

# Cellular Versus Acellular Grafts for Diabetic Foot Ulcers: Altering the Protocol to Improve Recruitment to a Comparative Efficacy Trial



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Top 10 Fellow and Resident Grant Winner at the 8th Cosmetic Surgery Forum

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## RESIDENT PEARL

- Deciding on the appropriate wound care regimen for diabetic foot ulcers is difficult given the vast amount of wound products on the market. This head-to-head clinical trial compared the use of an expensive cellular matrix and an inexpensive acellular matrix relative to the standard of care. We hope that this study will help to guide therapy based on cost-effectiveness of wound adjuncts without compromising patient care.

Diabetic foot ulcers (DFUs) have a substantial impact on public health. The standard of care (SOC) for DFUs consists of a multidisciplinary approach involving glycemic control, wound care with debridement of necrotic tissue, application of a moist dressing, infection control, use of off-loading devices, and patient education. New therapeutic devices aim to target the extracellular matrix (ECM) that is impaired in DFU; however, there is insufficient data on the effectiveness of such therapies along with lack of evidence on their

long-term effectiveness. We hypothesized that there is no difference in healing between the cellular matrix and an acellular matrix relative to SOC. To test this hypothesis, we conducted a randomized, single-blind clinical trial in patients with nonhealing DFUs that included 3 treatment arms: (1) SOC, (2) SOC plus a bioengineered ECM with living fibroblasts, and (3) SOC plus a bioengineered ECM devoid of cells. Our trial currently is closed for enrollment, as we have reached our target population size. Amendments to the protocol were made to help reach this threshold.

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Chronic diabetic foot ulcers (DFUs) remain a serious therapeutic challenge worldwide.<sup>1-2</sup> Patients with DFUs are at higher risk for infections, which may lead to limb loss.<sup>1-5</sup> In fact, 1 in 6 patients with DFUs will undergo an amputation.<sup>6</sup> The long-term consequences of DFUs are numerous and can severely affect patients' quality of life, including loss of productivity.<sup>7</sup> The current standard of care for DFUs consists of debridement of the necrotic tissue, application of a moist dressing, and use of

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The authors report no conflict of interest.

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This study was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) with the identifier NCT01450943.

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an off-loading device that protects the wound from pressure or trauma related to ambulation and other acts of daily living.<sup>4-6,8</sup> Unfortunately, studies have shown that the best standard of care (SOC) only heals 30% of DFUs after 20 weeks of therapy.<sup>9</sup> With the estimated cost per episode of care approaching \$40,000, DFUs remain a costly and important problem.<sup>10</sup>

The altered extracellular matrix (ECM) in DFUs has been a target for the development of new therapeutic devices that provide a new matrix that is either devoid of cells or can be enriched with fibroblasts.<sup>8,11</sup> These bioengineered skin substitutes stimulate the growth of new vessels and generate cytokines essential for tissue repair. In 2013, Lev-Tov et al<sup>12</sup> published this study protocol (Dermagraft Oasis Longitudinal Comparative Efficacy [DOLCE] trial) to compare the effectiveness of 2 advanced wound care devices, specifically to evaluate the clinical efficacy of a cellular matrix versus an acellular matrix, which we have amended. The cellular matrix used in the study is a dermal substitute composed of viable newborn foreskin fibroblasts seeded onto a bioabsorbable polyglactin mesh on which fibroblasts generate an ECM.<sup>13,14</sup> It is supplied frozen and requires specific thawing steps prior to application. The recommended regimen for treatment of DFUs for this cellular matrix is 8 weekly applications.<sup>13,14</sup> In 2016, the cost of the product was reported as \$1411 per 5.0×7.5-cm sheet.<sup>15</sup> The acellular matrix product used in the study is a bioabsorbable ECM that is derived from porcine small intestinal submucosa.<sup>16,17</sup> It is stored at room temperature and has a long shelf life, with a current price of \$112.6 for a 3.0×3.5-cm single-layer fenestrated sheet (\$1126.60 per box of 10 sheets). The industry-supported randomized controlled trials for each of these devices have reported a 20% added benefit in the rate of wound closure at week 12 compared to SOC.<sup>14,17</sup> However, our hypothesis is that these therapeutic devices will yield equivalent clinical outcomes, each being equally more effective than SOC, supporting the wider adoption of the less expensive, cell-free matrix device that has a longer shelf life and is easier to apply.

This article provides the interim report of the trial (registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) with the identifier NCT01450943) described in the published protocol and initiated in 2011,<sup>12</sup> focusing on elements that required modification during the trial's duration.

## Methods

**Study Protocol**—The clinical trial was approved by the Veterans' Affairs Institutional Research and Development Committee and their institutional review board. This study was funded by the Veteran's Administration Merit Award (#10554640), which was awarded to 2 of the investigators (S.E.D. and R.R.I.). Eligible veterans were recruited from all 7 sites of the VA Northern California Healthcare System. This trial is a randomized, single-blinded,

3-armed, controlled clinical equivalence trial comparing the effectiveness of an SOC treatment, cellular ECM, and acellular ECM.

**Study Products**—The SOC dressing applied in the clinical trial included a sterile antimicrobial gel, a non-adherent dressing, and gauze.<sup>12</sup> The SOC dressing also was used as a secondary dressing for the active treatment arms. Bacitracin antibiotic ointment was used as an alternative for patients with allergy to iodine.<sup>12</sup>

**Randomization**—The inclusion and exclusion criteria were previously outlined.<sup>12</sup> After a 2-week screening phase to exclude rapid healers, patients were randomized into a treatment arm and entered the active phase for 12 weeks. Patients then were seen once monthly for 16 weeks in a follow-up phase.<sup>12</sup>

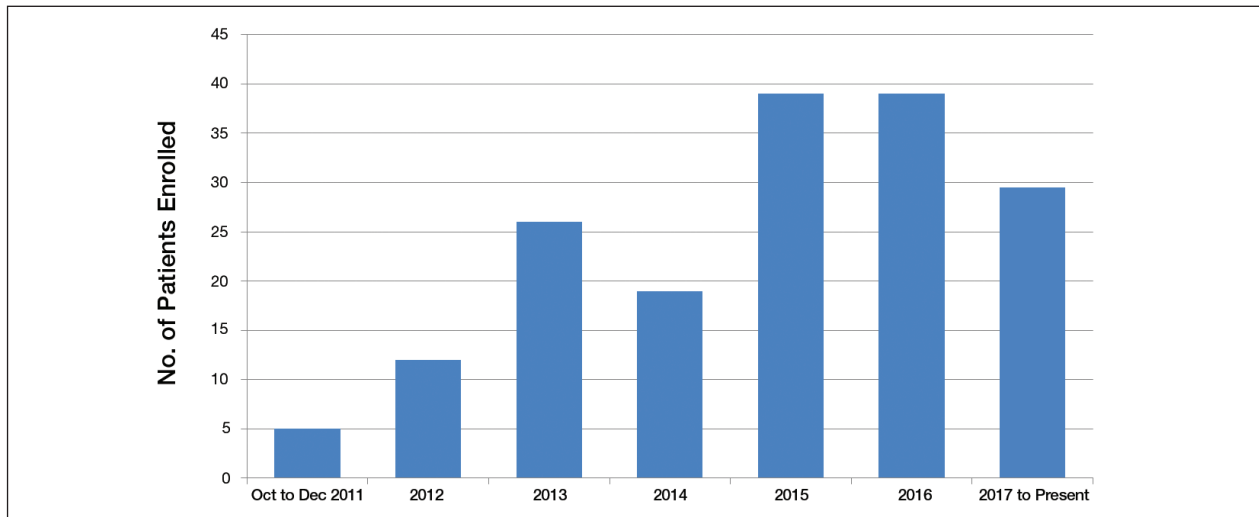
**Primary and Secondary Outcomes**—The primary outcome was complete wound closure by week 12.<sup>12</sup> Complete healing was defined as full reepithelialization with no drainage or dressing requirement. The secondary outcomes included healing at 28 weeks, rate of healing, ulcer recurrence at week 20, association of wound healing with ulcer characteristics or patients' characteristic, incidence of adverse events, and cost-effectiveness of each treatment compared to the SOC arm.<sup>12</sup>

**Statistical Analysis**—To detect a 25% difference in the incidence of ulcer closure between the 2 study groups and the SOC group, the estimation of the sample size was based on 80% power with a significance level of 0.05. Specifically, it was expected that 50% of the cellular and acellular matrix groups and 25% of the SOC group would reach complete wound closure. The protocol indicated that 57 participants would be enrolled in each arm (total of 171 participants). Lev-Tov et al<sup>12</sup> discussed the statistical analysis in more detail.

## Results

**Study Protocol Amendments**—Given the number of diabetic patients in the US veteran population, we anticipated that there would be enough participants meeting the inclusion and exclusion criteria; however, because of the difficulty with recruitment, the initial study criteria were modified. The study was initially designed to incorporate DFUs with a minimum size of 1.0 cm<sup>2</sup>.<sup>12</sup> The study investigators noted that within the veteran population, many diabetic patients with DFUs had ulcers that were too small to meet the inclusion criteria; thus, these patients could not be captured in the trial. However, those small ulcers would stall for months, which prompted the decision to change this major exclusion criterion to allow patients with a wound size greater than 0.5 cm<sup>2</sup> (versus 1.0 cm<sup>2</sup>) to be recruited. Enrollment of participants also was extended to include nonveterans.

Another limiting criterion was the percentage of total hemoglobin level for hemoglobin A<sub>1C</sub> (HbA<sub>1C</sub>). The study was originally established to include participants with an HbA<sub>1C</sub> level of 10% of total hemoglobin or below.<sup>12</sup> Unfortunately, the majority of the potential participants



Total patient enrollment to date.

had values substantially higher, and thus could not be enrolled in the trial, requiring another amendment to the study protocol in 2014, which was approved to include patients with an HbA<sub>1c</sub> level less than 12% of total hemoglobin. This change contributed considerably to the noted increase in enrollment rates in 2015, which almost doubled relative to enrollment under the original exclusion criteria (Figure).

The study has screened more than 600 patients. Among them, 137 were assessed for eligibility; 71 were excluded for various reasons, including screen failure (eg, decrease in wound size by >40% during the 2-week screening phase), loss to follow-up, and adverse events. Sixty-six participants reached the primary outcome at week 12, while 55 participants completed the study (19 in the SOC group; 18 in the cellular matrix group; 18 in the acellular matrix group).

We have stopped enrolling patients from all sites and the community, as we have reached our target enrollment.

### Comment

One of the challenges of clinical trials is the recruitment of an adequate number of participants within an appropriate time frame, which is explained by Lasagna's Law,<sup>18</sup> a well-described phenomenon whereby the investigator overestimates the number of potential participants available to meet the inclusion criteria. This so-called funnel-effect was partly encountered in our selection process. A review of the veteran population with DFUs seemed to be more than adequate to fulfill the sample size; however, some important participant-related factors also played a substantial role. The criterion for minimum ulcer size of 1.0 cm<sup>2</sup> was comparable to other trials<sup>8</sup> but was a major limiting factor in our study. Many participants already were established with either the podiatry or multispecialty wound clinics, and they had small DFUs, which

were stalling for months. Thus, by decreasing the lesion size needed for inclusion, our trial benefited from this subset population.

In addition, the Veterans' Affairs network centralizes health information, making it readily available to all providers participating in their care. As a result, patients with diabetes mellitus typically are seen by a primary care physician along with an endocrinologist, a diabetic nurse, and/or a dietician. Despite the collaboration with an interdisciplinary team, the glycemic control of the participants remains an issue along with other psychosocial factors that are deterrents in patient compliance. As a result, patients with poorly controlled diabetes and an HbA<sub>1c</sub> level above 10% (and less than 12%) of total hemoglobin who were initially excluded from the study were reincluded after modifying the inclusion criteria. Some patients were interested in joining the study, but physical limitations (eg, impaired mobility) prompted their decision not to join the trial, even though they met all the inclusion criteria.

As far as research-related factors that could affect participation, it is notable that most of the patients were retired; thus, the interventions did not cause additional burden of taking time off from work or loss of productivity. Although randomization could be a deterrent in many clinical trials, the majority of patients were willing to participate without demanding to be assigned to a particular treatment group. Some research-related factors that were an impediment to patient enrollment included the time to travel and the associated expenses, but our trial was designed to offer a small stipend for travel reimbursement (up to \$400) to mitigate such factors.

There are many factors that are intertwined and can lead to enrollment and/or attrition rates. It was critical for our team to make some adjustment without compromising the controlled nature of a randomized trial.

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