuccessful prosthetic fitting trials. This will include a minimum of at least 5 different socket adjustments. This can include re-casting the residual limb, providing pressure relieves within the socket, changing the alignment of the prosthetic components to alter ground reactive forces, and adding padding to pressure sensitive areas. Likewise, subjects using assistive devices must have received a minimum of 3 months of unsuccessful assistive device adjustments. This information pertaining to the history of prosthetic fit attempts may be received from referral physician, prosthetics and/or orthotics direct report and/or subject self-report and/or medical record review.10.) Subjects should have an approximate range of the defect volume between 5cc to as much as 300cc. if the defect is a very local soft tissue deficiency over a pressure point. (The volume of the defect correlates with moderate or severe intolerability of the prosthesis)11.) Subjects must have a current relationship with a prosthetist and/or Assistive device Technician. 12.) Subjects who have a history of cancer to an affected limb that results in a surgical amputation maybe eligible.13.) Subjects who have a history of embolus to the affected limb that results in surgical amputation maybe eligible

- 3.14 Exclusion Criteria: List the specific criteria for exclusion of potential subjects from participation.1. Age less than 18 years2. Patient has inability to provide informed consent process.3. Amputated limb area intended for treatment has open wounds or tunneling4. Active drainage or active infection unresolved with one course of antibiotic treatment.5. Active infection anywhere in the body6. Diagnosed with cancer within the last 12 months and /or presently receiving chemotherapy or radiation treatment7. Known coagulopathy symptoms /diagnosis8. Systemic disease that would render the fat harvest and injection procedure, along with associated anesthesia, unsafe to the patient (e.g., scleroderma, lupus, vasculatures, collagen disease etc.)9. Pregnancy10. History of Diabetes Mellitus11. History of severe peripheral arterial disease12. Subjects with an Axis I DSM-IV diagnosis (e.g., Schizophrenia, Bipolar disorder) who are found to be clinically (i.e. medically) unstable at baseline. Individuals who manifest either: 1) evidence of currently active alcohol or psychoactive drug abuse or dependence on the SCID interview, or 2) a GAF score of 40 or lower due to any acute psychiatric symptomatology (e.g. suicidality, psychosis, severe depression or mania) will be reviewed by the Co-I for Psychosocial Assessment with the PI for determination of possible medical instability. Final determination of medically unstable status will be made by the PI on the basis of overall medical status and appropriateness for medical procedures; the patient may be considered ineligible for study participation per the Physician's discretion. 13.) Subjects with abnormal blood biochemistry or any other abnormal laboratory finding considered clinically significant in that it would deem the subject inappropriate for surgical procedures. This criterion will help to exclude subjects with severe nutritional deficiency, anemia, coagulopathy, renal and liver dysfunction, diabetes, and peripheral vascular



disease, as determined by the investigator (i.e. CBC with Differential, platelets, comprehensive metabolic panel to include electrolytes, bun/creatinine, liver function test and coagulation tests). As general safety measures, we will exclude patients with lab values listed below: Hct less than 30% INR greater than 1.8 Creatinine greater than 2.0 Bilirubin within the upper limit of normal Liver function tests (ALT, AST) greater than 2 times upper limit Albumin less than 2.0 Platelets less than 70 14) Subjects who per the clinical discretion of the investigator, would not be appropriate for the study. (e.g. a potential medication and/ or medical diagnosis that is not captured in above exclusion, but which could render the subject's participation in the study unsafe, or would have an adverse effect on fat metabolism or fat healing).

- 3.15 Will HIV serostatus be evaluated specifically for the purpose of participation in this research study? \* No If Yes, provide a justification:

[reviewer notes~]

#### Section 4 - Subject Recruitment and Informed Consent Procedures

- 4.1 Select all recruitment methods to be used to identify potential subjects:

Advertisements

Pitt + Me

Other Strategies: Described below

There are no items to display

#### Advertisements

Upload the advertisements for review:

Name	Modified Date
Study FLYER UL	9/12/2017 12:52 PM
TV advertisement script 7.10.2015	7/10/2015 1:12 PM
AMP 30 Flyer 9.13.2017	9/19/2017 1:13 PM
Trialspark questionnaire	9/13/2017 7:59 AM

Amp 30 Telephone Script	7/20/2015 4:23 PM
TrialSpark landing page	9/13/2017 7:58 AM
Pitt+Me	3/23/2017 12:12 PM
AMP 30 audio visual TV Advertisement	9/8/2015 11:27 AM
PITT+ME video	9/12/2017 12:49 PM
TrialSpark Ad Preview	9/13/2017 8:00 AM

#### Honest Broker

Identify the name of the honest broker system and name of the specific individuals who will provide those services:

Specify the IRB-assigned honest broker system number (e.g., HB123456):

Upload the signed honest broker assurance agreement:

Name	Modified Date
There are no items to display	

#### Recruitment Letters and Scripts

Upload recruitment letters/scripts/text:

Name	Modified Date
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#### Research Registry

List the IRB approval number and title for each registry source:

- 4.2 Provide a detailed description of your recruitment methods, including identifying and initiating contact with participants:
- i. Dr. Rubin has developed a very close working relationships with Colonel Paul F. Pasquina, MD United States Army Medical Corps; Chief of the Integrated Department of Orthopaedics and Rehabilitation, Walter Reed National Military Medical Center. Col. Pasquina is responsible for the medical care of a significant number of amputated military personnel. He has already identified a number of potential candidates and will continue to actively assist in referring patients for the study. Given the high incidence of amputations from recent conflicts (over 1,100 patients), we anticipate that a majority of our subjects will be wounded warriors, and has communicated directly his support of this proposal. If the potential subject is referred to Dr. Rubin's practice for participation for this study, the initial introduction is from Dr. Pasquina and/or his staff member. If the patient wants to inquire further, a referral to Dr. Rubin for a more comprehensive introduction to the study is completed. The introduction of the study is documented in the medical record of the primary practice via written or document stickers which have been provided to local referral sources. Medical records may be sent from Dr. Pasquina and/or the referring MD or hand carried by the patient for Dr. Rubin's review at the time of the potential subject's visit. The purpose of this process is for discussion with the potential subject at the time of the visit, not for identification purposes / recruitment prior to the subject's arrival to Dr. Rubin's Plastic surgery practice.
- ii. Even in light of the strong relationship with military physicians treating amputees, we were advised by the military to also consider civilian subjects in order to accelerate the pace of the scientific investigation. If successful, the overlying goal is to transfer this technology to all Department of Defense facilities and physicians treating wounded warriors and other military and civilian medical care centers. Potential subjects military and civilian will be recruited using social media, advertisement (see section 4.1 for advertisements) to be placed throughout the Oakland, greater Pittsburgh area and nationally via our existing contacts with military and civilian support groups, Plastic surgery clinics/ Physician's offices local and national and throughout the University of Pittsburgh Medical Center facilities who treat potential subjects that may meet the study criteria. In addition, subjects may make initial contact with the PI and/or research staff through their accessing the UPMC Center for Innovation in Restorative Medicine's website and /or other social media methods used for subject recruitment to this clinical trial. Potential subjects may also be identified through the registration of this study with (Pitt+Me) formerly known as the CTSI Research Participant Registry. Pitt+Me is a program of the University of Pittsburgh's Clinical and Translational Science Institute (CTSI) that advertises thru social media and engages researchers, patients, and volunteers from the Greater Pittsburgh community as partners in research. Another method of social media recruitment is with the use of "TrialSpark" which is a data-driven, recruiting system. It uses data, analytics, machine-learning and social media to target certain demographics using social media ads. If a participant clicks on the ad, they are brought to a study landing page that contains study information. If interested in

participating, they have the option to register and complete a prescreen to see if they are eligible. For participants who register, their contact information (name, phone number) are stored in a backend system so that study teams can track contacts and eligibility. It stores information in a HIPAA compliant manner which will be described in more detail in section 5.15. Comments on the Facebook ads are not able to be disabled however they will be monitored by TrialSpark and deleted on a regular basis. Potential participants may learn about this study on clinicaltrials.gov and through postings within the military community (active commission and retired). If the potential subject is responding to an advertisement/posting within a military web-based network or through the above mentioned sources, the potential subject is requesting to be evaluated for the purpose of participation in this study and no records are reviewed prior to study consent or registry consent being obtained. The potential subject will call the research coordinator in response to the advertisement. The research coordinator, utilizing a telephone script will obtain and document into the research binder, the verbal consent of the potential subject for participation for the pre-screening activity. The research coordinator will only pre-screen potential subjects for eligibility criteria by phone. The research coordinator will also obtain information specific to the registration of the potential subject for the screening visit. If the potential subject meets this criteria their information will be reviewed with the PI for further action. The PI will make a final determination on continuing the evaluation process and the potential subject will be contacted for further coordination of a screening visit. It is common practice for other plastic surgeons and physicians to refer patients to Dr. Rubin at this tertiary care center. Dr. Rubin, through clinical conferences and discussions with a variety of clinical services and referral sources, has facilitated awareness of this study. If the potential subject is referred to Dr. Rubin's practice for participation for this study, the initial introduction is from the physician or clinical care team who is known to the potential participant. If the patient wants to inquire further, a referral to Dr. Rubin for a more comprehensive introduction to the study is completed. The introduction of the study is documented in the medical record of the primary practice via written or document stickers which have been provided to local referral sources. Medical records may be sent from the referring MD or hand carried by the patient for Dr. Rubin's review at the time of the potential subject's visit. The purpose of this process is for discussion with the potential subject at the time of the visit, not for identification purposes / recruitment prior to the subject's arrival to Dr. Rubin's Plastic surgery practice.

Note: Questions jump from 4.2 to 4.6 as questions 4.3-4.5 have been removed and the information is now captured in 4.1

[reviewer notes~]

Section 4 - Subject Recruitment and Informed Consent Procedures

4.6 Are you requesting a waiver to document informed consent for any or all participants, for any or all procedures? (e.g., a verbal or computerized consent script will be used, but the subjects will not be required to sign a written informed consent document. This is not a waiver to obtain consent.

\* Yes

4.6.1 Identify the specific research procedures and/or the specific subject populations for which you are requesting a waiver of the requirement to obtain a signed consent form.

Addressed below:

If not all, identify the specific procedures and/or subject populations for which you are requesting a waiver: Telephone screening procedure in response to advertisement/posters/flyers. The waiver for documentation of informed consent is being requested only for phone screening procedures for the introduction of the study and evaluation of inclusion and exclusion criteria.

4.6.2 Indicate which of the following regulatory criteria is applicable to your request for a waiver of the requirement to obtain a signed consent form.

45 CFR 46.117(c)(2)

45 CFR 46.117(c)(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

45 CFR 46.117(c)(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

4.6.2.1 Address why the specific research procedures for which you are requesting a waiver of the requirement to obtain a signed consent form present no more than minimal risk of harm to the research subjects:

The telephone screening process within the research study present no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. We believe the information being obtained

during the screening phone call is the same type of information that would be collected on patients setting up a routine well-visit appointment.

- 4.6.2.2 Justify why the research listed in 4.6.1 involves no procedures for which written informed consent is normally required outside of the research context:

The information collected during the screening phone call is a review of inclusion/exclusion criteria, introduction of the study, and involved the same type of information that would be collected on patients setting up a routine well-visit appointment. If the subject does not meet inclusion criteria, all the information collected during the telephone screening will be destroyed and the subject will be informed of this activity at the time of the phone screening.

- 4.6.3 Address the procedures that will be used and the information that will be provided (i.e., script) in obtaining and documenting the subjects' verbal informed consent for study participation:

Potential subjects will call the research coordinator in response to the advertisement. The research coordinator will read from the screening script with the pre screening criteria being reviewed. If the potential subject meets this criteria the potential subject's information will be reviewed with the PI for further action. The PI, with input from the study team, will make a final determination on continuing the evaluation process and the potential subject will be contacted for further coordination of a screening visit. Upon completion of the telephone interview, qualified and interested subjects will be instructed to come to the Aesthetic Surgery Center for the scheduled screening visit. At the time of the screening visit if the potential subject, after review of the informed consent document and upon resolution of any questions, then verbalizes continued interest in study participation, the principal investigator or co-investigator who is on the Investigational Review Board (IRB) approved research protocol and consent documents, and is a physician will obtain subject signature. The physician will then sign the Certification of Informed Consent Statement ensuring a Health Insurance Portability and Accountability Act (HIPAA)-compliant informed consent document for the study, thereby minimizing the possibility of coercion and undue influence. No research related activities would be conducted until a fully executed informed consent document is obtained.

Upload Scripts:

Name	Modified Date
AMP30 Telephone Screening Script	7.2.15 7/2/2015 11:27 AM

[reviewer notes~]

Section 4 - Subject Recruitment and Informed Consent Procedures

4.7 Are you requesting a waiver to obtain informed consent or an alteration of the informed consent process for any of the following?

\* No

4.7.1 If Yes, select the reason(s) for your request:

There are no items to display

General Requirements: The Federal Policy [45 CFR 46.116 (d)] specifies in order for a waiver of consent to be approved, the request must meet four criteria. For each request, you will be asked to provide a justification addressing how each of these criterion is met.

Medical record review for the identification of potential subjects:

The research involves no more than minimal risk to the subjects; [45 CFR 46.116 (d)(1)]

The waiver or alteration will not adversely affect the rights and welfare of the subjects;[45 CFR 46.116 (d)(2)]

The research could not practicably be carried out without the waiver or alteration;[45 CFR 46.116 (d)(3)]

Whenever appropriate, the subjects will be provided with additional pertinent information after participation; [45 CFR 46.116 (d)(4)]

Review of identifiable medical records: [Note: A waiver of HIPAA Authorization must be requested (2.14.2)] Include the approximate number of medical records and/or specimens that will be accessed and enter -1 in question 3.11 for the number of subjects to be enrolled.

The research involves no more than minimal risk to the subjects;[45 CFR 46.116 (d)(1)]

The waiver or alteration will not adversely affect the rights and welfare of the subjects;[45 CFR 46.116 (d)(2)]

The research could not practicably be carried out without the waiver or alteration;[45 CFR 46.116 (d)(3)]

Whenever appropriate, the subjects will be provided with additional pertinent information after participation.[45 CFR 46.116 (d)(4)]

#### Parental Permission and/or Child Assent

The research involves no more than minimal risk to the subjects;[45 CFR 46.116 (d)(1)]

The waiver or alteration will not adversely affect the rights and welfare of the subjects;[45 CFR 46.116 (d)(2)]

The research could not practicably be carried out without the waiver or alteration;[45 CFR 46.116 (d)(3)]

Whenever appropriate, the subjects will be provided with additional pertinent information after participation.[45 CFR 46.116 (d)(4)]

#### Alteration of informed consent process

The research involves no more than minimal risk to the subjects;[45 CFR 46.116 (d)(1)]

The waiver or alteration will not adversely affect the rights and welfare of the subjects;[45 CFR 46.116 (d)(2)]

The research could not practicably be carried out without the waiver or alteration;[45 CFR 46.116 (d)(3)]

aWhenever appropriate, the subjects will be provided with additional pertinent information after participation.[45 CFR 46.116 (d)(4)].

#### Other Minimal Risk activity



The research involves no more than minimal risk to the subjects;[45 CFR 46.116 (d)(1)]

The waiver or alteration will not adversely affect the rights and welfare of the subjects;[45 CFR 46.116 (d)(2)]

The research could not practicably be carried out without the waiver or alteration;[45 CFR 46.116 (d)(3)]

Whenever appropriate, the subjects will be provided with additional pertinent information after participation.[45 CFR 46.116 (d)(4)].

4.7.2 Under what circumstances (if any) will you obtain consent from some of these subjects?

[reviewer notes~]

#### Section 4 - Subject Recruitment and Informed Consent Procedures

4.8 Are you requesting an exception to the requirement to obtain informed consent for research involving the evaluation of an 'emergency' procedure?Note: This exception allows research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent.\* No

[reviewer notes~]

#### Section 4 - Subject Recruitment and Informed Consent Procedures

4.9 Upload all consent documents for watermarking:Draft Consent Forms for editing:

Name	Modified Date
RUBIN_AMP 30 ICF (Mod 23 11.7.2018)	11/8/2018 1:19 PM

Approved Consent Form(s):

Name	Modified Date
RUBIN_AMP 30 ICF (Mod 23 11.7.2018)	11/8/2018 1:20 PM

[reviewer notes~]

Section 4 - Subject Recruitment and Informed Consent Procedures

- 4.10 Will all potential adult subjects be capable of providing direct consent for study participation? \* Yes

Indicate why direct consent is not possible:

- 4.10.1 Provide a justification for the inclusion of adult subjects who are unable to provide direct consent for study participation.

- 4.10.2 Specify the criteria used to determine that a potential adult subject is not able to provide direct consent for participation and identify who will be responsible for that determination.

- 4.10.3 Will you obtain the potential adult subject's assent for study participation?

\*

If No, provide a justification for not obtaining assent:

- 4.10.4 Identify who will provide proxy consent for the participation of the decisionally impaired adult:

[reviewer notes~]

Section 4 - Subject Recruitment and Informed Consent Procedures

- 4.11 At what point will you obtain the informed consent of potential research subjects or their authorized representative? After performing certain of the screening procedures, but prior to performing any of the research interventions/interactions

If Other, address below:

- 4.11.1 Address why you feel that it is acceptable to defer obtaining written informed consent until after the screening procedures have been performed. We have requested a waiver for telephone pre-screening for all potential subject who call in to the center inquiring to the study. This pre-screen phone script allows defers informed consent only for questions pertaining to minimal eligibility criteria. This eliminates an unnecessary trip for the

potential subject (many of whom are out of state) if they do not meet minimal eligibility criteria (examples 18 years of age or older, traumatic injury).

- 4.11.2 Taking into account the nature of the study and subject population, indicate how the research team will ensure that subjects have sufficient time to decide whether to participate in this study. In addition, describe the steps that will be taken to minimize the possibility of coercion or undue influence.

A screening visit will be scheduled during the telephone pre-screening conversation with the research coordinator and the potential subject. This screening visit will take place at UPMC Aesthetic Plastic Surgery Center located at 3380 Boulevard of the Allies, Suite 158, Pittsburgh Pa. 15213 and will include review of the informed consent. The study investigator or co-investigator will discuss with the subject the nature of the research study, design schema, the risks and benefits, cost and payments and rights as a research subject participant. The potential subject will review the informed consent document allowing ample time to review all information and ask questions. Should the potential subject wish to take the consent and review it outside of the office setting or discuss with other family, medical personnel he/she will be able to leave the office and return at a later date. The study investigator will provide the potential subject a private area to conduct this informed consent document review prior to signing the informed consent. After this detailed discussion of the study and conclusion of any and all questions, the study investigator, who is a physician, will obtain informed consent. The research coordinator will document the consenting process into the research chart and prior to beginning any research activities provide a copy of the fully executed informed consent document to the subject for his or her records. No research related procedures will be performed before the informed consent has been obtained.

[reviewer notes~]

#### Section 4 - Subject Recruitment and Informed Consent Procedures

- 4.12 Describe the process that you will employ to ensure the subjects are fully informed about this research study. \* Addressed below: This description must include the following elements:

who from the research team will be involved in the consent process (both the discussion and documentation);

person who will provide consent or permission;

information communicated; and

any waiting period between informing the prospective participant about the study and obtaining consent

In addition, address the following if applicable based on your subject population:

process for child assent and parental permission

continued participation if a child subject turns 18 during participation

process for obtaining proxy consent and assent for decisionally impaired subjects

continued participation if subject regains capacity to consent

The study investigator or co-investigator will discuss with the subject the nature of the research study, design schema, the risks and benefits, cost and payments and their rights as a research subject. The potential subject will review the informed consent document allowing ample time to review all information and ask questions. The study investigator will provide the potential subject a private area to conduct this study document review prior to signing the informed consent. After this detailed discussion of the study and conclusion of any questions, the study investigator, who is a physician, will obtain informed consent. The research coordinator will document the consenting process and prior to beginning any research activities provide a copy of the fully executed informed consent document to the subject for his or her records. If a re-consenting process is required based on regulatory guidance, the subject will be re-consented at their next scheduled visit or at an interim visit determined to be necessary for subject safety. The research member will highlight all changes with the subject while providing opportunity for the subject to review these changes at their leisure and make an informed decision to continue or discontinue study participation based on these changes

4.13 Are you requesting an exception to either IRB policy related to the informed consent process?

For studies involving a drug, device or surgical procedures, a licensed physician who is a listed investigator is required to obtain the written informed consent unless an exception to this policy has been approved by the IRB

For all other studies, a listed investigator is required to obtain consent (Note: In order to request an exception to this policy, the study must be minimal risk)

\* No

If Yes, provide a justification and describe the qualifications of the individual who will obtain consent:

- 4.14 Will you inform research subjects about the outcome of this research study following its completion?\* No If Yes, describe the process to inform subjects of the results:

[reviewer notes~]

### Section 5 - Potential Risks and Benefits of Study Participation

- 5.1 Describe potential risks (physical, psychological, social, legal, economic or other) associated with screening procedures, research interventions/interactions, and follow-up/monitoring procedures performed specifically for this study: \*

View	Research Activity:	Chest X-ray
	Common Risks:	The chest x-ray is one of the lowest radiation exposure medical examinations performed today. The effective radiation dose from this procedure is about 0.1 mSv, which is about the same as the average person receives from background radiation in 10 days.
	Infrequent Risks:	No Value Entered
	Other Risks:	No Value Entered
View	Research Activity:	Clinical Interview (SCID)and psychosocial evaluations
	Common Risks:	A feeling of emotional discomfort for the participant while answering questions during the interview process or when answering the psychological questionnaires
	Infrequent Risks:	No Value Entered
	Other Risks:	No Value Entered
View	Research Activity:	Core Needle Biopsy
	Common Risks:	Bleeding: It is possible, though unusual to experience a bleeding episode during or after this procedure. Bruising

		may result after the biopsy due to capillary interruption, Redness, swelling, pain may result from the biopsy site.
	Infrequent Risks:	In rare cases: Infection is unusual after this biopsy procedure, should infection occur, additional treatment including antibiotics or surgery may result. Scar: the skin when healing occurs at the biopsy area may result in scarring.
	Other Risks:	Risk of nerve or vessel damage, due to alterations in the anatomy of this type of injury, reaction Lidocaine injected locally for the biopsy.
View	Research Activity:	CT Scans
	Common Risks:	No Value Entered
	Infrequent Risks:	No Value Entered
	Other Risks:	This study will involve exposure to radiation. The amount of radiation exposure that each patient will receive will be about 1.3 rem per scan (a total of 5.2 rem) with minimum exposure of other areas of the body. There is no minimum amount of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations or cancer. However, the risk associated with the amount of radiation exposure is felt to be low and comparable to everyday risks.
View	Research Activity:	Electrocardiogram (EKG)-
	Common Risks:	Irritation or redness at the sites of electrode patch placement. EKG is performed as necessary for preoperative screening, based upon medical history and UPMC anesthesia guidelines
	Infrequent Risks:	No Value Entered
	Other Risks:	No Value Entered

View	Research Activity:	Medical Record Review
	Common Risks:	No Value Entered
	Infrequent Risks:	Participation in this research study does involve the potential risks of a breach of confidentiality of the medical record information and associated privacy of the participants. 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.
	Other Risks:	No Value Entered
View	Research Activity:	MRI
	Common Risks:	No Value Entered
	Infrequent Risks:	No Value Entered
	Other Risks:	MRI uses a strong magnetic field and there is a risk of the scanner attracting metallic objects. Certain conditions will exclude you from having a MR study, including the presence or suspected presence of a heart pacemaker, aneurysm clip, ear implant, IUD, shrapnel or metallic fragments in or on the body or eyes, neuro-stimulators, or other metal devices. Dental fillings do not present a problem with MRI. No other serious effects have been reported from being in the 1.5 Tesla magnet, although vertigo (e.g., dizziness and nausea) has been reported at higher field strengths. To minimize these risks, you will be carefully screened for metallic objects that are in your body or your possession before entering the magnet room. The MRI and CT scans require you to lay still or flat in a small confined space for period of time, you may experience a feeling of becoming closed in or

		uncomfortable (claustrophobic). Should this experience occur you can immediately contact the technician and stop the procedure.
View	Research Activity:	Photographs
	Common Risks:	There may be feelings of embarrassment during the photographs
	Infrequent Risks:	Loss of Confidentiality
	Other Risks:	No Value Entered
View	Research Activity:	Prosthetic, Orthotic, and occupational therapy evaluations
	Common Risks:	No Value Entered
	Infrequent Risks:	During evaluation process, there is a risk that the patient may experience mild muscle discomfort/ pain, or muscle strain. These risks will be minimized by providing detailed explanations of the assessment technique prior to evaluation, allowing all evaluation activities to be stopped at any time. Subjects will be informed that they will need to communicate any discomfort that they experience during these evaluation sessions.
	Other Risks:	No Value Entered
View	Research Activity:	Risk of Breach of Confidentiality
	Common Risks:	No Value Entered
	Infrequent Risks:	No Value Entered
	Other Risks:	Participation in this research study does involve the potential risks of a breach of confidentiality of the medical record information and associated privacy of the participants. The study investigators will take steps to reduce these risks by: 1) removing direct participant



	<p>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.</p>
View	<p><b>Research Activity:</b> Surgical Anesthesia</p>
	<p><b>Common Risks:</b> General anesthesia affects the whole body; it is more likely to cause side effects than local or regional anesthesia. Nausea, vomiting side effects of general anesthesia are minor and can be easily managed</p>
	<p><b>Infrequent Risks:</b> Aspiration during anesthesia and surgery is very uncommon. General anesthesia suppresses the normal throat reflexes that prevent aspiration, such as swallowing, coughing, or gagging. Insertion or removal of airways may cause respiratory problems such as coughing; gagging; or muscle spasms in the voice box, or larynx (laryngospasm), or in the bronchial tubes in the lungs (bronchospasm). Insertion of airways also may cause an increase in blood pressure (hypertension) and heart rate (tachycardia). Other complications may include damage to teeth and lips, swelling in the larynx, sore throat, and hoarseness or temporary or permanent vocal cord damage caused by injury or irritation of the larynx. Although all types of anesthesia involve some risk, major side effects and complications from anesthesia are uncommon. Some people who are going to have general anesthesia express concern that they will not be completely unconscious but will "wake up" and have some awareness during the surgical procedure. Awareness during general anesthesia is very rare because anesthesia specialists devote careful attention and use many methods to prevent this. A rare, potentially fatal condition called malignant hyperthermia (MH) may be triggered by some anesthetics. The anesthetics most commonly associated with malignant hyperthermia include the inhalation anesthetics and the muscle relaxant</p>

	<p>medicines. Other serious risks of General anesthesia: These include changes in blood pressure or heart rate or rhythm, heart attack, or stroke. Death or serious illness or injury due solely to anesthesia is rare and is usually also related to complications from the surgery. Death occurs in about 1 in 250,000 people receiving general anesthesia, although risks are greater for those people with serious medical conditions.</p>
Other Risks:	No Value Entered
Research Activity:	Surgical Fat Grafting procedure
Common Risks:	<p>Change in appearance: Volume over-correction or under-correction of treated area may cause an undesirable appearance. Bruising and swelling may occur secondary to the manipulation of the instruments used to remove and place fat during the liposuction and fat grafting procedures. Skin Contour: While most transferred fat results in a natural feel, it is possible that some or all of the fat may become firm, hard or lumpy. If some of the fat does not survive the transfer it may result in fat necrosis (fat tissue death) causing firmness in the tissue. Oil cysts may also form at the site of the transferred fat. In addition to changes due to trauma, factors such as skin tone, fat deposits, bony prominences, and muscle tone may contribute to asymmetry in amputation stump. Pain: may occur after fat removal or grafting and is expected to resolve within the immediate post operative period.</p>
Infrequent Risks:	<p>Bleeding: It is possible, though unusual to experience a bleeding episode during or after this procedure. Should bleeding occur, it may require emergency treatment to drain accumulated blood (hematoma). Scarring: All invasive procedures produce scars, some more visible than others. Abnormal scars may occur both within the skin and within the deeper tissues. Scars may be unattractive and of different color than the surrounding skin. There is the possibility of visible marks from sutures used to close the wound. Additional treatment including surgery may be</p>

View

needed to treat scarring. Seroma: Although unlikely, a collection of fluid may appear at the site where the fat was removed. This is usually treated by draining the fluid with a needle. Infection: risk of infection may occur secondary to the multiple small incisions from the liposuction procedure. Infection is unusual after this procedure. Should infection occur, additional treatment including antibiotics or surgery may be necessary. Long term effect: subsequent changes in the shape or appearance of the area where the fat was removed or placed may occur as a result of aging, weight loss or gain, or other circumstances not related to the Fat grafting procedure. Chronic pain may occur rarely after fat removal or grafting. Unsatisfactory result: There is a possibility of unsatisfactory result from the procedure resulting in unacceptable visible deformities, loss of function, wound disruption, healing problems, and loss of sensation. Allergic reaction: In rare cases local allergies to tape, suture material, or topical preparations have been reported. Systemic reactions, which are more serious, may result from drugs used during the procedure. This is an extremely rare occurrence. Damage to deeper structures: Deeper structures such as nerves, blood vessels and muscles may be damaged during the course of this procedure. The injury to deeper structures may be temporary or permanent. Serious complications may include blood clots, partial collapse of lungs, pulmonary embolism, fat embolism, stroke, infection. Serious complications after fat grafting are rare such as blindness loss of vision, and/or death.

**Other Risks:**

Scarring: All invasive procedures produce scars, some more visible than others. although good wound healing after a procedure is expected, abnormal scars may occur both within the skin and within the deeper tissues. Scars may be unattractive and of different color than the surrounding skin. There is the possibility of visible marks from sutures used to close the wound. Scars may also limit motion and function. Additional treatment including surgery may be needed to treat scarring. Long term effect: subsequent changes in the shape or appearance of the area where the fat was removed or placed may occur as a result of aging, weight loss or gain, or other circumstances not related to the Fat grafting

	<p>procedure. Unsatisfactory result: There is a possibility of unsatisfactory result from the procedure resulting in unacceptable visible deformities, loss of function, wound disruption, healing problems, and loss of sensation. Allergic reaction: In rare cases local allergies to tape, suture material, or topical preparations have been reported. Systemic reactions, which are more serious, may result from drugs used during the procedure. Enriched Grafting Procedure: Subject randomized to the enriched fat grafting procedure will undergo additional operating time of up to 30 minutes</p>
View	<b>Research Activity:</b> Venipuncture
	<b>Common Risks:</b> mild pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising and soreness.
	<b>Infrequent Risks:</b> severe pain; swelling; possibly an infection from the actual injection; fainting.
	<b>Other Risks:</b> No Value Entered

There are no items to display

- 5.1.1 Describe the steps that will be taken to prevent or to minimize the severity of the potential risks: SCREENING PROCEDURES: For online screening via TrialSpark, data provided as part of the screening process are encrypted by Secure Socket Layer (SSL) software and stored in a secure database server. Subject will be in a private room for all research procedures and during the consenting process steps will be taken to maintain to protect the potential subject's PHI. All Study materials will be assigned a study ID code. No personal information will be on said study materials. All information obtained for the purpose of this clinical trial will be de-identified and will be assigned a study ID code. All paper files will be in a locked file cabinet within the Department of Plastic and Reconstructive Surgery offices. All computer based files will be encrypted and encoded for password protection. All research staff are trained in research conduct and compliance having completed all required research modules and have education in Good Clinical Practice in research. The Laboratory technicians and CT technicians are well-versed in the risks of their practice and thoroughly address the subject prior to each exam, inclusive of the risks of venipuncture procedure and risks of exposure to radiation. All exams will be

terminated should the subject expresses any concerns issues or discomfort.

**EXPERIMENTAL PROCEDURES AND FOLLOW UP PROCEDURES:**The plastic surgeons performing the fat graft procedures are highly trained and skilled with years of experience in fat grafting procedures. The anesthesiologists are highly trained. All research staff are trained in research conduct and compliance having completed all required research modules and have education in Good Clinical Practice in research. All research staff are trained in the use of the 2D cameras. The pictures will be taken in a timely manner so as not to prolong any possible discomfort for the subject. Also, the photographs will be de-identified and labeled with subject ID only. The photographs will be located within a secure database within a locked office. In addition to our screening and subsequent pregnancy tests, the CT technicians are well-versed in the risks and thoroughly question the subject prior to each exam, including excess exposure to radiation. All exams will be terminated as soon as the subject expresses any discomfort. The psychosocial and SCID evaluations will be conducted by the research technician. A clinically significant symptom elevation or increase on these measures will direct the technician to contact the clinical psychologist on the team (Dr. Haas) who will visit with the patient on-site to ascertain need for further evaluation and possible referral for mental health support services. The occupational therapists, and prosthetics team in this study are highly trained and skilled in their evaluations. They will use the tools and tests they deem appropriate for a patient. They will assess what a patient is capable of, what tests the patient can/can't perform adequately, and when to stop a test that a patient appears unable to perform

- 5.2 What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study? \* Addressed below:

Upon discovery the PI and/or co-investigator will notify the subject of any event that could be of clinical significance needing further evaluation, or of a diagnosis of any unexpected disease or condition that occurred during the conduct of the study's research procedures. The study investigator will at the time of discovering the event contact the referring physician or primary physician for further evaluation of the event. Should the event be of a critical nature needing immediate intervention, the study investigator or co-investigator will proceed with immediate clinical intervention and screening procedures will be concluded. HO is not grounds for exclusion and we wish to be able to study subjects with Heterotopic Ossification (HO). HO is prevalent in extremity amputation wounds in military trauma. ii. If HO is present, we will ascertain that HO remains stable and does continue to increase in volume, as documented by CT imaging of stabilization. iii. Medical management will be instituted with NSAIDS as indicated and appropriate for the patient. iv. We will then determine if the HO is the primary source of pain, or causing erosion of skin on physical exam. Fat grafting over the HO will be performed as part of study provided that: HO is ruled out as primary source of pain through clinical exam, and HO is deeper and not eroding through skin, allowing adequate fat coverage. v. It is anticipated that adding more soft tissue coverage over HO will be beneficial. vi. If elective excision of

HO is required, that procedure will be performed in the first stage with 3 month recovery period before fat grafting.

- 5.3 All the risk questions (screening, intervention/interaction, follow-up) have been merged into one question (5.1).

[reviewer notes~]

#### Section 5 - Potential Risks and Benefits of Study Participation

- 5.4 Do any of the research procedures pose a physical or clinically significant psychological risk to women who are or may be pregnant or to a fetus?\* Yes

- 5.4.1 List the research procedures that pose a risk to pregnant women or fetuses:

CT Scans, Surgery and Anesthesia for the fat graft surgery

- 5.4.2 Describe the steps that will be taken to rule out pregnancy prior to exposing women of child-bearing potential to the research procedures that pose a risk to pregnant women or fetuses:

All participants who are women of child bearing potential will receive a urine pregnancy dip test at screening and prior to any CT scans and surgical procedure. Subjects who are WOCBP during participation in this clinical trial will be counseled on the risks of pregnancy and importance of avoiding pregnancy while enrolled in this study; pregnancy will result in their removal from the clinical trial.

- 5.4.3 Describe the measures to prevent pregnancy, and their required duration of use, that will be discussed with women of child-bearing potential during and following exposure to research procedures:

All participants who are women of child bearing potential will receive a urine pregnancy dip test at screening and prior to any CT scans and surgical procedure. Furthermore, patients will be counseled on the risks of pregnancy and importance of avoiding pregnancy while enrolled in this study and that pregnancy will result in their removal from the clinical trial

[reviewer notes~]

#### Section 5 - Potential Risks and Benefits of Study Participation

5.5 Do any of the research procedures pose a potential risk of causing genetic mutations that could lead to birth defects?\* No

5.5.1 List the research procedures that pose a potential risk of genetic mutations/birth defects:

5.5.2 Describe the measures to prevent pregnancy, and their required duration of use, in female subjects and female partners of male subjects during and following exposure to research procedures:

[reviewer notes~]

#### Section 5 - Potential Risks and Benefits of Study Participation

5.6 Are there any alternative procedures or courses of treatment which may be of benefit to the subject if they choose not to participate in this study?\* Yes - Describe below:

If Yes, describe in detail: Alternative treatments include prosthetic implants and standard surgical flap reconstruction/revision surgery.

[reviewer notes~]

#### Section 5 - Potential Risks and Benefits of Study Participation

5.7 Describe the specific endpoints (e.g., adverse reactions/events, failure to demonstrate effectiveness, disease progression) or other circumstances (e.g., subject's failure to follow study procedures) that will result in discontinuing a subject's participation?\* Describe below:

Development of complications (e.g., adverse reactions/events, failure to demonstrate effectiveness, disease progression and severe infection at the surgery site) or other circumstances (e.g., subject's failure to follow study procedures, noncompliance of all research visits) that obscure the ability to evaluate the results of the implant will result in discontinuing a subject's participation. All data regarding complications will be captured and adverse event reporting will be conducted through all the appropriate and required regulatory channels inclusive of any and all treatment required and medical course following complication. In every case in which it is possible to do functional evaluation, regardless of complications, the intended outcomes will be measured.

[reviewer notes~]

#### Section 5 - Potential Risks and Benefits of Study Participation

5.8 Will any individuals other than the investigators/research staff involved in the conduct of this research study and authorized representatives of the University Research Conduct and Compliance Office (RCCO) be permitted access to research data/documents (including medical record information) associated with the conduct of this research study?\* Yes

5.8.1 Identify the 'external' persons or entity who may have access to research data/documents and the purpose of this access:

FDA, Department of Defense and their contracted entities will review and/or obtain identifiable information; which may include the subject's identifiable medical information related to participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for preparing required scientific analyses of the research data. Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include subject's identifiable medical information) related to their participation in this research study for the purpose of (1) fulfilling orders, made by investigators, for hospital and health care services (e.g. laboratory tests) associated with this research study participation, (2) addressing correct payment for tests and procedures ordered by the investigators, and/or (3) for internal hospital operations (i.e. quality assurance). This research study will result in identifiable information that will be placed into the subject's medical records held at UPMC. The nature of the identifiable information resulting from the subject's participation in this research study that will be recorded in their medical record will be derived from the medical/surgical (fat grafting procedure). Psychiatric interview information will be entered into the medical record only if it is important to ensure the subject's medical/physical safety. In unusual cases, the investigators may be required to release identifiable information (which may include subject identifiable medical information) related to their participation in this research study in response to an order from a court of law. If the investigators learn that the subject or someone with whom the subject are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

5.8.2 Will these 'external' persons or entity have access to identifiable research data/documents?

\*Yes - Describe below:

If Yes, describe how they will protect the confidentiality of the research data: While the study funding source, Department of Defense (DOD), FDA and contracted entities understands the importance of maintaining the confidentiality of the identifiable research and medical information, the UPMC and the University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by these sources. Data



and samples resulting from this research study may be shared with other investigators in the future, and all information will be de-identified prior to the sharing of this information.

5.9 Has or will a Federal Certificate of Confidentiality be obtained for this research study?

\* No

5.10 Question has been moved to 5.17

5.11 Question has been moved to 5.16

[reviewer notes-]

#### Section 5 - Potential Risks and Benefits of Study Participation

5.12 Does participation in this research study offer the potential for direct benefit to the research subjects? Yes - Describe the direct benefit that subjects may receive as a result of study participation. Indicate if all, or only certain, of the subjects may derive this potential benefit. Describe the benefit: Fat grafting procedures performed for clinical purposes have been associated with positive results in improving the appearance of patients; it is also anticipated to improve pain related to inadequate soft tissue coverage. In this case, subjects are likely to have a visible improvement in their limb deformities, with the potential of improved prosthetic fit and comfort, resulting in improved mobility. Additionally, these improvements may have a positive impact on quality of life, as assessed by the instruments used in this study. Although we can not guarantee a positive outcome from this research fat grafting procedure, there may be a direct benefit to the research subject from his/her participation in this research study. In addition, this research may provide a greater understanding of the effects of fat grafting over time.

5.13 Describe the data and safety monitoring plan associated with this study. If the research study involves multiple sites, the plan must address both a local and central review process. Data Safety Monitoring Plan The Data Safety and Monitoring Plan for this trial will consist of two parts. A Local Data and Safety Monitoring Plan will be implemented by the Principal Investigator to ensure that there are no changes in the risk/benefit ratio during the course of the study and that confidentiality of research data is maintained. This DSMB will consist of the PI, Co-Investigators and study personnel who will meet and discuss monthly the study (e.g., study goals and modifications of those goals; subject recruitment and retention; progress in data coding and analysis; documentation, identification of adverse events or research subject complaints; violations of confidentiality) and address

any issues or concerns at that time. Minutes will be kept for these meetings and will be maintained in the study DSMB binder. Any instances of adverse events will be reported immediately to the University of Pittsburgh IRB in accordance with the guidance on the IRB website. The annual IRB renewal for this study will include a summary report of the Data and Safety Monitoring Plan findings from the study for the prior year. We will include the following information at the time of the IRB renewal regarding the frequency of the monitoring, the dates that the monthly meetings took place, a summary of the cumulative adverse events, external factors or relevant information that might have an impact on the safety or ethics of the study, and final conclusions regarding changes to the anticipated risk/benefit ratio to study participation and final recommendations related to the continuation, changing, or termination of the study. The protocol will not be initiated until written notification of approval of the research project is issued by the HRPO. A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. 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 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. All other amendments must be submitted with the continuing review report. All unanticipated problems involving risk to subjects or others must be promptly reported by phone (301-619-2165), by email (HRPO@amedd.army.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, 504 Scott Street Fort Detrick, Maryland 21702-5012. 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. A copy of the continuing review report and the re-approval notification by the UP IRB must be submitted to the HRPO as soon as possible after receipt of approval. Please note that the HRPO also conducts random audits at the time of continuing review and additional information and documentation may be requested at that time. The final study report submitted to the UP 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. 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. Accurate and complete study records will be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. All research records are stored in a confidential manner so as to protect the confidentiality of subject information. Per DoD Directive 3216.02, all greater than minimal risk studies require a Medical Monitor. The USAMRMC ORP HRPO also reserves the authority to require assignment of a Medical Monitor for those protocols assessed as presenting no greater than minimal risk to the subjects participating in the study. The second part of the DSMP will be the inclusion of an Independent Data Safety Monitoring Board (IDSMB). This IDSMB will convene once a year or as needed for review of all unanticipated events, adverse events, and serious adverse events affecting the risk to the human subject or others. The members of the IDSMB include Drs. Ernest Manders and James Russavage who are all present faculty members within the Department of Plastic Surgery at the University of Pittsburgh, without any involvement in this research protocol, they are not under the supervision of the PI or have a conflict of interest. Dr Manders, a member of the Independent Data Safety and Monitoring Board (IDSMB) will act as the Research Monitor for this study; he is available on site to respond to any urgent or emergency situations that may arise during the study and to serve as the subject advocate. The Research Monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the Research Monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The Research Monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. The Medical Monitor has the authority to stop the research at any time; he /she can remove individuals from the study, and take any steps necessary to protect the safety and well being of participants until the IRB has time to assess the study. This IDSMB will evaluate any adverse events and research staff adherence to subject confidentiality and de-identification processes. The IDSMB members will discuss, if necessary, any changes to the risk/benefit ratio of this study for the PI's report to the local IRB of all reporting adverse events, external factors or relevant information that might have an impact on the safety or ethics of the study, and final conclusions regarding changes to the anticipated risk/benefit ratio to study participation and final recommendations related to the continuation, changing, or termination of the study as outlined by the University of Pittsburgh IRB.

[reviewer notes~]

## Section 5 - Potential Risks and Benefits of Study Participation

- 5.14 What precautions will be used to ensure subject privacy is respected? (e.g. the research intervention will be conducted in a private room; the collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected, drapes or other barriers will be used for subjects who are required to disrobe)

All aspects of the study will be performed in a private room, including the consenting process, exams, urine pregnancy testing, questionnaires, photographs, CT scan, laboratory blood draw and the fat grafting procedure. The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected, drapes or other barriers will be used for subjects who are required to disrobe.

- 5.15 What precautions will be used to maintain the confidentiality of identifiable information? (e.g., paper-based records will be kept in a secure location and only be accessible to personnel involved in the study, computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords, prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information, whenever feasible, identifiers will be removed from study-related information, precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys, audio and/or video recordings of subjects will be transcribed and then destroyed to eliminate audible identification of subjects)

Participation in this research study does involve the potential risks of a breach of confidentiality of the medical record information and associated privacy of the participants. 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. Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study, computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords, prior to access to any study-related information, whenever feasible, identifiers will be removed from study-related information, precautions are in place to ensure the data is secure by using password restricted and folder level access by permission only on UPMC servers. Reference to sample: All research samples will be stored to include assigned code numbers, and any information linking these code numbers to the corresponding subjects' identities will be kept in a separate, secure location located in the security manned Biomedical Science Tower at the University of Pittsburgh, Should the subject decide to withdraw or be withdrawn from study participation, the already collected samples will then be rendered anonymous, i.e., the link between the code and the identity will be destroyed.

If the subject requests that the samples be destroyed and the link to the samples has not yet been rendered anonymous, we will destroy the samples. However if link to the samples were already rendered anonymous prior to the subject's request, we will not be able to identify the subject's samples making it impossible to destroy them. It is the Principal Investigator's intention to make subject de-identified information available to secondary investigators after all research study testing has been completed. These associated subject information will not include subject identifiers. The photographs will be housed as electronic files within the Canfield camera system. The system is password protected and is located within the locked offices of the Aesthetic Plastic Surgery Center located at 3380 Boulevard of the Allies, suite 180 Pittsburgh pa 15213. While the photographs will be labeled with an ID code, there is a risk of loss of confidentiality. Digital recording (i.e. photography or video) are being collected from any and all portions of the subject's pre-operative, operative, and post-operative course of treatment. These may include, but not be limited to, videos of personal interviews, functional assessment testing and clinical exams or photos of follow up clinical course, biopsies, etc. and will be de-identified and stored indefinitely in a secure password protected location on the UPMC server. These digital recordings and/or photos may be used for medical education and training, publication, and media reports – and, in any mode of transmission, including and not limited to: print, e-mail, television, internet, etc. While photograph will be de-identified, video recordings will remain identifiable. Regarding the use of these digital recordings for education, training, publication and storage purposes, the subject will not be identified by name, only by a unique code number. The subject's identifiable features in these photographs will be blacked out (i.e., eyes, facial features, etc.). Regarding the use of the subjects digital recordings for media purposes, the subject may be identified by name, but permission from the subject will be obtained in a separate consent document prior to the recordings being obtained (Media consent). The subjects are not required to give this permission and can refuse at any time after giving consent to these digital recordings being obtained and can still participate in this study without permitting these recordings. All data entered on TrialSpark as part of the registration process (e.g., email address, personal information) is subject to TrialSpark's extensive security protocol. Study-specific information, including data acquired during the study, may be accessed by engineers on an as needed basis to troubleshoot a technical issue (duplicate registrations, error in date entry format). TrialSpark maintains a protective privacy policy in reference to e-mail addresses, personal information, and any additional data entered on TrialSpark. TrialSpark does not sell or make available specific information about clients or their data with third-parties. The Secure Socket Layer (SSL) software, which encrypts all inputted information, keeps the information private. TrialSpark backend servers are stored at secure data centers. TrialSpark complies with the U.S. and E.U. Safe Harbor Framework and the U.S. and Swiss Safe Harbor Framework, expounded upon by the U.S. Department of Commerce. Further, TrialSpark complies with the Safe Harbor Privacy Principles of notice, choice, onward transfer, security, data integrity, access, and enforcement. All of the information collected is stored in a HIPAA compliant database with additional encryption, virtual, and physical safeguards. Data is encrypted at transfer and at rest.

- 5.16 If the subject withdraws from the study, describe what, if anything, will happen to the subject's research data or biological specimens.

Any identifiable research or medical information recorded for, or resulting from, a subject's participation in this research study prior to the date that the subject formally withdrew his/her consent will continue to be used and disclosed by the investigators for the purposes described above. All research samples will be stored to include assigned code numbers, and any information linking these code numbers to the corresponding subjects' identities will be kept in a separate, secure location located in the Department of Plastic Surgery at the University of Pittsburgh. Should the subject decide to withdraw or be withdrawn from study participation, the already collected samples and all digital recordings will be kept and will be rendered anonymous, i.e., the link between the code and the identity will be destroyed. If the subject requests that the samples be destroyed and the link to the samples has not yet been rendered anonymous, we will destroy the samples. However if link to the samples were already rendered anonymous prior to the subject's request, we will not be able to identify the subject's samples making it impossible to destroy them. All samples and digital recordings collected during their participation in this clinical trial, upon their early withdraw from the study, will be kept and not destroyed, but processed specifically as outlined in the research design for this trial. Upon the subject's withdrawal from the study, should they specifically request that their biological samples collected for research purposes be destroyed, we will stop all testing and destroy any remaining unprocessed samples. It is the Principal Investigator's intention to make subject de-identified information available to secondary investigators after all research study testing has been completed. These associated subject information will not include subject identifiers. Subjects will be instructed that they may choose to withdraw from this study at any time, but it is important that they continue to be monitored by a physician after they receive the research Fat grafting procedure in order to ensure their safety. It is also important for the subject to contact study personnel if they later experience any side effects that they might feel are related to the research study.

- 5.17 Following the required data retention period, describe the procedures utilized to protect subject confidentiality. (e.g., destruction of research records; removal of identifiers; destruction of linkage code information; secured long-term retention)

After the data retention period, research records will be destroyed, all samples will be de-identified, and all linkage codes will be destroyed. This will leave behind no identifiable patient information to trace tissue samples (which will be stored indefinitely) back to the subject. Digital recording (i.e. photography or video) are being collected from any and all portions of the subject's pre-operative, operative, and post-operative course of treatment. These may include, but not be limited to, videos of personal interviews, functional assessment testing and clinical exams or photos of follow up clinical course, biopsies, etc. and will be de-identified and stored indefinitely in a secure password protected location on the UPMC server. These digital recordings and/or photos may be used for medical education and training, publication, and media reports – and, in any mode of transmission, including and not limited to: print, e-mail, television, internet,

etc. While photograph will be de-identified, video recordings will remain identifiable. Regarding the use of these digital recordings for education, training, publication and storage purposes, the subject will not be identified by name, only by a unique code number. The subject's identifiable features in these photographs will be blacked out (i.e., eyes, facial features, etc.). Regarding the use of the subjects digital recordings for media purposes, the subject may be identified by name, but permission from the subject will be obtained in a separate consent document prior to the recordings being obtained (Media consent). The subjects are not required to give this permission and can refuse at any time after giving consent to these digital recordings being obtained and can still participate in this study without permitting these recordings.

[reviewer notes~]

## Section 6 - Costs and Payments

6.1 Will research subjects or their insurance providers be charged for any of the procedures (e.g., screening procedures, research procedures, follow-up procedures) performed for the purpose of this research study?\* No

6.1.1 Specify what research procedures will be billed to the subject or insurance provider:

6.1.2 Provide a justification for billing subjects or insurance providers for procedures that are performed solely for the purpose of the research study.

6.1.3 Will subjects or insurance providers be billed for the investigational drug or device being evaluated or used in this research study?

\*

Provide assurance that the FDA has given approval for the sponsor of this research study to charge investigators for the investigational drug or device.

If this is an investigational device, indicate if the Health Care Financing Administration has designated it as a Class B medical device.

\*

- 6.1.4 Address the contingencies that are in place to ensure that potential subjects, who may desire to participate in this research study but are not able to bear this personal financial risk, will be afforded access to study participation.

[reviewer notes~]

## Section 6 - Costs and Payments

- 6.2 Will subjects be compensated in any way for their participation in this research study?\* Yes
- 6.2.1 Describe the amount of payment or other remuneration offered for complete participation in this research study. The subject will be compensated for their participation \$104.00 /day upon completion of each study visit. The payment is intended to cover minor expenses (i.e. meals, parking, post-operative meds, tolls, etc.) which may be encountered and could be associated with subject's participation in this clinical trial. The subject's reasonable travel expenses will be reimbursed for round trip air fare coverage or for ground mileage coverage at \$0.55 per mile from the subject's place of residence to the UPMC Anesthetic Plastic Surgery Center or UPMC hospital/ overnight housing facility. The details of reimbursement will vary from person to person and will be discussed during each visit. Proper supporting documentation for mileage reimbursement is demonstrated by trip tickets or a MapQuest inquiry from the subject's place of residence to the study site displaying round trip mileage. Per visit travel may include air fare coverage round trip booked through the University of Pittsburgh travel agency(ies) from the subject's place of residence to the UPMC Anesthetic Plastic Surgery Center or UPMC hospital/facility in lieu of round trip mileage. The subject will be reimbursed with the per diem rate using the UPMC "WE PAY" system at the time of each visit. DoD personnel may receive compensation for research activities only if the research activities take place outside of scheduled work hours. The subject's participation may lead to new inventions or products. If the investigators are able to develop new products from the research use of the subject's tissue or biological sample, there are currently no plans to share with the subject any money or other rewards that may result from the development of these new products.
- 6.2.2 Describe the amount and term of payment or other remuneration that will be provided for partial completion of this research study. Study subjects will be compensated for their participation in the research study on a per diem total rate of \$104.00/day. The subjects



will receive the payment of \$104.00/day for each completed or partially completed visit at the time that the subject is present for their last study visit.

[reviewer notes~]

## Section 7 - Qualifications of Investigators and Sources of Research Study

- 7.1 Summarize the qualifications and expertise of the principal investigator and listed co-investigators to perform the procedures outlined in this research study. Principal Investigator/ Study Staff: J. Peter Rubin, MD, Founding Chair of the Department of Plastic Surgery at the University of Pittsburgh, is the principal investigator. Dr. Rubin has a very successful track record of implementing Department of Defense clinical trials under programs including the Biomedical Translational Initiative, the Armed Forces Institute of Regenerative Medicine, and the Office of Technology Transfer Clinical Trials Program. He is an internationally recognized board certified plastic and reconstructive surgeon, as well as a scientific researcher with an active basic science laboratory (Co-Director of the Adipose Stem Cell Center) and funding from the National Institutes of Health. As Principal Investigator, Dr. Rubin has significant experience with fat grafting techniques for reconstructive applications. He will provide medical oversight for study subjects, responsible for review and meeting of subject research study eligibility criteria, consenting process, research study procedures, overall protection of human subject risks and benefits, performance of clinical trial conduct and compliance maintaining GCP. Dr. Rubin will work directly with military officers to start the process of transferring the technology for broad use while the study is underway. Sydney Coleman, MD is a renowned plastic surgeon having over 20 years of expertise in the fat grafting procedure. Dr. Coleman is the inventor of the Coleman Cannula System which is the instrumentation being used with this research surgical procedure. He will serve as a technical consultant and attend operative procedures where his expertise will be used to enhance this project. Kacey G. Marra, PhD, Associate Professor of Surgery and Co-Director of the Adipose Stem Cell Center, University of Pittsburgh, is an expert in the area of adipose research experience. Dr. Marra completed undergraduate and graduate studies at the University of Pittsburgh in Chemistry and Organic Chemistry respectively. In 1996-7, she was a post-doctoral fellow at the Emory University School of Medicine, with advisor Elliot Chaikof, M.D., Ph.D. At Emory, Dr. Marra worked on the synthesis of novel synthetic blood vessels. Dr. Marra has almost 10 years of adipose research experience. As a co-investigator she will oversee the basic science laboratory assays and be responsible for the oversight of all lab processing, maintenance and storage during the life of the study for all research biological

samples collected for as well as participate in data analysis and manuscript preparation.

Gretchen Haas, PhD, Dr. Haas is Associate Professor of Psychiatry and Director of the Family and Psychosocial Studies Program at the University of Pittsburgh School of Medicine and Director of the Mental Illness Research, Education and Clinical Center (MIRECC) at the VA Pittsburgh Healthcare System. Dr. Haas is a psychologist with extensive experience working with veterans, and specializes in measures of social function. She has a track record as PI of NIH-funded research on suicidal behavior and the clinical epidemiology of major psychiatric disorders (schizophrenia and other psychoses). As Director of the Clinical Cores for two NIH-funded research Centers at the University of Pittsburgh (Center for the Study of Suicidal Behavior and the Conte Center for the Neuroscience of Mental Disorders-Schizophrenia) and a VA-funded Center of Excellence (MIRECC) she has provided leadership in the clinical and psychosocial assessment of individuals with psychiatric disorders and healthy (non-psychiatric) individuals. As Director of the VAPHS MIRECC, she has led the development of novel collaborative research and clinical demonstration projects for the assessment of suicidal behavior in veterans, and the treatment of veterans with comorbid mental health and substance use disorders. As a nationally recognized expert in clinical assessment, she serves on the Executive Committee of the VHA's MyHealtheVet internet Web Development group providing consultation on the development of tools for self-assessment of clinical symptoms, psychosocial functioning and quality of life among recently returning military personnel and veterans. As a co-investigator with extensive experience in measuring quality of life in wounded warriors, she is responsible for and will oversee all the psychosocial measures, initial and ongoing evaluations associated with this trial. She will design and oversee the quality of life assessments, analyze the data, and assist in manuscript preparation. Jeffrey Gusenoff, MD is Co-Director of the Life After Weight Loss Program and Visiting Associate Professor of Surgery in the Division of Plastic Surgery at UPMC. He completed his undergraduate and medical school training at The Johns Hopkins University in 1998 and 2002. His residency in General and Plastic Surgery was at the University of Rochester School of Medicine in Rochester, NY, and he graduated in 2007. This was followed by a fellowship in Post-Bariatric Body Contouring with J. Peter Rubin, MD at the University of Pittsburgh Medical Center. From 2008 until 2012, Dr. Gusenoff was an Assistant Professor of Surgery and Director of the Life After Weight Loss Program at the University of Rochester Medical Center. His research experience includes extensive clinical outcomes research. As a principle/co-investigator, he will provide clinical oversight for study subjects, will be responsible for collection of information assessing the research study eligibility criteria, consenting process, research study procedures, overall protection of human subject risks and benefits, performance of clinical trial conduct and compliance maintaining GCP. Diana Mermon, MS holds a Master's degree in Counseling with a master's level Certification in Education. Diana has over 10 years of research experience and will conduct the subject's clinical interview and the quality of life assessments. Elizabeth Radomsky, PhD, is a clinical psychologist with extensive experience and specific training and expertise in the use of neuropsychological assessments and diagnostic and

psychopathology rating instruments. She has over 25 years of research experience. She will be responsible for conducting the subject's clinical interview and the quality of life assessments at baseline and follow-up assessments. Albert Donnenberg, PhD, Since 1998, Dr. Donnenberg has also been the director of University of Pittsburgh Cancer Institute's (UPCI) Flow Cytometry Facility. Additionally, he is currently the Deputy Director of the Stem Cell Transplantation (SCT) Program and Director of UPCI Bone Marrow Processing Laboratory. Dr. Donnenberg graduated with a B.A. in Philosophy from the University of Colorado in 1973. Following the completion of his Ph.D. in Infectious Disease Epidemiology from Johns Hopkins University School Public Health in 1980, Dr. Donnenberg served as a Research Fellow in Oncology at Johns Hopkins University School of Medicine until 1982. Dr. Donnenberg is the recipient of multiple awards for his research efforts at the university. Among his honors are induction into the Delta Omega Honorary Public Health Society and his receipt of a 1988 - 1993 Carter-Wallace Fellowship for AIDS Research. Most recently, he was honored as a visiting fellow at the Institute Pasteur in Paris in 1994. As the director of University of Pittsburgh Cancer Institute's (UPCI) Flow Cytometry Facility and Deputy Director of the Stem Cell Transplantation (SCT) Program and Director of UPCI Bone Marrow Processing Laboratory, he will have oversight of the cell processing of the adipose tissue, and oversee the flow cytometry studies within the GMP hematopoietic stem cell laboratory, analyze the data, and assist in manuscript preparation. Vera Svobodova Donnenberg, PhD, Assistant Professor of Surgery, University of Pittsburgh, is a co-investigator who will oversee the flow cytometry analysis of the cell product and will directly supervise all technical aspects of the flow cytometry studies and ensure quality control. Dr. Donnenberg research focuses on flow cytometry, broncho-alveolar lavage fluid, and the analysis of dendritic cell subsets. Dr. Donnenberg has written over 75 publications, abstracts and other scientific presentations. Dr. Donnenberg is a member of several professional and scientific societies including the American College of Clinical Pharmacology, American Association for Cancer Research, and the International Society for Analytical Cytology. Rory Cooper, PhD, received his B.S. and M.Eng degrees in electrical engineering from California Polytechnic State University, San Luis Obispo in 1985 and 1986, respectively. He received the Ph.D. degree in electrical and computer engineering with a concentration in bioengineering from University of California at Santa Barbara in 1989. He is FISA & Paralyzed Veterans of America (PVA) Chair and Distinguished Professor of the Department of Rehabilitation Science and Technology(RST), and professor of Bioengineering, Mechanical Engineering, Physical Medicine & Rehab, and Orthopedic Surgery at the University of Pittsburgh. Dr. Cooper is Founding Director and VA Senior Research Career Scientist of the VA Rehabilitation Research and Development Center of Excellence in Pittsburgh. He is also the Co-Director of the NSF Quality of Life Technology Engineering Research Center, a joint effort between the University of Pittsburgh and Carnegie Mellon University. Dr. Cooper will serve as a co-investigator with extensive experience in the care of amputees and prosthetic design. Dr. Cooper will direct the preoperative and postoperative evaluation of the subjects. He will have overall coordination and interpretation of the functional and anatomical changes for the

prosthetic design with supervision of RST personnel. Sara Peterson, MBA, CPO, a certificate in Orthotics and Prosthetics from Century College, St. Paul, MN in 1993 and worked continually as an Orthotist/Prosthetist from 1993-2009, and obtained ABC Certification in 1999. In 2009, hired as lead prosthetic instructor at the University of Pittsburgh to help start the Master's of Science in Prosthetics and Orthotics, which recently received National Commission on Orthotics and Prosthetic Education (NCOPE) certification. In parallel with these duties as an instructor and Prosthetics Coordinator, she is a PhD student in the Department of Rehabilitation Science & Technology at Pitt. Ms. Peterson's role on this project will be with the Prosthetic fitting, administration of the surveys, and functional assessments/ measurements. Patsy Simon, RN, BS, CCRC, CCRA Director, Regulatory and Clinical Affairs for the UPMC Center for Innovation in Restorative Medicine, Department of Plastic Surgery at the University of Pittsburgh. Ms. Simon has over 30 years of clinical nursing experience with 15 years of expertise in clinical research trial conduct and compliance. She has regulatory expertise with federal, industry and investigator sponsored clinical trials along with experience in federal IND and IDE application development and oversight. Ms. Simon's role on this project is the direct management of regulatory and clinical operations and oversight of the clinical team focusing on adherence to federal regulations, conduct, and compliance with good clinical practice (GCP). Karen Foley, RN, BSN, CCRC has several years of regulatory and clinical research experience. Her study role will be to actively perform research related activities, access medical records and databases, as well as submission of regulatory documents to the University of Pittsburgh IRB associated with the conduct and compliance of a clinical trial. Isaac James, MS has a year of laboratory experience within the BST Adipose Stem Cell Laboratory. As co-investigator on this study he will be responsible for obtaining lipoaspirate from the operative area and transporting specimens to the laboratory (BST and HSC) for processing and analysis. Theresa Marie Crytzer, DPT, ATP is an Assistant Professor, University of Pittsburgh, School of Health and Rehabilitation Sciences, Rehabilitation Science & Technology. Dr. Crytzer received her Doctor of Physical Therapy, Graduate School of Physical Therapy, Slippery Rock University, Slippery Rock, PA on 200 and completed her Certificate in Clinical Research, University of Pittsburgh, Institute of Clinical Research, in 2011. Danielle Minter, PhD is employed by University of Pittsburgh, Department of Plastic Surgery as a Research Data Manager. As a co-investigator, she will be responsible for data collection and building and managing research databases. Mark Asher Schusterman, MD is employed by UPMC and a member of the Department of Plastic Surgery. As a co-investigator, he is responsible for collection of information assessing the research study eligibility criteria and consenting process, research study procedures, overall protection of human subject risks and benefits, performance of clinical trial conduct and compliance maintaining GCP. Francesco Egro, MD is employed by UPMC and a member of the Department of Plastic Surgery. As a co-investigator, he is responsible for collection of information assessing the research study eligibility criteria and consenting process, research study procedures, overall protection of human subject risks and benefits, performance of clinical trial conduct and compliance maintaining GCP. Wendy

Chen, MD is employed by UPMC and a member of the Department of Plastic Surgery. As a co-investigator, she is responsible for collection of information assessing the research study eligibility criteria and consenting process, research study procedures, overall protection of human subject risks and benefits, performance of clinical trial conduct and compliance maintaining GCP. Stephanie Dreifuss-Farber, MD is employed by UPMC and a member of the Department of Plastic Surgery. As a co-investigator, she is responsible for collection of information assessing the research study eligibility criteria and consenting process, research study procedures, overall protection of human subject risks and benefits, performance of clinical trial conduct and compliance maintaining GCP. Joanna Ng-Glazier, MD is employed by UPMC and a member of the Department of Plastic Surgery. As a co-investigator, she is responsible for collection of information assessing the research study eligibility criteria and consenting process, research study procedures, overall protection of human subject risks and benefits, performance of clinical trial conduct and compliance maintaining GCP. David Turer, MD is employed by UPMC and a member of the Department of Plastic Surgery. As a co-investigator, he is responsible for collection of information assessing the research study eligibility criteria and consenting process, research study procedures, overall protection of human subject risks and benefits, performance of clinical trial conduct and compliance maintaining GCP.

[reviewer notes-]

## Section 7 - Qualifications of Investigators and Sources of Study Support

### 7.2 Indicate all sources of support for this research study.\*

#### Selections

Federal: Upload a copy of the entire grant application (including the cover sheet) if our site is the awardee institution; for federal contracts, upload a copy of the research plan

There are no items to display

If Federal support, provide the sponsor information:

Federal sponsor	Grant Title	Grant number	Awardee institution	Federal grant application
View DOD	Adipose Stromal Cell Enriched Autologous Fat Grafting for Treating Pain at Amputation Sites	W81XWH-12-DMRDP-CTA-RPS	University of Pittsburgh	Amp 30 DoD grant(0.01)

For projects not supported by a federal grant, upload the research plan that was submitted for funding:

Name Modified Date

If Industry support, provide the sponsor information and level of support:

If Foundation support, provide the sponsor information:

If Other support, provide the support information and level of support:

[reviewer notes-]

### Section 7 - Qualifications of Investigators and Sources of Research Study

7.3 Is this study funded in part or whole by a PHS Agency?

\* No

Does any investigator\* involved in this study (select all that apply):

Name
<input type="checkbox"/> A. Have a financial interest (aggregated value of equity and remuneration** during the past or next twelve months) in a publicly-traded entity that either sponsors*** this research or owns the technology being evaluated or developed that exceeds \$5,000 but not \$10,000?
<input type="checkbox"/> B. Have a financial interest (aggregated value of equity and remuneration during the past or next twelve months) in a publicly-traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds \$10,000?
<input type="checkbox"/> C. Receive remuneration (during the past or next twelve months) from a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds \$5,000 but not \$10,000?
<input type="checkbox"/> D. Receive remuneration (during the past or next twelve months) from a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds \$10,000?
<input type="checkbox"/> E. Have equity in a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed?

- ☐ A. Have a financial interest (aggregated value of equity and remuneration\*\* during the past or next twelve months) in a publicly-traded entity that either sponsors\*\*\* this research or owns the technology being evaluated or developed that exceeds \$5,000 but not \$10,000?

- ☐ B. Have a financial interest (aggregated value of equity and remuneration during the past or next twelve months) in a publicly-traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds \$10,000?

- ☐ C. Receive remuneration (during the past or next twelve months) from a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds \$5,000 but not \$10,000?

- ☐ D. Receive remuneration (during the past or next twelve months) from a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds \$10,000?

- ☐ E. Have equity in a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed?

- ☐ F. Receive reimbursement or sponsorship of travel expenses (for one trip or a series of trips during the past or next twelve months) by an outside entity that either
- ☐ sponsors this research or owns the technology being evaluated or developed that exceeds \$5,000?
- 
- ☐ G. Have rights as either the author or inventor of intellectual property being evaluated or developed in this research that is the subject of an issued patent or
- ☐ has been optioned or licensed to an entity?
- 
- ☐ H. Have an officer or management position\*\*\*\* with a Licensed Start-up Company overseen by the COI Committee that either sponsors this research or owns the technology being evaluated or developed?
- ☐
- 
- ☐ I. Receive compensation of any amount when the value of the compensation would be affected by the outcome of this research, such as compensation that is explicitly greater for a favorable outcome than for an unfavorable outcome or compensation in the form of an equity interest in the entity that either sponsors this research or owns the technology being evaluated or developed?
- ☐
- 
- ☐ None of the above options apply and there are no other financial conflicts of
- ☐ interest in the conduct of this research.

There are no items to display

\*Investigator means the PI, co-investigators, and any other member of the study team, regardless of title, who participates in the design, conduct, or reporting of this research, as well as his/her spouse, registered domestic partner, dependents, or other members of his/her household. The PI is responsible for ensuring that s/he and all other relevant members of the study team review the above questions describing Significant Financial Interests.

\*\*such as salary, consulting fees, honoraria, or paid authorship

\*\*\*through the provision of funds, drugs, devices, or other support for this research

\*\*\*\*Such as serving on the Board of Directors or Board of Managers or a position that carries a fiduciary responsibility to the company (e.g., CEO, CFO, CTO, or CMO).

Does any investigator\* involved in this study (select all that apply):

## Name

- ☐ A. Have equity in a publicly-traded entity that either sponsors\*\* this research or owns the technology being evaluated or developed that exceeds a 5% ownership interest or a current value of \$10,000?
- ☐ B. Have equity in a non-publicly-traded entity that either sponsors this research or owns the technology being evaluated or developed?
- ☐ C. Receive salary, consulting fees, honoraria, royalties or other remuneration from an entity that either sponsors this research or owns the technology being evaluated or developed that is expected to exceed \$10,000 during the past or next 12 months?
- ☒ D. Have rights as either the author or inventor of intellectual property being evaluated or developed in this research that is the subject of an issued patent or has been optioned or licensed to an entity?
- ☐ E. Have an officer or management position\*\*\*\* with a Licensed Start-up Company overseen by the COI Committee that either sponsors this research or owns the technology being evaluated or developed?
- ☐ F. Receive compensation of any amount when the value of the compensation would be affected by the outcome of this research, such as compensation that is explicitly greater for a favorable outcome than for an unfavorable outcome or compensation in the form of an equity interest in the entity that either sponsors this research or owns the technology being evaluated or developed?
- ☐ None of the above options apply and there are no other financial conflicts of interest in the conduct of this research.

There are no items to display

\*Investigator means the PI, co-investigators, and any other member of the study team, regardless of title, who participates in the design, conduct, or reporting of this research, as well as his/her spouse, registered domestic partner, dependents, or other members of his/her household. The PI is responsible for ensuring that s/he and all other relevant members of the study team review the above questions describing Significant Financial Interests.

\*\*through the provision of funds, drugs, devices, or other support for this research

\*\*\*\*Such as serving on the Board of Directors or Board of Managers or a position that carries a fiduciary responsibility to the company (e.g., CEO, CFO, CTO, or CMO).



	Section: Section 7 - Qualifications and Source(s) of Support
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7.3.1 Provide the name of the investigator(s) and describe the nature of the Significant Financial Interest(s): Sydney Coleman, MD

7.3.2 If you selected A, B, C, or E, please complete a Standard Conflict of Interest Management Plan and submit it with your protocol. Please provide all of the requested information, including the correct protocol number and title. Incomplete, inaccurate, or unsigned forms will have to be edited and replaced.

For all other financial interests (D or F), the COI Office will work with you to develop an appropriate COI Management Plan.

7.3.2 If you selected B, D, E, or H, please complete a Standard Conflict of Interest Management Plan and submit it with your protocol. Please provide all of the requested information, including the correct protocol number and title. Incomplete, inaccurate, or unsigned forms will have to be edited and replaced.

For all other financial interests (A, C, F, or G), the COI Office will work with you to develop an appropriate COI Management Plan.

\*

Name	Modified Date
COI management plan for Dr. Coleman	11/15/2013 2:54 PM

	Section: Supporting Documentation
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[reviewer notes~]

Supporting Documentation Section

References and Other Attachments

Additional documents:

Please use the Add button to the left to upload additional documents if needed.

Name	Modified Date	Version
2005-13-R5 Procedure for Rapid Endotoxin Testing	8/8/2012 8:10 AM	0.01
2008-02-R0 Procedure for Manual Nucleated Cell Counting and Viability Determination Using Trypan Blue	8/8/2012 8:10 AM	0.01
DoD communication regarding enrollment hold 3.6.2018	5/14/2018 4:17 PM	0.01
Dr. Donnenberg Letter in support	7/24/2012 2:45 PM	0.01
Grant Application Package	7/17/2012 8:27 AM	0.01
References	7/23/2012 12:33 PM	0.01
STEM CELL TGI processing SOP.pdf	10/4/2013 1:12 PM	0.01

[reviewer notes~]

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

"Applicable clinical trials" are required by federal law to be registered in ClinicalTrials.gov.

Applicable Clinical Trials (ACTs) are studies that meet the following criteria:

The study is an interventional study AND

The study intervention is a drug, biologic, medical device, radiation or genetic AND

The Study is not Phase 0 or 1 AND

The study has at least one site in the United States or is conducted under an investigational new drug application or investigational device exemption

NIH Policy

Effective January 18, 2017, revised NIH Policy requires that all clinical trials funded in whole or in part by the NIH be registered and results information posted on ClinicalTrials.gov.

As defined by the NIH, a clinical trial is:

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health related biomedical or behavioral outcomes.

The NIH Policy extends beyond the Food and Drug Administration Amendment Act (FDAAA 801) requirements in that it requires registration and results reporting of:

clinical trials of behavioral, surgical and other types of health and medical interventions

phase 1 studies of drugs and biological products

small feasibility studies of device products

Failure to submit all required registration and results information requested on ClinicalTrials.gov can jeopardize University grant funding, the future funding of the grantee and subject the University of Pittsburgh to future monetary penalties.

In addition, to promote transparency of the clinical trials process, the International Committee of Medical Journal Editors (ICMJE) has established a policy requiring the entry of clinical trials in a public registry, such as ClinicalTrials.gov, prior to subject enrollment as a condition of consideration for publication of the trial results.

\* Based on the above information, will this study be registered in ClinicalTrials.gov? Yes

Who will serve as the Responsible Party? UPMC/Pitt Investigator or IND/IDE Pitt Sponsor Why are you registering your study? (Check all that apply)

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It is required for publication by the International Committee of Medical Journal Editors (Registration is required in a publically available, searchable database system prior to informed consent being obtained from the first study participant)

There are no items to display

If you are not yet registered and need to establish an account for the PI or other research staff that may need to access the record, please send an email to the University of Pittsburgh PRS administrator at [ctgov@pitt.edu](mailto:ctgov@pitt.edu) with the following information for each individual:

Full name

Telephone number

Pitt or UPMC email address

If you have any questions or concerns, please email us at [ctgov@pitt.edu](mailto:ctgov@pitt.edu).

To find out additional information about how to register your study go to:  
<https://www.clinicaltrials.gov/ct2/manage-recs/how-register>