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Design and Rationale of an Adaptive Multisite Randomized Crossover Trial in Wagner Grade 1 Diabetic Foot Ulcers

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ABSTRACT

Background: Randomized controlled trials in wound care are frequently challenged by heterogeneous patient populations, variability in the application of standard care, and ethical concerns related to prolonged exposure to ineffective therapy. These challenges are particularly pronounced in diabetic foot ulcer research, where ischemia, neuropathy, infection, and biofilm may independently influence healing outcomes and confound treatment effects.

Aims: To describe the design and methodological rationale of a multisite, adaptive randomized controlled trial evaluating a three-dimensional acellular collagen matrix (3D-ACM) plus standardized care compared with standardized care alone in Wagner grade 1 diabetic foot ulcers and surgical wound dehiscence below the malleolus.

Methods: Adults undergo a standardized two-week run-in period with protocolized standard care prior to randomization. Participants are randomized 1:1 to receive investigational treatment plus standardized care or standardized care alone. The primary endpoint is complete re-epithelialization of the index wound by week 12, confirmed at two consecutive visits. Achievement of ≥50% percentage area reduction at week 4 is assessed as a key secondary endpoint. Participants assigned to standardized care alone undergo a mandatory futility assessment at week 8; those with ≤50% percentage area reduction may cross over to investigational treatment beginning at the subsequent visit. A Bayesian assurance-based framework supports adaptive sample size determination and interim evaluation. Exploratory endpoints include tissue oximetry, thermography, and bacterial fluorescence imaging to assess potential mechanistic contributors to healing and non-healing.

Results: Enrollment and follow-up are ongoing. This manuscript focuses on trial design, ethical considerations, and statistical planning rather than treatment efficacy.

Conclusion: This adaptive crossover trial integrates methodological rigor with ethical responsiveness by combining standardized care, objective futility-based crossover criteria, Bayesian adaptive planning, and prospective mechanistic assessment. The framework may serve as a model for future trials evaluating advanced biologic therapies in complex wound populations.

Keywords: acellular collagen matrix; adaptive trial design; bacterial fluorescence imaging; biofilm; crossover design; diabetic foot ulcer; perfusion imaging; randomized controlled trial; registry; standardized care; wound healing

Introduction

Diabetic foot ulcers (DFUs) remain a major cause of morbidity, hospitalization, and lower-extremity amputation worldwide. Approximately 15–25% of individuals with diabetes will develop a foot ulcer during their lifetime, and recurrence rates remain high despite contemporary management strategies.[1,2] Impaired wound healing substantially increases the risk of infection, hospitalization, and limb loss, contributing to significant healthcare utilization and cost burden.[1-3]

Despite advances in wound-care technologies, randomized controlled trials (RCTs) in DFUs continue to face substantial design and execution challenges. Patient heterogeneity, inconsistent application of standard care, and variability in wound assessment practices contribute to wide dispersion in outcomes and limit interpretability across studies.[4-6,34] Ethical concerns also arise when participants assigned to control arms demonstrate minimal progress yet remain on standard care alone for prolonged periods, particularly in populations at elevated risk for infection and amputation.[4,5]

Traditional parallel-group trial designs often lack mechanisms to prospectively identify early non-responders or adapt treatment pathways in response to inadequate healing. Early percentage area reduction (PAR) has been shown to reliably predict subsequent wound closure, and failure to achieve predefined reduction thresholds is associated with poor healing outcomes.[7-9] Nevertheless, many trials do not formally incorporate these validated early metrics into governance or decision-making frameworks. As a result, participants may continue ineffective therapy for extended durations, and clinically meaningful distinctions between responders and non-responders may be obscured.

In addition, mechanistic contributors to healing and non-healing, including tissue perfusion adequacy, inflammatory burden, and bacterial bioburden, are rarely assessed in a standardized or systematic manner within randomized trials.[10,11,30] When such factors are evaluated, they are often measured inconsistently or retrospectively, limiting their utility for understanding treatment response, refining eligibility criteria, or informing future trial design. Increasing recognition of biofilm-related chronicity further underscores the importance of incorporating objective mechanistic assessments into contemporary wound research.[12,13]

Advanced biologic matrices have demonstrated improved healing rates compared with standard care alone in multiple randomized trials and meta-analyses; however, pooled closure rates in control arms remain modest even under optimized care conditions.[14-17] These findings highlight both the therapeutic promise of advanced biologic matrices and the persistent methodological limitations of conventional trial designs in this area. Real-world evidence analyses further suggest variability in outcomes across care settings, reinforcing the need for rigorous yet pragmatic trial frameworks.[18,19] Collectively, this body of evidence supports the development of study designs that preserve internal validity while incorporating adaptive, ethically responsive features and objective criteria for treatment modification.

This study evaluates a 3D-ACM used in conjunction with standardized care versus standardized care alone for the treatment of Wagner grade 1 diabetic foot ulcers and surgical wound dehiscence below the malleolus.[20] The revised protocol introduces several design features intended to address the limitations described above, including expansion to a multisite enrollment model, adoption of a Bayesian assurance-based statistical framework, implementation of an objective futility-based crossover rule governed by validated early healing metrics, and prospective collection of exploratory imaging endpoints. Together, these elements are intended to enhance interpretability, strengthen ethical responsiveness, and generate clinically informative data relevant to wound-care research.

Methods

STUDY DESIGN

This study is a multisite, adaptive, randomized controlled trial conducted under a single master protocol reviewed and approved by an independent Institutional Review Board.[20] The trial evaluates the effectiveness of a 3D-ACM used in conjunction with standardized care compared with standardized care alone for the treatment of Wagner grade 1 diabetic foot ulcers and surgical wound dehiscence below the malleolus.

The study is conducted across multiple clinical sites to enhance generalizability and mitigate site-specific variability in patient populations and wound-care practices. Multisite enrollment improves external validity while maintaining standardized protocol oversight.[21] All participating centers adhere to a uniform protocol specifying eligibility criteria, standardized care requirements, wound assessment procedures, and follow-up schedules to promote consistency in trial conduct and outcome assessment.[20]

The protocol incorporates adaptive design elements intended to address ethical and methodological challenges common to wound-care trials. These include a standardized two-week run-in period prior to randomization, objective criteria for early identification of inadequate healing, and a prespecified crossover mechanism for participants assigned to standardized care alone who meet futility criteria. In addition, the study employs a Bayesian assurance-based statistical framework to support adaptive sample size determination and interim evaluation while preserving the integrity and interpretability of the randomized comparison.[22-25] Adaptive clinical trial methodology and Bayesian inference have been increasingly recognized as appropriate approaches for addressing uncertainty and heterogeneity in complex clinical settings.[23-26]

Centralized medical monitoring is conducted through a Clinical Research Associate (CRA) provided by the sponsor to ensure consistent oversight of safety, protocol adherence, and data integrity across participating sites. Day-to-day conduct of the study is overseen by the local principal investigators at each center.[20]

In parallel with the randomized controlled trial, a prospective registry is conducted to capture patients who do not meet eligibility criteria for randomization but are treated under standardized clinical conditions. Registries provide structured real-world data that complement randomized evidence and enhance understanding of treatment performance across broader clinical populations.[27,28,33] Registry data are analyzed descriptively and separately from randomized comparisons and do not contribute to primary efficacy inference.

STUDY POPULATION

Eligible participants are adults aged 18 years or older with a Wagner grade 1 diabetic foot ulcer or a dehisced surgical wound located below the malleolus, measuring between 1 and 20 cm^2 following sharp debridement and demonstrating adequate perfusion as determined by noninvasive vascular assessment.[2,20] Limiting enrollment to Wagner grade 1 wounds is intended to reduce heterogeneity related to infection and deep tissue involvement, thereby improving interpretability of treatment effects while maintaining relevance to a clinically common and challenging wound population.[2,9]

Key exclusion criteria include evidence of uncontrolled local or systemic infection, advanced ischemia, or medical conditions likely to impair wound healing or interfere with protocol adherence, such as severe metabolic derangement or inability to comply with prescribed offloading requirements.[8,9,20] Participants whose wounds demonstrate excessive improvement during the standardized run-in period are excluded from randomization, as early rapid healing may obscure detection of treatment-related differences and confound evaluation of adaptive design elements.[7,8,20]

Collectively, these eligibility criteria are designed to balance internal validity with external applicability

by enrolling a population at meaningful risk for delayed healing, while minimizing confounding factors that could independently drive wound closure or treatment failure.[2,8,9]

RUN-IN PERIOD AND RANDOMIZATION

All participants complete a standardized two-week run-in period prior to randomization. During this phase, protocolized standard care is applied uniformly across sites, and serial wound measurements are obtained to document PAR and establish baseline healing trajectories.[7,8,20] The run-in period is intended to normalize wound-care practices, reduce inter-site variability, and identify wounds that demonstrate rapid early improvement under standardized care alone.

Participants whose wounds exhibit excessive improvement during the run-in period are excluded from randomization, as early spontaneous healing may obscure detection of treatment-related differences and confound evaluation of adaptive trial features.[7,8,20] This enrichment strategy is designed to increase the likelihood of observing clinically meaningful treatment effects while preserving clinical relevance and avoiding unnecessary exposure to investigational therapy.

Eligible participants who complete the run-in phase are randomized in a 1:1 ratio to receive investigational treatment plus standardized care or standardized care alone. Randomization is stratified by study site to account for potential differences in patient populations and clinical practice patterns across participating centers, thereby improving balance between treatment arms and supporting interpretability of outcomes in a multisite setting.[20]

INTERVENTIONS

Standardized care is applied in both treatment arms throughout the study and is prospectively defined within the protocol to minimize inter-site variability and ensure consistency of background therapy.[20] Standardized care includes regular sharp debridement performed at each treatment visit, infection assessment and management in accordance with established clinical guidelines, use of moisture-balanced dressings selected according to predefined criteria, and offloading using a standardized controlled ankle-walking boot.[2,8,9,29] Compression therapy is applied when clinically indicated based on vascular assessment and wound characteristics.[8]

Participants randomized to the investigational arm receive topical application of a 3D-ACM in addition to standardized care.[14-17,20] The matrix is applied at weekly intervals during the initial treatment phase, transitioning to biweekly application if complete wound closure has not yet occurred and continued treatment is clinically appropriate. This application schedule is intended to balance consistent biologic exposure with practical considerations related to wound response and visit burden.

Participants randomized to standardized care alone continue protocolized background therapy unless they meet predefined criteria for crossover. Crossover eligibility is governed by objective futility criteria assessed at week 8, as specified in the protocol, rather than investigator discretion.[20] This approach is intended to preserve the integrity of the randomized comparison while limiting prolonged exposure to ineffective therapy and addressing ethical considerations inherent to chronic wound trials.[7,27]

ENDPOINTS

The primary endpoint is complete re-epithelialization of the index wound by week 12, defined as intact epithelial coverage with no drainage and no requirement for wound dressings, confirmed at two consecutive study visits.[20] This definition is intended to provide a clinically meaningful and durable measure of wound closure while reducing misclassification associated with transient epithelial coverage or early recurrence.[7,13,20]

A key secondary endpoint is achievement of ≥50% PAR at week 4.[7-9] Early PAR has been consistently shown to predict subsequent wound closure and is incorporated prospectively in this study both as a clinically informative outcome and as an objective basis for adaptive decision-making.[7-9] Additional

secondary endpoints include time to complete closure, durability of closure over follow-up, and safety outcomes, including adverse events related to treatment and wound progression.[20]

Exploratory endpoints are included to assess potential mechanistic contributors to healing and non-healing that are not captured by surface area measurements alone. These include tissue oximetry and thermography assessed using the MIMOSA imaging system, as well as evaluation of bacterial load and bioburden using fluorescence imaging.[10,11,21] These imaging modalities are collected prospectively and analyzed descriptively to explore associations between perfusion, bacterial burden, and healing trajectories. Exploratory endpoints are hypothesis-generating and do not contribute to primary or key secondary efficacy analyses.

CROSSOVER DESIGN

Participants randomized to standardized care alone undergo a mandatory futility assessment at week 8, at which time PAR is calculated relative to baseline measurements.[20] Participants demonstrating ≤50% PAR meet the prespecified futility criterion and are eligible to cross over to investigational treatment beginning at the next scheduled visit.[7,20] This crossover determination is objective and protocol-driven and is not subject to investigator discretion, thereby reducing bias and preserving the interpretability of the randomized comparison.

The futility-based crossover mechanism is designed to address ethical concerns associated with prolonged exposure to ineffective therapy in chronic wound populations while maintaining methodological rigor.[4,7] By using an early, validated surrogate of healing response to govern crossover eligibility, the study seeks to balance patient protection with the need for a robust control comparison during the primary evaluation window.[7-9]

Participants whose wounds remain unhealed at week 12 may also elect optional crossover at the conclusion of the primary treatment phase. Data collected following crossover at week 12 are analyzed descriptively as secondary outcomes only and are excluded from the primary efficacy analysis to preserve internal validity.[7,20] This two-tiered crossover approach allows ethical access to investigational therapy while clearly delineating randomized and post-randomized data for analytical purposes.

STATISTICAL FRAMEWORK

The study employs a Bayesian statistical framework incorporating assurance-based sample size justification, hierarchical evidence synthesis, and prespecified interim analyses.[22-26] This approach addresses the inherent uncertainty and heterogeneity common to wound-care trials by formally integrating prior evidence and updating inference as data accrue, while maintaining transparency and interpretability. Adaptive designs and Bayesian methods have been increasingly recommended in complex clinical settings where treatment effects may vary and traditional fixed-sample approaches may be inefficient.[23-26]

Sample size planning is based on Bayesian assurance, which estimates the probability that the study will achieve its predefined success criteria given plausible treatment effects informed by prior randomized trials and meta-analyses of matrix-based therapies.[18,22] This framework permits adaptive refinement of enrollment targets in response to interim data, thereby reducing the risk of underpowered or unnecessarily large trials while preserving methodological rigor.

Primary efficacy analyses are conducted in the intention-to-treat population using data collected prior to any crossover, thereby maintaining the integrity of the randomized comparison.[20,28] Data obtained following futility-based or optional crossover are analyzed separately as secondary or exploratory outcomes and do not contribute to primary endpoint inference. This analytical separation is critical to avoiding bias introduced by treatment switching while still capturing clinically relevant information regarding post-crossover healing trajectories.[4,28]

Detailed statistical methods, including prior specification, interim monitoring rules, and handling

of missing data, are prespecified in a standalone Statistical Analysis Plan finalized prior to database lock. The approach to missing data aligns with established methodological recommendations for randomized trials.[32] Trial design and reporting considerations are informed by contemporary guidance on adaptive trials and randomized study transparency.[23,31] Furthermore, incorporation of registry-based contextual data reflects principles of pragmatic trial design intended to enhance external validity while preserving internal control.[35,36]

Resuts

Enrollment and follow-up are ongoing at the time of manuscript preparation. As this manuscript focuses on study design, methodological rationale, and analytical planning, no efficacy or safety outcomes are reported herein. Final analyses will be conducted after database lock in accordance with the prespecified Statistical Analysis Plan.

Discussion

This study addresses several persistent limitations of DFU trials identified in prior methodological and clinical literature, including patient heterogeneity, inconsistent background care, ethical concerns related to prolonged nonresponse, and limited incorporation of adaptive design principles.[4-6] By combining multisite enrollment with prospectively defined standardized care requirements, the protocol seeks to enhance external validity while reducing inter-site variability that can obscure treatment effects in wound-care research.[6,35]

A central and distinguishing feature of the design is the incorporation of an objective, PAR–based futility criterion to govern crossover eligibility. Use of a prespecified week-8 threshold based on validated early healing metrics allows timely identification of participants unlikely to achieve closure under standardized care alone, while avoiding investigator discretion that could introduce bias.[7-9,20] This approach provides an ethically responsive mechanism to limit prolonged exposure to ineffective therapy while preserving the integrity of the randomized comparison during the primary evaluation window.[4,27]

The Bayesian assurance-based statistical framework further differentiates this study from conventional fixed-sample designs. By incorporating prior evidence from randomized trials and meta-analyses of matrix-based therapies, the assurance approach allows adaptive refinement of sample size and interim evaluation while maintaining interpretability and methodological rigor.[18,22-26] This framework is particularly well suited to wound-care trials, where treatment effects and healing trajectories are often heterogeneous and difficult to estimate reliably using traditional frequentist assumptions.[23-26]

In addition to clinical endpoints, the protocol includes prospective collection of exploratory imaging data, including tissue oximetry, thermography, and bacterial fluorescence imaging. These modalities offer an opportunity to examine mechanistic contributors to healing and non-healing, such as perfusion adequacy and bacterial burden, that are not captured by surface area measurements alone.[10,11,12] Although exploratory in nature, these data may inform hypothesis generation, future endpoint selection, and refinement of adaptive criteria in subsequent studies.

The design introduces analytical complexity, particularly with respect to treatment crossover and adaptive decision-making. However, explicit separation of randomized and post-crossover data in primary efficacy analyses preserves internal validity, while secondary and exploratory analyses capture clinically relevant outcomes following treatment modification.[20,28] This structured analytical approach aligns with contemporary recommendations for adaptive trial reporting and methodological transparency.[23,31] Collectively, the framework balances scientific rigor with patient-centered considerations and reflects evolving best practices in the design of ethically responsive randomized trials in chronic wound populations.[4,6]

Conclusion

This protocol describes an adaptive, multisite randomized controlled trial evaluating a 3D-ACM in adults with Wagner grade 1 diabetic foot ulcers. By integrating prospectively defined standardized care, an objective futility-based crossover mechanism, Bayesian assurance-based adaptive planning, and exploratory imaging endpoints, the design seeks to generate robust and interpretable efficacy data while addressing ethical and methodological challenges inherent to wound-care research.

The incorporation of validated early healing metrics to guide crossover decisions, explicit separation of randomized and post-crossover analyses, and parallel conduct of a prospective registry collectively reflect a pragmatic and ethically responsive framework. The registry component provides complementary real-world data that may enhance contextual interpretation and external applicability while preserving the internal validity of the randomized comparison. Taken together, this integrated approach may serve as a model for future trials evaluating advanced biologic therapies in complex wound populations.

Conflicts of Interest:

The author reports a consultancy relationship with Reprise Biomedical, Inc. No other conflicts of interest related to this work are declared.

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Ethics statement:

This study was conducted in accordance with the principles of the Declaration of Helsinki. The randomized controlled trial protocol was reviewed and approved by the WCG Institutional Review Board. Written informed consent was obtained from all participants prior to enrollment, including consent for the collection, analysis, and publication of study data and accompanying clinical images.

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