CLINICAL STUDY PROTOCOL

A Pilot Safety and Efficacy Study of DermGEN Dermal Regeneration Scaffold for the Treatment of Diabetic Foot Ulcers

Test product:	DermGEN
Clinical study phase:	Feasibility
Sponsor:	DeCell Technologies Inc.
Sponsor's scientific expert**:**	Paul F. Gratzer, Ph.D., P.Eng. President and CEO Office: (902) 442-4668 Cell: (902) 223-2179 Fax: (902) 494-6621 Email: pfgratzer@decelltechnologies.com www.decelltechnologies.com
Sponsor's clinical expert:	Mark A. Glazebrook, MD FRCSC Orthopedic Surgeon

Protocol number: DCL-DFU11

Version: 5.0

Date: 28 March 2016

STUDY IDENTIFICATION DATA

Short Title	DermGEN DFU Study 11
Study Code	DCL-DFU11
Phase	1
Sponsor	DeCell Technologies, Inc.
Test Product	DermGEN
Dose/Route of Administration	Topical
CRO/Study Centre	DeCell Technologies, Inc.
Principal Investigator	Mark Glazebrook, MD PhD FRCSC
Version	5.0
Medical Monitor	R. Eric McAllister, MD DPhil
Date	28 March 2016

CONFIDENTIALITY STATEMENT

This protocol contains information that is confidential and proprietary to DeCell Technologies, Inc. ("DeCell") This information is being provided to you for the purpose of conducting a clinical study for DeCell. You may disclose the contents of this protocol to study personnel under your supervision who need to know the contents for this purpose, as well as to your Institutional Review Board(s) or Ethics Committee(s), subject to the following condition: The contents of this protocol may not be disclosed to any other person or entity without the prior written permission of DeCell, and may not be used for any purpose other than the conduct of this study. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, you will give prompt notice to DeCell of any such disclosure.

Any supplemental information that may be added to this document is also confidential and proprietary to DeCell and must be kept in confidence in the same manner as the contents of this protocol.

Any person who receives this protocol without due authorization from DeCell is requested to return it to DeCell or to promptly destroy it.

REVISION HISTORY

Version	Date	By	Description
3.0	24 Jun 2014	P. F. Gratzer	First circulated version, and with ethics approval. No patients enrolled under this version at St. Michael's Hospital.
4.0	08 Feb 2016	R. E. McAllister	Reformat without changes to protocol; circulated for comments.
4.A	08 Feb 2016	R. E. McAllister	Modify wording, no material changes to protocol
4B	09 Feb 2016	R. E. McAllister	Further modify wording, no material changes to protocol
4C	09 Feb 2016	R. E. McAllister	Alter methodology to promote study objectives more efficiently
4D	09 Feb 2016	R. E. McAllister	Incorporate comments and suggestions.
5.0	28 Mar 2016	R. E. McAllister	Revised circulated version. This is the first version to be implemented at the St. Michael's Hospital site. Changes from version 3.0 are: (a) Formatted to resemble ICH and FDA templates (b) One replacement application of DermGEN is permitted, if warranted. (c) Now provides for experience with up to 3 patients excluded from the study analysis, before finalizing procedures. (d) Now specifically allows inclusion of patients with DFU healing after treatment of underlying osteomyelitis. (e) Allows for vacuum-assisted closure device over the wound. (f) Utilizes the SF-12 questionnaire in place of the SF-36, and LUMT document in place of MDLUC-AQ.

SPONSOR APPROVAL PAGE

A Pilot Safety and Efficacy Study of DermGEN Dermal Regeneration Scaffold for the Treatment of Diabetic Foot Ulcers

Version: 5.0

Date: 28 March 2016

Approved for DeCell Technologies, Inc. by:

P.F Gratzer, PhD Date:

INVESTIGATOR PROTOCOL AGREEMENT PAGE

A Pilot Safety and Efficacy Study of DermGEN Dermal Regeneration Scaffold for the Treatment of Diabetic Foot Ulcers

I agree, as an Investigator conducting this study:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, with any future amendments, and with any other written study conduct procedures provided and reviewed and approved by DeCell Technologies, Inc. ("DeCell")
- Not to implement any significant deviations from or changes to the protocol without agreement from the sponsor and prior review and the written approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard to the patients, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational product, as described in this protocol, and any other information provided by the sponsor including, but not limited to, the current Investigator's Brochure or equivalent document provided by DeCell.
- That I am aware of, and will comply with, Good Clinical Practices (GCP) and all applicable regulatory requirements, including the regulations governing the use of controlled substances and devices.
- To ensure that all persons assisting me with the study are adequately informed about the investigational product, and that they are qualified to perform their study related duties and functions, as described in the protocol.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply details about the Qualified Investigator's ownership interest in the sponsor or the study drug, and more generally about his/her financial ties with the sponsor. DeCell will obtain and disclose any relevant information in this regard solely for the purpose of complying with regulatory requirements. Hence, I:
  - Agree to supply DeCell with all information regarding ownership interest and financial ties with that company (including those of my spouse and dependent children);
  - Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study; and
  - Agree that DeCell may disclose this information about such ownership interests and financial ties to regulatory authorities.

Principal Investigator's Name: _____
(please print)

_____ _____
Principal Investigator's Signature Date

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ACRONYMS & ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
bpm	Beats per minute
CRF	Case Report Form
CNS	Central Nervous System
CV	Cardiovascular
ECG	Electrocardiogram
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl transpeptidase
$HbA1_c$	Glycohaemoglobin
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board, or Ethics Review Committee, or similar entity
i.v.	Intravenous
LDH	Lactate Dehydrogenase
LUMT	Leg Ulcer Measurement Tool
SAE	Serious Adverse Event

1. STUDY BACKGROUND

1.1 Study Rationale

The number of people afflicted by diabetes is increasing significantly every year worldwide, with an estimated 366 million affected in 2011 that is projected to reach 439 million by 2030 — approximately 10% of the world's adult population. Of that population, up to 25% are expected to have chronic foot ulcers which can lead to significant complications: 85% of lower extremity amputations are an end result of diabetic ulcers[2]. This equates to a limb being amputated somewhere in the world every 20 seconds due to diabetes[3,4]. In Canada, 9 million people are diabetic and between 1.35 and 2.25 million will suffer from chronic foot ulcers[5]. In Nova Scotia, which has one of the highest rates of diabetes in Canada, more than 98,000 people are affected by diabetes, with between 14,700 and 24,500 people afflicted with chronic foot ulcers[6,7]. In addition, the problem of diabetes-related ulcers in Nova Scotia is projected to grow, with the number of people with diabetes increasing by at least 3% by 2020.

The most common form and first line of treatment for chronic diabetic foot ulcers is the use of weekly debridement. Patients are assessed initially to determine which detriments to healing (infection, vascular insufficiency, uncontrolled diabetes, smoking, poor nutrition, deformity and poor offloading) of an ulcer may be present. These detriments are then treated for optimization over the ensuing weeks to months. During this time, patients will have local wound care with debridement and the wound will be cleaned of any infected and necrotic tissue, using sharp debridement until a pristine bleeding wound is obtained. The wound site is then wrapped with a non-adherent and moist dressing followed by dry gauze, and the site is protected from weight-bearing (i.e., is off-loaded). This procedure is repeated at set intervals until the wound either heals, or (once all detriments to healing have been optimized and the wound has not healed) treatment is determined to be futile. The success rate for complete wound closure with standard care is very low and variable, with a range from single digit percentage to as high as 50%, and if healing does occur, it takes on average 8 to 9.5 weeks[8,9]. However, previous studies have shown that reduction in the area of the chronic wound during the first four weeks of treatment is a predictor of complete healing at 12 weeks[10]. Diabetic foot ulcers that persist more than 4 weeks have 5-fold higher risk of infection[11]. Development of an infection in a foot ulcer increases the risk for hospitalization 55.7 times and the risk for amputation 155 times[11]. Any wound that remains unhealed after 4 weeks is cause for concern, as it is associated with worse outcomes, including amputations[12].

Costs associated with treating diabetic foot ulcers range by country and region, but in all cases are a major economic burden. For example, in the U.S. in 2007, $116 billion was directly spent on diabetes, with at least 33% of these costs linked to the treatment of diabetic foot ulcers with an average cost per ulcer episode of $13,179. In Canada, the average cost of treating a diabetic foot ulcer is $10,736, with more than $150 million in total spent annually[5].

Although standard of care is the most widely used treatment for diabetic foot ulcers and the main form of treatment in Canada, there are a number of advanced wound care products available to the clinician. Most products fall under the category of a biologic dressing ranging from cell-containing living skin analogs such as Apligraf® (Organogenesis) and Dermagraft® (Shire) to tissue-derived decellularized scaffolds like GraftJacket® decellularized human dermis (Wright Medical), Oasis® porcine small intestinal submucosa (Smith and Nephew), and EpiFix® dehydrated human amnionic membrane (MiMedix). These products are designed and promoted as wound healing and tissue regeneration matrices that, once applied to the patient, are integrated with and then resorbed by the patient’s body. The use of these treatments, however, has been limited due to their prohibitive cost and inconsistent clinical performance. For example, market leaders Apligraf®, Dermagraft®, and Graftjacket® range in price from $1,500-$2,500 USD for a 2” x 2” graft.

Most importantly, although initial limited clinical studies used to prove effectiveness for marketing and reimbursement purposes were successful, performance of these products in general use has proven to be far less successful. The most expensive (and cell-based) products, Apligraf® and Dermagraft® are in fact not incorporated after application, and eventually are sloughed off the wound due to death of the cellular material within the graft. Further, even when successful, they have required from 6 to 10 reapplications of the product in order to achieve a wound closure rate of 35-55%[14]. In the case of Dermagraft®, costs of manufacture, poor sales, and a recent failed clinical trial for venous ulcers prompted Shire to sell Dermagraft® assets to Organogenesis with a loss of $650 million USD[15]. In the case of the ultimate market leader in terms of sales, GraftJacket® decellularized human dermis (Wright Medical), inconsistent and low rates of healing have been attributed to the failure to adequately remove donor cell materials (DNA/RNA, HLA cell membrane proteins) while preserving the natural architecture of the remaining extracellular matrix (ECM) scaffold[16,17]. The presence of cell remnants and disruption of tissue architecture increases inflammatory reactions both in-vitro and in-vivo, leading to inadequate and incomplete healing[18,19]. It should be noted that only Dermagraft® has been approved for use in Canada, and treatment of most diabetic foot ulcer patients in Canada consists of debridement alone.

In order to address this unmet need for a safe, consistent, and effective treatment for diabetic foot ulcers, a new start-up company located in Halifax, DeCell Technologies Inc. ("DeCell"), has developed its product DermGEN, a sterile, highly-purified, decellularized regeneration scaffold derived from donated human skin. This product and company have spun out of research conducted by Dr. Paul Gratzer (School of Biomedical Engineering, Dept. of Surgery) at Dalhousie University. Dr. Gratzer's patent pending decellularization technology has been shown to be superior to others in achieving very high levels of cellular material removal (95-99%) including DNA/RNA, HLADR, HLA-ABC, and cytoskeletal proteins beta-actin and vimentin[20]. In addition, the process maintains the natural composition and architecture of the ECM while creating a validated sterile product (See Appendix 1, Figures 1-5, Table 1). Using an immune-competent rat biocompatibility model (ASTM standard F1408 -97) and directly comparing DermGEN to the leading competitor Graftjacket®, there was consistent superiority as DermGEN demonstrated lower inflammation, more-rapid vascularization, and better tissue remodeling at 1, 3 and 9 weeks post-surgery (See Appendix 1, Figures 6-14). It should be noted that a more rigorous model was used here with excellent results, as human tissue was implanted into a rat (that is, a xenograft). In practice, the human decellularized dermis will be used to treat human patients and therefore would be a much better situation with transplantation within the same species (i.e., an allograft). DeCell Technologies Inc. has already received approval from Health Canada to use DermGEN in humans (See Appendix 2).

The purpose of this clinical trail is to perform a limited pilot study, the first study in man to assess the effectiveness and safety of DermGEN in the treatment of non-healing diabetic foot ulcers (DFU), as a preliminary to studies in larger populations and different wound types. This will be a one-arm prospective study with control comparisons made to historical data for standard of care treatment of DFU's (debridement, sterile moist bandages, off-loading of the foot) obtained within the Multi-Disciplinary Leg Ulcer Clinic (MDLUC) at the QEII Hospital. This study in Halifax will be mirrored in one other participating health care center in Toronto, with each center enrolling 5-10 patients for a total of 20 patients. Funding for this trial will be from a recently awarded (January 2014) CIHR Proof of Principle (POP) II Grant with Dr. Mark Glazebrook (Orthopaedic Surgeon, QEII Hospital) as Principal Investigator and Dr. Paul Gratzer (Associate Professor, Biomedical Engineering and CEO of DeCell Technologies Inc.) as the industrial sponsor.

Since previous studies have shown that reduction in the area of the chronic wound during the first four weeks of treatment is a predictor of complete healing at 12 weeks[10] and that DFU's persisting more than 4 weeks have 5-fold higher risk of infection[11], we will be determining and comparing the reduction of wound size for our study at 1 and 4 weeks. Our primary outcome measures will be the proportion of patients with

complete healing at 12 and 20 weeks. Time to complete healing, incidence of recurrence of ulcer, incidence of adverse events, wound characterization, and mean and median wound size will also be documented and compared over the 20-week scope of the study.

Given the current standard of care for diabetic foot ulcers, DermGEN may be transformative to a new standard of care that will have a great impact on the lives and wellness of diabetic Canadians. The dramatic statistic of a limb being amputated somewhere in the world every 20 seconds due to diabetes is simply unacceptable. Having a cost-effective product like DermGEN available to clinicians could truly alter this appalling outcome.

1.2 Pre-clinical in vitro Data

See Investigators' Brochure.

1.3 Pre-Clinical in vivo Data

See Investigators' Brochure.

1.4 Safety Considerations

DermGEN is expected to be a safe wound covering, with a favourable risk-benefit ratio as outlined below.

1.4.1 Harms

Possible complications with the use of DermGEN include maceration, specific or non-specific immune response, graft infection, graft resorption, or graft non-integration. Given the nature of the treatment and location and type of wound being treated, most adverse events may be stopped through the cessation of treatment with DermGEN.

1.4.2 Benefits

The possible benefits of the proposed study include a faster, more effective, and more cost effective resolution of a chronic diabetic foot ulcer.

1.4.3 Financial Compensation

Patients enrolling in this study receive no financial reward for participation. The study treatment is provided at no cost.

2. STUDY OBJECTIVES

The purpose of this clinical trail is to perform a limited pilot study to indicate the safety and effectiveness of DermGEN in the treatment of non-healing diabetic foot ulcers (DFU).

Adverse events incidence is the only objective regarded as a safety issue.

2.1 Primary Objectives

Primary Outcome Measures:

1. Mean and median reduction in wound area in the first 4 weeks.
2. Proportion with complete healing in the first 12 weeks. (*Complete healing is defined as 100% epithelialization without drainage*.)
3. Incidence of adverse events.
4. Impact of treatment, as measured by LUMT (Leg Ulcer Measurement Tool) and SF12 (See Investigational Plan, below)

2.2 Secondary Objectives

Secondary Outcome Measures:

1. Proportion with complete healing at any time point
2. Time to first-measured complete healing
3. Incidence of recurrence after complete healing
4. Change in wound characteristics
5. Mean and median reduction in wound area at 12 weeks

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is an interventional, single-arm, prospective study of DermGEN applied to diabetic foot ulcers.

The study treatment will be conducted for a total of up to 20 weeks, and 15-20 patients will be enrolled.

In order for the treatment team to gain experience with the sizing and application of DermGEN and the most suitable off-loading methodology, the first one to three patients may have differing closure procedures, and will not be included in the per-protocol analysis of the study (although all safety data will be reported). Thereafter, the team will specify a single regimen of procedures, dressing types, and off-loading methodology to be used for all subsequent patients.

3.1.1 Screening Procedures (Days -28 to -1)

Potential subjects will be screened during the 4 weeks preceding Day 0 to determine if they meet the inclusion and exclusion criteria, and if all criteria are satisfied, will be eligible to participate in the clinical trial. All general and indication-specific entry criteria must be met before study entry. Subjects who enter the trial will be provided with an Ethics Committee approved written informed consent for review and signature (See Appendix 3).

3.1.2 Clinic Admission (Day 0)

After enrollment and an initial assessment (time zero data), patients will be treated with DermGEN decellularized human dermal matrix. Following standard of care procedures, the wound will be debrided to provide healthy tissue margins and a bleeding wound bed. A 4 cm x 4 cm piece of DermGEN will be prepared by sizing to approximately 2-3 mm past the margins of the ulcer with the dermal side in contact with the wound bed, and securing it to the wound with sutures.

A non-adherent dressing will be used to cover the DermGEN graft, followed by a moisture retentive dressing and either (a) a compressive dressing; or (b) a vacuum-assisted wound closure dressing ("VAC-Assist"). All patients will have the same brands and types of dressings applied, except for the first 1 to 3 patients treated (see final paragraph, section 3.1 above).

3.1.3 Subsequent Clinic Visits (Weeks 1, 2, 3, 4, 12, and 20)

Follow up visits will be at 1, 2, 3, 4, and 12 and 20 weeks and as required for clinical care of active detriments to healing and local wound care.

The LUMT will be administered at each of the 1, 2, 3, 4, and 12 and 20 weeks FU visits in order to capture data relevant to the study. The SF-12 survey will be administered at time 0, 4, 12 and 20 weeks post-treatment.

Digital photography will be utilized to capture the appearance and size of the ulcer at each visit. Clinic photographs will be taken with the digital camera supplied by DeCell. Other photographs to demonstrate the condition of the wound between clinic visits may be taken with any digital camera (including smartphones), and a measuring ruler must be visible in each picture. Patients and caregivers are to be encouraged to take their own photographs if the wound ever becomes uncovered or visibly stained – again ensuring that some ruler appears in the photos – and copies should be provided to the study staff.

Dressing changes will occur at each visit, and a record of these changes kept. All patients will receive appropriate wound off-loading using a device appropriate to ulcer location. All post-treatment complications will be recorded on the appropriate case report form.

Patients with complications that may be managed by further treatment, for example antibiotic administration or reapplication of another DermGEN graft, will remain in the study.

For any subject who requests study withdrawal or is withdrawn by the investigator, the reason for study discontinuance will be recorded by the Principal Investigator on the appropriate case report form.

3.2 Dose Selection and Use

DermGEN will be applied on Day 0, following the directions for use.

If at a subsequent visit the product material is deteriorating, then the investigator may, at his discretion, remove the remaining product material, prepare the wound bed appropriately, and apply one new DermGEN treatment. In such cases, the remaining course of the study will continue unchanged, and the patient's last visit will still be at Week 20.

The reasons for any second application of DermGEN must be carefully documented, together with before and after photographs showing the deteriorating specimen in situ before removal and also the new specimen in place prior to applying new dressings.

4. STUDY POPULATION

4.1 General Considerations

A total of 15-20 patients will be enrolled for the study, with patients enrolled in each of the following participating centers: Halifax and Toronto.

Ages will include 18 and older from both sexes. Potential subjects will be screened to determine if they meet the inclusion and exclusion criteria and if all entry criteria are achieved, will be eligible to participate in the clinical trial. All general and indication-specific entry criteria must be met before study entry. Subjects who enter the trial will be provided with an Ethics Committee approved written informed consent for review and signature.

4.2 Inclusion Criteria

A subject will be considered eligible to participate in this study if each of the following inclusion criteria is satisfied:

1. Patient with documented stable Type I or II diabetes ($HbA1_C$ >7.0 within 1 month prior to Day 0).
2. Patient's ulcer has been present for a minimum of 2 weeks as of Day 0.
3. Study ulcer has healed <30% in size during the 2 weeks prior to Day 0.
4. Ulcer area is ≥1 cm^2 prior to debridement at Day 0 of study.
5. Ulcer extends through dermis and into subcutaneous tissue but without exposure of muscle, tendon, bone or joint capsule.
6. Ulcer is free of necrotic debris and clinical infection, and is comprised of healthy vascular tissue suitable for skin grafting on Day 0.
7. Patient has adequate circulation to the foot as evidenced by palpable pulse or pulse detectable with Doppler ultrasound, and lack of visible cyanosis in skin bordering the ulcer.
8. Female patients are not pregnant at time of, or during study.
9. Patient and caregiver ready and willing to participate and comply with follow-up regime.
10. Patient or legal representative has read and signed the Institutional Ethics Review Board approved informed consent form.

4.3 Exclusion Criteria

A subject will not be considered eligible to participate in this study if any one of the following exclusion criteria is satisfied:

1. Evidence of gangrene on affected foot.

2. Ulcer is over Charcot deformity (fractures or dislocation).
3. Ulcer is non-diabetic in etiology.
4. Ulcer has tunnels or sinus tracts that cannot be completely debrided.
5. Medical condition(s) that in the Investigator's opinion make the patient inappropriate for study
6. Patient has/had malignant disease not in remission for 5 years or more
7. Patient has acute or chronic hepatitis, cirrhosis, serum albumin <2.0 gm/dL, or has alkaline phosphatase or LDH at twice the normal upper limit
8. Patient receiving oral or parenteral corticosteroids, immunosuppression or cytotoxic agents, or is anticipated to require such agents during study
9. Patient received radiation therapy within 30 days of Day 0 of study
10. Patient has AIDS or is infected with HIV
11. Patient has participated in another study using investigational drug(s) or device within the previous 30 days
12. Obvious clinical signs and symptoms of ongoing cellulitis or osteomyelitis
13. Patient has any other condition which seriously compromises their ability to complete the study
14. Patient has known allergies to antibiotics, such as penicillin and streptomycin
15. Patient has a history of bleeding disorder
16. Patient received elective osseous procedures to the study foot within 30 days prior to screening visit, *except* that patients whose DFU overlies an area of treated osteomyelitis may be included, providing there exists a suitable base for application of the DermGEN.

4.4 Concomitant Medications

In general, there is no reason to expect medications to interact with DermGEN. Only medications considered prejudicial to wound healing are prohibited. These include, but are not necessarily restricted to, the following:

- Corticosteroids, either topical near the ulcer, or systemic
- Immunosuppressive drugs of any type, either topical near the ulcer, or systemic
- Anti-infective agents used topically, if believed to be cytotoxic

Patients will remain on all medications prescribed to treat their diabetes and associated conditions as determined at the point of enrolment. If there are any changes to a patient's medication (dosing, new medications, alternate medications) during the study, this will be noted in the patient's study file and reviewed by the study supervising clinician to determine continued eligibility of the patient in the study. Patients with complications that may be managed by further treatment, for example antibiotic administration or reapplication of another DermGEN graft, will remain in the study.

4.5 Dietary and Other Restrictions

None. A prudent diet for control of diabetes is encouraged.

4.6 Subject Completion and Withdrawal

4.6.1 Subject Completion

Patients will be required to attend all scheduled appointments specified for the study. If required, appointments may be re-scheduled within a week of the original appointment date. Patients will be required to adhere to home care regimes as provided verbally and in writing by their clinician, including dressing changes, off-loading of the affected limb, and immediate reporting of adverse events such as infection, continued bleeding, excessive inflammation and pain.

4.6.2 Subject Withdrawal

Any subject who voluntarily withdraws (e.g., withdrawal of consent) or is discontinued (e.g., as a result of an AE) from the study prior to the completion of all assessments will be considered as having withdrawn from the study.

Subjects may be withdrawn from the study under any of the following circumstances:

- (i) patient is non-compliant with home care regime (e.g. not wearing off-loading cast),
- (ii) presence of recurrent, untreatable infection,
- (iii) patient develops illness after enrollment that may unduly affect ulcer healing,
- (iv) patient requires more than one re-treatment with DermGEN

When an event such as a family emergency, a transient intercurrent illness (such as a cold) unrelated to study medication, or a remediable act of non-compliance prevents a subject from participating in a scheduled visit but the subject wishes to continue in the study, then with the agreement of the investigator, the clinical staff may attempt to reschedule the visit and retain the subject in the study.

If a subject is prematurely discontinued from participation in the study for any reason after treatment has begun, the investigator or designee must make every effort to perform the assessments scheduled for the Follow-Up Visit (section 6.5.1). The reason for withdrawal will be recorded in the CRF and the subject's medical record.

5. INVESTIGATIONAL MATERIAL INFORMATION

5.1 Investigational Material Identification

Donor human skin received from certified tissue banks will have a unique identifier assigned by the tissue bank. After decellularization processing by DeCell Technologies Inc., each piece of decellularized skin will be given a unique product code assigned by DeCell that will allow tracing to donor tissue received from tissue banks.

5.2 Packaging and Labelling

DermGEN will be provided in a hydrated form stored at room temperature. It will be supplied within a sterile, sealed specimen container containing phosphate buffered saline solution containing streptomycin/penicillin.

DermGEN will be labelled with a product code that will identify it with a specific date of manufacture and tissue source. The product name, DeCell Technologies Inc. logo, and date of manufacture will also appear on the label separately as well as the following text: "Store at room temperature. Do not re-sterilize. Do not freeze. Do not re-seal. Not for sale, for sanctioned clinical trial only. Use aseptic technique to open packaging and handle product inside."

5.3 Handling and Storage

Shipping in the container provided requires no special handling procedures.

As prescribed on the package label, the product should be stored at room temperature. It should not be re-sterilized, re-frozen, or re-sealed. If not used within 4 hours, it should be discarded according to locally-approved procedures. It is not for sale, and is for sanctioned clinical trial use only.

Use aseptic technique to open packaging and handle product inside.

5.3.1 Receipt of Study Product by Clinical Site

Upon receipt by the study site, the clinical site staff will examine the shipment to verify it has been received in acceptable condition.

5.4 Dispensing

The study product will be dispensed and administered according to study specific procedures. Only subjects participating in the study will receive it. Only authorized clinical staff may supply or administer it.

5.5 Accountability Procedures

Clinic records will be maintained to capture the following information:

a) Quantity received,
b) The current quantity on site,
c) Quantity used on each subject,
d) Quantity removed from stock but not dispensed (e.g., damaged, dropped, spilled), and
e) Quantity remaining at the end of the study and retained, returned, or destroyed, as per the sponsor's instructions.

5.6 Method of Assigning Treatments

All patients enrolled in the study will receive similar treatment. There is no blinding of treatment assignments.

6. STUDY PROCEDURES & ASSESSMENTS

6.1 Study Procedures

6.1.1 Screening (Day −28 to −1)

Patients may be enrolled in the study at or any time after initial presentation if it can be documented that they comply with all inclusion and exclusion criteria. (Enrollment day is designated as Day 0.) The investigator or designee will discuss with each subject the nature of the study, its requirements, and its restrictions. Written informed consent will be obtained prior to the performance of any protocol-specific procedures

The following will be required during the Screening period to determine eligibility:

- Informed consent
- Subject demographics
- Medical history
- Review of concomitant medication
- Relevant physical examination
- Vital signs
- Clinical laboratory tests
- Hepatitis B, Hepatitis C, and HIV screening
- Review of inclusion and exclusion criteria and study restrictions

6.1.2 Enrollment (Day 0)

After enrollment and an initial assessment including the Leg Ulcer Measurement Tool [LUMT] (see Appendix 4), patients will be treated with DermGEN decellularized human dermal matrix. Following standard of care procedures, the wound will be debrided to provide healthy tissue margins and a bleeding wound bed. A 4 cm x 4 cm piece of DermGEN will be prepared by sizing to approximately 2-3 mm past the margins of the ulcer and securing to the wound with sutures ensuring that the dermal side is in contact with the wound bed. [*The dermal side of DermGEN can be identified by the following: (i) apply a drop of blood or contact with blood from the wound bed to one surface of the graft; (ii) rinse blood off with sterile saline; (iii) if blood does not wash off entirely, this is the dermal side—the epidermal side will not retain visible quantities of blood.*] A non-adherent dressing will be used to cover the DermGEN graft, followed by (a) a moisture retentive dressing and a compressive dressing, or (b) dressings as specified for use by all patients, once the first 1 to 3 patients have been treated (see section 3.1, above). Suitable off-loading will also be provided, with careful instructions for use.

6.1.3 Follow-up Procedures (Week 1 to Week 20)

Follow up visits will be at Weeks 1, 2, 3, 4, and 12 and 20, and as required for clinical care of active detriments to healing and local wound care. The Leg Ulcer Measurement Tool [LUMT] will be completed at each of the Weeks 1, 2, 3, 4, 12, & 20 follow-up visits in order to capture data relevant to the study. In addition, digital photography will be utilized to capture the appearance and size of the ulcer at each visit. The SF-12 survey will be administered at Day 0, and at the Weeks 4, 12 and 20 visits.

Dressing management will follow and a record of all changes will be kept. All patients will receive wound off-loading using a device appropriate to ulcer location.

All post-treatment complications will be recorded on the appropriate case report form. Patients with complications that may be managed by further treatment, for example antibiotic administration or application of one replacement DermGEN graft, will remain in the study.

For any subject who requests study withdrawal or is withdrawn by the investigator, the reason for study discontinuance will be recorded by the Principal Investigator on the appropriate case report form. Stopping treatment or withdrawal from the study will occur when:

- (i) patient is non-compliant with home care regime (e.g. not wearing off-loading cast),
- (ii) presence of recurrent, untreatable infection,
- (iii) patient develops illness after enrollment that may unduly affect ulcer healing,
- (iv) patient requires more than one re-treatment with DermGEN

6.1.4 Compliance

Patients will be required to attend all scheduled appointments required for the study. If required, appointments may be re-scheduled within a week of the original appointment date. Patients will be required to adhere to home care regimes as provided verbally and in writing by their clinician including dressing changes, off-loading of the affected limb, and immediate reporting of adverse events such as infection, continued bleeding, excessive inflammation and pain. Patients will be encouraged to take their own photographs of any untoward signs.

6.2 Safety Assessments

6.2.1 Physical Examination

A relevant physical examination assessing the subject's overall health and physical condition will be will be performed at every visit.

6.2.2 Adverse Events

All AEs occurring after the subject has signed the ICF until the end of the Follow-up period will be recorded. AEs present at first dosing or any AE identified prior to first dosing will be recorded in the source documentation as Baseline Signs and Symptoms.

AEs will be ascertained on the basis of volunteered signs or symptoms and on clinical observation and assessment at study visits. Spontaneous AEs will be recorded as such, and AEs will also be elicited by clinical site staff using non-leading questions at designated time points.

All SAEs will be followed until resolved or until a stable status has been achieved.

6.2.3 Clinical Laboratory Assessments

Patients must have recent $HbA1_c$ data in order to qualify for enrollment, and be not excluded on other health grounds. A repeat $HbA1_c$ will be obtained at the end of study (or withdrawal) visit for each patient, as well.

Other laboratory data obtained during the study as part of usual care should be available for audit by the sponsor during the study and for 6 months after; but no specific testing is required by this protocol.

Laboratory safety data will be reviewed by the investigator or designee as part of usual care.

6.2.4 Medication History

All medications (prescription and non-prescription, herbal medications, or investigational drugs) taken by the subjects during the 14 days prior to Screening and during the remainder of the study will be recorded in the source documentation. The reported medications will be reviewed and evaluated by the investigator or designee to determine if they affect the subject's eligibility to participate in the study.

6.2.5 Concomitant Medications

Patients will remain on all medications prescribed to treat their diabetes and associated conditions as determined at the time of enrolment. If there are any changes to a patient's medication (dosing, new medications, alternate medications) during the study, this will be noted in the patient's study file and reviewed by the study supervising clinician to determine continued eligibility of the patient in the study.

6.3 Efficacy Assessments

6.3.1 Primary Outcome Measurements are the following:

1. Mean and median reduction in wound area in the first 4 weeks
2. Proportion with complete healing in the first 12 weeks. (Complete healing is defined as 100% epithelialization without drainage.)
3. Incidence of adverse events
4. Impact of treatment, as measured by LUMT and SF-12.

6.3.1.1 Wound Size

Wound size will be assessed:

a) By direct measurement of largest and smallest dimensions; and

b) By estimation from a photograph with a measurement scale shown beside the wound. Photographs should be taken from a distance of approximately 6 inches, and from vertically above the centre of the ulcer.

6.3.1.2 Impact of Treatment

The impact of treatment will be analyzed using the LUMT and the Short-Form Health Survey (SF-12), both reliable and validated outcome measures.

The Leg Ulcer Measurement Tool (LUMT) provides numerical scale grading of clinician- and patient-rated domains (see Appendix 4).

The short form health survey (SF-12) is a 12-question assessment of mental and physical health and quality of life outcomes. (See Appendix 5)

6.3.2 Secondary Outcome Measurements include the following:

1. Time to complete healing
2. Time to first-measured complete healing
3. Incidence of recurrence after complete healing
4. Change in wound characteristics over time
5. Mean and median reduction in wound area at 12 weeks

7. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

7.1 Statistical and Analytical Plans

7.1.1 Analysis Populations

Safety population: all subjects will be included in the analysis for safety.

Efficacy population: all subjects excepting the first 1 to 3 (i.e. those treated before standardization of procedures) will be included in the analysis to seek efficacy signals.

7.1.2 General Statistical Considerations

This small study is not expected to support statistical conclusions. Descriptive statistics will be used throughout.

7.1.3 Planned Analyses

7.1.3.1 Analysis of Safety Assessments

Safety data include treatment-emergent AEs, physical exams, and clinical laboratory assessments.

Narrative summary reports will constitute the adverse event database, with simple summary analysis. Systemic effects are not expected due to DermGEN alone, and such AE's may be expected to be caused by the underlying ulcer. All serious AE's will be reported as required by GCP, and will be described in full in the final study report.

7.1.3.2 Analysis of Efficacy Assessments

Photographic, narrative, and laboratory data will be examined in various ways to seek a signal of efficacy. Conclusions may be used to design more rigorous efficacy investigations in one or more subsequent studies.

7.1.3.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will include age, ethnic origin, height, weight, and BMI. Other baseline information will include relevant medical and surgical history, and prior and concomitant medications. Descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum) for continuous variables, and the proportion of subjects for categorical variables will be

presented for demographic and baseline characteristics using the safety population. No formal statistical comparison between the groups will be performed.

All important deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be described. Relevant medical and surgical history will be listed.

7.2 Determination of Sample Size

The sample size chosen for this study was based upon precedent set by other first in human studies of similar nature and was not based on power calculations.

8. STUDY ADMINISTRATION

8.1 Data Collection and Database Construction

For all data collected on the CRF, source documentation should be available at the site. A source document checklist will be used to identify the source data for all data points collected.

For the clinical trial, DeCell Technologies will assign a unique identifier for each patient enrolled in the study and this identifier will be used on all Case Report Forms (CRFs) and any other documents sent to DeCell throughout the study. Information collected under the unique identifier for each patient will be devoid of any specific personal information that may directly identify an individual. Only each clinician's study coordinator and the clinicians themselves participating in the study will know the identity of their patients and their assigned unique study identifier for traceability. DeCell Technologies will know the unique patient identifier and unique product code of decellularized skin used to treat the patient for traceability. Data for the study will be captured on a paper version of CRFs and sent to DeCell Technologies who will enter all the data into an electronic database created in Microsoft Excel© that will be encrypted with a password. Access to the database will only be made available to the Halifax-based Study Coordinator, the P.I. of each participating site, and DeCell Technologies Inc.

8.2 Regulatory and Ethical Considerations

8.2.1 Ethical Conduct of the Study

This study will be conducted in accordance with GCP and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable local laws and regulations. This may include an inspection by the sponsor representatives and/or regulatory authority representatives at any time.

8.2.2 Notification to Primary Care Physician

If agreed to by the subject, the investigator or designee will notify the subject's primary care physician of the subject's participation in the study. The primary care physician may contact the investigator for any further information regarding the subject's participation in the study.

8.2.3 Regulatory Authority Approval

In accordance with any applicable local regulations, the sponsor or designee will obtain approval from the appropriate regulatory agency prior to a site initiating the study in that country or jurisdiction.

8.2.4 Ethics Approval

It is the investigator's responsibility to ensure that this protocol is reviewed and approved by the appropriate Ethical Review Committee or Institutional Review Board (IRB).

The IRB must also review and approve the site's ICF and any other written information provided to the subject, prior to the enrollment of subjects; and any advertisement that will be used for subject recruitment. The investigator or designee must forward to the sponsor copies of the IRB approval and the approved informed consent materials, which the sponsor must receive prior to the start of the study.

If during the study, it is necessary to amend study documentation (e.g., protocol, ICF, etc.), the investigator or designee will be responsible for ensuring that the IRB reviews and approves these amended documents. IRB approval of the amended ICF must be obtained before new subjects consent to take part in the study, using this version of the form. Copies of the IRB approval of the amended ICF and the approved amended ICF must be forwarded to the sponsor as soon as available.

8.2.5 Subject Informed Consent

All relevant study information will be summarized in an informed consent form (completed in collaboration with the sites) provided by DeCell. The investigator or designee will explain all relevant aspects of the study to the patients prior to entry unto the study (i.e., before any examinations and procedures associated with the selection for the study are performed or any study-specific data is records on study-specific forms).

The patient will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for their decision.

Then the patient and investigator or designee will sign and date the form. The patient will receive a copy of the signed and dated form.

The signed informed consent form will remain in the investigator site file, or if locally required in the patient's note/file of the medical institution. If informed consent is obtained on the date the study specific procedures are performed, the study record or the patient's clinical record must clearly show that information consent was obtained prior to these procedures.

The informed consent form and any other written information provided to the patient will be revised whenever important new information becomes available that may be relevant to the consent, or if there is an amendment to the protocol that necessitates a change to the content of the written informed consent form. The investigator will inform the patient of the changes in a timely manner and will ask the patient to confirm participation in the study by signing the revised informed consent form. Revised informed consent forms must receive the IRB's approval before implementation.

Patient information (both locally and from participating sites) will be identified by a study number. Patient identifiers (name, health card number, and hospital specific identifying numbers) will not be included in study records. Patients will be coded by a number indicating the site and chronological number of enrollment at that site.

8.2.6 Principal Investigator Reporting Requirements

In accordance with applicable local regulatory requirements, the investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her clinical site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

8.3 Privacy

All records identifying the patient will be kept confidential and to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to DeCell. Only the patient's study number will be recorded in the CRF. If the patient's name appears on any other document, it will be anonymized. Study data stored in a computer will be handled in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of DeCell, the IRB, or regulatory authorities may inspect their medical records to verify collected information and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data and health information protection laws. If the results are published, the patient's identity will remain confidential. The principal investigator at each site will maintain a list to enable patients to be identified.

8.3.1 Subject Identifiers

De-identified study data will be collected via paper CRF and transferred to DeCell. Subjects will be assigned a study number and this will be used for documentation throughout the clinical trial. This number and the patient's initials are the only identification that will be used on data collection forms. Study records, paper and electronic, will be kept in a secure location at the clinical site and/or hospital record department.

8.3.2 Access and Disclosure of Personal Information

Study data will be entered into a secured electronic database stored at DeCell Technologies' main office on a password protected computer, with separate password required to access the database. The database will be backed-up with encryption to an external local and off-site hard-drive. Only study staff and DeCell will have access to this data. The electronic database will track subjects by an assigned 5-digit number and subject initials. No identifying information is entered into the database system. The subject's assigned 5-digit number will be the only identifier used on all correspondence to DeCell.

The following personnel will have access to the personal information: members of the IRB of record, the study staff at each site as outlined in the delegation log, and quality assurance staff and auditors.

8.3.3 Release of Subject Information

The results of this study will be reported in such a manner that subjects will not be identifiable in any way. Published reports or presentations will refer to grouped data or coded individual data and not to any identifiable individuals. Study reports sent to the sponsor or regulatory agencies will not include subject names.

8.3.4 Consent for Collection, Access, Use and Disclosure of Subject Information

By signing the ICF, the subject consents to the collection, access, use, and disclosure of his or her information as described in that document. If a subject withdraws consent, some of the subject's information may still be collected, used, and disclosed by those involved in this study per applicable laws.

8.4 Study Monitoring

8.4.1 Study Monitoring by Compliance Auditors

All study data will be reviewed by the Scientific Advisory Board (SAB) of DeCell Technologies Inc.

DeCell may conduct an audit to ensure compliance with GCP and regulatory authorities. The investigator/institution will be informed of the audit outcome. In addition, inspections by regulatory health authority representatives, funding agency, or ethics review board might occur and the site will notify DeCell immediately.

The investigator/institution agrees to allow the auditor or inspector direct access to all the relevant documents and allocate time to the auditor/inspector to discuss any findings.

8.4.2 Study Monitoring by Sponsor

In accordance with GCP, DeCell's representatives will review the protocol, study requirements and responsibilities with the site staff including identification or source data items. DeCell will monitor the site to verify that data are authentic, accurate, complete and that the safety and rights of participating patients are being protected. In addition, it will assess if the study is conducted in accordance with the latest version of the protocol and study agreements. The investigator and representative of the institution (where applicable) agree to allow the monitor direct access to all relevant documents.

8.5 Principal Investigator's Data Responsibility

The principal investigator of each site must sign the protocol signature sheet before recruitment may start at the respective center. Likewise, all protocol amendments/integrated protocols must be signed and dated by the principal investigator before coming into effect at their respective center. A complete list of all participating centers and their investigator as well as all required signature documents, will be maintained in DeCell's study file.

The investigators and key personnel will be listed in the study file.

All other study personnel are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term "the investigator" is noted in the protocol text, it may refer to either the principal investigator at the site or an appropriately qualified, trained and delegated individual of the investigational site.

8.6 Study and Site Closure

This study may be terminated early if adverse events directly related to the use of DermGEN are observed within a significant number of patients.

8.7 Subject Compensation and Indemnification

Subjects will not be compensated for participation in the study.

8.8 Publication Policy

DeCell is committed to the results of every study it performs. DeCell in collaboration with the participating investigators will be responsible for publication and presentation strategy. All publications will follow institutional and tri-council policies and will be based on data released and agreed to by DeCell. The synopsis of the study protocol has been made available on the Internet at www.clinicaltrials.gov.

9. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All post -treatment complications and adverse events will be recorded on the appropriate case report form.

This study may be terminated early if adverse events directly related to the use of DermGEN are observed within a significant number of patients.

The investigator or designee and clinical site staff are responsible for the detection, documentation, and reporting of events meeting the definition of an AE or SAE.

9.1 Definitions

9.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and may not necessarily have a causal relationship with the administered treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. During the study, an AE can also occur outside the time that the investigational product(s) was given (e.g., during a washout period).

Pre-existing conditions, diseases, or disorders are not considered AEs unless there is a change in intensity, frequency, or quality.

9.1.2 Serious Adverse Events and Serious Unexpected Adverse Events

A SAE is any untoward medical occurrence that

- results in death,
- is life-threatening (at the time of the event),

- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A serious and unexpected AE is SAE that is not identified in nature, severity, or frequency in the risk information set out in the Product Monograph or on the label of the investigational material.

9.1.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Clinically significant abnormal laboratory findings (e.g., from clinical chemistry, hematology, or urinalysis) or other abnormal assessments (e.g., from vital signs or ECG) that are judged as clinically significant by the investigator or designee will be recorded as AEs or SAEs, if they meet the definitions provided in Sections 9.1.1 and 9.1.2. Furthermore, clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal findings associated with the disease being studied that are present at the start of the study and do not worsen will not be reported as AEs or SAEs, unless the investigator or designee judges them as more severe than expected for the subject's condition.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

9.2 Evaluation of Adverse Events and Serious Adverse Events

9.2.1 Classification of Adverse Event Severity

The investigator or designee is responsible for making an assessment as to the severity of an AE (see Table 1). If there is insufficient information to determine severity, the AE must still be reported.

Table 1. Classifications for Adverse Event Severity

Classification	Definition
Mild	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An event that is alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living or significantly affects clinical status. The event poses a significant risk of harm to the subject and hospitalization may be required.

9.2.2 Classification of Adverse Event Causality

For each recorded AE, the investigator or designee must make an assessment of causality based on the following criteria (see Table 3) to determine the relationship between the AE and study material.

Table 2. Classifications for Adverse Event Causality (i.e., relationship to study drug)

Classification	Definition
Unrelated	The AE or SAE is judged to be *clearly and incontrovertibly due only to extraneous causes* (e.g., disease, environment, etc.) and do not meet the criteria for study drug relationship listed under probable, possible, or unlikely.
Unlikely	The AE or SAE is *unlikely* related to the study drug, when the AE or SAE ▪ does not follow a reasonable temporal sequence from administration of the study drug ▪ may readily have been produced by the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject ▪ does not follow a known pattern of response to the study material ▪ does not reappear or worsen when the study material is re-administered
Possible	The AE or SAE is *possibly related* to the study material, when the connection to the study material appears unlikely but cannot be ruled out with certainty. This causal relationship is assigned when the AE or SAE ▪ follows a reasonable temporal sequence from administration of the study material ▪ may have been produced by the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject ▪ follows a pattern of response to the suspected study material
Probable	The AE or SAE *probably related* to the study material, when the connection to study material can be made with a high degree of certainty. This causal relationship is assigned when the AE or SAE ▪ follows a reasonable temporal sequence from administration of the study material ▪ cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject. ▪ disappears or decreases on cessation or reduction in dose (note that are important exceptions when an AE or SAE does not disappear upon discontinuation of the study material, yet relatedness clearly exists, e.g., bone marrow depression or tardive dyskinesias) ▪ follows a known pattern of response to the suspected study material reappears upon re-challenge

9.3 Reporting Procedures

9.3.1 Contacting Sponsor Regarding Safety

When issues regarding safety arise (e.g., SAE or a serious unexpected AE), the sponsor must be contacted within an appropriate timeframe.

DeCell assumes responsibility for appropriate reporting of AEs to the regulatory authorities. DeCell will also report to each investigator all SAEs that are unlisted and associated with the use of the study product. The investigator must report these events to the appropriate IRB that approved the protocol (unless otherwise required and documented by the IRB).

9.3.2 Reporting Period

AEs and SAEs will be assessed and recorded in the source documentation from the time of first contact with the subject (e.g., at the Screening) until the end of the Follow-Up phase of the study. AEs that occur after medical screening and prior to administration of the first dose of study drug will be recorded in the source documentation as Baseline Signs and Symptoms.

All unresolved AEs will be followed up for a minimum of 14 days after the subject's final study visit, unless the investigator's judgment dictates otherwise, the event has resolved or stabilized before the 14-day period, or the subject is lost to follow-up. All SAEs will be followed until resolved or until a stable status has been achieved.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects that occur following the Follow-up period. However, if the investigator or designee learns of any AE or SAE at any time after a subject has been discharged from the study and the event is considered as reasonably related to the study drug, the investigator will notify DeCell.

9.3.3 Any Adverse Event

All post-treatment complications and adverse events will be recorded on the appropriate case report form.

9.3.4 Any Serious Adverse Event

Any SAE—expected or unexpected, irrespective of relationship to study treatments, including death due to any cause—experienced by a study subject will be reported to DeCell by the investigator or designee within **24 hours** of learning of the event.

All additional follow-up evaluations for SAEs will be reported to DeCell.

9.3.5 Follow-Up of Adverse Events and Serious Adverse Events

All AEs and SAEs that have not resolved by the end of the study or have not resolved upon discontinuation of the subject's participation in the study must be followed-up until one of the following occurs:

- the event resolves
- the event stabilizes
- the event returns to a baseline value, if a baseline value is available

- the event can be attributed to agents other than the study drug or to factors unrelated to study conduct

When it becomes unlikely that any additional information can be obtained (e.g., subject or health care practitioner refuses to provide additional information, the subject is lost to follow-up), the investigator or designee will ensure that the follow-up includes any pertinent supplemental investigations (e.g., laboratory tests or investigations, histopathological examinations or consultation with other health care professionals) to elucidate the nature and/or causality of the AE or SAE.

9.4 Insurance for Patients

DeCell maintains clinical trial insurance for this study in accordance with the laws and regulations of Canada.

10. REFERENCES

(1) International Diabetes Federation (IWGDF), (2012)

(2) Rogers et al, JAPMA, 2008;98:166

(3) The Lancet (cover), Nov. 2005

(4) Armstrong, et al, Diabetes Care 2013, In Press

(5) Canadian Diabetes Association Website, Accessed February 2014

(6) Canadian Diabetes Association, "At the Tipping Point: Diabetes in Nova Scotia", 2013

(7) Canadian Diabetes Association, Website News, "Diabetes Wellness Plan is on the Election Agenda in Nova Scotia", Monday, Sept. 16, 2013

(8) "The Diabetic Foot in Nova Scotia: Challenges and Opportunities", May 2007, Diabetes Care Program of Nova Scotia

(9) "Audit of Time Taken to Heal Diabetic Foot Ulcers" Robertshaw, L, Robertshaw, D.A., and Whyte, I., Practical Diabetes Int., 2001; 18(1):6-9,

(10) "Percent Change in Wound Area of Diabetic Foot Ulcers Over a 4-week Period is a Robust Predictor of Complete Healing in a 12-week Prospective Trial." Sheehan P, Jones P, Caselli A, et al. Diabetes Care 2003; 26(6): 1879-82.

(11) "Risk Factors for Foot Infections in Individuals With Diabetes." Lavery et al., Diabetes Care. 2006; 29:1288-93.

(12) "Consensus development conference on diabetic foot wound care: April 7-8,1999,Boston, MA. American Diabetes Association. Diabetes Care." 1999;22(8):1354-1360.

(13) "The Costs of Diabetic Foot: The Economic case for the Limb Salvage Team" Driver, V.R., Fabbi, M., Lavery, L.A., and Gibbons, G. J. Vasc. Surg. 2010; 52:17S-22S

(14) "Advanced Wound Care Therapies for Nonhealing Diabetic, Venous, and Arterial Ulcers: A Systematic Review" Greer, N., Foman, N.A., MacDonald, R., Dorrian, J., Fitzgerals, P., Rutks, I., and Wilt, T.J. Annals of Internal Medicine 2013;159:532-542

(15) "Shire Executes Agreement to Divest Dermagraft", Shire press release, January 17, 2014

(16) "Quantification of DNA in Biologic Scaffold Materials" Gilbert, T.W., Freund, J.M, and Badylak, S.F., J Surg Res 2009; 152:135-19

(17) "In-Vivo and In-Vitro Histological Evaluation of Two Commercially Available Acellular Dermal Matrices" Faleris, J.A., Hernandez, R.M.C., Wetzel, W., Dodds, R., Greenspan, D.C. Hernia 2011;15:147-156

18) "Human Monocyte Activation by Biologic and Biodegradable Meshes In Vitro" Orenstein, S., Quao, Y., Kaur, M., Klueh, U., Kreutzer, D., Novitsky, Y. Surg Endosc 2009; 24:805-811

(19) "In Vitro Acitvation of Human Peripheral Blood Mononuclear Cells Induces by Human Biologic Meshes" Orenstein, S., Quao, Y., Kaur, M., Klueh, U., Kreutzer, D., Novitsky, Y., J Surg Res 2010; 158:10-14

(20) “Methods for Tissue Decellularization”, Paul Frank Gratzer, Canadian Application, International Reference no. PCT/IB2077/001538, Entry date August 21, 2012; “Methods for Tissue Decellularization”, Paul Frank Gratzer, U.S. Application no. 13/580,367, Entry date August 21, 2012

(21) Guidance for Industry Chronic Cutaneous Ulcer and Burn Wounds —Developing Products for Treatment , U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), June 2006

(22) “The Use of an Acellular Dermal Regenerative Tissue Matrix in the Treatment of Lower Extremity Wounds: A Prospective 16-week Pilot Study” Brigido, S.A., Int Wound J, 2006;3:181—187

(23) “Benchmarks for Interpretation of Score Differences on the SF-36 Health Survey for Patients with Diabetes.” Bjorner, J.B., Wolden, M.L., Gundgaard, J., and Miller, K.A. Value in Health 2013; 16: 993-1000

(24) “Digital Imaging of Wounds: Are Measurements Reproducible Among Observers?” Quan SY, Lazarus GS, Kohli AR, et al. Int J Low Extrem Wounds 2007; 6:245–8.

(25) “Surrogate End Points for the Treatment of Diabetic Neuropathic Foot Ulcers” Margolis, D.J., Gelfand, J.M., Hoffstad, O., and Berlin, J.A. Diabetes Care 2003; 26:1696-1700

(26) “Healing of Diabetic Neuropathic Foot Ulcers Receiving Standard of Care: A Meta-Analysis” Margolis, DJ., Kantor, J., and Berkin, J.A. Diabetes Care 1999;22:692-695

11. APPENDICES

If not included with this version, please refer to earlier versions of the protocol for appendices referenced herein.

APPENDIX 1: DermGEN Characteristics

APPENDIX 2: Health Canada's Approval To Use DermGEN

APPENDIX 3: Informed Consent Document

APPENDIX 4: The Leg Ulcer Measurement Tool [LUMT]

Leg Ulcer Measurement Tool (LUMT)

Clinician Rated Domains					
Exudate Type	0 None 1 Serosanguinoues 2 Serous 3 Seropurulent 4 Purulent		Granulation tissue type	0 Healed 1 Bright beefy red 2 Dusky pink 3 Pale 4 Absent	
Exudate Amount	0 None 1 Scant 2 Small 3 Moderate 4 Copious		Granulation tissue amount	0 Healed 1 76 to 100% of wound bed 2 51 to 75% of wound bed 3 26 to 50% of wound bed 4 0 to 25% of wound bed	
Size (from edge of advancing border of epithelium) (length x width)	0 Healed 1 <2.5 cm2 2 2.5-5.0 cm2 3 5.1-10.0 cm2 4 10.1 cm2 or more		Edges	0 Healed 1 >/= 50% advancing border of epithelium or indistinct borders 2 <50% advancing border of epithelium 3 Attached, no advancing border of epithelium 4 Unattached or undermined	
Depth (tissue layers)	0 Healed 1 Partial thickness skin loss 2 Full thickness 3 Tendon/joint capsule visible 4 Probes to bone		Periulder skin: -callus -dermatitis (pale) -maceration -induration -erythema -purple blanchable -purple non-blanchable -skin dehydration	Number of factors affected: 0 None 1 One only 2 Two or three 3 Four or five 4 Six or more	
Undermining (greatest at _____ o'clock)	0 0 cm 1 >0-0.4 cm 2 >0.4-0.9 cm 3 >0.9 – 1.4 cm 4 >1.5 cm		Leg edema type	0 None 1 Non-pitting/firm 2 Pitting 3 Fibrosis or lipodermasclerosis 4 Indurated	
Necrotic tissue type	0 None 1 Loose white to yellow shough 2 attached white to yellow shough or fibrin 3 soft gret to black eschar 4 hard dry black eschar		Leg edema location	0 None 1 Localized periulcer 2 Foot, including ankle 3 To mid calf 4 To knee	
Necrotic tissue amount	0 None visible 1 1 to 25% of wound bed 2 26 to 50% of wound bed 3 51 to 75% of wound bed 4 76-100% of wound bed		Assessment of bioburden	0 Healed 1 Lightly colonized 2 Heavily colonized 3 Localized infection 4 Systemic infection	

Leg Ulcer Measurement Tool (LUMT)

Patient (Proxy) Rated Domains		
Pain amount (as it relates to the leg ulcer) *Rate your pain experience in the last 24 hours on a scale from 0 to 10, where 0 is "no pain" and 10 is the "worst pain*	Numerical rating scale (0-10) 0 None 1 1-2 2 3-4 3 5-7 4 >7	
Pain frequency (as it relates to the leg ulcer) *Which of the following best describes how often you have had pain in the last 24 hours?*	0 None 1 Occasional 2 Position dependent 3 Constant 4 Disturbs sleep	
Quality of life (as it relates to the leg ulcer) *How do you feel about the quality of your life at the present time?*	0 Delighted 1 Satisfied 2 Mixed 3 Dissatisfied 4 Terrible	

Total Clinician Rated Domains
Total Patient Rated Domains

APPENDIX 5: The SF-12 Health Survey

SF-12 Health Survey

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. **Answer each question by choosing just one answer**. If you are unsure how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

☐1 Excellent ☐2 Very good ☐3 Good ☐4 Fair ☐5 Poor

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	YES, limited a lot	YES, limited a little	NO, not limited at all
2. **Moderate activities** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	☐1	☐2	☐3
3. Climbing **several** flights of stairs.	☐1	☐2	☐3

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	YES	NO
4. **Accomplished less** than you would like.	☐1	☐2
5. Were limited in the **kind** of work or other activities.	☐1	☐2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	YES	NO
6. **Accomplished less** than you would like.	☐1	☐2
7. Did work or activities **less carefully than usual**.	☐1	☐2

8. During the past 4 weeks, how much did pain interfere with your normal work (including work outside the home and housework)?

☐1 Not at all ☐2 A little bit ☐3 Moderately ☐4 Quite a bit ☐5 Extremely

These questions are about how you have been feeling during the past 4 weeks.
For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm & peaceful?	☐1	☐2	☐3	☐4	☐5	☐6
10. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5	☐6
11. Have you felt down-hearted and blue?	☐1	☐2	☐3	☐4	☐5	☐6

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

☐1 All of the time ☐2 Most of the time ☐3 Some of the time ☐4 A little of the time ☐5 None of the time

Clinical Trial

Informed Consent Form

STUDY TITLE: A Pilot Safety and Efficacy Study of DermGEN Dermal Regeneration Scaffold for the Treatment of Diabetic Foot Ulcers

CLINICAL STUDY REGISTRATION NUMBER**:** NCT02184455.

PRINCIPAL Dr Mark Glazebrook

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STUDY SPONSOR: DeCell Technologies Inc.

FUNDING AGENCY**:** DeCell Technologies Inc. , CIHR

1. Introduction

You have been invited to take part in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This informed consent form explains the study.
You may take as much time as you wish to decide whether or not to participate. Feel free to discuss it with your friends and family, or your family doctor. The study staff will tell you if there are any study timelines for making your decision

Please ask the study staff or the principal investigator to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

The researchers will:

- Discuss the study with you
- Answer your questions
- Keep confidential any information which could identify you personally
- Be available during the study to deal with problems and answer questions

You are being asked to consider participating in this study because you have a diabetic foot ulcer and may benefit from this new grafting product.

If you decide not to take part or if you leave the study early, your usual health care will not be affected.

2. Why is this study being conducted?

You are being asked to take part in this study because you are being treated for a diabetic foot ulcer. This study is being done to compare this treatment to existing treatment of diabetic foot ulcers and compare the time it takes for these ulcers to heal.

3. What Is Being Tested?

The purpose of this clinical trial is to perform a limited pilot study (which means a small number of patients (20) to determine the effectiveness and safety of DermGEN graft material in the treatment of non-healing diabetic foot ulcers.

4. How Long Will I Be In The Study?

After enrollment in this study, your doctor will ask you to visit the clinic for several follow up visits. These visits will happen at: 1, 2, 3, 4, 12, 20 weeks, the last study visit will be 6 months from the date of your first visit. Each follow-up appointment will take 30-60 minutes or less.

5. How Many People Will Take Part In This Study?

A total of 20 patients will be enrolled in this study, with patients enrolled in each of the following participating centers: Halifax and Toronto. The study will be centrally managed at the Halifax site. Twelve (12) patients will be enrolled locally at the Halifax Infirmary site and eight (8) at the Toronto site.

6. How Is The Study Being Done?

Prior to being enrolled for participation in the study, you will be asked to read and voluntarily sign this Informed Consent. Your surgeon will explain the application of the DermGen graft and the procedure with you. You will have an opportunity to ask and receive answers from your surgeon about any questions you may have regarding the procedure, the graft, this research study, or this document. You will undergo routine tests and procedures for your diabetes and your diabetic ulcer at your clinic appointment, including baseline blood work and a physical examination of your effected foot. As part of this study you will be asked to answer questions about your pain, function and general health at each visit. Following the completion of your medical evaluation, you will be scheduled for the application of the graft material. In this study, you will receive the same treatment as other patients enrolled in this study. Each follow-up appointment will take 30-60 minutes or less. You will be asked to return to the QEII for 6 visits over the next 6 months. A record of your diabetic ulcer will be kept by the research staff at each visit.

7. What Will Happen If I Take Part In This Study?

SCREENING

If you want to be in this study and sign this consent form, you will be asked to have some tests done to see if you can take part. This is called screening. It is possible that the tests will show that you can't be in the study. There may be other tests done as part of usual care. The research team will discuss these with you.

The research study screening tests that will be done are:

- General Health Assessment – your doctor will examine your foot ulcer and review standard blood work to confirm you are eligible for this study.

STUDY

We will do the following as part of the trial:

Visit	Visit 1 Baseline	Visit 2 Week1	Visit 3 Week 2	Visit 4 Week3	Visit 5 Week 4	Visit 6 Week 12	Visit 7 Week 20
Time	30 min	60 min	30 min	30 min	30 min	30 min	30 min
Informed consent	X						
Medical history Review (MDLUC Hx form)	X				X	X	X
Ulcer assessment record. (including digital record) -Photograph	X	X	X	X	X	X	X
Questionnaires SF 36	X				X	X	X
Review and report adverse events		X	X	X	X	X	X
Application of graft		X					

- Foot Exam – your doctor will examine your foot ulcer for signs of infection, circulatory status, the size of your foot ulcer at each visit.
- A photograph will be done of the diabetic ulcer at each visit.
- The questionnaires you will answer at visits 1,5,6,7
- Application of the graft to the diabetic ulcer at visit 2

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FOLLOW UP

These visits will happen at: 1, 2, 3, 4, 12, 20 weeks, the last study visit will be 6 months from the date of your first visit.

Of course you may ask not to have further tests done or to participate in any additional trial procedures at any time.

It is important that you tell the Principal Investigator about any drugs or medicines you are taking or wish to take. You must also tell the Principal Investigator about anything unusual that is happening with your health. This includes any medical problems that seem to be getting worse. If you have to see another doctor or have to go to a hospital, you must let the doctors know that you are in a research study. You should also tell your own doctor as quickly as possible, for your safety.

8. What About Birth Control and Pregnancy?

The effects of study *device on* unborn babies or sperm are unknown. You should not take part in this study if you are pregnant or planning to become pregnant.

Birth Control: If you and your partner are of childbearing potential (physically able to have children) and you are sexually active, it is important that you practice an acceptable method of birth control during this study

Pregnancy: If you get pregnant during the study you may need to stop participating in the study.

9. Are There Risks To The Study?

There are risks with this, or any study. To give you the most complete information available, we have listed many *possible* risks, which may appear alarming. We do not want to alarm you but we do want to make sure that if you decide to try the study, you have had a chance to think about the risks carefully. Please also be aware that there may be risks in participating in this study that we do not know about yet.

Possible complications with the use of the DermGEN graft include the following;
Uncommon "Uncommon risks (1 or more out of every 1000 people but less than 1 out of every 100 people have experienced the following):"

- Maceration which is softening of the skin due to prolonged exposure to wetness
- specific or non-specific immune response
- infection
- the graft does not adhere to the surface

Given the nature of the treatment and location and type of wound being treated, most adverse events may be stopped through the cessation of treatment with graft removal..

QUESTIONNAIRES: You may find the interviews and questionnaires you receive during the course of the study upsetting or distressing. You may not like all of the questions that you will be asked. You do not have to answer those questions you find too distressing.

The study *device* may interfere with medications, both prescribed and over the counter that you are currently taking. You should ask the Principal Investigator if the study *device* could interfere with your medications before consenting to be in this study. You should also consult with the Principal Investigator or members of the research team before taking any new medications.

You will be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the study staff.

10. Are There Benefits Of Participating In This Study?

You may or may not benefit directly from participating in this study. Your participation may help other people with a diabetic ulcer in the future.

11. Are There Other Choices?

If you decide not to participate in this study, other treatment choices may be available. Your other choices may include:

- Getting treatment or care for your diabetic ulcer without being in a study

Talk to your doctor about your choices before you decide if you will take part in this study.

New devices become available for this sort of condition at different times and in different parts of the world. Like many other hospitals, we do not feel it is helpful to test more than one experimental treatment for the same condition at the same time in the same person. This could even be dangerous. So you will not undergo two experimental procedures during the same time period.

You are free to seek other opinions or choices in other hospitals or cities if you wish.

12. What Happens at the End of the Study?

You will be followed by your othopaedic surgeon after the study end as part of clinical practice. There is no charge for this device.

13. What Are My Responsibilities?

As a study participant you will be expected to:

- Follow the directions of the Principal Investigator
- Report all medications being taken or that you plan on taking
- Report any changes in your health to the Principal Investigator
- Report any problems that you experience that you think might be related to participating in the study
- Return for scheduled appointments.

14. Can My Participation in this Study End Early?

The study sponsor, the Capital Health Research Ethics Board, Health Canada, or the Principal Investigator have the right to stop patient recruitment or cancel the study at any time.

The principal investigator may decide to remove you from this study without your consent for any of the following reasons:

- The treatment does not work for you;
- You do not follow the directions of the Principal Investigator;
- In the opinion of the Principal Investigator you are experiencing side effects that are harmful to your health or well-being;
- There is new information that shows that being in this study is not in your best interests;
- You plan to become pregnant, plan to discontinue acceptable birth control, or you become pregnant.
- When there is evidence that the study should be stopped due to safety reasons or lack of treatment effect (when the treatment is not working well).

If you are removed from this study, a member of the study team/principal investigator will discuss the reasons with you and plans will be made for your continued care outside of the study.

You can also choose to end your participation at any time without having to provide a reason. If you choose to withdraw from this study by providing notice to the study doctor, your choice will have no effect on your current or future medical treatment and healthcare. Your health records may be examined in connection with this study or further analyses related to it. Your health records will only be made available as described above. However the above agencies, including the sponsor, will only look at and use study related records up to the date of your withdrawal from the study, except where it is necessary to ensure that the study is scientifically reliable and to report side effects associated with the study medication as required by regulatory authorities.

If you withdraw your consent, the information about you that was/were collected before you left the study will still be used. No new information about you will be collected without your permission.

15. What About New Information?

It is possible that new information may become available while you are in the study about some new treatment for your condition. You will be told about any other new information that might affect your health, welfare, or willingness to stay in the study and will be asked whether you wish to continue taking part in the study or not.

16. Will It Cost Me Anything?

Compensation

You will not have to pay for any study device while participating in this study; you will not be paid to be in the study.

Research Related Injury

If you become ill or injured as a direct result of participating in this study, necessary medical treatment will be available at no additional cost to you. Your signature on this form only indicates that you have understood to your satisfaction the information regarding your participation in the study and agree to participate in the study. In no way does this waive your legal rights nor release the Principal Investigator, the research team, the study sponsor or involved institutions from their legal and professional responsibilities.

17. What About My Privacy and Confidentiality?

Protecting your privacy is an important part of this study. Every effort to protect your privacy will be made. No identifying information (such as your name or hospital number)

will be sent outside of this health care facility. If the results of this study are presented to the public, nobody will be able to tell that you were in the study.

However, complete privacy cannot be guaranteed. For example, the investigator may be required by law to allow access to research records. A copy of this consent form will be put in your health record. Your family doctor will be told that you are taking part in this study.

If you decide to participate in this study, the investigator(s) and study staff will look at your personal health information and collect only the information they need for this study. "Personal health information" is health information about you that could identify you because it includes information such as your;

- Name,
- Address,
- Telephone number,
- Age or month/year of birth (MM/YY),
- Information from the study interviews and questionnaires;
- New and existing medical records, or
- The types, dates and results of various tests and procedures.

When you sign this consent form, you give us permission to:

- Collect information from you
- Collect information from your health record
- Share information with the people conducting the study
- Share information with the people responsible for protecting your safety while participating in this research.

<u>Access to Records</u>

Other people, during visits to this health care facility, may need to look at your personal health information to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines. These people might include:

- DeCell Technologies Inc., the company that makes the DermGen graft, and its representatives and partner companies (inside and outside of Canada);
- The Capital Health Research Ethics Board (CHREB) and people working for or with the CHREB because they oversee the ethical conduct of research studies at Capital Health;
- Representatives of Health Canada, the group of people who oversee the use of drugs in research in Canada.

Use of Your Study Information

The research team will collect and use only the information they need to judge the safety and usefulness of the device. The sponsor and companies working for and with the sponsor will use the information collected about you during the study, only for scientific research purposes. “Study data" is health information about you that is collected for the study, but that does not directly identify you.

Any study data about you that is sent outside of Capital Health will have a code and will not contain your name or address, or any information that directly identifies you.

You also allow the collection, reporting and transfer of your anonymous personal health information and study data to:

- The sponsor and companies working for and with the sponsor; and
- Regulatory authorities within and outside Canada.

Study data that is sent outside of the hospital will be used for the research purposes explained in this consent form. The investigator(s), study staff and the other people listed above will keep the information they see or receive about you confidential, to the extent permitted by applicable laws. Even though the risk of identifying you from the study data is very small, it can never be completely eliminated.

The research team will keep any personal health information about you in a secure and confidential location for 7 years and then destroy it according to Capital Health policy. Your personal health information will not be shared with others without your permission.

After your part in the study ends, we may continue to review your health records for safety and data accuracy until the study is finished.

When the results of this study are published, your identity will not be disclosed.

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of the results of this study, please contact Trish Francis RN Orthopedic Research dept @ 902 473 5993.
The Research Ethics Board and people working for or with the Research Ethics Board may also contact you personally for quality assurance purposes.

Your Access to Records

You may ask the study doctor to see the information that has been collected about you. You may ask to make corrections to this information by talking with a member of the research team.

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

18. Declaration of Financial Interest

The sponsor is reimbursing the Principal Investigator and/or the Principal Investigator's institution to conduct this study. The amount of payment is sufficient to cover the costs of conducting the study.

19. What About Questions or Problems?

For further information about the study call Dr. Mark Glazebrook. Dr. Glazebrook is in charge of this study at this hospital (*he* is the "Principal Investigator"). Dr. Mark Glazebrook's work telephone number is (902) 473-5993. If you experience any symptoms or possible side effects or other medical problems, please let the Principal Investigator know immediately.

If you can't reach the Principal Investigator, or it is after regular business hours, speak to the emergency physician on call. The afterhour's number is **(902) 473-2222.**
This doctor may not be the one you usually see while in this study. Please call the Principal Investigator or research coordinator the next business day to tell them about the possible side effects or other medical problems you experienced.

The Principal Investigator is Dr. Mark Glazebrook
Telephone: (902) 473-7137
Your Research Coordinator is Trish Francis RN.
Telephone: (902) 473-5993

20. What Are My Rights?

You have the right to receive all information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction before you make any decision. You also have the right to ask questions and to receive answers throughout this study.

After you have signed this consent form you will be given a copy.
If you have any questions about your rights as a research participant, contact the **Patient Representative** at **(902) 473-2133**.

In the next part you will be asked if you agree (consent) to join this study. If the answer is "yes", you will need to sign the form.

21. Consent Form Signature Page

I have reviewed all of the information in this consent form related to the trial called:
A Pilot Safety and Efficacy Study of DermGEN Dermal Regeneration Scaffold for the Treatment of Diabetic Foot Ulcers

I have been given the opportunity to discuss this study. All of my questions have been answered to my satisfaction. I authorize access to my personal health information, medical record and research study data as explained in this form.

This signature on this consent form means that I agree to take part in this study. I understand that I am free to withdraw at any time without affecting my future care.

_____	_____	____ / _____ / ___
Signature of Participant	Name (Printed)	Year Month Day*
_____	_____	____ / _____ / ___
Witness to Participant's Signature	Name (Printed)	Year Month Day*
_____	_____	____ / _____ / ___
Signature of Investigator	Name (Printed)	Year Month Day*
_____	_____	____ / _____ / ___
Signature of Person Conducting Consent Discussion	Name (Printed)	Year Month Day*
_____	_____	____ / _____ / ___
Signature of Participant's Substitute Decision Maker	Name (Printed)	Year Month Day*

If the consent discussion has been conducted in a language other than English, please indicate:

_____
Language

_____	_____	____ / _____ / ___
Signature of Translator	Name (Printed)	Year Month Day*

Note: Please fill in the dates personally

I Will Be Given a Signed Copy of This Consent Form
Thank you for your time and patience!