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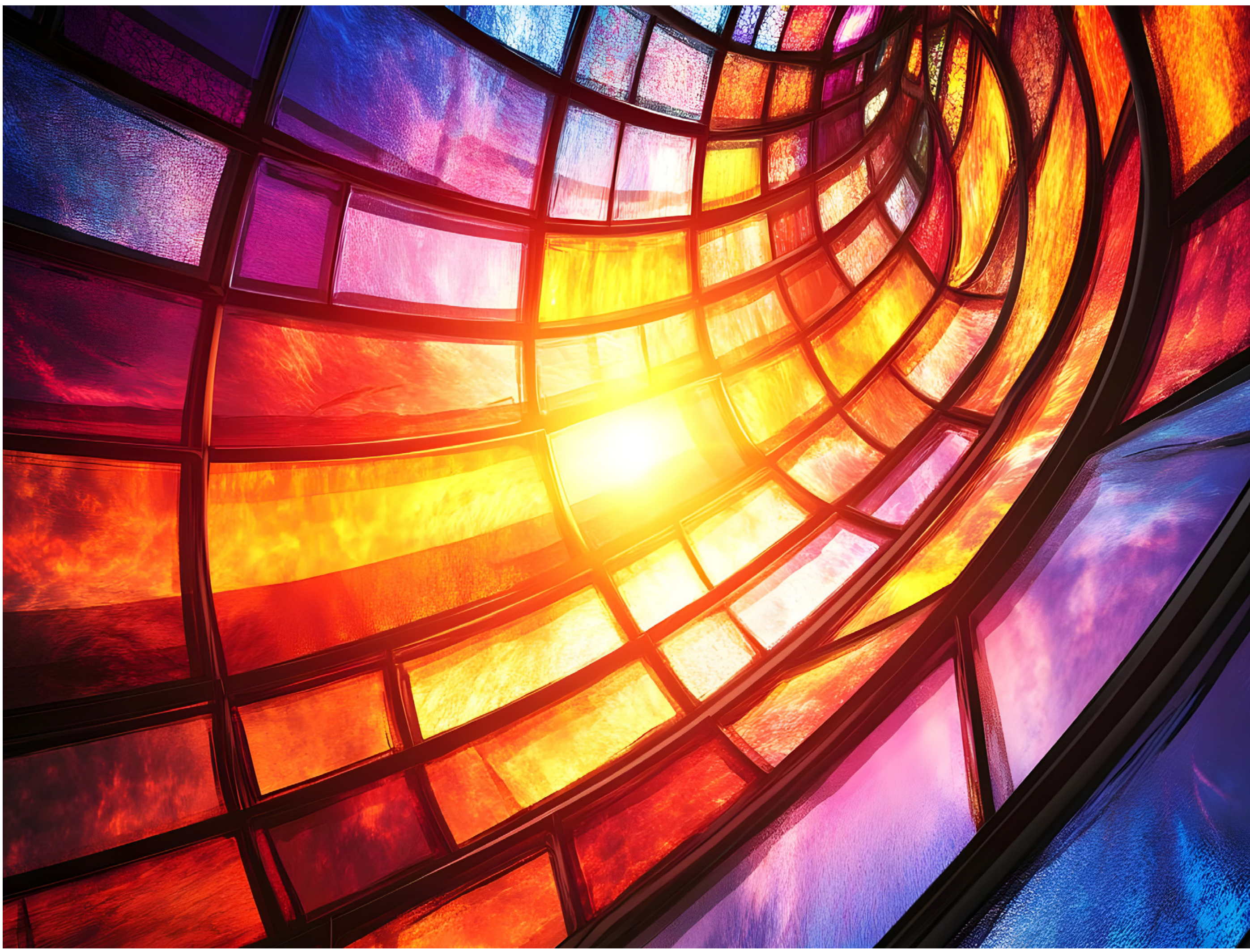
CAMPs evidence compendium



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CAMPs compendium

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Establishing a shared framework for advanced wound care

As former Co-Vice Chairs of the 2025 Cellular, Acellular, and Matrix-like Products (CAMPs) Conference, we are honoured to introduce this compendium, which highlights key research and developments in this rapidly evolving field. Over the past decade, the field of advanced wound care has matured from offering promising adjuncts to a rigorously studied, standards-driven pillar of wound repair and regeneration. The *Journal of Wound Care* (*JWC*) has been instrumental in that evolution, advancing both the language and the evidence base we rely on in a variety of settings: outpatient clinics, extended care facilities, assisted living, patient homes, as well as the operating theatre. In 2023, *JWC*, at the request of Dr William Tettelbach, codified the term 'CAMPs', replacing a patchwork of legacy labels ('skin substitutes', 'cellular/tissue products') with a unifying definition that reflects diverse mechanisms of action and a far broader set of indications than hard-to-heal ulcers alone. That consensus clarified what CAMPs are, and just as importantly, what they are for.

Since then, the journal has continued to sharpen best practices. The most recent *JWC* position work reframes CAMPs not as a salvage manoeuvre but as an early, intentional component of comprehensive care, including acute surgical and traumatic wounds, when microenvironment, not just biomechanics, must be restored. These updates provide pragmatic guidance on patient selection, product choice across cellular, acellular and hybrid matrices, and the thoughtful use of adjuncts, such as negative pressure wound therapy, to stabilise grafts or matrices. The same work also maps the regulatory pathways clinicians navigate (Premarket Approval (PMA), 510(k), and §361 Human Cell and Tissue Product (HCT/P)), making it clear how the composition, scientific mechanism, clinical impact and regulatory status should inform how a given product is integrated into the plan of care.

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Across indications, the through-line in *JWC's* recent literature is earlier, smarter deployment. When CAMPs are introduced in step with integral debridement, infection control, oedema management, and offloading or compression, not after these foundations have failed, healing accelerates, complications fall, and quality of life improves. This isn't just biologically intuitive; it is economically credible. *JWC* has summarised growing datasets, such as real-world Medicare claims data, showing fewer amputations, readmissions, emergency visits and lower overall costs when CAMPs are applied judiciously and early. This message resonates with clinicians and payers alike.

Equally important, the journal has not shied away from the remaining gaps. Authors have called for the design of better randomised trials in targeted populations, transparent reporting of product characteristics and application techniques, and registry-level surveillance to capture real-world safety, effectiveness and durability. Those calls are practical and actionable: they ask us to document what we do, to compare and elevate the standard of care, in addition to building the longitudinal datasets that turn promising case series into confident standards of care.

Policy and language are also advancing. *JWC* has compared emerging coverage frameworks with the clinical evidence and urged the community to keep terminology and policy aligned with science, so that a clinician's decision to deploy a CAMP is driven first by evidence, which in certain circumstances may be translational, and patient goals, then reinforced by coherent coding and reimbursement. Education has kept pace: over the last year, *JWC's* CAMPs-focused programming has expanded, reflecting a maturing, multidisciplinary consensus about when, where and how these technologies add value.

This compendium stands on that foundation. You will find summaries of the latest prospective clinical studies that test CAMPs against hard outcomes (closure, time to closure, recurrence, quality of life), retrospective analyses of real-world data leading to applicable real-world evidence and pragmatic guidance on stitching product choice to patient pathophysiology: granulation deficits that may benefit from amniotic-derived allograft; epithelialisation lags that respond to dermal constructs; and complex defects where three-dimensional scaffolds can bridge dead space and shorten the reconstructive ladder. Just as the journal emphasises, product selection is not brand-driven but mechanism-driven; anatomy, perfusion, bioburden and mechanical forces determine the tool.

Our charge to readers is simple. First, adopt the common language of CAMPs. Shared terms accelerate shared learning. Second, integrate CAMPs early, when the clinical presentation calls for it, within a disciplined care bundle that includes meticulous wound bed preparation and offloading or compression. Third, measure what matters: closure, function, quality of life, recurrence, utilisation and cost. Finally, contribute to the evidence stream. Publish your protocols, your comparators and your outcomes. Registries and pragmatic trials will ensure that, two conferences from now, our 'best practice' chapters are even more precise, equitable and durable than they are today.

On behalf of the CAMPs faculty and the *JWC* team, thank you for the work you do for people living with hard-to-heal and complex wounds. May the pages that follow help you match the right matrix to the right moment—and bring your patients to closure sooner, more safely and with fewer compromises. **JWC**

Safeguarding access, fiscal responsibility and innovation: a comprehensive reimbursement framework for CAMPs to preserve the Medicare Trust Fund

Executive summary: This manuscript presents a unified and comprehensive policy framework addressing the flat-fee reimbursement model for skin substitutes, also referred to as cellular, acellular, and matrix-like products (CAMPs), proposed by the Centers for Medicare & Medicaid Services (CMS). These products are vital to treating hard-to-heal wounds, which disproportionately affect older patients, and those patients who are disabled and medically underserved. While CMS aims to curtail excessive spending and introduce payment consistency, the current proposal threatens access to life-saving therapies, endangers patient outcomes, and may destabilise clinical delivery infrastructures and manufacturing ecosystems critical to wound care.

Declaration of interest: This study was sponsored by Tiger BioSciences, US. WHT and TT were supported by an honorarium by Tiger BioSciences. The remaining authors have no conflicts of interest to declare.

CAMPs • Local Coverage Determination • wound • wound care • wound dressing • wound healing

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While the Centers for Medicare & Medicaid Services (CMS)'s proposed reforms aim to reduce costs, improve consistency, and strengthen accountability in the use of cellular, acellular, and matrix-like products (CAMPs), stakeholders remain concerned that certain elements of the current framework may unintentionally undermine patient care and programme sustainability. To guide ongoing refinement, the following key concerns highlight areas where adjustments are essential to preserve access, support innovation, and protect the long-term solvency of the Medicare Trust Fund.

Key concerns

- **Waste, fraud and abuse:** these actions contribute to most of the rising spending on CAMPs, as evidenced by >$900 million USD in federal indictments[1] and an additional $2.6 billion USD in likely inappropriate billing practices. Addressing this concentrated misuse through targeted policy reform, not artificial cost constraints, is a solution pathway that would provide the greatest benefit to Medicare enrolees and support the long-term solvency of the Medicare Trust Fund
- **Financial sustainability:** a reimbursement amount set below the acquisition cost of CAMPs undermines the financial viability of care delivery in both facility settings (also referred to as hospital outpatient departments (HOPDs)) and non-facility settings (which include private office-based practices, post-acute care (PAC) and advanced mobile wound care practices (AMWCP)).[2] When reimbursement fails to cover the cost of therapy, providers may be forced to restrict access or shift care toward facilities that are exempt from reimbursement ceilings, creating fragmentation in care delivery
- **Access and equity:** the proposed initial reimbursement cap of $125.38 USD/cm² for CAMPs that do not have Biologics License Applications status risks restricting or eliminating access to high-performing but higher-cost

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CAMPs, especially for patients with complex, hard-to-heal or large-area wounds. This disproportionately impacts rural hospitals, safety-net clinics, and underserved populations that already face significant barriers to advanced wound care technologies. Studies have shown that socioeconomic disparities contribute to differences in hard-to-heal wound care outcomes, which are closely linked to access limitations,[3] including limited access to biologically active therapies and other advanced modalities[4]

- **Clinical appropriateness:** a flat-rate pricing model introduces a one-size-fits-all reimbursement methodology that disregards clinical nuance and disease severity. Lower-cost therapies are not supported by evidence demonstrating equivalence to more effective biologic or composite CAMPs, such as placenta-derived allografts, which have been shown to significantly reduce mortality, recurrence and adverse outcomes in patients with lower extremity diabetic ulcers (LEDUs) or venous leg ulcers (VLUs).[5,6] This approach will erode years of progress in evidence-based wound care protocols, especially for LEDUs, VLUs and pressure injury (PI) ulcers, for which tailored approaches are essential
- **Systemic impact:** unstudied access limitations have the potential to increase costly adverse outcomes, including amputations, emergency department (ED) visits, intensive care unit (ICU) admissions, and even mortality from sepsis and wound-related infections. Longitudinal studies have shown that timely access to advanced wound care, such as CAMPs, reduces 30-day hospitalisation rates and long-term care costs.[6,7] Without safeguards, the CMS proposal risks raising net Medicare spending over time while compromising beneficiary quality of life.[8]

Drawing on extensive Medicare claims data, clinical trial outcomes, economic modelling and real-world evidence (RWE), the authors demonstrate how the proposed reimbursement framework will lead to unintended negative consequences, particularly for rural and PAC settings. The authors propose a modified policy, summarised in Table 1.

Introduction

The wound care stakeholder community recognises and appreciates the ongoing commitment of CMS to improving value, transparency and sustainability across Medicare Part B services. The community further acknowledges that the agency has taken meaningful steps in recent years to address longstanding challenges related to waste, rising costs, pricing variability, and potential abuse of advanced wound care technologies. The proposed future-effective CAMPs Local Coverage Determinations (LCDs) and transition to a flat-rate reimbursement framework for CAMPs reflect a sincere effort to reduce costs, simplify billing and improve

Table 1. Proposed policy modifications

Proposal	Description	Anticipated impact
Reform oversight practices	Transition from broad, retrospective audits to a targeted, data-driven oversight model that employs real-time usage data, intensity-of-use metrics and provider-level outlier detection. Implementing advanced, AI-enabled monitoring systems will enable earlier identification of irregular patterns, reduce administrative burden, and improve the effectiveness of fraud, waste and abuse prevention efforts	>$38 billion USD in cost savings over 10 years by eliminating fraud, waste and abuse without relying on artificial pricing constraints
Rescission of the future-effective CAMPs LCDs	Halt implementation of proposed LCDs that create unnecessary access restrictions and administrative barriers for Medicare beneficiaries	Preserves timely access to medically necessary wound care therapies and prevents harm to vulnerable patient populations
Adopt a revised flat-fee reimbursement rate	Implement a flat-fee rate of $478–704 USD/cm^2, aligned with clinical effectiveness, economic sustainability and real-world manufacturing costs	Based on projected 2025 spending on CAMPs, implementing a flat-fee reimbursement model leads to >$100 billion USD in Medicare savings over the next decade while preserving patient access to advanced therapies
Maintain equity across care settings	Ensure access to CAMPs is maintained in AMWCP, PAC, rural and underserved settings, through policies that support flexible delivery models	Improves access for immobile and underserved patients, ensures equity in care delivery
Develop a clinically sensible, evidence-based coverage determination policy	Implementation of an evidence-based, clinically sensible coverage determination policy, plausibly through the National Coverage Determination pathway, to standardise best practices and reduce administrative burden	National consistency, reduced administrative burden and improved clarity for providers
Monitor outcomes and refine policy	Enable longitudinal data-sharing between CMS and providers to assess effectiveness of CAMPs, recurrence rates, amputations and quality of life metrics	Improves best practice adoption, benchmarks clinical performance and supports continuous policy refinement
Protect innovation	Align reimbursement for next-generation wound care technologies with their demonstrated clinical value and manufacturing complexity	Stabilising the cost structure preserves R&D pipelines and fosters scalable, high-impact innovation, while incentivising entrepreneurs to address the growing need for next-generation solutions

AI—artificial intelligence; AMWCP—advanced mobile wound care practices; CAMPs—cellular, acellular, and matrix-like products; CMS—Centers for Medicare & Medicaid Services; LCDs—Local Coverage Determinations; PAC—post-acute care; R&D—research and development payment consistency across sites of service. However, there are concerns that the current proposal will unintentionally destabilise crucial care delivery models and diminish access to clinically proven treatment options, particularly for the most medically vulnerable Medicare beneficiaries. This document aims to build upon the agency's reform goals by offering RWE and clinical insight to support a reimbursement model that safeguards fiscal integrity and preserves favourable patient outcomes.

Policy background and context

Medicare spending on CAMPs has escalated over the past decade, prompting growing concerns about overuse, fraud, abuse and incomplete Average Sales Price (ASP) reporting.[9] These concerns echo broader issues raised by the Medicare Payment Advisory Commission, which has identified persistent weaknesses in ASP-based payment systems, particularly their susceptibility to pricing opacity and site-of-service payment disparities.[10]

While the proposed future-effective CAMPs LCDs remain on hold due to unresolved stakeholder concerns,[11] CMS has continued to pursue alternative cost-containment strategies. On 14 July 2025, CMS proposed a shift to a flat-fee reimbursement model under the Medicare Physician Fee Schedule (PFS), thereby removing product-specific ASP pricing and standardising CAMPs reimbursement as an 'incident-to' supply. This model would apply to CAMPs applications in non-facility settings, where providers bear the full cost of care and are reimbursed under Medicare's PFS Relative Value Unit (RVU) system. Covered place-of-service (POS) settings include: private physician offices (POS 11); AMWCPs (POS 15); home-based care (POS 12); assisted living facilities (POS 13); skilled nursing facilities (SNF) (POS 31); and nursing facilities (POS 32). These changes would apply regardless of the acquisition cost or regulatory classification (i.e., Premarket Approval, 510(k), or 361 HCT/P) for the CAMPs product.

Directly afterward, CMS issued the CY 2026 Outpatient Prospective Payment System (OPPS) and ambulatory surgical centre (ASC) Payment System Proposed Rule to update Medicare payment policies and rates for HOPDs and ASCs. Although reimbursement mechanisms differ between the OPPS and PFS, with OPPS relying on Ambulatory Payment Classifications to trigger payment, CMS proposes to align with the PFS model by adopting a per-unit reimbursement approach for CAMPs in facility settings. This shift aims to establish a consistent payment policy across care sites, which CMS describes as treating CAMPs uniformly across different outpatient care settings, to the extent permitted by applicable law.

Although this reform intends to simplify reimbursement, it neglects real-world costs related to patient access, care delivery logistics and clinical complexity. CMS's initial proposed CAMPs flat-rate reimbursement of \$125.38 USD/cm² applies regardless of acquisition cost or wound severity, yet only considers HOPD costs, not all care settings, when arriving at the reimbursement amount. This financial pressure favours lower-cost products over clinically superior options. Compounding this concern is the fact that the majority of CAMPs applications now occur in non-facility settings, where immobile patients typically reside, yet were not represented in the claims-based pricing model proposed by CMS.

Clinical risks and equity concerns

- Hard-to-heal wounds, particularly PI ulcers, LEDUs and VLUs, are increasingly affecting younger patients with underlying conditions such as diabetes. These comorbid conditions carry high risks of amputation, sepsis and death.[6,12] Creating unintentional barriers to early, effective healing has the opposite effect, increasing lifetime care costs, prolonging disability, and diminishing the likelihood of patients returning to work[11]
- Flat-rate reimbursement incentivises the selection of cheaper, less-effective products, undermining personalised, evidence-based care
- Underserved communities and AMWCPs which have significantly expanded access since 2020, will be disproportionately harmed
- RWE shows that CAMPs reduce recurrence rates by up to 91%, mortality by 26%, and adverse events by up to 71% in high-risk patients[5,6,11,12]
- Studies have documented disparities in access and outcomes based on ethnicity, rurality and income, factors that will likely be exacerbated by reimbursement ceilings that fail to account for variation across care delivery environments.[3,4]

Methods

A comprehensive policy and outcomes analysis was conducted, integrating retrospective 2016–2024 Medicare claims data, with a primary focus on 2020–2024, along with economic modelling and real-world clinical outcomes from previously published studies on CAMPs. The analysis included wound care episodes for beneficiaries with PI ulcers, LEDUs and VLUs. LEDU episodes required confirmation of a diabetes diagnosis, while VLU episodes required confirmation of chronic venous insufficiency, with International Classification of Diseases (ICD)-10 codes used for patient identification, ulcer definitions and other outcomes. Outcomes evaluated included ED visits, hospitalisations, readmissions and total episode costs.

Margin analyses were conducted using the proposed 2026 flat-rate reimbursement values and compared against historical payment rates under the ASP pricing and HOPD bundled payment systems. Additional modelling assessed site-of-service impacts and access trends based on publicly available CMS proposed rules, Medicare Administrative Contractor (MAC) LCD proposals, and peer-reviewed health economic studies.

Box 1. Reimbursement comparisons

A. Current 'bundled' HOPD reimbursement	
APC 5054 (CPT 15271)*	*$1829.23
CMS payment (78% of total)	$1426.80
Cost of CAMPs applied	–$500.00
Facility net gain	**$926.80**
B. CMS proposed Physician Fee Schedule in non-facility settings	
Product reimbursement (4cm² × $125.38 USD/cm²)	$501.52
Application procedure (e.g., CPT 15271)	$150.00
Total allowable reimbursement	$651.52
CMS Payment (78% of total)	**$508.19**
C. Proposed Physician Fee Schedule in the facility setting	
Product reimbursement (4cm² × $125.38 USD/cm²)	$501.52
Application procedure (e.g., CPT 15271)†	$746.61
Cost of CAMP applied	–$500.00
Total allowable reimbursement	$748.13
CMS Payment (78% of total)	**$583.54**

*depending on the local wage index; †proposed facility application fee;
APC—ambulatory payment classification; CAMPs—cellular, acellular, and matrix-like products; CMS—Centers for Medicare & Medicaid Services; CPT—current procedural terminology; HOPD—hospital outpatient department; $—US dollars

Results

Policy impacts

CMS does not intend to implement PFS through the Medicare hospital OPPS bundled payment structure, although the proposed rate is based on Medicare claims data from HOPD or facility settings. The proposal does not use any data from the physician's office/mobile clinic setting, where, for several years, the bulk of CAMPs use has occurred. Instead, CAMPs reimbursement would be folded into the procedure's practice expense RVUs as a flat-rate supply input, eliminating separate payment for individual products and creating a site-neutral cost assumption. This policy creates strong financial incentives to select lower-cost CAMPs, despite a lack of evidence showing they provide clinical outcomes equivalent to those of currently used options supported by RWE and robust clinical research.[5] This will also lead to selective patient avoidance, where access to care is restricted because providers are unwilling to treat patients with larger, more complex wounds that require more resources to achieve functional recovery. The current bundling in the hospital outpatient site of service has demonstrated this effect for over a decade.

Under the proposed 2026 flat-rate model, total reimbursement for a 4cm² CAMPs application in a private physician's office would be $508.19 USD (Box 1B). The resulting gross margins across various product acquisition costs in non-facility settings are shown in Box 2. While these margins may appear adequate for lower-cost products, they fail to support the full cost of wound care delivery in both the private office and PAC settings (Box 3). For PAC providers, particularly those serving complex or underserved populations, the diminishing gross margins will prove unsustainable.

Even if CAMPs reach prices as low as $75 USD/cm² under the proposed flat-rate reimbursement model, AMWCPs would need to more than double their salaried advanced practice providers (APPs)'s daily patient load just to break even. Considering operational barriers, especially travel time between patient visits, which can average 4.5 hours daily in the Midwest, along with documentation, home care delivery logistics and operational needs, such visit volumes are operationally unrealistic.

A typical AMWCP based in the Midwest employs APPs with an average total compensation (salary plus benefits) of $225,000 USD per year. In this model, a productive APP can see approximately 12 patients per day over 260 working days per year (approximately 3120 patient visits per year), with approximately 2% (62 patients) requiring CAMPs (operational and cost data contributed by Wound Care Plus, US). At an average of 12 applications per patient, this equates to 744 CAMP applications per year. Under the proposed flat rate of $125.38 USD/cm² plus a $150 USD application fee, using an average wound size of 4cm² and a product acquisition cost of $100 USD/cm², each application would generate a margin of $251.52 USD, resulting in $187,131 USD in annual gross margin from CAMPs. When distributed across the provider's entire caseload, this equates to only approximately $60 USD per total patient visit, insufficient to cover an APP's compensation, let alone the additional operational costs outlined in Box 3, meaning the programme would operate at a deficit. By contrast, at $704/cm² plus a $150 application fee, with the same wound size and a product acquisition cost of $564/cm², each application would generate a $710 margin, yielding $527,040 annually from CAMPs. This equates to roughly $169 per patient visit, a level far more likely to cover APP compensation and essential operating expenses, thereby sustaining programme

Box 2. Impact of proposed Physician Fee Schedule on gross margins in non-facility settings

Product cost	Gross margin	% margin
$220 USD/cm² ($880 USD)	–$371.81 USD	–42.3
$160 USD/cm² ($640 USD)	–$131.81 USD	–20.6
$135 USD/cm² ($540 USD)	–$31.81 USD	–5.9
$75 USD/cm² ($300 USD)	$208.19 USD	+69.4

Note: Gross margin = Centers for Medicare & Medicaid Services payment (78% of total) – production acquisition cost

Box 3. Costs associated with wound care delivery

Staffing and logistical costs: medical assistant, registered nurse and advanced practice provider (APP) staffing, communications (telephones, tablets etc.) with responsible parties (patient, primary care physicians, facilities, manufacturer etc), travel time between patient visits
Compliance/regulatory and insurance costs: staff to submit for insurance verification before application, electronic medical record licensing required for appropriate documentation, coding and credentialling costs, billing costs, regulatory compliance, practice expense; medical malpractice/professional liability, audit defence, legal costs for contracting with distributors
Educational and training costs: ongoing education to the patient; direct daily caregiver staff, provider training
Wound care application costs: wound care supplies; product shipment to the provider; time to affix the product to the wound and dressing to cover the product

viability and preserving Medicare beneficiary access to advanced wound care.

The risk to Medicare beneficiaries is clear: economic pressures will once again drive product selection based on financial margins rather than clinical need, only now in the opposite direction. Instead of overuse of high-priced products, the wound care stakeholder community faces underuse of clinically appropriate options, undermining both therapeutic best practices and patient outcomes. Moreover, if AMWCPs are unable to remain financially viable under the proposed reimbursement structure, entire care delivery models will collapse, eliminating access for homebound or transportation-limited patients. This creates substantial barriers to care that have not been observed since before 2020, and puts vulnerable Medicare beneficiaries at risk of preventable complications, hospitalisations, avoidable amputations and, in some cases, mortality.

To understand how the proposed reimbursement changes might drive these access limitations relative to facility-based wound care clinics, consider the following example under the current HOPD reimbursement model: a 4cm² LEDU treated with a $500 USD ($125 USD/cm²) CAMP provides a net gain of $926.80 USD, versus the proposed $583.54 USD (Box 1A, 1C). If implemented, the proposed 2026 flat-rate model with a facility-fixed application fee (Box 1C) incentivises providers to substitute lower-cost CAMPs to avoid financial loss. To illustrate the system-wide impact, consider a health system that operates 10 HOPD wound care clinics (Box 3). Under the proposed payment structure, substituting a $500 USD CAMP into the new reimbursement framework results in a revenue drop of $343.26 USD per application. At just 350 applications per clinic per year (a total of 3500 CAMP applications annually), the system would collectively experience over $1.2 million USD in lost reimbursement (Box 4). This reduction is not abstract; faced with sustained negative margins, healthcare leadership will take corrective actions that often include staff cuts, reduced clinic hours and limits on the types of patients served. These measures decrease clinical capacity and restrict access to care for Medicare beneficiaries, who rely on continuity of advanced treatment.

The most consequential impact of these economic pressures is not on manufacturers or markets, but on Medicare beneficiaries themselves. When policies aimed at cost containment fail to account for clinical realities, it is patients with hard-to-heal wounds who bear the most significant burden. Reductions in price per cm², when implemented without accompanying economic analysis or clinical foresight, increase barriers to access, particularly for susceptible populations. As research has shown, cost-shifting without appropriate safeguards leads to reduced access and greater financial vulnerability, further compounding the risks faced by these patients.[8] These access limitations are associated with higher rates of major and minor amputations, ED visits, hospital admissions, ICU stays, severe infections, such as sepsis, and elevated mortality rates.[5,7,12,13] Likewise, acute reconstruction for patients with trauma, burn and cancer will, paradoxically, require more expensive and higher-risk interventions, such as muscle flaps and free tissue transfer, followed by prolonged stays in SNF facilities, acute rehabilitation hospitals, extended outpatient rehabilitation and home health services.

Box 4. Example facility impact of proposed physician fee

Per application	
Proposed payment structure	$583.54
Prior bundled rate margin	$926.80
Revenue change	**–$343.26**
Extended to (3500 (annual CAMP applications) × (–$343.26)) = –$1,201,410	

$—US dollars; CAMP—cellular, acellular, and matrix-like product

Recent Medicare analyses confirm that when CAMPs are withheld or inappropriately limited, patient outcomes worsen while healthcare use and overall costs rise.[11,14] A 2024 real-world study of >450,000 Medicare wound episodes found that placenta-derived allografts were associated with significantly improved clinical outcomes across LEDUs and VLUs. Compared to the standard of care, treatment with these CAMPs reduced one-year mortality by 26% in LEDUs and 23% in VLUs, reduced recurrence by up to 91%, and lowered overall adverse outcomes by as much as 71%.[5] A 2021 study of >3400 patients found that those with hard-to-heal ulcers had a 74% higher risk of long-term mortality than matched controls, with the hazard ratio (HR) rising to 2.85 among patients with arterial leg ulcers and 1.49 for VLUs.[15] In critically ill populations, the presence of a PI ulcer has been shown to increase the 28-day mortality risk by 30% (HR 1.30) in patients with sepsis,[16] and among older patient populations with a stage 3–4 PI ulcer the mortality risk is almost doubled (pooled HR 1.78–1.96).[17] These data underscore the potentially life-threatening consequences of delayed or fragmented care. If AMWCP and other PAC programmes are destabilised by reduced reimbursement, it will disproportionately impact medically fragile patients for whom early, consistent intervention often determines limb salvage and survival. A 2019 CMS-sponsored evaluation of a prior authorisation model for hyperbaric oxygen therapy found increases in amputations and ED visits in some populations, while total Medicare spending did not decline, despite reductions in service use, highlighting the risk of cost containment strategies that unintentionally shift care burdens without improving outcomes.[18] These findings underscore the importance of maintaining access to advanced therapies, such as CAMPs, with proven effectiveness in the Medicare population, particularly when caring for patients at high risk for limb loss or death.

Disproportionate billing practices: a key factor in CAMPs cost burden on the Medicare Trust Fund

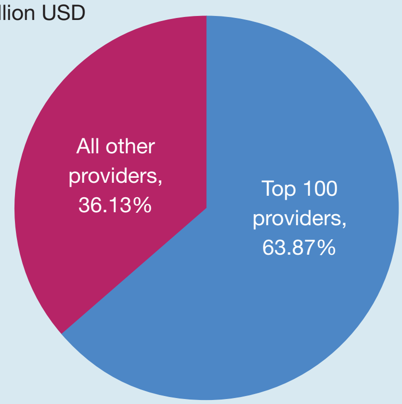
In 2023, two providers were indicted for $900 million USD in fraudulent CAMPs billing.[19,20] These cases underscore that a disproportionate share of Medicare's cost escalation may be driven by a small number of high-risk providers, rather than systemic misuse across the broader clinician community. Analysis of 2023 Medicare claims data demonstrated that 26% of total CAMPs spending came from just the top 10 providers in non-facility settings, compared to only 5% in facility settings. When expanded to the top 100 providers, the disparity becomes even more pronounced, accounting for an astounding approximately 64% of non-facility spending versus just 19% in the facility setting (Fig 1). To put this in perspective, fewer than 3% of non-facility providers billing for CAMPs applications are responsible for 63.9% of all CMS spending in this category, while the remaining 97.3% of providers account for just 36.1% of spending. This extreme concentration of use underscores that the primary cost drivers are a very small subset of high-intensity providers, rather than the broader wound care community.

Given that total private office and PAC spending reached approximately $3.8 billion USD in 2023,[11] these 100 providers were responsible for a staggering $2.43 billion USD, largely attributable to waste, fraud or abuse. Anecdotal reports suggest this trend has continued to escalate. Further analysis shows that 63.87% of spending came from just 44.5% of the billable units, with an average cost per patient of $346,906, 24.5-times higher than the average for other providers (Table 2). Additional red flags include the fact that the top 100 non-facility providers applied CAMPs to each patient more than twice as often as others. This intensity was also reflected in service frequency: they represented 14.4% of all CAMP service dates while treating just 6.7% of patients, signalling a pattern of more intensive and potentially excessive use. A policy solution that focuses on these outlier behaviours, not on artificial cost constraints or application restrictions, will deliver the greatest benefit to Medicare beneficiaries and preserve the Trust Fund's long-term solvency.

The appropriate use of CAMPs is well supported in the medical literature. It has long been recognised in the surgical community, with placenta-derived tissues featured in major plastic surgery references, such as *Plastic Surgery: Principles and Practice* by John Staige Davis, *Wound Repair* by Earle Peacock, and the *Plastic Surgery* (5th edn) series by Peter Neligan. Despite this longstanding clinical acceptance, these standards have yet to be broadly integrated into Medicare policy or routine clinical practice.[21–23] In contrast, inappropriate use of CAMPs has contributed to documented instances of waste, fraud and abuse, issues that undermine both clinical quality and fiscal stewardship within Medicare.[1,20]

Consider one example, that of a 78-year-old female patient who was treated for a VLU over 114 days. During her episode of care, applications of CAMPs were performed without a single debridement being recorded. On 10 occasions, CAMPs were applied on a day following a previous application, exemplifying wasteful practice. In total, 28 CAMP applications occurred (one every four days). Since approximately 290cm² was billed per application (range: 192–300cm²), CMS paid approximately $274,561 USD per application (range: $151,000–317,000 USD) for a shocking total of $7 million USD.

Fig 1. Percentage of Centers for Medicare & Medicaid Services payments to non-facility place of service for 3694 National Provider Identifiers in 2023 totalled $3.8 billion USD



Policy enforcement (or lack thereof) may be another culprit. While the Office of the Inspector General and other legal bodies have indicted a few 'bad actors', the analysis in this article attributes easily identifiable, expensive deviations from good practice to 100 providers or fewer countrywide. This suggests that the entire industry is being upended by the actions of <3% of providers in 2023. This is not a recommendation to triple the number of audits. Audits, and the clawbacks they often trigger, impose substantial administrative and financial burdens on CMS as well as on providers and manufacturers (Box 3). Rather, targeted oversight, capable of identifying fraud, waste and clinical outliers, is both appropriate and necessary. If designed to flag high-risk usage patterns, a programme like CMS's Wasteful and Inappropriate Service Reduction Model, which combines advanced technologies, such as artificial intelligence and machine learning, with clinical reviews, would, in real time, significantly reduce overuse, abuse and fraud with CAMPs reimbursement.

With compelling evidence highlighting its unfavourable impacts on access and outcomes for

Table 2. Comparisons of non-facility provider impacts on the Medicare Trust Fund

Category	The top 100 providers	All other providers
% of CMS CAMPs spending	63.9	36.1
% of CAMPs patients	6.7	93.3
% of services (on unique dates)	14.4	85.6
% of billable units	44.5	55.5
Average size of CAMP, cm²	56.7	11.9
Average cost/patient, $ USD	346,906	14,123

CAMPs—cellular, acellular, and matrix-like products; CMS—Centers for Medicare & Medicaid Services beneficiaries,[11,14] federal and legislative decision-makers should strongly consider rescinding the proposed future-effective CAMPs LCDs for the treatment of LEDUs and VLUs (L39764), and support the development of a redrafted coverage determination policy guided by nationally recognised, extensively published wound care experts. Such a framework should be grounded in peer-reviewed evidence and real-world clinical experience to support best practices in the application of CAMPs. The wound care stakeholder community urges CMS to establish a well-designed National Coverage Determination that codifies consistent, evidence-based practices across a range of wound types and sizes if rescission of the LCDs by the MACs is not secured before their implementation on 1 January 2026. A well-designed coverage policy, paired with a flat-fee reimbursement model, would establish clear clinical standards, accelerate adoption of appropriate care, eliminate fraud and abuse, and reduce the need for costly and burdensome audits. Over the past five years, there has been a growing consensus on the need to replace the current reimbursement structure, which too often steers treatment decisions based on financial incentives, with a model rooted in clinical appropriateness, favourable patient outcomes and healthcare value.

Factors driving CAMPs pricing

The projected financial pressures, along with the unfavourable consequences of restricting access for Medicare beneficiaries, underscore the urgency of addressing the broader systemic factors driving CAMPs pricing. To that end, the authors outline the key contributors to the current crisis: inflation, product complexity, rising demand and policy loopholes. When surveyed, >50 wound care stakeholders, consisting of professional associations, frontline healthcare delivery companies, including providers, and manufacturers of wound care-related products, were aligned in the belief that a flat-rate reimbursement model, grounded in data and clinical consensus, is the most viable strategy to preserve the Medicare Trust Fund while reducing CAMP-related expenditures.

Inflation in the US rose sharply between 2019 and 2025, with the Consumer Price Index for All Urban Consumers (CPI-U) increasing from 251.7 to approximately 317.8, a cumulative rise of approximately 26.3%, according to Bureau of Labor Statistics data.[24] While inflationary pressures have since moderated, actual prices have not meaningfully declined. Any attempt to artificially constrain costs through drastic reimbursement reductions will likely shift the procurement of CAMPs overseas, particularly for human tissue-derived products. This raises serious concerns about quality assurance, tissue sourcing, and adherence to standard operating procedures in countries with endemic infectious diseases and less stringent regulatory oversight. Although labour costs abroad may be lower, outsourcing CAMPs processing would further erode the security and integrity of the domestic supply chain and displace US-based jobs. CAMPs also play a vital role in burn and trauma care, making their availability a matter of national security. Reliance on overseas production can result in extended lead times for product sourcing. In the event of a mass casualty, such as one caused by a terrorist attack, this delay, compounded by the possibility that the US market may not be prioritised,

Table 3. Full cost burden ($ USD), justifying CAMP reimbursement range of $478–704 USD/cm²

Cost category	Entry-scale estimate (per cm²)	Late-stage estimate (per cm²)	Description
Clinical trials and R&D	$115	$185	Amortised cost of $11.5–15 million USD in past and future R&D over 3 years at early-stage volume (240,000–500,000cm²)
Procurement, manufacturing and processing	$38	$59	Includes GMP production, quality assurance/quality control, raw materials, tissue preparation, production batch loss and sterile packaging
SG&A expenses (including inflation)	$132	$151	Overhead for ~100 employees at $150,000 USD average salary, adjusted for inflation
Regulatory, legal and compliance	$37	$50	US FDA engagement, IP, safety monitoring, tissue bank compliance, audit readiness
Marketing, education and access	$95	$143	Sales force, provider education, payer contracting and outreach
Insurance, risk and fixed costs	$30	$70	Product liability insurance, risk mitigation, professional service fees
Subtotal (fully burdened cost)	$447	$658	Total cost to sustain product in market prior to margin
+ Margin (industry standard)	$31 (7%)	$46 (7%)	Operating margin to support reinvestment, future R&D, capital stability and pipeline continuity
Total justified reimbursement	$478 per cm²	$704 per cm²	Full reimbursement range needed to maintain innovation and ensure access for Medicare patients

FDA—Food and Drug Administration; GMP—good manufacturing practice; IP—intellectual property; R&D—research and development; SG&A—selling, general and administrative

Fig 2. Adjusted cellular, acellular, and matrix-like product (CAMP) units sold in the private office and post-acute care settings (2020–2025): polynomial projection

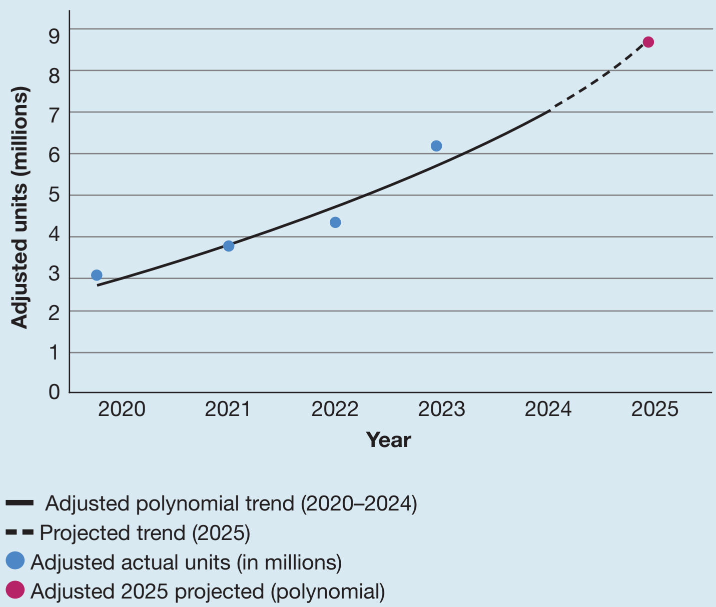
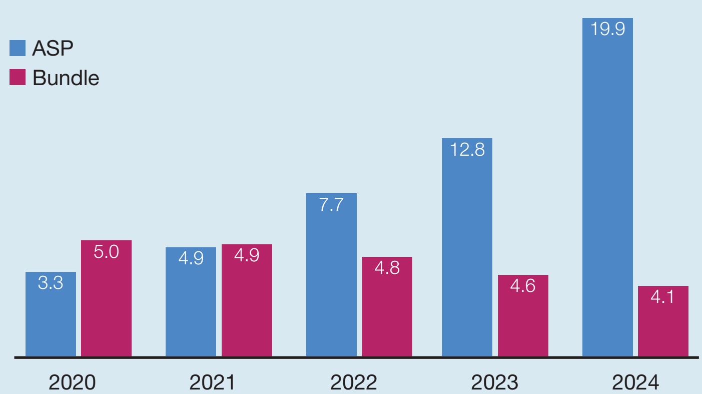


Fig 3. Patients with pressure injury ulcers treated with cellular, acellular, and matrix-like products (CAMPs) by year and payment type. Bundle payment model represents the hospital outpatient department setting. The average sales price (ASP) payment model represents the private office and post-acute care settings (values in thousands)



could severely limit the ability to scale supply rapidly. This underscores the need for a resilient, responsive and domestically anchored supply chain that can support federal emergency response objectives under the National Response Framework.

Companies that established their workforces before the recent inflation surge were able to scale up under more stable labour conditions. In contrast, newer entrants over the last five years have had to navigate elevated wage demands and a constrained labour pool, especially for skilled clinical, regulatory and biomanufacturing roles, placing them at a competitive disadvantage. This dynamic creates an uneven playing field and threatens to destabilise a critical domestic industry at a time when resilient, secure and compliant supply chains are more essential than ever.

Sustaining improvements in patient outcomes and access is heavily reliant on preserving the innovation pipeline that makes these advanced treatments possible. Innovation is the cornerstone of expanding access to advanced medical technologies that favourably impact Medicare beneficiaries. However, bringing these advancements to market often generates significant costs, including selling, general and administrative expenses, research and development, regulatory engagement, payer education, provider training and ongoing compliance infrastructure. While these investments are essential to ensuring equitable access and improved outcomes, they also add meaningful costs to the operating structure of stakeholders, driving innovation in both the manufacturing and healthcare delivery arenas. As an example, unavailable less than a decade ago, a patient's own cells can now be cultured and fabricated into three-dimensional-printed constructs, an important breakthrough for treating wounds in burn and trauma victims, with high prospects in warfighter scenarios.[25–27] Other solutions, such as synthetics, multilayered CAMPs, the development of alternative preservation techniques, or wound-specific targeted engineering offer increases in stimulatory regulatory factors, improvements in extracellular matrix architectures, and more efficient delivery systems for deeper wounds.

To bring novel CAMPs to market and sustain their availability, manufacturers incur comprehensive and layered cost burdens, including clinical trials, good manufacturing practices, regulatory compliance, provider education, payer engagement, patient awareness initiatives, marketing, and sales and administrative infrastructure. These expenses, compounded by modest commercialisation volumes and ongoing inflationary pressure, result in a fully burdened per-unit cost ranging from \$447–658 USD/cm². These estimates are derived from a cost framework informed by industry benchmarks and representative, publicly available data. However, when factoring in a sustainable operating margin to support future innovation or development and ensure long-term viability, the total justified reimbursement range rises to \$478–704 USD/cm², as detailed in Table 3.

- The early-stage estimate of \$478 USD/cm² reflects the minimum viable reimbursement needed to support access to a novel CAMP at early-stage scale, assuming relatively efficient operations and controlled input costs
- The full-scale estimate of \$704 USD/cm² reflects the full economic burden when accounting for broader clinical development requirements, manufacturing complexity and commercialisation ramp-up, particularly before economies of scale have been achieved.

As these technologies evolve and become more complex, the costs of innovation become increasingly difficult to forecast. However, a reimbursement rate below this range ($478–704 USD/cm²) would suppress innovation, restrict Medicare patient access to clinically superior therapies of the future, and anchor market value to legacy products that no longer bear the burden of ongoing investment. Policymakers must recognise that reimbursement models rooted in outdated cost structures are incompatible with sustaining the advanced technologies and real-world infrastructure demands of modern wound care, which, in the long-term outlook, reduces the overall spend on the Medicare Trust Fund.[7,13]

It is projected that, by the end of 2025, the adoption of CAMPs as an effective treatment option will have increased by as much as six million units since 2020 (Fig 2). As the US population ages and comorbidities such as diabetes increase in prevalence, policymakers along with wound care providers will experience a continued rise in wound prevalence resulting in more patients being treated and increases in the types of wounds seen. For example, since 2020, the number of Medicare beneficiaries diagnosed with a PI ulcer who received CAMPs during their episode of care has steadily grown in frequency to levels not seen before the COVID-19 pandemic (Fig 3). This upsurge most likely corresponds to the simultaneous growth of community-centred wound care delivery, AMWCP, in the PAC setting.

From 2020 to 2025, AMWCPs have significantly expanded healthcare delivery to underserved Medicare beneficiaries with PI ulcers, conditions that, before the COVID-19 pandemic, were often inadequately addressed due to immobility and the absence of an effective support network. AMWCPs now bring wound care onsite to the most at-risk Medicare beneficiaries. This, in large part, made the economics of travel time between patient visits in AMWCPs achievable through the evidence-based adoption of medically proven technologies, such as CAMPs, to treat PI ulcers, VLUs and LEDUs.

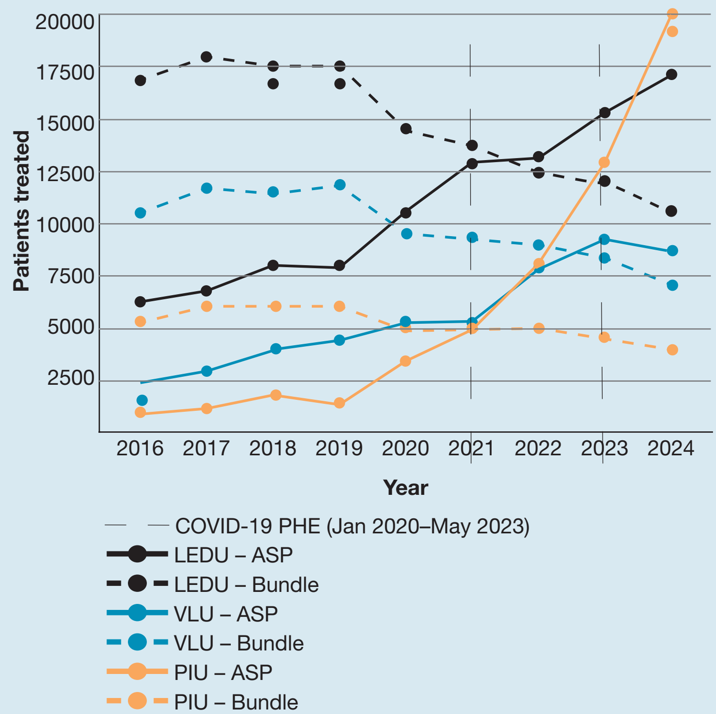
The danger of reducing healthcare expenditure by unduly slashing the reimbursement of CAMPs based on historic or pre-pandemic precedents without strategically considering the long-term consequences has recently been highlighted.[11] Medicare claims data from 2016–2024 have revealed a general trend of decreased treatment of wounds, starting just before the COVID-19 pandemic, in the facility setting, which has been tethered to an increase in the private office and onsite PAC settings (Fig 4).

This surge reflects a market adapting to rising demand for effective treatment of hard-to-heal wounds, even under artificial downward pressure. Proposals restricting reimbursement eligibility from >200 CAMPs to <20 will severely disrupt the supply–demand balance, limit patient access and destabilise the broader wound care ecosystem. As the dominant payer in the wound care space, Medicare plays a central role in shaping market dynamics and access to CAMPs. However, it has also raised criticism for incentivising the use of more expensive treatments in non-facility settings and restricting the ability to treat larger wounds in the HOPD setting. Prior coverage policies that impose rigid limits on the number of CAMPs applications have failed to account for patients with larger or more complex wounds, complications such as cellulitis or wound infections, and even significant compounded comorbidities.[11] Taken together, the evidence presented in this manuscript indicates that the most effective approach is a flat-rate pricing structure that provides an entry point for new technologies in line with their developmental costs, while sustaining established CAMPs through commercialisation ramp-up before economies of scale have been realised.

Adopting a flat-rate reimbursement schedule would yield substantial savings to the Medicare programme. Based on projected 2025 Medicare spending on CAMPs in the private office and PAC settings of $15.38 billion USD, implementing a flat-rate reimbursement of $704 USD/cm² (CMS portion: $549.12 USD/cm²) would result in:

- An immediate 69% reduction in Medicare CAMPs expenditures
- In the private office and PAC settings, an estimated cost saving of up to $10.57 billion USD in the first year of implementation
- A projected 10-year saving of up to $105.7 billion USD.

Fig 4. Patients treated with cellular, acellular, and matrix-like products (CAMPs) by aetiology and reimbursement type (average sales price (ASP) versus bundle). Bundle payment type represents the hospital outpatient department setting. ASP payment model represents the private office and post-acute care settings. PHE—public health emergency; PIU—pressure injury ulcer; LEDU—lower extremity diabetic ulcer; VLU—venous leg ulcer



Conclusion

The efforts of CMS to modernise reimbursement for wound care are commendable. Yet, the proposed flat-fee structure fails to account for the diversity of CAMPs, their real-world effectiveness and the operational realities of delivering care. The wound care stakeholder community urges CMS and federal policymakers to adopt, as a matter of urgency, a refined, data-driven approach that integrates clinical appropriateness, economic sustainability and access equity. Notably, <3% of non-facility wound care providers using CAMPs in their treatment regimen are responsible for nearly two-thirds of CMS spending in this category, underscoring the need for targeted oversight of high-intensity outliers rather than across-the-board payment cuts that risk harming access for the majority of beneficiaries. A refined, evidence-based reimbursement approach, combined with a clear coverage determination policy, will preserve patient access, drive best practices, incentivise innovation, reduce unnecessary audits, and protect the long-term sustainability of the Medicare Trust Fund while concurrently generating >$100 billion USD in projected savings over 10 years. These savings are even greater when the avoided downstream costs from improved healing and reduced complications in Medicare and Medicare Advantage patients with hard-to-heal LEDUs treated with CAMPs are simultaneously taken into account.[7] Broad consensus exists across the wound care community in support of policy reform that balances fiscal stewardship with equitable access to advanced care for Medicare beneficiaries. **JWC**

Acknowledgments

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The overlooked epidemic: the importance of treating 'other' open wounds in wound medicine

Abstract: In the field of wound medicine and surgery significant attention is devoted to well-defined hard-to-heal (chronic) wounds, such as diabetic foot ulcers (DFUs), venous leg ulcers (VLUs) and pressure ulcers (PUs). These conditions dominate research, clinical guidelines and resource allocation, due to their clear aetiologies and high prevalence among specific patient populations. However, a substantial category of wounds—often labelled as 'other' open wounds under International Classification of Diseases (ICD)-10 codes—remain underappreciated and frequently excluded from analyses. These include non-specific open wounds without a particular aetiology, as well as surgical and trauma wounds that persist in outpatient settings without evolving into more specialised diagnoses. This opinion piece—building on the reimbursement framework proposed by Tettelbach et al.—argues that neglecting these 'other' wounds perpetuates inefficiencies in healthcare, exacerbates patient suffering and inflates economic burdens. By integrating comprehensive treatment strategies for all open wounds, regardless of aetiology, we can improve patient outcomes, reduce costs and advance equitable wound care interventions.

Declaration of interest: The authors have no conflicts of interest to declare.

Open wounds represent a critical challenge in modern healthcare, affecting millions of people worldwide and imposing substantial clinical and financial strains.[1] According to International Classification of Diseases (ICD)-10, open wounds are primarily coded under categories such as: S01 (head); S11 (neck); S21 (thorax); S31 (abdomen, lower back, pelvis, and external genitals); S41 (shoulder and upper arm); S51 (elbow and forearm); S61 (wrist, hand, and fingers); S71 (hip and thigh); S81 (knee and lower leg); S91 (ankle, foot, and toes); T01 (multiple body regions); and others including T09.1, T11.1, T13.1 and T14.1 for unspecified levels or regions.[2,3] These codes encompass a broad spectrum of injuries, from lacerations and punctures to bites and avulsions, often requiring extensions for episode of care (e.g., initial, subsequent or sequela).

While DFUs, VLUs and PUs (also known as pressure injuries) receive targeted interventions—supported by extensive evidence-based protocols—'other' open wounds are frequently sidelined. These wounds lack a 'specific aetiology', making them outliers in studies that prioritise categorical data.[4,5] Surgical incisions and traumatic injuries, for example, may heal uneventfully in acute settings but transition to hard-to-heal (chronic) open wounds in outpatient care when complications arise without a refined diagnosis.[6] This exclusion not only causes an underestimation of the true burden of wound care but also hinders the development of holistic management approaches. As an opinion piece, this paper—building on the reimbursement framework proposed by Tettelbach et al.,[7] and published in this edition of *JWC*—posits that treating 'other' open wounds with the same rigour as their more prominent counterparts is essential for patient-centred care and systemic efficiency.

Categorising open wounds is an interesting exercise. Hard-to-heal wounds are typically categorised by aetiology: DFUs stem from neuropathy and possibly poor circulation in patients with diabetes; VLUs arise from venous insufficiency; and PUs result from prolonged pressure on immobilised individuals.[8] These types dominate wound medicine literature because their causes are identifiable, allowing for aetiology-specific treatment, such as offloading for DFUs or compression therapy for VLUs, and improved offloading surfaces for PUs.

In contrast, 'other' open wounds defy neat categorisation. They include acute injuries that become hard-to-heal due to infection, poor healing environments or comorbidities, without fitting into the above categories.[9] Surgical wounds, classified as 'clean', 'clean–contaminated', 'contaminated', or 'dirty' based on intraoperative conditions, often heal by primary intention but can dehisce or persist as open wounds in outpatient follow-up. Trauma wounds, such as abrasions, lacerations or punctures from accidents, similarly start as acute but may linger if not properly managed, especially in resource-limited settings.[9] Patients with autoimmune and haematological disorders may have their own wounds that wax and

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wane with their disease (e.g., rheumatoid arthritis, sickle cell anaemia).

The outpatient context exacerbates this issue. Postoperative or post-trauma patients discharged to ambulatory care may present with wounds that no longer qualify for surgical codes but remain open, leading to ICD-10 open wound designations. This reclassification highlights a gap—while acute care focuses on closure, outpatient management deals with persistence, yet resources skew toward aetiology-specific wounds.

Prevalence and economic burden

The scope of hard-to-heal wounds is vast, affecting approximately 2–2.5% of the US population—equating to millions of individuals.[10,11] In Medicare beneficiaries alone, the annual cost of wound care exceeds $28 billion USD, with surgical wounds and 'other' open wounds contributing significantly.[12] Globally, particularly in tropical regions, wound care burdens healthcare systems with high prevalence rates and costs averaging thousands of dollars per patient over years.[13,14]

'Other' open wounds amplify this burden. Studies indicate that non-specific wounds, including those from trauma and surgery, account for a notable portion of outpatient visits but are underrepresented in cost analyses.[15] In primary care, hard-to-heal wounds—including these 'other'—impose significant financial strains, with increasing prevalence due to an ageing population and comorbidities.[16] Fife et al.[17] conducted extensive research in the domain of wound care. The findings indicated a significant distribution of various types of outpatient wounds in wound centres. The studies revealed that in one set of wound centres, DFUs accounted for approximately 15%, VLUs 11%, PUs 15%, postoperative complications 21%, and atypical wounds 21%, while arterial and traumatic wounds comprised the remainder.

Carpenter et al.[18] conducted comprehensive retrospective research evaluating healing rates and percentage area reduction across various wound types, including DFUs, VLUs, surgical wounds, trauma wounds and 'other' open wounds, all treated with cellular and/or tissue-based products (CTPs). The study reported an overall healing rate of approximately 51% across all wound aetiologies, with notable outcomes of 44% for surgical wounds, 63% for trauma wounds, and 61% for 'other' open wounds within the ICD-10 'S' and 'T' categories. These findings underscore the critical need to prioritise the often-overlooked category of 'other' open wounds with the same rigorous attention and care as more extensively studied wound types, such as DFUs, VLUs and PUs, to ensure optimal healing outcomes across all wound aetiologies.

Why 'other' open wounds are overlooked

The exclusion of non-specific open wounds from analyses stems from methodological preferences: studies favour homogeneous cohorts for robust data, sidelining heterogeneous 'other' categories. This bias perpetuates a cycle where evidence for treating these wounds lags, discouraging investment.[19] Additionally, reimbursement policies often prioritise aetiology-specific codes, leaving 'other' open wounds underfunded in outpatient settings.[20]

Surgical and trauma wounds exemplify this oversight. Initially managed acutely, they may become hard-to-heal in outpatient care due to infection or delayed healing, yet lack dedicated protocols beyond general open wound guidelines. This results in suboptimal outcomes, including higher infection rates and prolonged healing times.[21]

All wounds, regardless of aetiology, should undergo thorough evaluation to identify and address impediments to healing, such as infection, poor vascularity or nutritional deficiencies. Once these barriers are resolved, each wound should be treated with the same meticulous care as an open wound, employing evidence-based interventions, such as CTPs. By systematically reducing barriers to healing, we establish the essential foundation for optimising outcomes across all open wounds, ensuring equitable and effective treatment for every patient.

The imperative for comprehensive treatment

Treating 'other' open wounds is not optional—it is vital for preventing complications such as infections, which can lead to amputations or sepsis. Proper care, including debridement, dressings and negative pressure wound therapy, accelerates healing, reduces pain and improves patient quality of life. Economically, early intervention curtails costs; untreated wounds escalate expenses through hospitalisation and extended care.[22]

For surgical and trauma wounds, outpatient strategies, such as irrigation, autologous grafts and biofilm management, are underused but effective. It is imperative for wound medicine and surgery to shift from aetiology silos to a unified framework, incorporating all 'other' open wounds into research policy. This inclusivity would foster innovation, such as advanced dressings for non-specific cases, and ensure equitable access.

There also needs to be a better understanding of diagnosis and treatment of the underlying aetiology of those wounds we do treat. This is particularly true of VLUs, where many practitioners treat wounds that look like a VLU without diagnosing the venous pathology let alone treat the disease. No one would treat breast cancer because it looks like breast cancer; multiple tests would be undertaken to reach a confirmed diagnosis before implementing any form of treatment.

Collaborative care must include those often underutilised specialties including haematology, rheumatology, infectious disease and pharmacology.

Conclusion

While the broad categories of DFUs, VLUs, PUs, post-surgical, post-traumatic, atypical and ischaemic wounds will help with ensuring that the treatment of the underlying aetiology is diagnosed and addressed thoroughly, we must recognise that the 'other' open wounds (post-surgical, post traumatic and atypical) under ICD-10 codes are not mere footnotes—they are a silent epidemic demanding attention. By overlooking them, we risk perpetuating disparities in care and inflating burdens on patients and systems. It is time for clinicians, researchers and policymakers to advocate for inclusive analyses, refined classifications and robust treatment protocols. Embracing these hard-to-heal 'other' open wounds as integral to wound medicine and surgery will not only heal individuals but also strengthen healthcare resilience. Future studies must prioritise this category to unlock improved outcomes for all. JWC

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Dehydrated Amnion Chorion Membrane versus standard of care for diabetic foot ulcers: a randomised controlled trial

Objective: Diabetic foot ulcers (DFUs) continue to challenge wound care practitioners. This prospective, multicentre, randomised controlled trial (RCT) evaluated the effectiveness of a dehydrated Amnion Chorion Membrane (dACM) (Organogenesis Inc., US) versus standard of care (SoC) alone in complex DFUs in a challenging patient population.
Method: Subjects with a DFU extending into dermis, subcutaneous tissue, tendon, capsule, bone or joint were enrolled in a 12-week trial. They were allocated equally to two treatment groups: dACM (plus SoC); or SoC alone. The primary endpoint was frequency of wound closure determined by a Cox analysis that adjusted for duration and wound area. Kaplan–Meier analysis was used to determine median time to complete wound closure (CWC).
Results: The cohort comprised 218 patients, and these were split equally between the two treatment groups with 109 patients in each. A Cox analysis showed that the estimated frequency of wound closure for the dACM plus SoC group was statistically superior to the SoC alone group at week 4 (12% versus 8%), week 6 (22% versus 11%), week 8 (31% versus 21%), week 10 (42% versus 27%) and week 12 (50% versus 35%), respectively (p=0.04). The computed hazard ratio (1.48 (confidence interval: 0.95, 2.29) showed a 48% greater probability of wound closure in favour of the dACM group. Median time to wound closure for dACM-treated ulcers was 84 days compared to 'not achieved' in the SoC-treated group (i.e., ≥50% of SoC-treated DFUs failed to heal by week 12; p=0.04).
Conclusion: In an adequately powered DFU RCT, dACM increased the frequency, decreased the median time, and improved the probability of CWC when compared with SoC alone. dACM demonstrated beneficial effects in DFUs in a complex patient population.
Declaration of interest: This study was funded by Organogenesis Inc., US. JC serves as a consultant and speaker for Organogenesis. RDD serves as a speaker for Organogenesis. OMA and MLS serve as consultants for Organogenesis. The authors have no other conflicts of interest to declare.

CAMPs • chronic wounds • dACM • dehydrated Amnion Chorion Membrane • diabetic foot ulcers • placental allograft • wound • wound care • wound dressing • wound healing

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Prevalence of diabetes in the US has continually increased over the past two decades, peaking at 11.6% of the population in 2021.[1] There are an estimated 37.3 million individuals with diabetes in the US, 28.7 million of whom have a confirmed diagnosis.[2–4] The presence of diabetes carries increased risk for development of lower extremity ulcers, primarily through development of peripheral neuropathy and ischaemia from peripheral vascular disease.[5,6] Minor injuries to the skin may go unnoticed and develop into a diabetic foot ulcer (DFU). Patients with diabetes are estimated to carry a 25% lifetime risk of developing a DFU.[4] In the US, the estimated overall incidence of DFUs ranges from 6–13% of patients with diabetes, with >1 million having a hard-to-heal DFU (an ulcer persisting for >6 weeks).[7–9] Among patients with diabetes, >50% of DFUs have been reported to remain unhealed after 12 months. These patients carry a 40% risk of infection for every six months that their wounds remain unhealed.[8,10,11] In the worst case, this may lead to lower limb amputation. Approximately 28 out of every 10,000 patients with diabetes will undergo amputation, with up to 85% of all non-traumatic amputations being attributable to DFUs.[12,13] In the event of amputation, the 5-year mortality risk is higher than that of many common forms of cancer.[14–16]

The negative health consequences associated with DFUs are paired with potential for high financial burden. The estimated individual cost of care related to a DFU is $4595 USD per ulcer episode, up to $28,000–$31,000 USD for the two years following diagnosis, and $8659 USD annually thereafter.[16,17] This equates to approximately $9–13 billion USD in annual financial burden to private and public insurance payers.[17,18] In the event of a below-the-knee amputation, individual costs can exceed $50,000 USD, even before associated costs such as prolonged hospital stay, rehabilitation and prosthesis.[19] Overall, the longer a DFU persists, the higher the risk for negative health outcomes and high financial burden to the patient. This warrants a treatment that can significantly reduce time to complete wound closure (CWC) for DFUs, as both negative health outcomes and high financial burden issues persist with standard of care (SoC).

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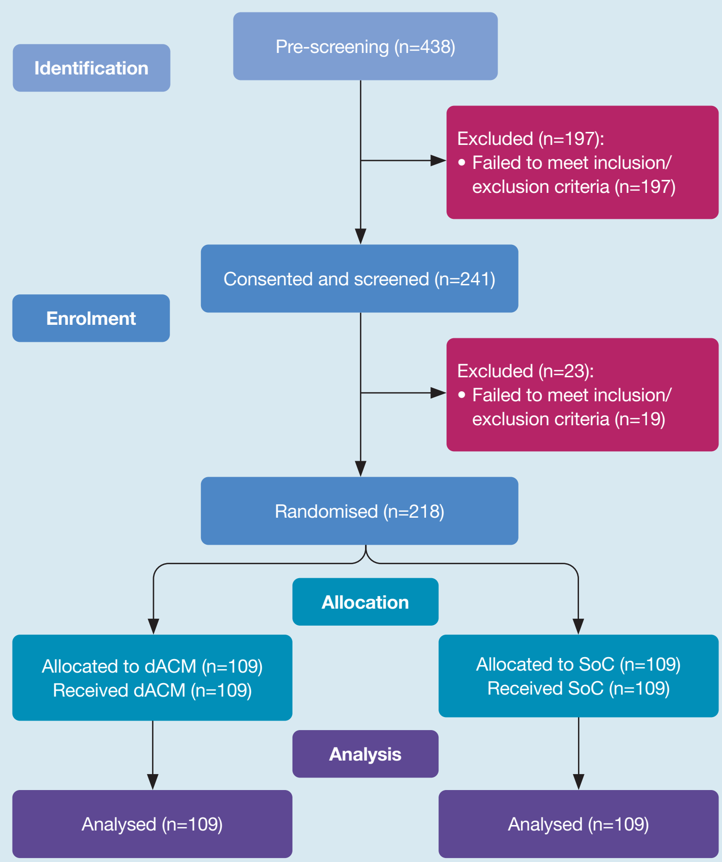
Current SoC for DFUs involves offloading, debridement, dressing application to maintain a moist wound environment, infection management, surgery when appropriate, and prevention of recurrence.[20–22] While capable of achieving healing, <50% of DFUs receiving SoC attain CWC in 12–16 weeks.[23–26] In this situation, wound care guideline recommendations include incorporation of adjuvant therapies to aid in management of the wound environment.[22] Specifically, much emphasis has been placed on Cellular and/or Tissue-based Products (CTPs), or Cellular, Acellular and Matrix-like Products (CAMPs), which include placental membrane allografts.

Following the advent of cryopreservation and dehydration in the late 1990s, use of placental allografts became prominent in wound care.[27] Through different processing and preservation techniques, the composition and inherent properties of the amnion and/or chorion layers are able to be retained, and have been shown to support wound healing.[8,24,27] Contained within the amnion and chorion are numerous growth factors, cytokines, collagens, proteoglycans, glycoproteins and hyaluronic acid.[28–33] A wide range of growth factors, in addition to matrix proteins contained within dehydrated Amnion Chorion Membrane (dACM), have been identified.[31,32] In vitro analysis further identified that dACM caused a significant reduction in matrix metalloprotease activity. In addition, proliferation of human dermal fibroblasts, human keratinocytes, and human microvascular endothelial cells occurred after these cells were cultured in dACM-conditioned media.[31,32]

dACM (NuShield; Organogenesis Inc., US) is a human placental allograft tissue composed of amnion and chorion, derived from donated birth tissue, that retains native extracellular matrix (ECM) scaffolding and proteins.[34] dACM contains ECM proteins including collagen, fibronectin, hyaluronic acid and laminin.[31] In addition, dACM contains numerous types of growth factors, proteins and cytokines.[31] dACM is intended for use as a protective barrier in the management of acute and hard-to-heal wounds and is regulated as human cells, tissues, and cellular and tissue-based products (HCT/Ps; Food and Drug Administration (FDA) classification) solely under Section 361 of the Public Health Service Act as defined in 21 CFR Part 1271.[34] A previous retrospective analysis and case series have indicated potential efficacy for the use of dACM in DFUs when paired with SoC.[35,36]

The purpose of this randomised controlled trial (RCT) was to assess the clinical effectiveness outcomes of dACM for the management of DFUs.

Fig 1. CONSORT flow diagram. dACM—dehydrated Amnion Chorion Membrane; SoC—standard of care



Method

Ethical approval and patient consent

This study was conducted in accordance with the specifications of the protocol and in accordance with principles consistent with Good Clinical Practice, 21 CFR 312, ICH E6, HIPAA regulations in 45 CFR Part 164. Advarra IRB, US acted as the central institutional review board (IRB) for the study. Advarra is registered with the FDA and the Office for Human Research Protections (OHRP) (IRB Organization Number, 0000635; IRB Registration Number, 0000971). Subjects read, understood and signed an IRB-approved written informed consent prior to undergoing study activities. Treatment records included subject ID (with ulcer care centre of treatment) and study treatment; subject baseline age and sex; and ulcer area, depth and volume at all study visits.

Study design

This prospective, randomised, controlled multicentre study compared dACM plus SoC to SoC alone in subjects with hard-to-heal DFUs (Clinical trial: NCT03855514). dACM was used along with SoC on DFUs of >6 weeks' duration (self-reported duration of four weeks plus two weeks of screening) which had not adequately responded to conventional ulcer therapy and could extend into dermis, subcutaneous tissue, tendon, capsule, bone or joint. dACM was applied at the wound care facility according to the prescribing information. Eligible subjects were between 18–85 years of age with a DFU that had not healed with conventional therapy for ≥6 weeks and whose surface area was between 0.5–25cm^2. For subjects with multiple DFUs, a designated 'index ulcer' was prospectively identified by the investigator at day –14. In subjects with multiple ulcers, the most severe ulcer that met study requirements was designated as the index ulcer. Once eligibility was confirmed, subjects were randomised 1:1 to the following groups:

- Group 1: dACM plus SoC
- Group 2: SoC alone

Following screening and randomisation, subjects were seen weekly for up to 12 weeks. Week 12 was the timepoint used for the determination of primary and secondary efficacy endpoints.

dACM: the investigational treatment material

dACM manufacturing, recovery and processing of donated tissues were performed in accordance with all federal, state and local regulations, including the US FDA regulations 21 CFR 1270 and 1271. Placentas were donated with informed consent after planned Caesarean sections, and all processing was completed in accordance with the FDA's Good Tissue Practices (GTP) and American Association of Tissue Banks (AATB) standards. All donors were screened for medical issues, social issues, and communicable diseases that could affect donor suitability. Serological testing for bacterial, viral and infectious diseases were performed on blood specimens from each donor and exceeded the requirements of the FDA and the AATB. Viral testing included antibodies to HIV-1, HIV-2, HTLV-1, HTLV-2, hepatitis B core and hepatitis C. Tests for HIV-1 nucleic acid, hepatitis B surface antigen and other adventitious viruses and pathogens were also conducted.

Group 1: dACM plus SoC

Subjects who were randomised to Group 1 received, in addition to SoC, dACM sized to cover the entire wound. Ulcers were prepared using standard methods that included sharp debridement (by curette or scalpel) to ensure that the ulcer area was free of debris and necrotic tissue. Ulcer beds and peri-ulcer areas were cleansed with normal, sterile saline solution. dACM was applied and fixated directly on the open ulcer bed with the chorion side in contact with the wound per manufacturer specifications at weekly intervals at the discretion of the investigator, or until the DFU was healed. This was followed by application of outer dressings.

Group 2: SoC alone

Subjects randomised to Group 2 did not receive dACM on the index ulcer. The SoC for DFU included debridement, offloading of the ulcer, management of infection, and maintenance of appropriate cleansing at the time of each dressing change. Surgical or sharp debridement was performed to remove all necrotic and devitalised tissue, as well as surrounding callus, extending to healthy viable tissue. Following debridement, the ulcer was thoroughly cleansed with saline and gently dried with gauze. Standard dressings were restricted to those that provided exudate control and allowed for a moist wound environment. Control subjects were also seen weekly for up to 12 weeks to determine efficacy endpoints.

Inclusion and exclusion criteria and the general study population

The general study population included a total of 218 subjects with DFUs. The inclusion and exclusion criteria defined in the protocol applied to all subjects (Fig 1).

All subjects in both groups were instructed to avoid weight-bearing on the affected foot throughout the duration of the study. All subjects were required to offload their DFU with a protocol-approved offloading device from the time of their screening visit (e.g., fixed ankle walker boot, pressure-relieving footwear or shoe modifications).

Inclusion criteria

The study population comprised subjects with:

- Type I or II diabetes with a DFU of ≥6 weeks' duration that was unresponsive to SoC
- A DFU extending into dermis, subcutaneous tissue, tendon, capsule, bone or joint
- Well controlled glucose levels with HbA1c <10% and an ulcer between 0.5–25cm^2
- Minimum age of 18 years
- Adequate lower extremity perfusion as evidenced by transcutaneous oxygen measurement or a skin perfusion pressure measurement of ≥45mmHg, or an ankle–brachial index between 0.6–1.3 or a toe–brachial index ≥0.6
- No evidence of unresolved gross soft tissue infection or osteomyelitis as ruled out by X-rays, computerised tomography (CT) scan or magnetic resonance imaging (MRI)
- No evidence of underlying comorbid conditions that would adversely affect wound closure (cancer, Raynaud's syndrome, severe venous insufficiency or uncorrected arterial insufficiency)
- Abstinence from concomitant medications that would compromise wound closure (cytotoxic drugs or chemotherapeutics).

Exclusion criteria

- Evidence of skin cancer within or adjacent to the ulcer site
- Symptoms of osteomyelitis
- Disorders that would affect patient safety in the trial (e.g., malignant melanoma)
- Cellulitis
- Ulcers with sinus tracts
- Active deep vein thrombosis
- Uncontrolled diabetes
- Renal impairment (creatinine >2.5mg/dl)
- Hepatic impairment (≥2×upper limit of normal (ULN))
- Haematological compromise.

During the 2-week run-in period, the ulcers were debrided and offloaded using per protocol footwear. Ulcers that healed by 20% or more were excluded from the trial.

Randomisation
This was a 1:1 computerised randomisation (Group 1: Group 2). The randomisation was stratified by baseline wound area, <4cm^2 in stratum 1 and ≥4cm^2 in stratum 2. This ensured that equal numbers of subjects in the dACM plus SoC and SoC alone treatment groups were included in both wound size groups.

Sample size
It was expected that approximately 50% of subjects in the dACM plus SoC treatment group and 30% of subjects in the SoC only treatment group would demonstrate CWC by week 12. In order to achieve 80% power to detect this difference, a total of 220 subjects (110 in each group) were required for the primary analysis. A log-rank test with a two-sided significance level of 0.05 was used for this calculation.

Intent-to-treat (ITT) population
All subjects who received SoC only or dACM plus SoC after randomisation, and had at least one post-baseline assessment, were included in the ITT population. The ITT population was the primary analysis population for clinical efficacy endpoints.

Data collection
Investigators were responsible for collecting and accurately recording the clinical data generated for this study in electronic case report forms. Wound measurements were made by ruler. Measurements of the DFU length were from 'head to toe' at the longest point. Measurements of the width were from side to side at the widest point that was perpendicular to the length. Area was computed by multiplying length by width. Accurate records of the clinical data generated from this study were maintained according to Good Clinical Practices requirements.

Analysis software
Data analysis, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations were performed primarily using SAS (release 9.4 or higher) for Windows (SAS Institute Inc., US). No other software was necessary.

Study endpoints
Primary efficacy endpoint:
- Time to and frequency of CWC by or at 12 weeks.

Key secondary endpoints:
- Mean percentage change from baseline in wound area at week 12
- Proportion of subjects achieving ≥40% wound closure by or at week 6.

Table 1. Patient characteristics

	dACM + SoC	SoC	p-value*
Number of patients	109	109	
Age			0.12
Mean±SD	60.14±10.39	57.84±10.98	
Median	61.57	57.34	
Sex, n (%)			0.50
Male	85 (78.0)	90 (82.6)	
Female	24 (22.0)	19 (17.4)	
BMI			0.38
Mean±SD	32.56±7.88	33.54±8.39	
Median	30.90	32.60	
Number of DFUs per patient			0.50
Mean±SD	1.30±0.62	1.20±0.51	
Median	1.00	1.00	
DFUs per patient, categorical, n (%)			0.12
Single wound	96 (86.5)	86 (78.2)	
Multiple wounds	15 (13.5)	24 (21.8)	

*For continuous variables, the p-value is from a two-sided, two sample t test, testing for a difference in means between treatments. For categorical variables, the p-value is from a two-sided Fisher's exact test testing for a difference in proportions between treatments. BMI—body mass index; dACM—dehydrated Amnion Chorion Membrane; DFU—diabetic foot ulcer; SD—standard deviation; SoC—standard of care

Statistical methods
All efficacy analyses were completed using ITT populations.

Primary efficacy analysis
The time to the first reported CWC of the index wound was summarised using the Kaplan–Meier method. The follow-up time was censored at the week 12 visit or early termination visit if a subject did not achieve CWC. The median time to CWC (and other quartiles), along with the percentage of subjects achieving CWC at each time point, was presented along with two-sided 95% confidence intervals (CIs). The estimated Kaplan–Meier curves will also be displayed by plotting histograms of healing over time. Treatments were compared using log-rank tests stratified by baseline wound area (<4cm^2 or ≥4cm^2). As a sensitivity analysis, a Cox proportional hazards regression model was also used to estimate the hazard ratio and associated 95% CI, adjusting for baseline wound area and index ulcer duration at baseline.

Key secondary efficacy analyses
Mean percentage change from baseline in wound area at week 12
The mean percentage change at 12 weeks from baseline was analysed for treatment, baseline wound area (<4cm^2 or ≥4cm^2), and the treatment-by-week interaction. Study week was included in the model as

Fig 2. Percentage of all diabetic foot ulcers with complete wound closure (n=218). dACM—dehydrated Amnion Chorion Membrane; SoC—standard of care

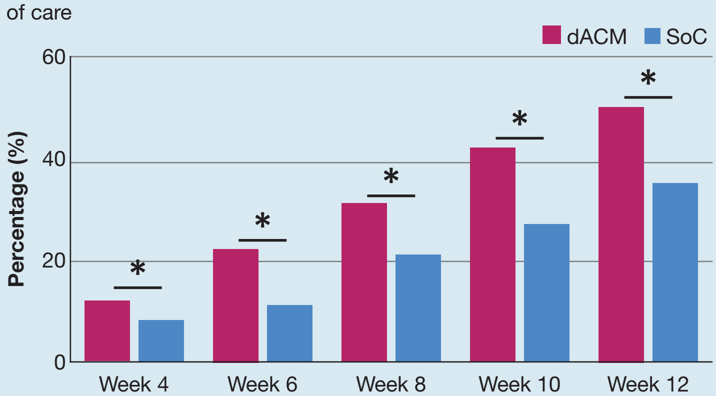


Fig 3. Percentage of all diabetic foot ulcers <4cm^2 with complete wound closure (n=157). dACM—dehydrated Amnion Chorion Membrane; SoC—standard of care

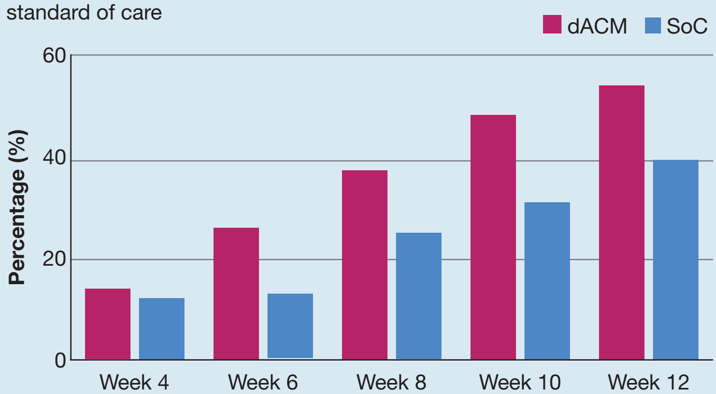
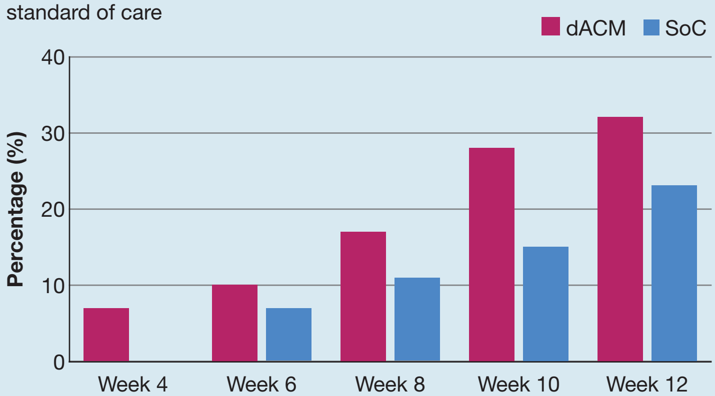


Fig 4. Percentage of all diabetic foot ulcers ≥4cm^2 with complete wound closure (n=61). dACM—dehydrated Amnion Chorion Membrane; SoC—standard of care



a categorical variable (weeks 1–12) along with the treatment-by-week interaction.

Proportion of subjects achieving ≥40% wound closure at by or at week 6 from baseline

The number and percentage of subjects reported to have a percentage change from baseline in surface area ≥40% were summarised by treatment group and baseline wound area category (<4cm^2 or ≥4cm^2).

Results

Patient population and baseline wound characteristics

Baseline patient characteristics are shown in Table 1. The mean age across treatment groups was 57.8–60.1 years, with men representing the majority of patients treated (male: 80.3%; female, 19.7%). The average body mass index (BMI) was approximately 33.1kg/m^2, and the majority of patients had only one wound (83.5%). Baseline wound characteristics (Table 2) showed mean wound sizes of 4.3 and 4.4cm^2, and mean wound durations of 8.0 and 9.1 months for dACM plus SoC- and SoC-treated groups, respectively. These were not statistically significantly different (p=0.59). Almost all (98%) of the wounds were debrided within the four weeks prior to first treatment of dACM plus SoC or SoC alone (p=1.00) (Table 2).

Treatment characteristics

There were no differences between the dACM plus SoC- and the SoC-treated groups in the frequency or number of uses of SoC (p=1.00). Both groups received SoC on a weekly basis for up to 12 weeks. As shown in Table 3, only the investigational treatment group received dACM. dACM-treated wounds received on average 8.7 applications, with 98% of DFUs receiving multiple applications. For wounds receiving multiple dACM applications, the median interval between applications was 6.5 days. Treatment with hyperbaric oxygen (HBO) or negative pressure wound therapy (NPWT) within 28 days prior to initial use of dACM or SoC occurred infrequently (4.5% versus 1.8%, hyperbaric oxygen therapy (HBOT); 6.3% versus 7.3%, NPWT for dACM- and SoC-treated subjects, respectively). Use of HBOT and NPWT was comparable between treatment groups (Table 3). Neither HBOT nor NPWT were allowed from day 1 through week 12 during the trial.

Complete wound closure (CWC)

Primary analysis: CWC in the overall population (n=218)

Kaplan–Meier analysis found dACM treatment significantly improved the median time to CWC (p=0.04), achieving the endpoint in 84 days compared to the SoC-treated DFUs that did not achieve a Kaplan–Meier median time to CWC by week 12 (end of study; EOS); (Table 4, Fig 2). The estimated frequency of CWC for dACM compared to SoC was statistically significantly improved at week 4 (12% versus 8%), week 6 (22% versus 11%), week 8 (31% versus 21%), week 10 (42% versus 27%), and week 12 (50% versus 35%) (p=0.04). The differences (shown in Fig 2) in percentage CWC between groups demonstrate improvements (p=0.04) in favour of dACM that range between 43% and 100% (mean: 61%). Cox proportional hazards regression analysis showed that dACM treatment increased the probability of CWC by 48% compared with SoC treatment alone (HR=1.48 (95% CI: 0.95, 2.29)) (Table 4).

Secondary analyses

Secondary analyses of CWC for stratum 1 (DFUs <4cm²) and stratum 2 (DFUs ≥4cm²)

Stratified randomisation ensured equal distribution within each stratum by group. Kaplan–Meier and Cox analyses of all subjects (n=218) was performed by SAS-combined strata computations (stratum 1, n=157; stratum 2, n=61). Neither stratum 1 nor stratum 2 showed sufficient power to demonstrate statistically significant results at a level of p<0.05. Stratification was used to adjust for potential study bias due to potential imbalances in DFU size between the dACM plus SoC and SoC alone groups.

Stratum 1 CWC (DFUs <4cm²) (n=157)

Fig 3 and Table 4 show CWC results for subjects in stratum 1. Kaplan–Meier analysis found dACM treatment resulted in a median time to CWC of 72 days compared to the SoC-treated DFUs that did not achieve a Kaplan–Meier median time to CWC by week 12 (EOS) (p=0.06). The estimated frequency of CWC for dACM compared to SoC was improved at week 4 (14% versus 12%), week 6 (26% versus 13%), week 8 (37% versus 25%), week 10 (48% versus 31%) and week 12 (54% versus 39%) (p=0.06). The differences in percentage CWC between groups (Fig 3) showed improvements in favour of dACM that ranged between 17–100% (mean: 52%). Cox proportional hazards regression analysis showed that dACM treatment increased the probability of CWC by 50% compared with SoC treatment alone (HR=1.50 (95% CI: 0.93, 2.43)) (Table 4).

Stratum 2 CWC (DFUs ≥4cm²) (n=61)

Fig 4 and Table 4 show CWC results for subjects in stratum 2. Kaplan–Meier analysis found dACM treatment resulted in median times to CWC that were not achieved by EOS. However, for the dACM plus SoC group ≥4cm², the 95% CI for median time to CWC was between 74.0–90.0 days (Table 4, Fig 4). SoC-treated DFUs did not achieve a Kaplan–Meier median time to CWC by week 12 (EOS). A 95% CI, therefore, was not applicable (NA; i.e., unable to be computed) (Table 4). The estimated frequency of CWC for dACM compared to SoC was improved at week 4 (7% versus 0%), week 6 (10% versus 7%), week 8 (17% versus 11%), week 10 (28% versus 15%) and week 2 (32% versus 23%). The differences in percentage CWC between groups (Fig 4) show improvements in favour of dACM that range between 39–87% (mean: 56%). Cox proportional hazards regression analysis showed that dACM treatment increased the probability of CWC by 9% compared with SoC treatment (HR=1.09 (95% CI: 0.37, 3.15) (Table 4).

Mean percentage change from baseline in wound area at week 12: all subjects

The mean percentage reduction in wound area from baseline for dACM versus SoC was significantly improved at week 12 (72% versus 21%; p=0.0075) (n=218).

Table 2. Baseline DFU characteristics

	dACM + SoC	SoC	p-value*
Number of patients	109	109	
Index wound area, n (%)	109	109	1.00
<4cm²	79 (72.5)	78 (71.6)	
≥4cm²	30 (27.5)	31 (28.4)	
Wound area, cm², n†	111	110	0.89
Mean±SD	4.31±6.67	4.44±7.32	
Median	1.80	1.98	
Wound depth, mm, n	109	109	
Mean±SD	2.36±3.08	2.21±1.83	0.67
Median	2.00	2.00	
Wound duration, months, n	109	109	0.59
Mean±SD	7.98±16.57	9.08±12.96	
Median	3.00	4.00	
Wound location, n (%)	109	109	
Dorsal	14 (12.6)	13 (11.8)	1.00
Plantar	72 (64.9)	79 (71.8)	0.31
Toe	28 (25.2)	11 (10.0)	<0.01
Midfoot	34 (30.6)	42 (38.2)	0.26
Hindfoot	4 (3.6)	4 (3.6)	1.00
Ankle	2 (1.8)	2 (1.8)	1.00
Heel	7 (6.3)	9 (8.2)	0.61
Debridement, n (%)†‡	111	110	1.00
Yes	108 (97.3)	108 (98.2)	
No/unknown	3 (2.7)	2 (1.8)	
NPWT, n (%)†‡	111	110	0.80
Yes	7 (6.3)	8 (7.3)	
No/unknown	104 (93.7)	102 (92.7)	

*For continuous variables, the p-value is from a two-sided, two sample t test, testing for a difference in means between treatments. For categorical variables, the p-value is from a two-sided Fisher's exact test testing for a difference in proportions between treatments; †Safety population: 3 patients were randomised but not treated; ‡ Within 4 weeks prior to first treatment. dACM—dehydrated Amnion Chorion Membrane; DFU—diabetic foot ulcer; NPWT—negative pressure wound therapy; SD—standard deviation; SoC—standard of care

Proportion of subjects achieving ≥40% wound closure by or at week 6 from baseline by strata

Stratum 1: Results summarised by baseline wound area category <4cm² and treatment group (n=157)

The percentage of subjects with wound closure ≥40% by or at week 6 for dACM versus SoC was 79.7% versus 61.5% (p=0.0125).

Table 3. Treatment characteristics

	dACM + SoC	SoC	p-value*
Number of patients	109	109	
Number of dACM treatment applications, n	109	NA	NA
Mean±SD	8.70±3.84	NA	
Median	9.00	NA	
dACM Applications, n (%)	109	NA	NA
Single	2 (1.8)	NA	
Multiple	107 (98.2)	NA	
Interval between dACM applications, days	109	NA	NA
Mean±SD	6.67 ± 2.09	NA	
Median	6.50	NA	
HBOT, n (%)†‡	111	110	0.45
Yes	5 (4.5)	2 (1.8)	
No	106 (95.5)	108 (98.2)	
NPWT, n (%)†‡	111	110	0.80
Yes	7 (6.3)	8 (7.3)	
No	104 (93.7)	102 (92.7)	

*For continuous variables, the p-value is from a two-sided, two sample t test, testing for a difference in means between treatments. For categorical variables, the p-value is from a two-sided Fisher's exact test testing for a difference in proportions between treatments; †Safety population: 3 patients were randomised but not treated; ‡Within 4 weeks prior to first treatment. dACM—dehydrated Amnion Chorion Membrane; HBOT—hyperbaric oxygen therapy; NA—not applicable; NPWT—negative pressure wound therapy; SD—standard deviation; SoC—standard of care

Stratum 2: Results summarised by baseline wound area category ≥4cm^2 and treatment group (n=61)
The percentage of subjects with wound closure ≥40% by or at week 6 for dACM versus SoC was 80.0% versus 48.4% (p=0.0108).

Safety
dACM demonstrated a highly favourable safety profile in the trial. There were no adverse events or serious adverse events reported to be related to dACM.

Discussion

We have shown that the CWC rate was significantly increased in dACM-treated subjects compared with subjects treated with SoC alone in a challenging patient population with DFUs of >6 weeks' duration extending into dermis, subcutaneous tissue, tendon, capsule, bone or joint. This was accompanied by a significant reduction in the median time required to heal the ulcer. The hazard ratio for CWC for a dACM-treated patient was 1.48 compared with a patient treated with SoC alone during the 12 weeks of the study. The treatment of hard-to-heal DFUs requires a multidisciplinary approach that involves surgical debridement of the ulcer area, adequate offloading of the foot, treatment of infection, and maintenance of a moist wound environment.[37–40] Rigorously enforced compliance with the clinical protocol helped ensure that these requirements were met. Healing rates for our control group were similar to SoC healing rates reported in previous trials.[8,41–43] The use of dACM should be considered as an adjunct to the currently recommended SoC and not as a substitute for it.

Ulcer recurrence is common in patients with diabetes, and a history of previous foot ulceration is a strong predicting factor for the development of foot ulceration in the future.[44] No dACM-treated DFUs that healed in this trial were reported to have reopened over the 3-month period of observation. This finding suggests that supporting healing with the application of dACM may result in closed wounds that are at least as durable as wounds that healed strictly by secondary intention. Improvements in our understanding of the wound healing process have led to the development of various CAMPs or CTPs.[8,42,45–47] Combined use of these techniques may further improve wound healing rates, and large real-world evidence comparative effectiveness studies that include thousands of subjects treated at hundreds of wound care facilities may provide valuable, additional information.

Percentage of CWC and median time to CWC were statistically significantly superior in the dACM-treated group compared with the SoC-treated group (Fig 2, Table 4). CWC and median time to CWC were also more favourable in the patient cohorts of stratum 1 and stratum 2 (Fig 3, 4, Table 4). Hazard ratios indicated that dACM increased the probability of CWC by 48%, 50%, and 9% for all subjects, stratum 1 and stratum 2, respectively. Interestingly, dACM versus SoC mean percentage improvements in the frequencies of CWC were remarkably comparable for all subjects (n=218), stratum 1 (wound <4cm^2; n=157) and stratum 2 (wound ≥4cm^2; n=61). Specifically, mean percentage improvements in CWC comparing dACM to SoC were 61%, 52% and 56% for the entire study population, stratum 1 and stratum 2, respectively. These findings demonstrate that dACM was beneficial for a diverse population of DFUs categorised by size as 'large' and 'small' (Fig 2–4). Similarly, mean percentage wound closure proved favourable in the overall dACM-treated group compared with the SoC-treated group (72% versus 21%; p<0.05). Stratum 1 and stratum 2 demonstrated that the percentage of subjects with ≥40% wound closure was 80% versus 62% (stratum 1) and 49% (stratum 2) (both p-values<0.05). These results in partial area reductions are consistent with the relative proportions of subjects who healed in the trial and the time to healing for dACM versus SoC. The totality of evidence from this RCT shows favourable clinical outcomes for the use of dACM in a broad DFU complex patient population.

The primary endpoint (frequency of and time to wound closure; Kaplan–Meier analyses) results in this trial compared well to other published data on adjunctive ulcer care treatments categorised as CAMPs or CTPs. The pivotal study for FDA approval of a bilayered living cellular construct (BLCC; Apligraf, Organogenesis Inc., US) for the treatment of DFUs showed a frequency of wound closure of 56% and a median time to wound closure of 9 weeks.[42] dACM plus SoC showed similar results in this RCT with a frequency of wound closure of 50% at 12 weeks and a median time to wound closure of 12 weeks. In recent real-world data, comparative effectiveness research studies of CAMPs for the treatment of hard-to-heal ulcers, median times to wound closure have been variously reported as 26 weeks for dehydrated Human Amnion Chorion Membrane (dHACM; Epifix, MiMedx, Integra LifeSciences, US), 30 weeks for fetal bovine collagen dressing (FBCD; PriMatrix, Integra LifeSciences, US), and 43 weeks for acellular porcine small intestinal submucosa collagen dressing (SIS; Oasis, Smith+Nephew, US).[48–50]

In this DFU study, clinical outcomes showed beneficial efficacy effects with the use of dACM on ulcers both <4cm^2 and ≥4cm^2 when compared with SoC. These clinical benefits are likely due to preservation of dACM composition, including ECM scaffolding, and its use as a protective barrier to support healing in DFUs. The manufacturing of dACM occurs with minimal manipulation to the native placental membrane. Well-designed preclinical studies have shown that unmodified ECM, growth factors, and dehydrated differentiated and non-differentiated cellular structures are preserved.[31] An array of growth factors and cytokines are maintained and have been isolated from dACM-conditioned media in vitro.[31] In vivo, wound healing studies have demonstrated that dACM-treated groups had significantly increased expression of the pro-angiogenic genes including: fibronectin (FN1), ephrin A1 (EFNA1), transforming growth factor beta-3 (TGF 3), vascular endothelial growth factor C (VEGFC), thymidine phosphorylase (TYMP), thrombospondin 1 (THBS1), and serpin family E member 1 (SERPINE1).[32,51,52] Further, in vivo studies have demonstrated that many of the significant barriers to wound closure observed with the use of conventional dressings were overcome with the use of dACM.[53,54] Dehydration maintains structural stability[32] and this contrasts with other human amniotic membrane products with shorter shelf-lives that are variously manipulated by other cleansing and tissue processing steps.

The dACM efficacy results demonstrated in our RCT are consistent with RCT data reviewed in meta-analyses that have suggested potentially favourable healthcare economic outcomes with the use of placental membrane allografts in hard-to-heal wound management.[55,56] Use of CAMPs or CTPs has been associated with significant, positive economic outcomes in various wound care settings.[17,18] Findings suggest that use of CAMPs or CTPs for the management of DFUs may lower overall medical costs through reduced use of costly healthcare services.[57] Using electronic health records of a diverse group of subjects with hard-to-heal wounds, over 7000 ulcers in more than 5000 subjects were analysed.

Table 4. Kaplan–Meier and Cox proportional estimates of time to complete wound closure (CWC) by or at week 12; intention to treat (ITT) population*

	dACM (dACM + SoC)	SoC
Overall number of subjects, n (%)	109 (100)	109 (100)
Kaplan–Meier time to CWC, days		
25% of subjects	44 (log-rank p=0.04)	65
50% of subjects (median time to CWC)	84 (log-rank p=0.04)	NA
Cox ratio of dACM+SoC:SoC (95% CI)†	1.48 (0.95, 2.29)‡	NA NA
Stratum 1: Wound area <4cm²		
Number of subjects with baseline wound area <4cm², n (%)‡	79 (100)	78 (100)
Kaplan–Meier time to CWC, days		
25% of subjects	42.0 (log-rank p=0.06)	55.0
50% of subjects (median time to CWC)	72.0 (log-rank p=0.06)	NA
Cox ratio of dACM+SOC:SoC (95% CI)‡	1.50 (0.93, 2.43)	NA
Stratum 2: Wound area ≥4cm²		
Number of subjects with baseline wound area ≥4cm², n (%)‡	30 (100)	31 (100)
Kaplan–Meier time to CWC, days		
25% of subjects	69.0	NA
50% of subjects (median time to CWC)	(74.0, 90.0)	NA
Cox ratio of dACM+SOC:SoC (95% CI)‡	1.09 (0.37, 3.15)	NA

*ITT population comprises all subjects randomised and treated at study day 1. †The Cox model is adjusted for ulcer duration. Hazard ratios use SoC as reference and estimate hazards of dACM+SoC/SoC. ‡Both the log-rank test and Cox proportional hazard model are stratified by wound area <4cm² or ≥4cm² at baseline. CI—confidence interval; dACM—dehydrated Amnion Chorion Membrane; SoC—standard of care; NA—not achieved

Clinical outcomes were tracked, and costs of ulcer care using the database of the US Ulcer Registry were assessed. The DFU patient population evaluated was comparable to the DFU patient population in our dACM trial.[57] Reporting on the total number of subjects who did not achieve CWC, patients with hard-to-heal pressure ulcers made up 25% of the population, followed by 20% with post-surgical wounds, 14% with DFUs, 13% with trauma ulcers, radiation ulcers and various ulcers of mixed aetiology. Followed over five years, the patients were shown to accrue total direct costs to the medical system of over $29,249,500 USD for ulcer management alone. The costs of unhealed ulcers were reported to substantially increase from $4000 USD per patient at six months to $18,000 USD at two years and beyond.[57,58] All patients who entered this trial had longstanding, hard-to-heal ulcers that were refractive to routine treatments. Based upon literature documenting that CAMPs or CTPs with greater frequencies and accelerated times to CWC result in more cost-effective DFU wound management approaches, dACM may prove to be a promising, cost-effective adjunct to SoC for use in DFUs. Importantly, dACM-treated DFUs closed at a median time of 12 weeks and the healing rate by week 12 was 50%. SoC-treated DFUs did not achieve a median time to closure by 12 weeks, and the healing rate by week 12 was 35%. Further, the time to healing associated with dACM management of complex DFUs was appreciably less than the time to healing of other CTPs previously referenced.[48,50]

This was the first RCT of dACM to the authors' knowledge. The study was properly powered for the expected treatment effect size based on real-life use of the product. Longer term studies that analyse infections, osteomyelitis, ulcer recurrence rates, amputations (toe, foot, below-knee amputation and above-knee amputation) are suggested to determine the comparative cost-effectiveness of CAMPs or CTPs. Comparative effectiveness research studies in a real-world setting that include larger numbers of patients/centres and longer durations of follow-up hold the promise to further define the effectiveness of dACM compared with other amnion/chorion membrane allograft products.

Limitations

The limitations of this trial included the lack of blinding in using a CAMP or CTP as the primary wound contact material compared with routine dressings. Both investigators and patients in the trial were aware of treatment group assignment. However, stratified randomisation, statistical analyses by strata, and sensitivity analyses performed by Cox proportional hazards regression that adjusted for multiple variables mitigated imbalances between treatment groups for wound size as well as patient characteristics, wound characteristics, and treatment characteristics (e.g., offloading), and decreased many of the potential risks for bias often associated with open-label trials. All patients were offloaded in the study; however, offloading was not standardised. Methods of offloading other than fixed ankle boots were permitted at the discretion of the investigator only if patient safety would have been compromised. In those cases, another form of protocol-approved offloading treatment was performed. We also recognise that this study, like all RCTs, was intended to demonstrate efficacy, and as such was conducted under highly controlled conditions. This trial had high 'internal validity' because of randomisation, careful selection of participants, and a standardised treatment protocol across the 15 investigative sites. The objective of the study was to maximise the possibility of observing a treatment effect, if it existed.[59,60] While RCTs are considered level 1 evidence in determining if a product can actually work, future real-world data comparative effectiveness research studies to demonstrate clinical outcomes in a variety of wound care settings and in broader patient populations may be warranted.

Conclusion

We have demonstrated in a prospective RCT that the use of dACM resulted in a higher frequency of wound closure, decrease in time to healing, and higher probability of healing when compared with currently available SoC. dACM may be a very useful adjunct for the management of complex DFUs in a challenging patient population. **JWC**

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Reflective questions

- What are the advantages of using dehydrated Amnion Chorion Membrane plus standard of care (SoC) over SoC alone in the management of diabetic foot ulcers (DFUs)?
- How can healthcare providers use the results of this study when considering different options for complex DFUs?
- How does a reduction in time to wound closure benefit patients with DFUs?

Clinical experience depicting wound regression trends with carePATCH: a case series

Objective: The objective of this case series was to assess the clinical outcomes of standard of care (SoC) supplemented with carePATCH (ExtremityCare LLC, US) a dehydrated, dual-layer amniotic membrane allograft, in mediating hard-to-heal wounds that had failed to respond to SoC alone.
Method: Data were collected from electronic health records of patients seen between November 2023 and January 2025 at a single wound care provider group (WelsCare LLC, US). Patients aged ≥18 years with hard-to-heal wounds failing to achieve ≥50% surface area reduction within 30 days of documented SoC treatment were included. carePATCH was applied as an adjunct to SoC following debridement of the wound in accordance with best wound care practices. Changes in wound surface area, percentage area reduction (PAR) and clinical parameters were assessed at baseline, at final application and at one week post final application.
Results: A total of 13 patients (eight male, five female, mean age: 75.1 years) were included. A total of 13 wounds, including venous leg ulcers (n=6), pressure ulcers (n=5), post-surgical wounds (n=1) and venous stasis/arterial wounds (n=1) were evaluated. Median PAR (for all wounds combined) at final application was 77.4%, increasing to 100% at one week post final application. Statistical analysis demonstrated significant improvement in PAR outcomes (p=0.017 at final application; p=0.003 at one week post final application). Box-and-whisker plots revealed consistent surface area reduction across all wound types, with measurements remaining stable one week post final application.
Conclusion: This case series provides encouraging results for the use of carePATCH as an adjunct to SoC in mediating chronic wounds. Patient outcome data support positive clinical experiences with regard to wound regression.
Declaration of interest: The authors have no conflicts of interest to declare.

CAMPs • dual-layer placental allograft • hard-to-heal wounds • placental allograft • pressure ulcer • PU • venous leg ulcer • VLU • wound • wound barrier • wound care • wound covering

Hard-to-heal wounds can develop and worsen due to the complex interactions between underlying medical conditions and lifestyle factors; the root cause and appropriate route for healing can be complex and multifactorial. Medical conditions, such as diabetes, chronic venous insufficiency, peripheral artery disease and hypertension, impair proper circulation, thereby delaying the body's natural healing process.[1,2] Lifestyle considerations, including mobility limitations, nutritional deficiencies, obesity, inadequate wound site care (e.g., poor hygiene, footwear/site irritation), smoking and substance misuse can further contribute to wound chronicity.[1–3] Due to this aetiological complexity, standard of care (SoC) measures alone may be insufficient to support wound closure, thereby prompting the need for adjuvant wound care modalities such as allografts to facilitate positive wound healing and size regression trends.[2,3]

Research suggests that placenta-derived allografts, commonly classified under the term 'cellular, acellular, and matrix-like products' (CAMPs), have an observable impact on outcomes for various healing-resistant wounds and may serve as a beneficial adjunct to primary intervention methods, such as debridement of necrotic tissue, pathogenic suppression, moisture balance, compression therapy and pressure offloading.[4] These allografts can offer multimodal supplemental support by acting as a protective barrier, while also presenting natural properties that provide mechanical protection and growth factors to assist in the management of hard-to-heal wounds and support the overall healing cascade.[5–7]

Dual-layer amniotic membranes are a specific type of placenta-derived allograft that incorporate two laminated layers of amnion. These specific membranes are typically expected to provide a thick, robust composition with resistance to degradation in the wound bed, while also presenting a high density of cellular factors that may be favourable during wound management (including growth factors, cytokines and hyaluronic acid).[7] Dual-layer membranes provide exposure to a highly concentrated matrix of the amnion itself, and typically offer enhanced structural integrity and an increased concentration of bioactive factors compared with single-layer counterparts.[6,8]

The objective of this retrospective case series was to evaluate observed clinical outcomes for wounds,

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including pressure ulcers (PUs), venous leg ulcers (VLUs), surgical wounds and venous stasis-arterial wounds, with the use of carePATCH (ExtremityCare LLC, US), a dehydrated, dual-layer amniotic membrane allograft, as an adjunct to SoC. Observed outcomes included percentage surface area reduction (PAR) and wound surface area trends following the application of carePATCH.

Method

Study design

Data for this retrospective, observational case series were collected from electronic health records of patients seen between November 2023 and January 2025 at a single wound care provider group (WelsCare LLC, US).

Ethical approval and patient consent

This case series involving human participants was reviewed and approved by Advarra Institutional Review Board (IRB; Pro00089009; 8 August 2025). Using the Department of Health and Human Services regulations 45 CFR 46.104(d)(4), the IRB determined that this case series was exempt from IRB oversight. Research measures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1975, as amended in 2013.

The collection and evaluation of all protected patient health information was performed in a Health Insurance Portability and Accountability Act (HIPAA)-compliant manner. To protect the privacy and confidentiality of the patients, all identifiable information was anonymised. General written informed patient consent (which encompassed the use of data and imaging) was obtained by the patient provider.

Product compliance

carePATCH meets all criteria to be compliant with human cells, tissues and cellular and tissue-based products (HCT/P) that are regulated by the US Food and Drug Administration (FDA) under 21 CFR Part 1271 and Section 361 of the Public Health Service Act.

Patient qualification and data collection

Records of patients with one or more hard-to-heal wounds and who received applications of carePATCH were reviewed. Inclusion and exclusion criteria were applied to the patient records to ensure a well-defined study population of patients with hard-to-heal wound conditions.

The inclusion criteria were:

- Age ≥18 years
- Presence of one or more of a PU, DFU, VLU, surgical wound and/or venous stasis arterial wound
- Failure to achieve a ≥50% reduction in total surface area within 30 days following documented SoC treatment
- carePATCH applied once or more to the clinically diagnosed wound
- Wound duration of ≥30 days before the first carePATCH application.

Exclusion criteria were:

- Wounds with signs of unmanaged, active infection prior to allograft application
- Primary or adjunct use of allografts other than carePATCH during the course of application.

Wound assessments were performed and documented by the treating provider at baseline (before the first allograft application) and at each subsequent clinical visit. Wound dimensions were measured via Tissue Analytics (Net Health, US), a mobile wound imaging app specialising in wound tracking, and by using a sterile, single-use ruler. When a ruler was used, the wound surface area was calculated as length multiplied by width when it was placed externally over the wound. Wound depth was measured by gently inserting a sterile, cotton-tipped applicator at the deepest point of the wound, after which it was laid on a ruler to capture the depth value. Each wound was also photographed and digitally assessed via the Tissue Analytics program, which automatically calculates wound measurements. The provider reviewed and compared both manual and analytics-derived measurements to discern the most appropriate wound measurement and progression of the wound within the field.

Wound characteristics were systematically documented within progress notes, including date of wound onset, previous treatments, potential contributing and/or exacerbating factors and venous sufficiency. Further wound examination details included: assessments to identify infections; status of wound healing; percentage of the wound bed covered by granulation tissue, slough, and/or eschar; and exposure of any deep structures, such as fascia, tendon or bone. The level and type of wound exudate were also noted. The condition of the periwound skin was carefully assessed for signs of calluses, maceration, erythema, oedema or induration.[1]

Standardised patient profile data were abstracted from patient charts. This included: baseline demographics (age, biological sex, race); smoking status; history of diabetes; mobility classification; anatomical location of the wound; allograft application location; aetiology; and wound size measurements.

Allograft application

Before initiating allograft procedures, the provider reviewed each patient's clinical documentation to confirm that the application of allograft was deemed medically necessary. After which, insurance verification was received and the patient's verbal consent was obtained. Additionally, it was noted that allografts were applied to wounds that had failed to heal over time, even with the use of conservative SoC measures (e.g., offloading, dressing changes, over-the-counter aids, etc.). The application of the carePATCH allograft was performed as an outpatient procedure by a licensed wound care provider.

Application followed a sequence grounded in best practice for wound bed preparation and CAMPs application, which included the following steps:

- **Wound site preparation:** before application, and after removal of any dressings, the wound was cleansed with a 0.125% Dakin's solution. Wound bed debridement was performed either via soft gauze debridement to remove slough and exudate, or via sharp debridement of <20cm^2 using a dermal curette, with bleeding of subcutaneous tissue to remove necrotic and/or fibrotic tissue
- **Application preparation:** the most appropriate size of carePATCH allograft was selected for the application to minimise wastage. The allograft was removed from its sterile, dual-pouch packaging in an aseptic manner. As a dual-layer amnion product, carePATCH is non-side specific and could be placed with either surface in contact with the wound. The allograft size was chosen, as needed, to ensure an appropriate overlap on to the healthy periwound skin to anchor the graft while preventing wastage
- **Allograft application:** the allograft was placed directly on to the prepared wound bed. It was then gently hydrated with a saline-moistened, sterile cotton-tipped applicator to smooth the graft. This served to ensure uninterrupted contact between the allograft and the surface of the wound bed by removing any underlying air pockets or fluid. Minimal-to-no graft was wasted upon applications; where appropriate, the allograft was added into the wound to ensure the depth of the wound was covered.

Following application, a multilayer dressing system was employed to protect the allograft, manage exudate and provide a conducive healing-environment. For example, along with allograft placement, Anasept (Argentum Medical, US) and a layer of oil emulsion were applied in some cases along with a layer of Telfa (Cardinal Health, US) followed by alginate (or abdominal dressing (ABD) pads (Medline, China)) for possible drainage. The wound location site was then secured with a border foam dressing. Where applicable, U-cut foam (Shenzhen Tongzhou Technology Co. Ltd., China) was placed around the wound for offloading, and the area was secured with a silicone-bordered foam dressing. Additional wound protective dressings or modalities used included, but were not limited to, UNNA boots (Medline, Germany), Coban (3M, Germany), ABD pads and/or stockings.

Patients and their skilled nursing home or home-health providers were instructed to keep the dressing(s) clean and change them as prescribed at the end of each allograft application visit. Where applicable, instructions were given to remove all wound dressings down to the oil emulsion level, but not to remove the oil emulsion layer in order not to expose the graft residing beneath. Patients returned for weekly follow-up, and at each appointment the outer dressings were carefully removed and the wound was assessed. The decision to reapply carePATCH was at the discretion of the treating provider.

Statistical analysis

Data for this cohort population were analysed using Jmp software (Version 18; 2025; Jmp Statistical Discovery LLC, US). Descriptive statistics were used to summarise patient characteristics and outcomes whereas categorical variables are presented as counts and percentages. Where possible, interquartile ranges are presented to meaningfully illustrate the spread of the data and to provide a robust understanding of variability given the heterogeneity within patient populations and wound aetiologies. Each patient's interval phase is compared with his/her own baseline, which was captured as the measurement before initial allograft application. Additionally, interval-based trend analysis for timepoints of interest (e.g., at final allograft application) were presented to further summarise outcomes.

Results

Patient demographics and baseline wound characteristics

A total of 13 patients were identified to meet the inclusion and exclusion criteria during this retrospective review. The cohort consisted of eight male patients (61.5%) and five female patients (38.5%) with a mean age of 75.1±13.5 years (range: 49–94 years). A total of 11 patients were white, one was African American and one was a Pacific Islander. The majority of patients had never smoked (n=11, 84.6%), one patient smoked (7.7%) at the time of allograft application and one patient was a former smoker (7.7%). Of the 13 patients, six (46.2%) had a medical history of diabetes while seven (53.9%) did not. Patient population physical mobility (ambulatory) classifications are summarised in Table 1.

A total of 13 individual wounds in various wound locations were assessed. The wound categories included in this report were: VLUs (n=6, 46.2%); PUs (n=5, 38.5%); pressure/post-surgical wounds (n=1, 7.7%); and venous stasis and arterial wounds (each n=1, 7.7%). A flow diagram illustrating wound type by anatomical wound location is presented in Fig 1. No adverse events specific to the application of the placental allograft were observed within the patient records reviewed for this retrospective series. The number of allograft applications per wound category are presented in Table 2.

Surface area outcomes by wound aetiology

To quantitatively evaluate wound outcomes over time and provide a uniform framework for analysing changes in size, surface area measurements were collected at various intervals starting from immediately before until after final allograft application. The same intervals were assessed across all patients to maintain a standardised approach to data review and to allow for comparison of wound dimension trajectories.

Surface area outcomes were analysed separately for each wound category type. The independent analyses aid in illustrating the outcome variations per wound type along with the potential degree of impact the allograft can have on varying wound types. Box-and-whisker and linear regression plots for the different wound categories are shown in Figs 2 and 3.

Fig 2a shows the overall distribution trend change in wound surface area from the first allograft application to the final application and one week post final application, combining data from all wound types within this case series. The box-and-whisker plots demonstrate a clear distribution change in surface area between the initial and final application timepoints, indicating a positive clinical response. Notably, wound size regression remained relatively stable one week after the final application, suggesting that the observed attenuations for patients were sustained.

Fig 2b focuses exclusively on VLU wounds. Of the six patients with VLUs, there were two for whom the one-week post-application data were unavailable. This was due to the patients being transferred to another facility after the final allograft application was deemed completed. Thus, the final box plot in Fig 2b presents data for four patients at one week post final application.

Figs 2c,d relate to PUs; the sole distinction between the two plots is that Fig 2c includes all PU cases, including one patient whose grafting course was truncated prematurely due to a change in insurance provider. Fig 2c depicts the full scope of the data with the outlier, while Fig 2d depicts trend distribution without distortion. Furthermore, the box-and-whisker variability shown in Figs 2c,d can be attributed to the variety of wound sizes included within this patient population. The whiskers extend to capture the full range of measurement values (including outliers), reflecting the heterogeneity commonly observed in real-world clinical settings, illustrating the surface area attenuation trend across timepoints.

In Fig 3, two individual wound trajectories are shown, using linear regression to assess surface area changes across the intervals of interest, from immediately before the first allograft application through to one week post final application. For the venous stasis and arterial wound, the surface area demonstrated a clear downward trend with a coefficient of determination (R^2) of 0.91, suggesting consistent attenuation over the course of the carePATCH allograft application. The representative post-surgical wound depicted a more variable response, with an R^2 of 0.34, although the overall slope still reflected a net reduction in wound size.

Table 1. Patient mobility classifications at initial presentation

Ambulatory classification	Patients, n	Patients, %
Assistive device/aid needed	10	76.9
Limited but mobile	2	15.4
Mobile	1	7.7

Table 2. Allograft applications by wound type

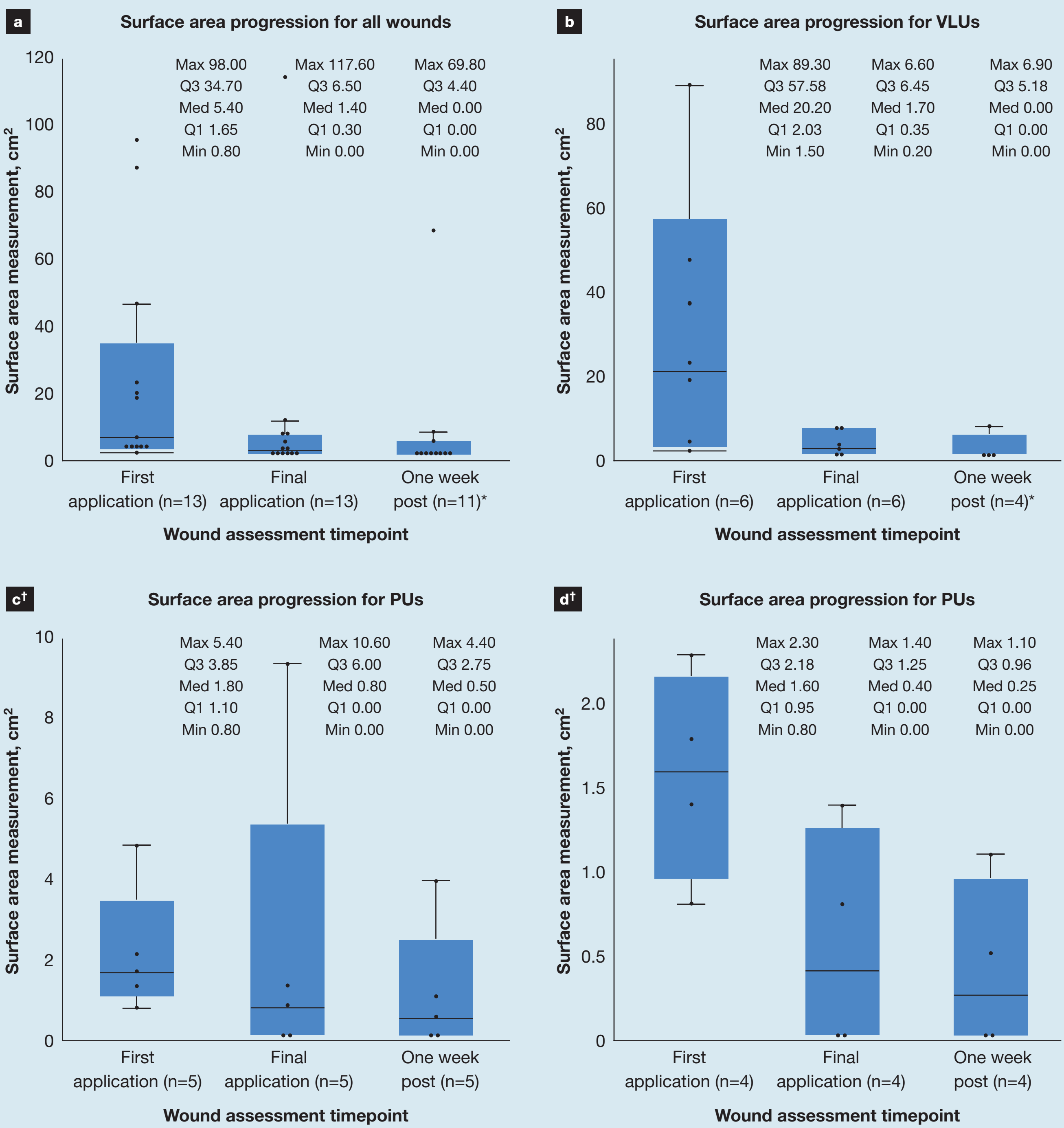
Wound type	Number of allograft applications		
	Mean±standard deviation	Minimum	Maximum
Venous leg ulcer	7.5±2.81	4	10
Pressure ulcer	6±2.55	3	9
Other	8.5±2.12	7	10

Percentage surface area reduction outcomes by wound aetiology

To further investigate the clinical outcomes of allograft application, wound outcomes were analysed as PAR. The resulting values from the PAR calculations demonstrate relative change and allow for a more robust, statistically normalised comparison to the initial wound size per patient compared with surface area calculations. The percentage reductions were computed separately per patient, per wound aetiology at the final visit prior to the allograft being applied, and at one week post final allograft application. Fig 4 presents PAR

Fig 1. Sankey diagram showing the patient counts and percentages per wound type and wound location within the study patient population

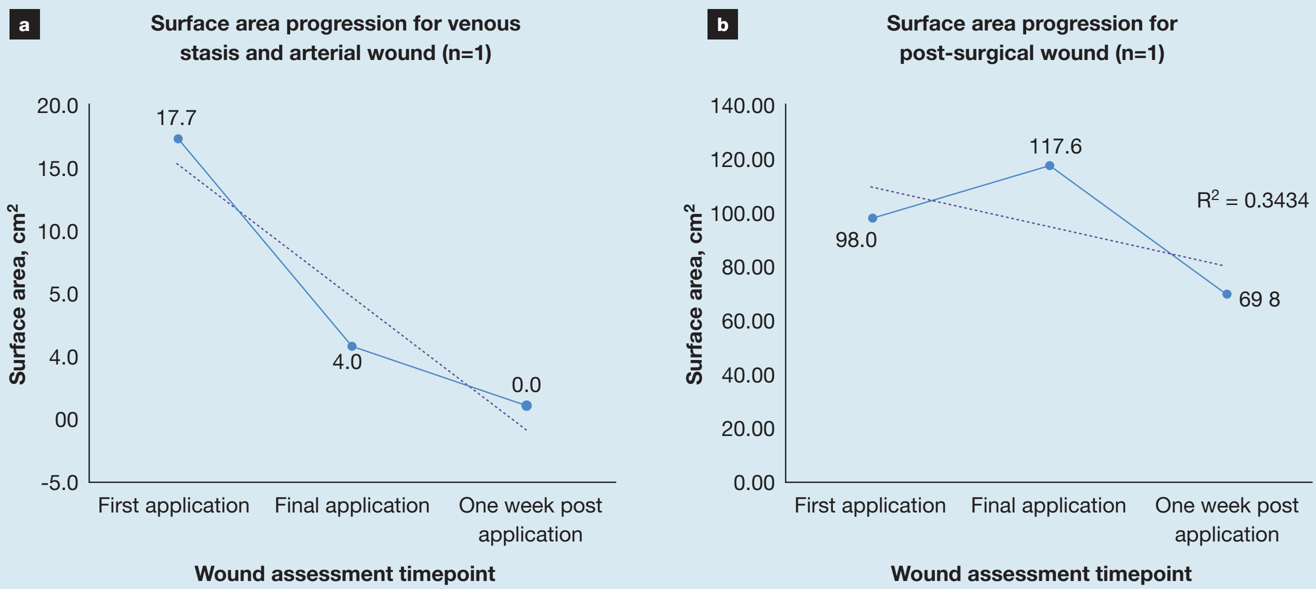
Fig 2. Box-and-whisker plot analyses showing wound surface area distribution across various timepoints. All wound data, highlighting a reduction in wound surface area from the first carePATCH allograft application to the final application, with measurements remaining stable through to one week post-final application **(a)**. Venous leg ulcers (VLUs) **(b)**. Pressure ulcers (PUs) **(c,d).** Max—maximum; Med—median; Min—minimum; Q—quarter



*Of the six patients with VLU, there were two for whom the one week post application data were unavailable due to the patients having been transferred to another facility after the final application of allograft was completed

†Fig 2c includes all patients with a PU (n=5), including one with a prematurely shortened application period due to insurance-related discontinuation, whereas Fig 2d excludes that patient (n=4). Fig 2c represents the full scope of the data, while Fig 2d allows for a clearer trend distribution without distortion

Fig 3. Linear regression plots illustrate surface area trends for a venous stasis and arterial wound **(a)** and a post-surgical wound **(b)**. Plots depict data attenuation trends across multiple timepoints, including before first allograft application through to one week post final application of carePATCH. Both wound types demonstrated an overall reduction in surface area over time. A slight increase in wound size was noted for the post-surgical wound prior to final allograft application; patient reports suggest this was not associated with an infection



per wound type (Fig 4b,c)—to illustrate the distinct size progression trajectories per aetiology for this particular patient population—and overall PAR with all wound types incorporated (Fig 4a). The latter is presented to support the idea of broad generalisability, which may be used to reinforce that the tissue technology has the potential for use across multiple wound aetiologies.

When reviewing all wound aetiologies together, the Wilcoxon signed-rank test resulted in a statistically significant p-value of 0.017 when assessing PAR data from the final visit, before the final carePATCH was applied (compared with a reference value of zero, the null hypothesis). Similarly, the same non-parametric test resulted in a statistically significant p-value of 0.003 when assessing PAR data from the one week post final allograft application timepoint.

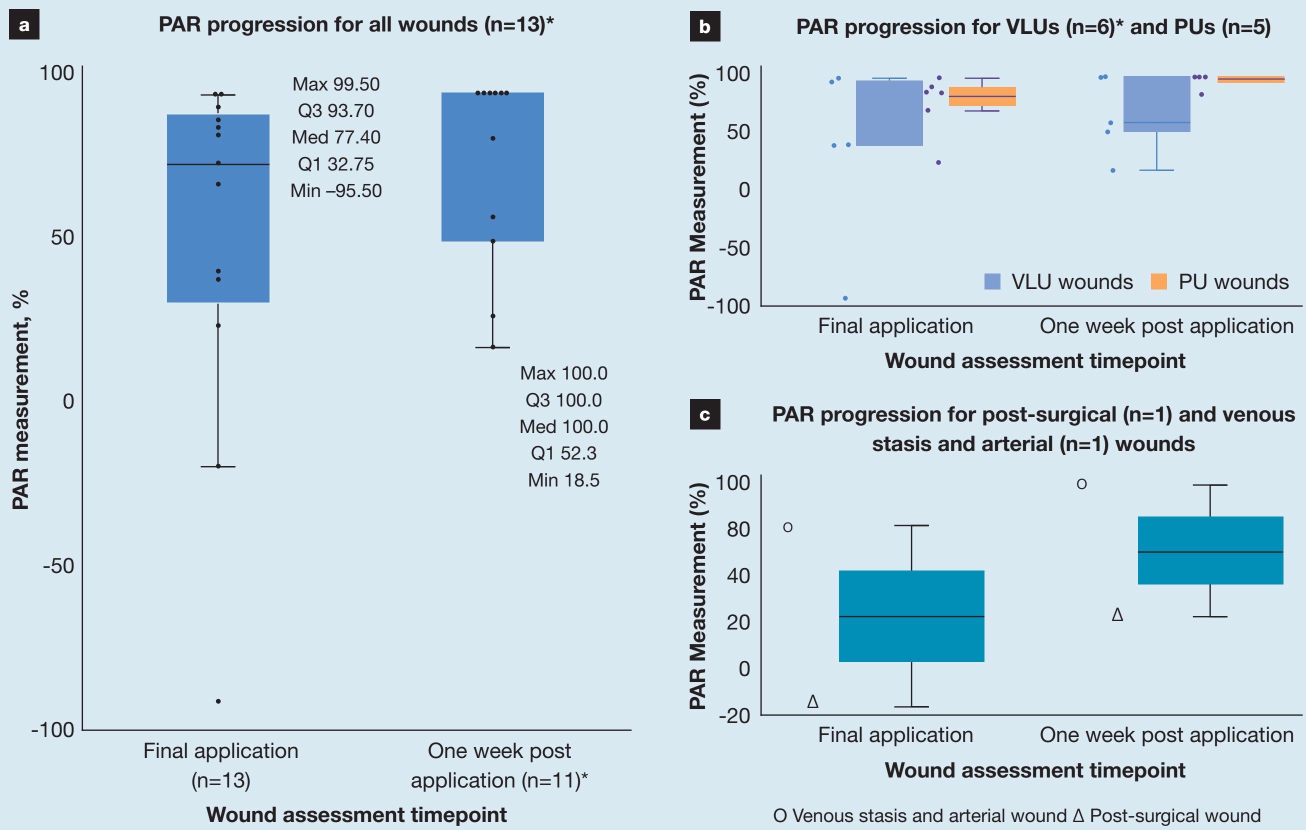
The box plots in Fig 4a depict the median PAR at the time of final application as 77.4%, while PAR at one week post final application increased to 100%. The PARs of 77.4% and 100% imply that, within the study population, at least half of the patients experienced a wound size reduction of greater than or equal to this value at their respective visit intervals. This reflects a substantial overall response to allograft applications in conjunction with SoC, suggesting that patients had meaningful clinical experiences. Albeit there is a difference in medians (77.4% versus 100%), the overlap observed in the interquartile ranges and the whiskers of each box plot suggests largely comparable PAR value distributions between the two wound assessment timepoints, meaning there are no substantial differences. Thus, results may be interpreted as illustrating that the overall degree of PAR was sustained through to one week post final allograft application. Figs 4b,c depict the same points as shown in Fig 4a, but segregated per wound aetiology.

Case presentations

Patient 1: VLU on the left lateral lower leg

An 88-year-old male patient with no history of smoking, limited mobility but denying any difficulty in walking, residing in an assisted living facility and participating in Home Health. He had a history of general muscle weakness, chronic venous congestion and hypertensive chronic kidney disease. The date of onset for the left lateral lower leg VLU was estimated by the patient to be approximately six months prior to initial allograft application. At initial onset, the wound demonstrated favourable outcomes to an advanced biologic (unrelated to this case series) and had almost achieved closure, per previous physician notes. However, the patient re-presented for wound care following a traumatic tear which reopened the wound (Fig 5). Previous wound treatments had included Home Health (a wide range of healthcare services available at home in the US for illness or injury, including wound care) and dressing changes. Prior to carePATCH application, upon examination of the full-thickness VLU, the following wound characteristics were noted: 90% beefy red granular tissue; 10% pink, slightly open epithelial tissue; no evidence of necrosis; no deep structures; with attached wound edges; and small-to-variable serosanguineous drainage. The patient received care for 22 days, after which, the

Fig 4. All wound data, within which the box-and-whisker plots depict datapoints for the majority of patients largely clustered around the 85–100% PAR range. The two negative PARs at –20% and –95.5% are patients who experienced some fluctuations at the final application timepoint but by the one week post final application the PAR was +28.7% and +18.5%, respectively. The patient with the –20% PAR had a post-surgical pressure wound on his left proximal posterior thigh/inferior buttock which was 98cm^2 prior to any allograft placement. The patient with –95.5% PAR had a stage 3 pressure ulcer on his left lateral hip/buttock which was 5.4cm^2 prior to any allograft placement. Of note, this patient's grafting course was truncated prematurely due to a change in insurance provider. There were no reports of infection for either patient during allograft placement visits **(a)**. Each of the wound aetiologies individually **(b,c)**. Max—maximum; Med—median; Min—minimum; PAR—percentage area reduction; PU—pressure ulcer; Q—quarter; VLU—venous leg ulcer



*Of the six patients with a VLU, there were two for whom the one week post application data were unavailable due to the patients having been transferred to another facility after the final application of allograft was completed

provider did not require further allograft application. The patient was not seen one week post final allograft application as he had been transferred to an extended care facility prior to the visit. At his final application visit, the wound was at a PAR of 87.3%.

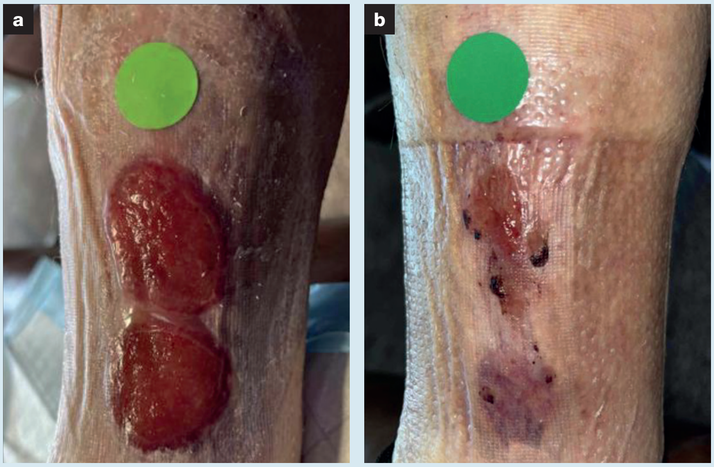
Patient 2: VLU on the left lateral shin, anterior aspect

A 94-year-old female patient with no history of smoking, requiring a walker for ambulation, residing in an assisted living facility and participating in Home Health. Past medical history noted mild oedema to lower extremities, depression, hypothyroidism, atrial fibrillation and unspecified macular degeneration. The patient was unsure of how the wound started (onset estimated to be approximately one month prior to allograft application) but mentioned it had increased in size over time, possibly due to venous stasis. Previous wound treatments included offloading, Home Health and dressing changes. Per physician discretion, conservative measures had failed to reduce the wound size and, as such, the non-healing wound had caused complications including chronic foot pain and instability while ambulating. Prior to carePATCH application, the overall following wound characteristics were noted: 90% beefy tissue; freedom from cellulitis, infection, tunnels and tracts, eschar and necrotic material; free of underlying osteomyelitis; extending into the dermis but without tendon, muscle, capsule or bone exposure. Allograft was applied weekly for nine weeks, at which time the wound was at a PAR of 99.5%, which increased to 100% at one week post final allograft application, as shown in Fig 6.

Patient 3: Venous stasis and arterial wound, right foot inferomedial

A 61-year-old female patient with no history of smoking and who was mobile. Past medical history indicated she had underlying diseases of venous insufficiency and suspected arterial insufficiency. Additional history of diabetes may have been exacerbating and delaying wound alleviation efforts. The patient reported that this wound initially presented almost four years previously, and that since then it had constantly required wound care. She had tried podiatry care, offloading, dressing changes and over-the-counter treatments, all of which had failed to reduce the wound size. The non-healing wound had caused complications including chronic foot pain and instability while ambulating. Prior to carePATCH application, the overall following characteristics were noted for this full-thickness wound: 100% beefy red granulation tissue; callused periwound; no exposed deep structures noted such as facia, tendon or bone; free of cellulitis, infection, tunnelling, undermining, eschar and necrotic material; and no sign of infection, erythema, oedema, drainage, pus or foul odour. Allograft was applied weekly for seven weeks, at which time the wound was at a PAR of 77.4%, which increased to 100% at one week post final allograft application, as shown in Fig 7.

Fig 5. Patient 1: an 88-year-old male patient with a venous leg ulcer of the left lateral lower leg. Wound measurement before first allograft application, 6.33×2.84×0cm **(a)**; before final allograft application, 21 days later, the wound measured 1.82×1.25×0cm **(b)**. After the final allograft application, the patient was transferred to the extended care facility



Discussion

VLUs, PUs and related hard-to-heal wounds affect a high number of patients, and create a substantial personal and economic burden to those affected as well as for providers seeking alternative modes of care beyond SoC. Estimates indicate that in the US, VLUs alone affect >600,000 people annually with costs that could exceed $15 billion USD, and that PUs are experienced by 1–3 million patients annually, with the national cost of hospital-acquired pressure ulcers alone potentially exceeding $27 billion USD.[9–12] As contemporary research continues to explore possible additional mechanisms of action, published literature has shown that placental-derived allografts could support wound healing through a variety of methods, including barrier protection and native growth factors.[6,13–20]

Despite careful attention and persistent care using SoC procedures, some pertinacious wounds remain unresolved over time. The most commonly captured wounds in human amniotic allograft clinical trials include DFUs, VLUs and PUs. For example, Snyder et al.[14] performed a multicentre study at eight clinical sites in the US that compared 15 patients with DFUs who received dehydrated amniotic membrane applications with 14 patients treated with SoC alone. Of patients in the amniotic membrane cohort, 35% achieved complete wound closure at or before week six, whereas no patients in the SoC-only cohort achieved wound closure across the same timeframe.

Fig 6. Patient 2: a 94-year-old female patient with a venous leg ulcer of the left lateral shin, anterior aspect. Wound measurement before first allograft application, 11.3×7.9×0.1cm **(a)**; before final allograft application 61 days later, the wound measured 0.6×0.7×0.2cm **(b)**; one week after final allograft application, wound size was 0×0×0cm **(c)**

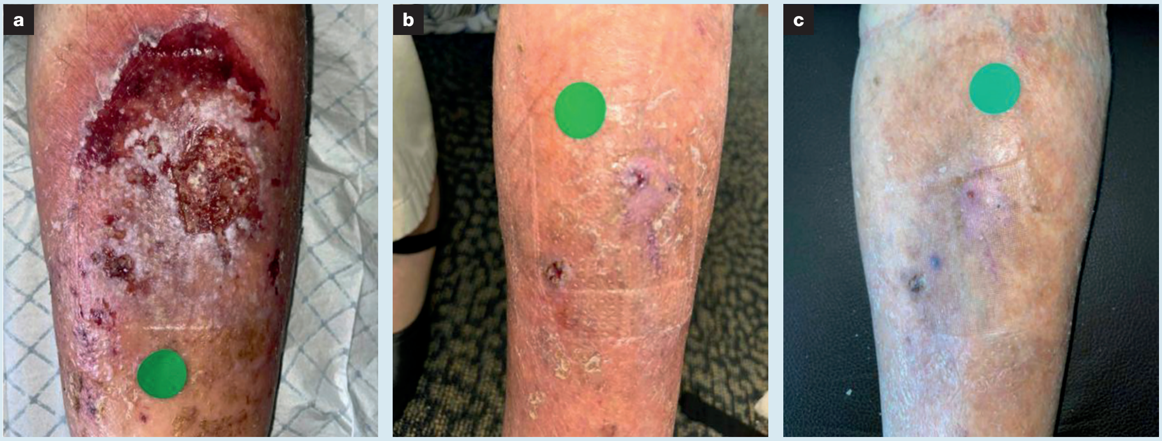


Fig 7. Patient 3: a 61-year-old female patient with venous stasis and arterial wound, right foot inferomedial. Wound measurement before first allograft application, 3.4×5.2×0.2cm **(a)**; before final allograft application, 48 days later, the wound measured 2×2×0.1cm **(b)**; one week after final allograft application, wound size was 0×0×0cm **(c)**

A case series by Regulski[21] assessed four patients, aged 69–85 years, with DFU, VLU or traumatic wounds which required from 1–8 applications of amniotic allografts before reaching 100% wound regression.

Lavery et al.[13] compared weekly and biweekly applications of a dehydrated amniotic membrane allograft, including a total of 40 patients with DFUs; this study found no difference in healing time between the two time cadences, but observed mean wound area reduction rates of $0.18\pm0.48cm^2$/week and $0.15\pm0.63cm^2$/week, respectively.

Ditmars et al.[22] performed a small, multicentre retrospective study that examined the use of dehydrated amniotic membrane on multi-aetiology, hard-to-heal wounds, which included four patients with VLUs (five wounds). The patients with VLUs required a mean of four applications to achieve a 50% reduction in wound size. VLUs showed a strong linear relationship between wound size reduction and care duration (R^2=0.644), and a steeper rate of resolution compared with DFUs also treated with allografts based on linear slope analysis.

The findings of the current study reinforce the possibility that use of dehydrated, dual-layer amniotic membrane allografts, such as carePATCH, can function as a beneficial adjunct for the management of hard-to-heal wounds. While data presented here are observational and retrospective in nature, patients with PU, VLU, post-surgical, plus venous stasis and arterial category wounds resistant to SoC methodologies alone were observed to experience a positive clinical response with the use of an amniotic membrane allograft. The allograft was noted to be well-tolerated by patients, with no allograft-related adverse events reported. Whether reviewing the box plots or linear regression data, across the patients and intervals evaluated, serial wound assessments revealed a measurable reduction in wound size. The findings here align with existing literature, which similarly weigh wound regression data via PAR and surface area values to depict allograft application response. It is worth noting that variations observed in per patient regression trends are unsurprising given the heterogeneity within real-world clinical settings, patient populations and wound aetiologies. While this study was not designed to evaluate defined PAR or surface area thresholds within set allograft application windows, the temporal comparisons from available data and their observed trends support the broad assertion that objective wound regression measurements observed in the 13 patients are clinically meaningful. Furthermore, the data findings highlight the relative stability of most wound measurements one week after the final carePATCH application, indicating sustained wound size attenuation for this cohort.

Given the results obtained from this small-scale study, it may still be posited that dual-layer amniotic allograft configurations, such as that used in the study, may confer certain advantages as an adjunct during care. Human amniotic membrane is a thin, collagen-rich tissue derived from the placental submucosa. Its framework, composed of collagen and the extracellular stromal matrix, are key components which add to the structural integrity in allograft-based wound coverings. Because of the manner in which carePATCH is minimally processed, the native physical integrity of the amnion layers is maintained and its dual layer configuration contributes to greater durability relative to single-layer amniotic allografts. Moreover, the pliability and thin profile of carePATCH may facilitate effective allograft placement, helping to ensure uninterrupted contact with the surface of the wound bed, and complete coverage of the wound.

Limitations

Further studies may improve understanding of the advantages conferred by the allograft used. As this study was conducted retrospectively, using pre-existing data, standardisation and statistical power methodologies used in prospective trial models were limited. Given that the performance of carePATCH was only evaluated using available patient data, in addition to limited patient analysis methods, this may also present survivorship bias. Additionally, for future studies, presenting cohorts from multiple clinics with key patient inclusion and exclusion criteria may help limit any referral and/or selection bias. For example, patients seen at this clinic may represent more complex cases referred for specialised care, thereby enriching the study population with more involuted hard-to-heal wounds for which the mitigation effect would be more pronounced. Finally, more robust, indication-specific studies that examine homogenous patient populations with particular histories, shared comorbidities or demographic commonalities may result in distinctive outcomes.

Conclusion

Within this 13-patient retrospective analysis assessing the supporting role of carePATCH, the results conveyed favourable trajectories for applications of the allograft used in conjunction with SoC. Even in the absence of a formal prospective study design, this small, real-world dataset was able to provide clinically meaningful insights into the use of placental tissue allografts. The findings support the need for continued emphasis on understanding the ability of placental allografts to impact recalcitrant or non-healing wounds, especially for patients who have experienced a prolonged period of stagnation on their road to recovery. JWC

Data availability statement
The data that supports the findings of the manuscript may be available from the corresponding author upon reasonable request that takes into account patient privacy requirements.

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The views expressed in the submitted article are of the author(s) and are not an official position of the organisation.

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Reflective questions

- Reviewing the published literature, are there certain patient-centred outcomes that should be assessed more in depth compared with others when amniotic placental allografts are applied as adjuncts? Examples include, quality of life, functional status, comfort, sense of self control and reduced interventions.
- Keeping varying wound aetiologies in mind, similar to those in this case series, how do you envision the role of amniotic placental allografts evolving as part of the broader advanced wound care landscape?
- Regardless of wound aetiology, wound location and population heterogeneity, the dual-layer amniotic placental allograft in this case series demonstrated meaningful trends favouring positive patient outcomes. In your experience, what unique advantages have you seen such allografts provide over other wound care modalities?

Efficacy of a full-thickness decellularised placental membrane allograft compared to standard of care in diabetic foot ulcers: a prospective, randomised controlled trial

Abstract: This multicentre, randomised controlled trial evaluated the efficacy and safety of adjunctive full-thickness decellularised placental membrane (FT-DPM) in treating persistent and recalcitrant diabetic foot ulcers (DFUs) compared to standard of care (SoC). A total of 57 patients were analysed in the treatment group; the study product was applied to the wound bed post debridement and left in place for 5–9 days. Some 51 patients received SoC only, including debridement and moist wound therapy with alginates, foams or hydrogels. All wounds were offloaded. The findings of this study showed that the FT-DPM significantly improved wound closure rates at 12 weeks compared to SoC (48% versus 27%, respectively; p=0.0499, per-protocol analysis), with a significant percentage area reduction (79% versus 56%, respectively; p<0.05). Mild and moderate adverse events were similar between groups, while serious adverse events were more frequent in the SoC group compared with the FT-DPM group (29% versus 2%, respectively); none were related to treatment. These findings suggest that FT-DPM is an effective and innovative treatment for hard-to-heal (chronic) DFUs, offering a superior option to SoC, particularly for wounds that resist conventional treatments. This approach has the potential to significantly improve patient outcomes and reduce the societal burden of hard-to-heal wounds.

Declaration of interest: This research was partially funded by LifeNet Health, US, the not-for-profit organisation that processes Matrion Full-Thickness Decellularized Placental Membrane. PMM serves as a key opinion leader for LifeNet Health. All other authors declare no conflict of interest regarding this research.

allograft dressings • amnion • diabetes • diabetic foot ulcer • placental membrane • randomised controlled trial • wound • wound care • wound dressing • wound healing

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Annually, >18 million people globally experience a diabetic foot ulcer (DFU).[1–3] The rising prevalence of diabetes has dramatically increased the incidence of these wounds, creating substantial social, economic and physical challenges.[4] Hard-to-heal (chronic) DFUs significantly strain global healthcare systems,[2,4] with increasing prevalence noted among the US Medicare beneficiary population.[5] In 2019, 16.4% of Medicare beneficiaries had a hard-to-heal wound, up from 14.5% in 2014, and costing Medicare as much as $597.4 million USD a year.[5]

Individuals with hard-to-heal wounds face not only physical pain but also disability, reduced productivity, and higher risks of depression, social isolation, amputation and death.[1,3,6] Effective treatments for these conditions are paramount to advancing patient care and alleviating broader societal burdens.

Treating DFUs presents numerous challenges. These wounds often resist conventional therapies, resulting in prolonged treatment times and frequent recurrences.[2] Infections can further complicate treatment, necessitating aggressive interventions, including surgery.[4] Systemic factors, such as poor circulation and immune dysfunction, exacerbate the difficulty of achieving complete wound closure.[5]

Allografts from live-birth tissue have become essential for wound and soft tissue repairs, including hard-to-heal lower extremity wounds, tendinopathies and dental-guided bone regeneration.[7–9] Within the amniotic sac, the placental membrane consists of two primary layers: the amnion and the chorion (Fig 1).[9–11]

The amnion includes the epithelium, basement membrane, compact layer, fibroblast layer and spongy layer, which contribute essential extracellular matrix (ECM) components, growth factors, cytokines and proteins.[9–12] However, the amnion alone lacks sufficient structure for providing a protective covering and contains only a small fraction of the prohealing factors found in the full placental membrane. Additionally,

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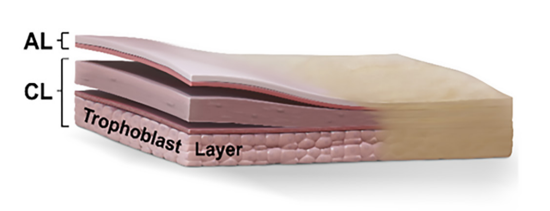
amnion-only grafts can be difficult to apply and may migrate from the intended site.[13]

The chorion consists of the cellular layer, reticular layer, pseudobasement membrane and trophoblast layer, which can be up to four times thicker than the combined amnion and other chorion layers.[9,10] Typically, the amnion and chorion layers are separated during processing, and the spongy and trophoblast layers are removed, reducing the abundance of biological factors by as much as 50–80% and resulting in thinner, less manageable grafts.[9,10,14]

A full-thickness decellularised placental membrane (FT-DPM) has been developed that includes the trophoblast layer to overcome the limitations observed with typical placental-derived allografts.[10] Unlike other allografts, FT-DPM undergoes a proprietary decellularisation process to remove donor cells while preserving all the placental membrane layers, the structural, porous ECM components, and critical biological factors for wound healing.[10,14,15] A murine subcutaneous model provided evidence that FT-DPM provides a natural scaffold that retains its structures upon implantation for up to 10 weeks while promoting host-cell infiltration, angiogenesis and tissue remodelling.[10]

Although previous studies have highlighted the potential of placental-derived allografts in wound closure, comprehensive data comparing these treatments to standard of care (SoC) are limited. As such, this present randomised controlled trial (RCT) aims to fill this evidence gap by evaluating the effectiveness of adjunctive FT-DPM versus SoC alone in treating persistent and treatment-resistant DFUs.

Fig 1. Cross-section of the placental membrane showing the amnion (AL), chorion (CL), and trophoblast layers. The amnion provides extracellular matrix components, and the thicker chorion and trophoblast layers enhance structural support and biological activity



Methods

Study design

This study was a multicentre, open, prospective, randomised controlled clinical trial designed to evaluate the efficacy of adjunctive FT-DPM compared to SoC alone (1:1 allocation ratio) in treating patients with persistent and recalcitrant DFUs at eight outpatient wound clinics in: California (four sites); New Mexico; Arizona; North Carolina; and Florida. The study enrolled patients from February 2022 through to March 2024.

Ethical approval and patient consent

The WIRB-Copernicus Group Institutional Review Board (IRB), US, approved the study protocol (approval number 20215453, 7 October 2021), which adhered to the 1975 Declaration of Helsinki. The trial was registered on Clinicaltrials.gov (NCT05087758). All patients completed the informed consent process, including providing a signature and date on the IRB-approved informed consent form. This consent allowed the sharing of all deidentified wound assessments with images in reports, presentations and manuscripts about the research study.

Hypothesis testing

Hypothesis testing was conducted using a two-sided alpha of 0.05 to determine that the use of FT-DPM in the treatment of DFUs offered a statistically significant better outcome than SoC, based on the proportion of wounds healed at 12 weeks. The sample size was calculated with GraphPad Prism 9.1.0 (GraphPad Software, Inc, US) based on an assumed 70% wound healing rate in the FT-DPM group and a 45% healing rate in the SoC group,[17,18] with an estimated 60 patients per group needed to achieve 80% power for a statistically significant result. The study aimed to enrol up to 140 patients to account for screen failures and non-adherence.

Table 1 lists the full inclusion and exclusion criteria. Patients were included in the study if they had a diagnosis of type 1 or 2 diabetes with a Wagner stage 1/2 DFU (1–25cm^2) of at least 30 days duration.

Exclusion criteria included evidence of unresolved gross soft-tissue infection or osteomyelitis, presence of inflammatory conditions or active cancer, and current treatment with immunosuppressants or radiotherapy

Screening, run-in phase and baseline visit

At the screening visit, patients were assessed for their eligibility, per Table 1 criteria, and eligible patients provided their written informed consent. The provider performed a complete physical examination with comprehensive wound assessment, recorded the complete medical and wound history and concomitant medications, and assessed for adequate circulation (by ankle–brachial pressure index or Doppler).

During the four-week run-in phase, all patients were assessed for eligibility and received weekly SoC treatment. SoC included: debridement; infection control; appropriate dressings; and offloading using surgical shoes and/or removable cast walkers. Each investigator was allowed to choose the type and brand of dressings and offloading equipment for their enrolled patients. Following debridement, moist wound therapy was applied, using alginates, foams or hydrogels, and the wound was covered with a gauze suitable for its moisture state.

At the baseline visit (week 1), the provider reassessed for study eligibility and repeated the screening assessments. Patients whose wounds demonstrated a significant reduction in size (>50%) during the run-in phase were excluded from the study, as they were considered likely to heal with SoC alone. The principal investigator at each site enrolled and randomised eligible

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• 21–80 years of age at the time of consent • Stable diabetes treatment for ≥30 days at baseline • Full-thickness, Wagner 1 or 2 DFU of the lower limb with a duration of ≥30 days • Wound area ≥1cm² and <25cm² and depth ≤9mm • Absence of wound infection based on Infectious Disease Society of America criteria[16] • Adequate circulation to the affected lower extremity, defined as at least one these criteria: – Transcutaneous oxygen measurement at the dorsum of the foot ≥30mmHg – Ankle–brachial pressure index >0.75 – At least biphasic Doppler arterial waveforms at the dorsalis pedis and posterior tibial arteries • Able to comply with offloading and dressing change requirements • Able to understand the study requirements, provide written informed consent, agree to abide by the study restrictions, and return to the site for the required assessments • Provided written authorisation for use and disclosure of protected health information • Had a life expectancy >6 months • Wound only dressed with concomitant materials approved for study	• Pregnant or lactating • Wound decreased in size ≥50% between the screening and baseline visits • >1 ulcer on target limb • Haemoglobin A1c >12% within 90 days of the screening visit • Serum creatinine concentrations ≥3.0mg/dl within 30 days prior to screening • Sensitivity to: lincomycin, polymyxin B sulfate, vancomycin, n-lauroyl sarcosinate, nuclease, and/or endonuclease • Wound treated with biomedical/topical growth factors or living skin equivalent within four weeks before the screening visit • Had uncontrolled connective tissue disease, immune disease, or malignancy • Received radiotherapy, systemic corticosteroids, or immunosuppressive/chemotherapeutic agents <30 days before the baseline visit • Have necrosis, purulence, or sinus tracts that could not be removed by debridement* • Underwent a revascularisation procedure in the treatment target limb <4 weeks before the baseline visit • Serum aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase levels >3× the normal upper limit within 30 days prior to screening • Had Charcot disease, peripheral vascular disease (>1 nonpalpable pulse on either foot), or any condition that, in the opinion of the investigator, placed the subject at undue risk or potentially jeopardised the quality of the data to be generated

*Assessed after run-in phase at baseline visit; DFU—diabetic foot ulcer

patients who passed the run-in phase, using sequential alternating treatments, into two groups: patients receiving FT-DPM; and those receiving SoC only.

Interventions

Immediately following enrolment at the baseline visit, patients entered a 12-week treatment phase. The FT-DPM group received a combination of the FT-DPM along with SoC. FT-DPM (Matrion, LifeNet Health, US) is a cellular and/or tissue-based product (CTP) derived from donated human birth tissue and includes both the amnion and chorion with the trophoblast layer (Fig 2).

Fig 2. Representative image of full-thickness, decellularised placental membrane grafts used in this study (Matrion, LifeNet Health, US)

To ensure sterility and safety, the material undergoes a proprietary decellularisation process that renders it acellular and uses low-dose gamma irradiation at an ultra-low temperature to achieve a sterility assurance level of 1×10^{-6} without impeding the physiochemical, CTP properties of the graft.

At each weekly visit, the FT-DPM graft was applied to the wound bed after thorough debridement using a sharp blade, scissors, or a hydrosurgery system (Versajet, Smith+Nephew, UK). The graft was rehydrated for up to five minutes using wound fluid or blood in the wound space, or with sterile isotonic solution, if necessary. During the application process, the appropriate size graft was selected to fit the debrided wound bed, with the amnion side facing up. Depending on the wound state, the graft was secured using sutures, sterile adhesive strips or bioadhesive before applying the secondary dressing. Appropriate, nonadherent dressings were used, such as oil emulsion dressings for dry wounds or more absorptive dressings for moist wounds. The FT-DPM graft was left in place for 5–9 days. Additional graft applications were administered per the investigator's discretion.

In the SoC group, patients received moist wound therapy with alginates, foams, or hydrogels. The wounds were covered with moist or dry gauze, as appropriate.

At each weekly treatment visit, debridement was performed as necessary and assessments were conducted to monitor wound closure, measure wound area, wound depth, and record any adverse events (AEs). At the end-of-study visit (or week 12), a physical examination was also performed and adequate circulation was reconfirmed. Wound areas were measured weekly using an electronic wound assessment system (ARANZ Silhouette, ARANZ Medical, New Zealand). In both groups, patients continued their offloading regimen and dressings were changed at each weekly visit until complete wound closure was observed, defined as 100% re-epithelialisation without drainage or dressing requirements. Closure was confirmed at a two-week follow-up visit.

All wounds that achieved closure entered a six-month follow-up phase, during which telephone calls occurred at two, four and six months to confirm that the wound remained closed, report AEs and review concomitant medications.

Outcome measures

The primary efficacy endpoint was the proportion of wounds closed in each group within the 12-week treatment phase.

Secondary efficacy endpoints included mean percentage area reduction (PAR) from baseline through 12 weeks, the proportion of wounds with ≥50% reduction in wound area at four weeks and weekly thereafter, and median time to heal through 12 weeks,

The rate of DFU infections was determined based on cultures containing $\geq 10^5$ microorganisms. The recurrence rate of DFUs during the follow-up period was also documented. Lastly, the total number of graft applications received per patient throughout the study duration was recorded.

Statistical analysis

Statistical analysis was performed using GraphPad Software. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Continuous data were summarised using descriptive statistics. Categorical data were summarised by frequencies and percentages.

Baseline comparability between treatment groups was determined by comparing demographic data and baseline disease characteristics. A modified-intention-to-treat (mITT) population and per-protocol (PP) population were used for the primary and secondary endpoint analyses. The mITT population included all patients who were randomised, received the allocated treatment for their DFU, and completed at least one week of treatment. The PP population included all patients who completed the study protocol and did not have any major protocol violations, defined as missing >3 visits, having a serious adverse event (SAE) involving hospitalisation in which PP wound care was not administered, and use of an expired product. The Cochrane–Mantel–Haenszel analysis was prescribed in the protocol to assess the primary efficacy endpoint (i.e., differences in proportion of patients with confirmed wound closure between groups), with the assumption that such potentially confounding covariates would be identified. Kaplan–Meier analysis was used to analyse time to heal. Continuous secondary endpoints were analysed using analysis of variance or analysis of covariance, as appropriate, followed by Fisher's least significant difference post-hoc test. The proportion of wounds with at least 50% area reduction at weeks 4 through 12 was analysed using Fisher's exact test with Bonferroni corrections for each timepoint. In cases where patients lost to follow-up or withdrawn from the study, the last observation carried forward was imputed.

Safety data were summarised by treatment group and visit, using descriptive statistics for the safety population. The safety population included all patients who were randomised, received treatment for their DFU, and had at least one post-baseline safety assessment. AEs were listed individually and summarised by preferred terms within a system organ class for each treatment group. The impact of treatment on infection rate, treatment-emergent AEs, and changes in vital signs and physical examinations were assessed regularly.

Results

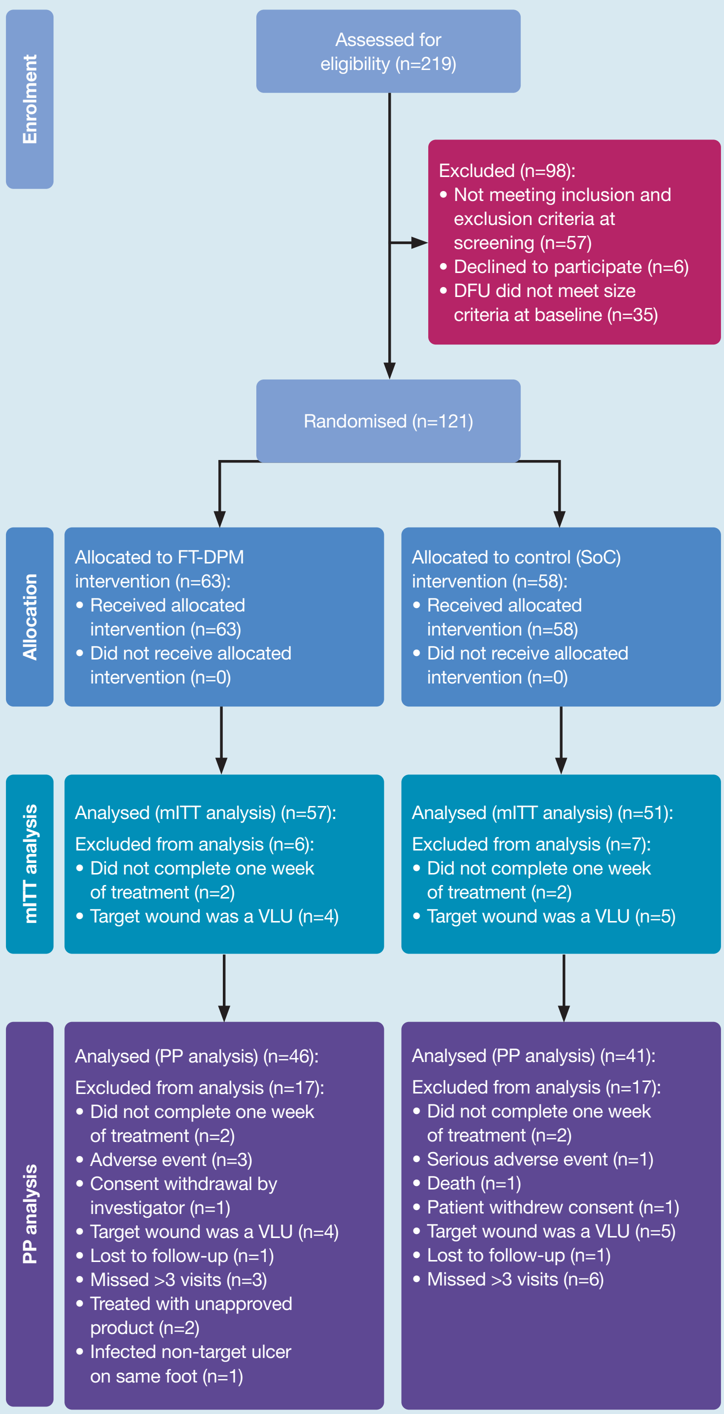
Baseline characteristics

Fig 3 summarises patient flow during this study, which began with screening on 11 February 2022 and ended with the last visit on 2 July 2024. Investigators screened 219 patients for eligibility; 98 (45%) were excluded, of whom 57 (58%) did not meet inclusion criteria at their screening visit, six (6.1%) declined to participate, and 35 (36%) were excluded after the four-week run-in phase, because their wound area decreased by at least 50%. After the run-in phase, 121 patients were enrolled, with 63 allocated to the FT-DPM group and 58 to the SoC group.

In each group, two patients discontinued the study after their baseline visit and did not complete at least one week of treatment. During the treatment phase, investigators discovered that the target wounds of four patients in the FT-DPM group and five in the SoC group were venous leg ulcers, and those patients were removed from analysis. Ultimately, the mITT population included 108 patients (57 in the FT-DPM group and 51 in the SoC group) following withdrawal of these patients (Fig 3).

Additionally, in the FT-DPM group: one patient was withdrawn from the trial by the investigator (the patient was unable to comply with the visit schedule); three patients discontinued due to the occurrence of AEs; and three patients had a major protocol violation (by missing at least three treatment visits/<75% compliance with the study visit schedule); two patients were treated with an unapproved CTP; one patient had an infected non-target ulcer on the same foot as the target ulcer; and one patient was lost to follow-up.

Fig 3. Patient flowchart. DFU—diabetic foot ulcer; FT-DPM—full-thickness, decellularised placental membrane graft; mITT—modified intention-to-treat; PP—per-protocol; SoC—standard of care; VLU—venous leg ulcer



In the SoC group: one patient died (unrelated to the study); one patient discontinued the trial due to an amputation (SAE); and six patients had a major protocol violation (by missing at least three treatment visits/<75% compliance with the study visit schedule). Therefore, the PP population comprised 87 patients (46 in the FT-DPM group and 41 in the SoC group) (Fig 3).

Patient and wound characteristics were similar and well-balanced between groups (Tables 2 and 3). In the FT-DPM group, the mean±standard deviation (SD) age was 60.2±10.3 years, compared to 57.7±9.2 years in the SoC group. Both groups were predominantly male (Table 2). The mean±SD wound area was 3.6±0.45cm^2 in the FT-DPM group and 4.7±0.76cm^2 in the SoC group (Table 3). The most common wound location at baseline was the plantar forefoot. The mean±SD wound duration was 10.1±11.4 months in the FT-DPM group and 8.4±7.9 months in the SoC group. In the mITT population, 96% of patients treated with FT-DPM and 100% of patients treated with SoC failed previous treatments. In the PP population, those numbers were 97% and 100% for FT-DPM and SoC, respectively.

Primary outcome

Due to there being no statistical group differences in baseline parameters (Tables 2 and 3), Fisher's exact test analysed the primary efficacy endpoint. For the mITT population, 22 (39%) of wounds closed at 12 weeks compared to 13 (26%) in the SoC group. This group difference was not significant. For the PP population, significantly more wounds closed in the FT-DPM group (n=22; 48%) compared to the SoC group (n=11; 27%) (p=0.0499). DFUs treated with FT-DPM were 1.8 times more likely to close than those treated with SoC. Fig 4 depicts a patient in the FT-DPM group whose wound healed.

Secondary outcomes

Fig 5a depicts the mean±standard error of the mean (SEM) percentage area reduction (PAR) in the mITT population during the study. The FT-DPM PAR was significantly greater than the SoC PAR at week 3 and at weeks 5 through 11 (p<0.05), with the greatest difference reported at week 8 (p<0.001). Fig 5b depicts the mean±SEM PAR in the PP population during the study. The FT-DPM PAR was significantly greater than the SoC PAR at weeks 3 through end of study (p<0.05), with the greatest differences reported at week 6, 8 and 11 (p<0.001).

For the mITT population, there were 31 (54%) wounds in the FT-DPM group with at least 50% PAR at four weeks compared to 21 (41%) wounds in the SoC group. For the PP population, there were 30 (63%) wounds in the FT-DPM with at least 50% PAR compared to 19 (46%) wounds in the SoC group. Group differences were not significant. Fig 6 depicts the proportion of wounds with at least 50% PAR from weeks 4 through 12. For the mITT population, the FT-DPM group had significantly more wounds with at least 50% PAR beginning at week 6 through to the end of the study (p<0.05). For the PP population, this difference became significant at week 8 (p<0.001) and remained so through to the end of the study (p<0.05).

The mean±SD number of FT-DPM applications at 12 weeks in the mITT population was 8.8±3.5. The mean±SD

Table 2. Patient baseline characteristics

Variable	PP population			mITT population		
	FT-DPM (n=46)*	SoC (n=41)	p-value†	FT-DPM (n=57)	SoC (n=51)	p-value
Patient age, years, mean±SD	60.2±10.3	57.7±9.2	0.2273	59.6±10.9	57.3±9.8	0.2469
Sex, n (%)	**–**	**–**	**0.0750**	**–**	**–**	**0.205**
Female	10 (22)	3 (7)	–	13 (23)	6 (12)	–
Male	36 (78)	38 (93)	–	44 (77)	45 (88)	–
BMI, kg/m^2, mean±SD	34.7±9.3	33.0±7.0	0.3514	34.7±9.6	33.4±8.4	0.4430
Ethnicity, n (%)	**–**	**–**	**1.000**	**–**	**–**	**0.876**
Hispanic or Latino	16 (35)	15 (37)	–	21 (37)	17 (33)	–
Other than Hispanic or Latino	29 (63)	25 (61)	–	34 (60)	33 (65)	–
Unknown	1 (2)	1 (2)	–	2 (3)	1 (2)	–
Race, n (%)	**–**	**–**	**0.838**	**–**	**–**	**0.842**
White	35 (76)	35 (85)	–	43 (75)	43 (84)	–
Black or African American	7 (15)	4 (10)	–	8 (14)	5 (10)	–
Asian	1 (2)	1 (2)	–	2 (3)	1 (2)	–
American Indian or Alaskan Native	1 (2)	0 (0)	–	1 (2)	1 (2)	–
Other	2 (4)	1 (2)	–	3 (5)	1 (2)	–
Diabetes, n (%)	**46 (100)**	**41 (100)**	**–**	**57 (100)**	**51 (100)**	**–**
Insulin	31 (67)	26 (63)	0.822	39 (68)	33(65)	0.689
Oral agents	35 (76)	26 (63)	0.244	43 (75)	33 (65)	0.292
Diet and exercise	9 (20)	8 (20)	1.000	10 (17)	10 (20)	0.809
Cancer history, n (%)	4 (9)	0 (0)	0.119	4 (7)	0 (0)	0.120
Prior revascularisation, n (%)	3 (6)	2 (5)	1.000	6 (10)	3 (6)	0.495
Tobacco history, n (%)	17 (37)	12 (29)	0.500	19 (33)	16 (31)	0.840

*Percentages were based on the number of patients in each group; †Differences between continuous variables were tested with two-sided t-tests and categorical variables with two-sided Fisher's exact tests, where p<0.05 was considered statistically significant; BMI—body mass index; FT-DPM—full-thickness decellularised placental membrane; mITT—modified-intention-to-treat; PP—per-protocol; SD—standard deviation; SoC—standard of care

number of applications in the PP population was 9.1±3.5.

Fig 7 depicts the Kaplan–Meier time to heal analysis. For the mITT population, the median time to heal was eight weeks for the FT-DPM group compared to nine weeks in the SoC group (Fig 7a). This group difference was not significant (hazard ratio (HR): 1.761; 95% confidence interval (CI): 0.9, 3.5). For the PP population, the median time to heal was six weeks in the FT-DPM group compared to nine weeks in the SoC group (Fig 7b). This difference was significant (HR: 2; 95% CI: 1, 4.0; p=0.0453).

Among the 22 patients who healed in the FT-DPM group, three (14%) had a DFU recurrence reported, two had a recurrence at the two-month follow-up visit, and one patient had a recurrence after four months. Among the 13 patients who healed in the SoC group, one (10%) patient had a DFU recurrence at the two-month follow-up visit.

Safety outcomes

Table 4 summarises AEs. There were 31 (54%) AEs in the FT-DPM group compared to 45 (88%) in the SoC group. The frequency of both mild and moderate AEs was similar in both groups. Only one mild AE (equating to temporary discomfort and inconvenience but which did interfere with normal daily activities or pose a significant risk to health) in the SoC group was procedure related. In the FT-DPM group, only one AE was related both to the procedure and to the FT-DPM; the wound developed cellulitis, which was resolved. SAEs were more frequent in the SoC group, with 29% of patients experiencing SAEs, compared to 4% in the FT-DPM group.

There was only one (2%) SAE in the FT-DPM, which was unrelated to the procedure or product. The patient developed cellulitis, requiring hospitalisation, and exited the trial early with suspected osteomyelitis. The

Table 3. Wound baseline characteristics

Variable	PP population			mITT population		
	FT-DPM (n=46)*	SoC (n=41)	p-value†	FT-DPM (n=57)	SoC (n=51)	p-value
Wound location, n (%)	**–**	**–**	**0.874**	**–**	**–**	**0.884**
Big toe	8 (17)	4 (10)	–	10 (17)	6 (12)	–
Plantar forefoot	20 (43)	18 (44)	–	24 (42)	23 (45)	–
Plantar heel	6 (13)	8 (19)	–	7 (12)	9 (18)	–
Dorsal surface	6 (13)	6 (15)	–	6 (10)	7 (14)	–
Medial	1 (2)	2 (5)	–	2 (3)	2 (4)	–
Lateral	4 (9)	3 (7)	–	7 (12)	4 (8)	–
Fifth toe	1 (2)	0 (0)	–	1 (2)	0 (0)	–
Wagner grade at screening, n (%)	**–**	**–**	**0.389**	**–**	**–**	**0.517**
Wagner 1	23 (50)	25 (61)	–	31 (54)	27 (53)	–
Wagner 2	23 (50)	16 (39)	–	26 (45)	24 (47)	–
Wound duration, months, mean±SD	10.1 (11.4)	8.4 (7.9)	0.4354	11.1 (13.6)	9.7 (17.1)	0.6465
Wound area at baseline, cm^2, mean±SD	3.59 (0.45)	4.74 (0.76)	0.1821	3.76 (0.44)	4.38 (0.62)	0.4180
Wet versus dry, n (%)	33 (72)	34 (82.9)	0.308	42 (74)	40 (78)	0.654
Prior failed treatment, (n) %	**44 (96)**	**41 (100)**	**0.496**	**55 (96)**	**51 (100)**	**0.497**
Debridement	44 (96)	41 (100)	0.496	55 (96)	51 (100)	0.497
Compression	20 (43)	20(49)	0.670	25 (44)	27 (53)	0.441
Pressure dressing	4 (9)	6 (15)	0.506	5 (9)	7 (14)	0.543
Offloading	35 (76)	28 (68)	0.476	45 (79)	36 (71)	0.376
Negative pressure wound therapy	2 (4)	4 (10)	0.415	4 (7)	4 (8)	1.000
Cellular and/or tissue-based products	8 (17)	7 (17)	1.000	10 (17)	2 (4)	0.610
Growth factors	1 (2)	1 (2)	1.000	1 (2)	1 (2)	1.000
Prior infection, n (%)	0 (0)	0 (0)	–	0 (0)	0 (0)	–

*Percentages were based on the number of patients in each group; †Differences between continuous variables were tested with two-sided t-tests and categorical variables with two-sided Fisher's exact tests, where p<0.05 was considered statistically significant; FT-DPM—full-thickness decellularised placental membrane; mITT—modified-intention-to-treat; PP—per-protocol; SD—standard deviation; SoC—standard of care

SoC group experienced 15 (29%) SAEs, two (13%) of which were procedure related. The procedure-related events included one case of sepsis affecting the target DFU and one case of osteomyelitis affecting the target DFUs; both resolved following hospitalisation. In total, five infections occurred during the treatment period (three (4%) in SoC and two (4%) in FT-DPM groups), including one moderate AE in the SoC group, which also led to the patients's early withdrawal.

Discussion

The results of this study appear to confirm that FT-DPM combined with SoC is almost twice as effective in treating persistent and recalcitrant DFUs than SoC alone. This RCT predominantly included patients with recalcitrant DFUs, which had persisted for >10 months on average after failing SoC and advanced treatments, including negative pressure wound therapy and other CTPs. The results of this study offer valuable insights into FT-DPM's potential to treat particularly challenging cases for which SoC or other CTPs are not effective. The demographic and wound characteristics of the study population were well-matched between the FT-DPM and SoC groups, ensuring comparability and reducing the likelihood of confounding factors influencing the results.

Fig 4. Patient: a 51-year-old male with type 2 diabetes treated with oral agents and insulin, and a Wagner Grade 1 diabetic foot ulcer (DFU) on the right, plantar forefoot. DFU onset occurred 11 months prior to the screening visit. Initial treatment included standard wound care with debridement, offloading and application of another cellular and/or tissue-based product. A full-thickness decellularised placental membrane application was used at baseline, week 1, week 2, week 7 and week 8. The wound at baseline with an area of 2.7cm² **(a)**. The wound had completely healed by week 9 **(b)**

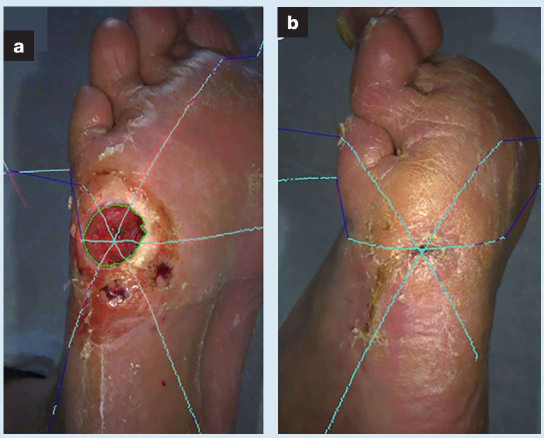


Fig 5. Mean±SEM PAR (mITT population); *p<0.05, **p<0.001, repeated-measures ANOVA with 'group' as the between-patients variable and 'week' as the within-patients variable (interaction p=0.0011), followed by Fisher's least significant difference post hoc tests for each week **(a)**. Mean±SEM PAR (PP population); *p<0.05, **p<0.001, repeated-measures ANOVA with 'group' as the between-patients variable and 'week' as the within-patients variable (interaction p=0.0001), followed by Fisher's least significant difference post hoc tests for each week **(b)**. ANOVA—analysis of variance; EOS—end-of-study (or week 12) visit; FT-DPM—full-thickness decellularized placental membrane; mITT = modified-intention-to-treat ; PAR—percentage area reduction; PP—per-protocol; SEM—standard error of the mean

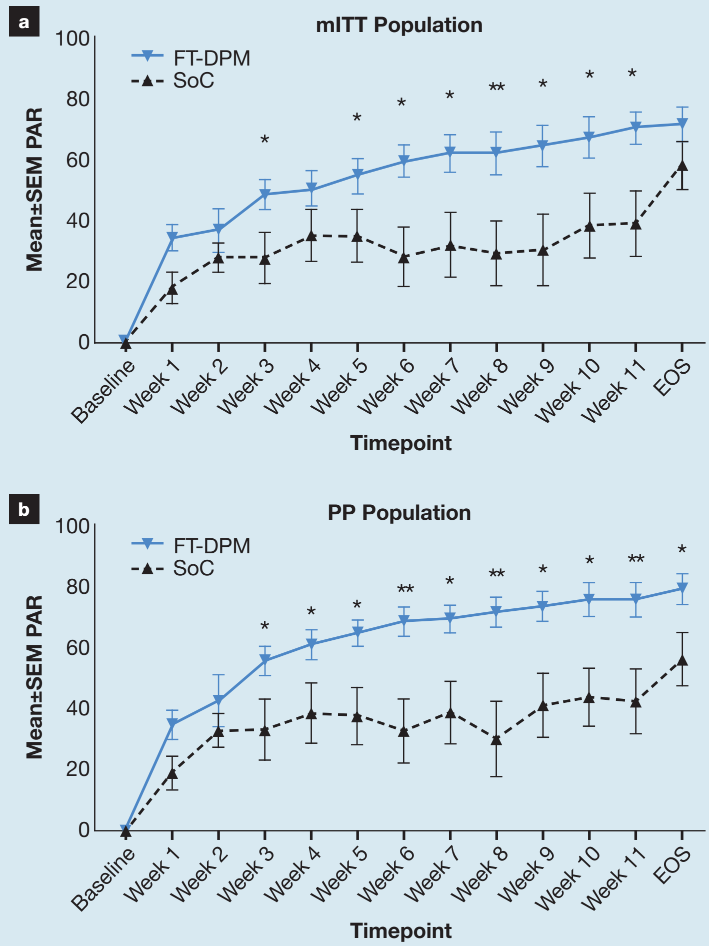


Table 4. Summary of treatment emergent adverse events (TEAEs) and serious adverse events in the safety population (n=108)

Adverse event	FT-DPM (n=57), n (%)	SoC (n=41), n (%)
Number of TEAEs	**31 (54)**	**45 (88)**
Related to procedure	1 (3)	1 (2)
Related to treatment	1 (3)	0 (0)
TEAE intensity		
Mild	24 (77)	25 (56)
Moderate	5 (16)	5 (11)
Severe	2 (7)	15 (33)
Serious adverse event	**1 (2)**	**15 (29)**
Related to procedure	0 (0)	2 (4)

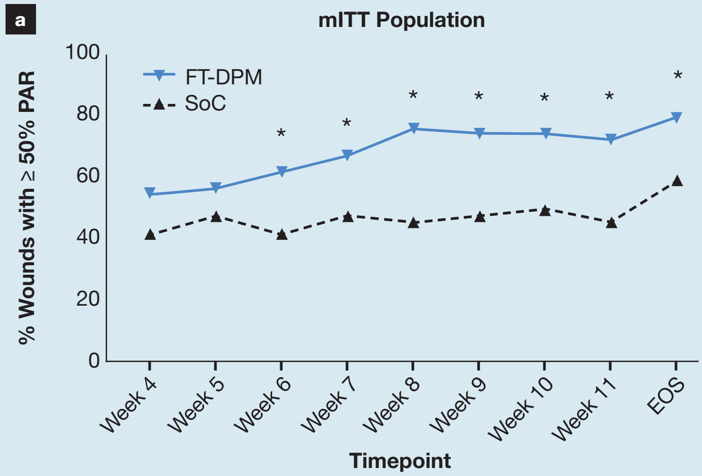
FT-DPM—full-thickness decellularised placental membrane; SoC—standard of care

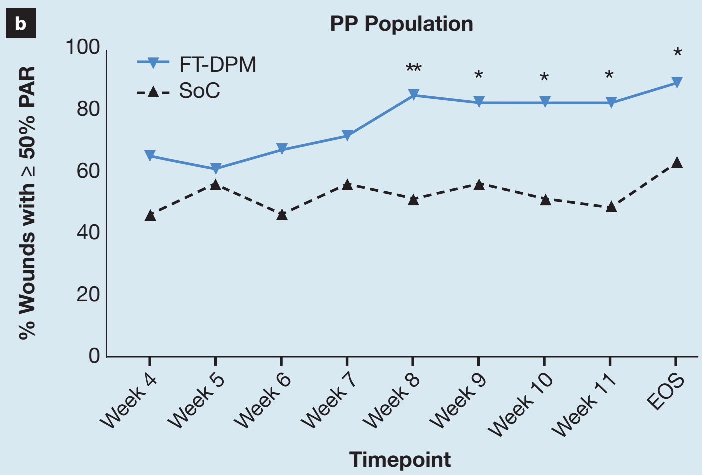
Efficacy outcomes

The primary outcome—wound closure rates at 12 weeks—demonstrated that FT-DPM improved wound closure rates compared to SoC, a trend that reached significance in the PP population (48% versus 27%, respectively; p=0.0499). Previous RCTs that evaluated the use of other placental membranes on DFUs have reported higher wound closure rates at 12 weeks. For example, a trial that evaluated the effect of aseptically processed dehydrated human amnion and chorion allograft (dHACA, AmnioBand, MTF Biologics, US) to tissue-engineered skin substitutes (TESS, Apligraf, Organogenesis, US) found that dHACA had superior healing rates with 90% (27/30) of DFUs closed compared to 40% (12/30) in the TESS group.[19] However, in addition to having a smaller sample size, this trial only allowed Wagner 1 ulcers, whereas approximately half the wounds treated with FT-DPM in this present study were Wagner 2 (Table 3).

In a single-arm trial evaluating a viable cryopreserved human placental membrane on 31 more severe DFUs with exposed deep structures, 59% of wounds closed.[20] In a smaller RCT comparing dHACA to SoC, 85% of DFUs healed at 12 weeks; however, only 20 were treated with dHACA.[21] The current study did not

Fig 6. Proportion of wounds with ≤50% PAR from weeks 4 through 12 (mITT Population); *p<0.05, Fisher's exact test with Bonferroni correction for each timepoint (a). Proportion of wounds with ≤50% PAR from weeks 4 through 12 (PP population); *p<0.05, ****p<0.001, Fisher's exact test with Bonferroni correction for each timepoint (b). EOS—end-of-study (or week 12) visit; FT-DPM—full-thickness decellularised placental membrane; mITT—modified-intention-to-treat; PP—per-protocol





evaluate offloading adherence, which could have negatively affected healing outcomes. For example, a retrospective study of viable placental membrane allografts (Grafix, Smith+Nephew, UK) reported slightly higher healing rates, noting that 20% of participants were non-adherent to offloading which increased to 45% among the non-healed wounds.[22] While the authors reported slightly higher healing rates with viable placental membrane (57% of hard-to-heal wounds closed), the majority of wounds (52%, 46/89) received other advanced modalities in combination with the placental membrane. In the current study, other advanced modalities were not allowed; additionally, 26% of wounds in the FT-DPM group failed prior advanced therapies (Table 3), which emphasises the treatment-resistant complexity of this wound population.

At four weeks, the majority of FT-DPM wounds had a PAR of at least 50% compared to less than half of SoC wounds, with significantly more wounds achieving a 50% PAR by week 6 in the mITT population (p<0.05) and by week 8 in the PP population (p<0.001). This significant difference persisted through to the end of the study, suggesting that FT-DPM accelerated healing rates and sustained healing effectiveness over time, which was further demonstrated by the fact that few closed wounds had recurrence during the six-month follow-up period. Faster healing rates are also shown with the median times to heal, with FT-DPM wounds healing in a median of 6–8 weeks, compared to nine weeks in the SoC group. These findings underscore the potential of FT-DPM as a superior treatment modality, particularly for patients with hard-to-heal wounds, such as DFUs, where prolonged duration is a common challenge.[23–25]

Safety considerations

The safety profile of FT-DPM was favourable and consistent with expectations. Mild and moderate AEs were comparable between the two groups and no SAEs were directly attributed to the FT-DPM treatment. The lower rate of SAEs in the FT-DPM group compared to the SoC group suggests that FT-DPM may be a safer option for patients with hard-to-heal DFUs. These findings support the use of FT-DPM as a viable and safe treatment option, particularly for persistent and recalcitrant ulcers. Future studies should continue to monitor long-term safety to further confirm these findings.

Limitations

The results of this study are promising; however, some limitations must be acknowledged. There were only 108 patients included in the mITT analysis, likely resulting in the study being underpowered. This was a consequence of protocol revisions made after the sample size calculation, which required that all wounds had be of at least 30 days' duration during the screening visit and had to enter the four-week run-in period. Although there were challenges due to missed visits, there was still statistically significant improvement for wound closure and PAR in wounds treated with FT-DPM. Furthermore, there were variations in the administration of SoC across the different study sites, as investigator training and standardisation of the SoC treatment were not uniformly applied. Investigators chose the type and brand of dressings and offloading equipment for their patients. For example, a surgical shoe was used at several sites for all enrolled patients even though current evidence base suggests that a cast walker is more effective at offloading. These discrepancies could have introduced variability in the outcomes, affecting the study's ability to accurately assess the efficacy of FT-DPM relative to SoC.

The design of the four-week run-in period was intended to allow the natural healing process to occur before evaluating the need for a CTP. During this phase, 35 patients were excluded due to significant reduction in wound size (≥50%), as they were deemed likely to heal with SoC alone, given that a 50% PAR at four weeks is a strong predictor of healing.[23–25] While this approach logically screened out wounds that did not require advanced treatment, it may have inadvertently excluded patients who, despite showing initial improvement, could have benefited from FT-DPM to further enhance the speed and quality of healing.

Conclusion

The findings of this RCT demonstrated that FT-DPM, when combined with SoC, was a more effective treatment for DFUs than SoC alone. The findings underscore the potential of FT-DPM to improve clinical outcomes for patients with hard-to-heal DFUs, including those that previously failed advanced modalities, such as prior CTPs. Initial findings from a further RCT, currently underway, have begun to confirm the superior and faster wound closure rates observed in the FT-DPM group compared to an active comparator. **JWC**

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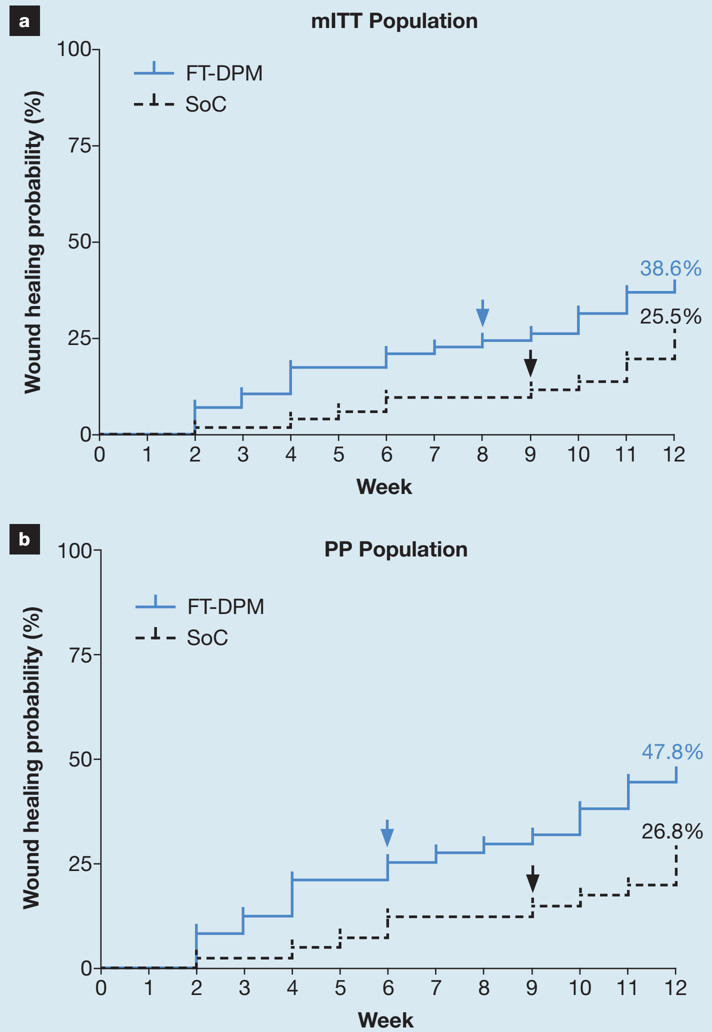
Reflective questions

- How was treatment with full-thickness decellularised placental membrane (FT-DPM), when combined with standard of care (SoC), a more effective treatment for diabetic foot ulcers (DFUs) than SoC alone?
- How do the healing rates demonstrated in this study compare with those studies of other placental membrane products?
- How might the protocol design of this study, with a four-week run-in period, have impacted the speed and quality of healing?

Fig 7. Kaplan–Meier mean time to heal. mITT population **(a)**; PP population **(b)**. Arrows indicate median time to heal. mITT—modified-intention-to-treat; PP—per-protocol



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Clinical use of DermaBind TL/FM as a wound covering for hard-to-heal wounds of various aetiologies: a case series

Objective: The purpose of this retrospective case series is to describe real-world clinical experience with DermaBind TL or FM, (HealthTech Wound Care, US), a dehydrated full-thickness placental membrane intended for homologous use as a protective wound covering in wounds of various aetiologies that failed to heal with standard of care (SoC).
Method: This retrospective observational, uncontrolled case series collected data from healthcare providers in the US. Eligible cases were patients, ≥18 years of age, with hard-to-heal wounds who received DermaBind TL or FM after having completed a minimum of four weeks of SoC without evidence of wound improvement. Data collected included patient demographics, wound characteristics and wound size.
Results: The cases of 27 patients encompassing 36 wounds were included. The average age of patients included was 72.4 years (range: 37–101 years). The majority of wounds were pressure ulcers (63.9%), followed by diabetic foot ulcers (19.4%) and venous leg ulcers (8.3%). Wound onset was, on average, 29 weeks prior to the first graft application with the placental membrane, and the average wound size was 34cm^2. Graft applications occurred weekly, with an average duration of treatment of 6.7 weeks. The observed average percentage surface area reduction across the 36 wounds was 69.1% (range: –17.6–100%). No adverse events were reported by the provider across all patient cases.
Conclusion: These observations describe the clinical use of DermaBind as a wound covering material consistent with its homologous natural protective role. Larger, prospective studies are warranted to further investigate its clinical use. The authors would like to stress that this non-randomised, retrospective uncontrolled case series was used to describe findings, such as number of grafts applied, observed percentage of surface area reduction and graft wasted, and not to demonstrate efficacy.
Declaration of interest: This research was funded by HealthTech Wound Care, US. Providers were compensated for the time spent completing required documentation. Education was provided by JM at HealthTech Wound Care on the required documents and portal training. Manuscript development was completed by HealthTech Wound Care. JM and DS are employees of HealthTech Wound Care, the manufacturer of DermaBind. MCS is a paid consultant of HealthTech Wound Care. Other authors listed are healthcare providers and not affiliated with HealthTech Wound Care other than using DermaBind when appropriate, based on medical necessity. There are no other conflicts of interest to declare.

chronic wounds • diabetic foot ulcer • full-thickness placental wound covering • hard-to-heal • venous leg ulcer • wound • wound care • wound dressing • wound healing

The wound healing process involves four phases: haemostasis, inflammation, proliferation and remodelling.[1] In the haemostasis phase, blood vessels constrict to decrease blood flow to the injury, the platelet plug forms and reinforces, and the coagulation cascade is activated.[1,2] The inflammation phase has a significant role in the wound healing process, and involves a complex and dynamic interplay of immune cells.[2,3] The proliferative phase includes the formation of granulation tissue and re-epithelialisation.[2,4] In the final stages of wound healing, collagen synthesis, turnover and organisation, as well as extracellular matrix remodelling take place.[1] When this process is interrupted, wound healing is impaired and can lead to wounds that persist past the typical healing time (around four weeks), leading to a hard-to-heal (chronic) wound.[3] Hard-to-heal wounds that do not demonstrate a percentage area reduction (PAR) of >50% by week four are a strong predictive factor for a wound becoming hard-to-heal.[5] Many individuals with hard-to-heal wounds have underlying medical conditions, such as diabetes, obesity or malnutrition, which complicate the wound healing process.[4] Factors that impair wound healing include oxygenation, infection, venous insufficiency, older age, restricted ambulation, medications, comorbidities, oncological treatments, or lifestyle habits, such as smoking or alcohol use.[4]

Hard-to-heal wound aetiologies include pressure ulcers (PUs), diabetic foot ulcers (DFUs), venous leg ulcers (VLUs) and arterial ulcers.[2,3] These hard-to-heal wounds

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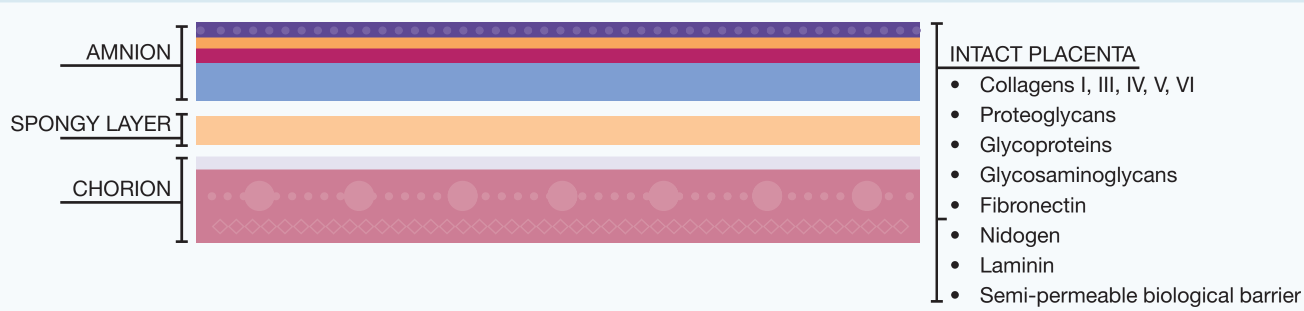
Fig 1. DermaBind TL/FM (HealthTech Wound Care, US) undergoes a proprietary preservation method, which retains all native layers of the placental membrane, including the amnion and chorion with the spongy layer intact



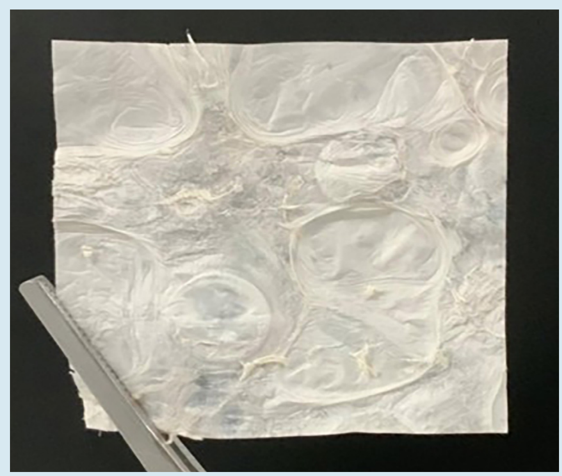
can lead to significant morbidity and mortality.[6] DFUs preceded 84% of diabetes-related lower limb amputations, annually worldwide.[7] More recent reports show that the five-year mortality rate for individuals with diabetes and foot ulceration is approximately 40%, increasing to 63% in individuals who have undergone an amputation.[8] Hard-to-heal wounds can also have negative effects on patients' social and mental wellbeing, causing emotional distress and social isolation.[9]

In the US, it is estimated that the quality of life of almost 2.5% of the total population is affected by hard-to-heal wounds.[9] Since older age is a factor that can affect wound healing, the older population has a higher prevalence of hard-to-heal wounds. In 2019, 16.4% of Medicare beneficiaries were impacted by hard-to-heal wounds. For this same year, expenditure for their care was $2.5 billion USD in the outpatient setting, $1.1 billion USD for home health, and $4.1 billion USD for physician offices.[10]

The primary principles of wound management include: tissue debridement; infection prevention and control; moisture balance; and assessment of the wound edges.[4,11] There are a number of additional clinical management strategies for hard-to-heal wounds. These include autologous platelet-rich plasma, hyperbaric oxygen therapy, negative pressure wound therapy (NPWT), growth factors, cell therapy and skin grafts.[4] With all types of wound classes and therapies, a wound covering must be used.[12]

Wound dressings, including gauze, bandage and cotton wool, can lead to dehydration and reinjury when removed, whereas allograft wound dressings, such as placental-derived coverings, can maintain a moist environment, manage exudate and protect against infections.[13,14] In the published literature, placental membranes have been reported to offer advantages in the management of exudative wounds. The fibrous extracellular matrix provides inherent absorptive properties while maintaining intimate contact with the wound bed.[14] Upon application, the dehydrated graft gradually rehydrates, which has been described as allowing modulation of wound fluid rather than oversaturation, thereby supporting moisture balance and helping to prevent periwound

Fig 2. DermaBind TL is a dehydrated placental membrane covering that preserves the comprehensive collagen matrix, glycoconjugates, and glycosaminoglycans. DermaBind TL/FM contains 400+ proteins, including collagens, fibrins, elastins, glycosaminoglycans, and glycoconjugates (image supplied by HealthTech Wound Care, US)



maceration.[15,16] These demonstrated advantages have made them a treatment option in more complicated wounds.[13] Clinical studies have demonstrated the value of placental-derived wound coverings in hard-to-heal wounds, including DFUs and VLUs.[4,17–19]

DermaBind TL and DermaBind FM (HealthTech Wound Care, US) are dehydrated, full-thickness, placental membranes intended for homologous use as a protective wound covering and contain 400+ proteins, including collagens, fibrins, elastins, glycosaminoglycans and glycoconjugates. A proprietary preservation method retains all native layers of the placental membrane, including the amnion and chorion with the spongy layer intact (Figs 1 and 2). The membrane grafts can be used as a protective wound covering on partial- or full-thickness acute or hard-to-heal wounds. The key differentiating factor between these two products is the unique notch on DermaBind FM that allows healthcare providers using the graft to distinguish between the top chorion layer and bottom amnion layer of the graft that comes into direct contact with the wound. DermaBind TL, on the other hand, has an orientation label on the graft packaging indicating appropriate application with amnion side down.

On 5 January 2023, the US Food and Drug Administration's (FDA) Tissue Reference Group (TRG) determined that DermaBind TL appeared to meet all four criteria under 21 (Code of Federal Regulations) CFR § 1271.10(a) based on the product's described processing[20] and intended homologous use as a wound covering for acute and hard-to-heal wounds. DermaBind TL qualifies for regulation solely under Section 361 of the [US] Public Health Service (PHS) Act and the regulations in 21 CFR Part 1271. On 3 November 2023, the FDA's TRG determined that DermaBind FM, when intended for use as a wound covering and to protect the wound from the external environment also appeared to meet the criteria for regulation solely under section 361 of the PHS Act and the regulation in 21 CFR Part 1271.

The purpose of this case series is to describe retrospective, uncontrolled, real-world clinical experience with DermaBind TL or FM as a protective wound covering in hard-to-heal wounds of various aetiologies that failed to heal with SoC.

Methods

Study design

Deidentified data were collected from included patients whose wounds had failed to heal after four weeks. Data collection took place in the US between 2023–2025. The providers were given one of three options:

- Completing a deidentified seven-page questionnaire
- Completing a deidentified Excel (Microsoft Corp., US) worksheet
- Uploading deidentified data for extraction by HealthTech Wound Care personnel.

Each provider was extensively trained on the case submissions, required documents, inclusion criteria and secure portal upload. Data were entered and reviewed independent of the providers and of HealthTech Wound Care.

Participants and eligibility

Healthcare professionals who focus on wound care management or who specialised in wound care were able to submit cases to be included in this retrospective study. Eligible participants were adults ≥18 years of age with hard-to-heal wounds treated in the US, and who had completed a minimum of four weeks of SoC without evidence of wound improvement.

Demographics and clinical data

Baseline demographic and clinical data collected, if available, included: age; sex; race; ethnicity; medical history; surgical history; social history (such as lifestyle habits, social circumstances); allergies; medications; and wound aetiology. For patients with diabetes, haemoglobin A1c (HbA1c) values were collected, if available. When applicable, ankle–brachial pressure index (ABPI) and/or toe–brachial pressure index (TBPI) were also recorded, in addition to other advanced imaging, such as non-invasive arterial Doppler.

Wound-specific data included wound location, duration, and confirmation of non-healing wounds following failed SoC. Product names and dates of use for failed treatment were also requested. Wound assessments were collected pre- and post-allograft application and included: date of visit; wound length; width; depth; surface area; wound bed tissue type; deepest exposed structure; exudate amount and type; periwound description; pain; signs of infection; presence of oedema and treatment; offloading modalities used; wound cleansing method; and dressing type.

Documentation of debridement used and wound images were recorded at each visit along with any adverse events, if applicable. Wound size was captured via planimetry, photographic analysis, and using the linear measurement method, depending on the providers' standard clinical practice. Measurements obtained were non-blinded and completed by the provider or a trained clinician. The numeric rating scale (NRS 0–10; where 0=no pain and 10=worst possible pain) was used to capture pain severity; some cases did not report pain values.

Due to the nature of this retrospective case study, wound assessment tools were not captured and these were not standardised across providers. However, providers used similar templates and/or questionnaires to the Bates-Jensen Wound Assessment tool for wound assessment[21] and the TIMERS (tissue; infection/inflammation; moisture; edge of wound; regeneration/repair of tissue; social factors) framework model for wound assessment and management,[22] proprietary developed tools, the digital wound management platform (eKare, US) or electronic health record (WoundExpert, US). Pre-graft wound assessments (tissue type, deepest exposed structure, exudate type and severity, periwound description and pain measures) were missing for wounds 1, 2, 9–12, 16 and 17). Pre-graft wound measurements were missing for wounds 6,9–12 and 16–19. Pre-graft wound images were missing for wounds 2, 9–12 and 16–19. The number of grafts applied, and wound onset were not documented for wound 2. Pain severity was not consistently reported at each visit by some providers. Results are presented descriptively, and no statistical analysis was performed.

Ethical approval and patient consent

Institutional Review Board approval was not required for this retrospective case study as patients had already been treated by their provider with DermaBind TL or FM based on medical necessity and failed conservative treatment. Patient consent was obtained by their provider for the use and release of deidentified data, and publication of photographs/images.

Wound management and DermaBind TL or FM application

After failing SoC for ≥4 weeks, wound bed preparation was completed and approved for full-thickness placental membrane application by the provider. The wounds were cleansed with either normal saline or a wound cleanser. The allograft was applied to the wound surface area and the graft was trimmed, if necessary. Rehydration was completed with normal saline or passive hydration. A non-adherent dressing was used with Adaptic (Solventum Corp., US), Xeroform (Covidien, US), Versatel (Medline, US) or other silicone contact layer, or with non-stick Telfa (Cardinal Health, US). Some providers secured the allograft with Steri-Strips (3M, US) while others secured the non-adherent dressings with Steri-Strips for additional securement; other providers chose not to use Steri-Strips. Skin preparation was used on the periwound in various cases. The next steps were use of a dry dressing, such as gauze, bordered gauze or foam. If the wound was on the lower extremity, roll gauze or Kerlix (Covidien, US) wrap was used. Compression therapy proceeded, if warranted, to the lower extremity. Visits were conducted weekly for new graft application and wound assessment. Providers completed sharp or mechanical debridement, if warranted, prior to the graft application; most completed serial sharp debridement weekly. In addition, a properly maintained wound bed, tissue quality, infection prevention, exudate management, compression therapy, aggressive offloading, elevation, management of underlying comorbidities, appropriate nutrition and optimisation of nutrition, and blood glucose control were documented.

Failed SoC included sharp and surgical debridement, Hydrogel (Cardinal Health, US), Medi-honey (Derma Sciences, New Zealand), Santyl (Smith+Nephew, US), silver nitrate, silver dressings and creams, povidone-iodine, alginates, collagen, non-adherent dressings, dry dressings, foams, or Unna's boot. Additional measures included: exudate management; maintaining a moist wound environment; compression therapy; elevation of lower extremities; frequent repositioning; aggressive offloading (low air loss mattress, wheelchair cushions, wedges, Charcot restraint orthotic walker (CROW) boot, postoperative shoe, total contact casting); optimising nutrition; blood glucose control; prevention of infection; or surgery, if warranted. Supplementation with Ensure (Abbott Laboratories, US), Pro-Stat (Nutricia, US), multivitamins, vitamin C, or zinc was used to ensure optimal nutrition. NPWT or vascular management were also used. Comorbidities were managed by the patient's primary care provider and required close observation in some patient cases at greater risk for limb loss.

Results

A total of 27 patient cases were collected encompassing 36 wounds. Healthcare providers that submitted cases included: two doctors of podiatric medicine; two doctors of medicine; eight nurse practitioners; and one physician assistant across the US. The average age of patients included was 72.4 years (range: 37–101 years), and 59.3% of the patients were female. On average, patients had >5 documented comorbidities. Additional baseline demographics can be found in Table 1.

The majority of wounds were PUs (63.9%), followed by DFUs (19.4%) and VLUs (8.3%). PUs were stages 2–4. DFUs were Wagner grade 2 and 3. VLUs were partial- and full-thickness. Additional wounds included full-thickness trauma injury and full-thickness post-necrotising fasciitis. The average wound size was 34cm^2. Wound onset was, on average, 29 weeks prior to first graft, with dates ranging from 2017 to 2025. Additional baseline wound characteristics can be found in Table 2. The locations of wounds included bilateral lower extremities, including foot and ankle, arm, sacrum, buttocks, coccyx, midback and hips.

Graft applications occurred weekly, for an average duration of treatment of 6.7 weeks (range: 2–15 weeks). Grafts were continued as deemed clinically appropriate by the provider. Visits were conducted in both the clinic and mobile wound care setting. In one patient, only two grafts were applied, separated by 32 days (wound 7); the patient was seen weekly for wound assessment, and wound care was provided with Adaptic dressing and rolled gauze applied to lower extremity wound. Additional treatment was received by two patients in conjunction with the allograft. In wounds 24 and 25, NPWT was applied, and in another patient with two wounds used plain packing strip packed into a tunnel while the allograft was used on the surface of the wound (wounds 13, 14).

Average percentage surface area reduction across the 36 wounds was 69.1% (range: –17.6–100%). Of the wounds, nine (25%) healed completely and, in total, 28 (77.8%) wounds had a ≥50% percentage reduction in surface area (Table 3). Of the remaining wounds, three

Table 1. Baseline characteristics

Demographics	Patients (n=27)
Age, years, mean	72.4
Female, n (%)	16 (59.3)
Past medical history, n (%)	
Diabetes	13 (48.1)
Hypertension	9 (33.3)
Peripheral artery disease	5 (18.5)
Venous insufficiency	2 (7.4)
Heart failure	4 (14.8)
End-stage renal disease	2 (7.4)
Bedbound	3 (11.1)
Paraplegia	2 (7.4)

Table 2. Baseline wound characteristics

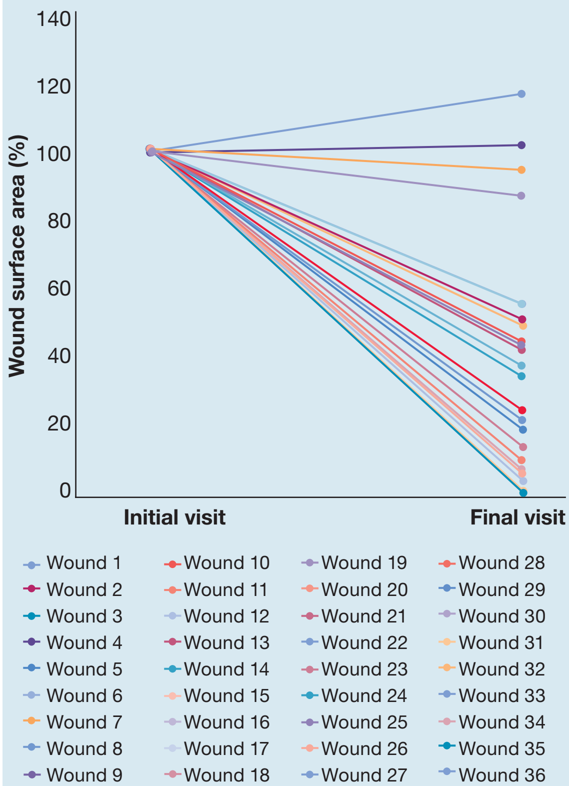
Characteristics	Wounds (n=36)
Surface area, cm^2, mean	34
Time since onset, weeks, mean	29
Wound aetiology, n (%)	
Pressure ulcer	23 (63.9)
Diabetic foot ulcer	7 (19.4)
Venous leg ulcer	3 (8.3)
Non-pressure hard-to-heal ulcer	1 (2.8)
Necrotising fasciitis	1 (2.8)
Traumatic injury	1 (2.8)

had between 40–49% reduction; two worsened (wound 9: –2.6% reduction; wound 17: –17.6% reduction), and three wounds remained at a similar surface area (wound 16: 12.2% reduction; wound 19: 12.1% reduction; wound 31: 4.8% reduction) (Fig 3). Figs 4–7 represent different wound aetiologies with various percentages of observed wound closure in patients included in the study.

Necrotic tissue, slough, granulation and re-epithelialisation were reported. Across all clinical cases, slough and necrotic tissue were able to be debrided before application of the full-thickness placental membrane. Exudate type and severity ranged from none to serous, serosanguineous or sanguineous with a severity of scant/mild or moderate. The deepest exposed structure in most wounds included subcutaneous tissue and fascia. In two patients (Patients S (wound 23) and T (wounds 24, 25 and 26)), muscle exposure was noted.

Methods for reporting pain varied across cases. In general, pain remained mild and consistent across therapy. No adverse events were documented in any of the patients.

Fig 3. Change in wound surface area (%) from first measurement to final follow-up. Change in wound surface area was normalised to percentage change, resulting in overlapping lines due to similar % changes in wounds 5 and 6; in wounds 4, 12 and 20; in wounds 7, 8, 15, 18, 27–30 and 35; in wounds 10, 22 and 25; in wounds 16 and 19; and in wounds 33 and 36



Discussion

In this observational experience—the application of the grafts as wound coverings—nine (25%) wounds were observed as completely healed. In total, 28 (77.8%) wounds had ≥50% reduction in surface area (including nine healed wounds). After thorough assessment and where SoC has failed, providing a placental graft, if deemed appropriate by the treating provider, may play a role in the wound healing process as a protective wound covering.

An area of interest for this study was the placement of appropriately sized grafts to serve as a covering layer over an open wound bed. Selecting a graft close to the wound size permitted minimal wastage. This approach was carried out in a manner consistent with placental homologous use, where the covering function of the grafts over the wound paralleled the placenta's natural role as a protective barrier to potentially support an environment that can promote the healing cascade.

When wounds fail to progress through the healing phases in an orderly fashion, hard-to-heal wounds persist. Each wound is unique, given the wound aetiology and the comorbidities of the patient. Hard-to-heal wounds are complex and require a multidisciplinary approach in addition to using advanced modalities. Not every patient will require or be an acceptable candidate for this protective wound covering. If underlying comorbidities and wound bed preparation are not managed appropriately, progression to wound healing will not be observed, and this can result in delayed wound healing. These considerations emphasise the importance of looking at the patient as a whole and not disregarding other patient-related factors when treating these complex wounds.

The patients included in this retrospective case series had many comorbidities requiring clinical management, with, on average, ≥5 comorbidities per patient. This is likely an underestimation, as some patients had no or few documented medical histories. Despite this likely under-reporting, the number of comorbidities emphasises the complexity of these clinical cases. Many of the comorbidities, such as diabetes, can negatively impact

Table 3. Wound characteristics and clinical course

Patient	Wound	Age, years	Sex	Wound aetiology	Stage/Wagner grade/ partial- or full thickness	Wound location	Time from wound onset to graft application, weeks	Duration of graft application, weeks	Initial surface area, cm^2	Surface area at final follow-up provided, cm^2	Surface area reduction cm^2	Surface area reduction %
A	1	64	M	DFU	WG 2	Right foot	32	5	1.2	0.04	1.16	96.7
B	2	70	F	PU	NR	Sacral	NR	4	38	16	22	57.9
C	3	84	F	PU	Stage 3	Sacral	61	14	16.2	0.01	16.19	99.9
D	4	99	F	PU	Stage 3	Right leg	9	15	20.72	1.2	19.52	94.2
E	5	74	F	VLU	FT	Right lower leg	365	10	460	256.5	203.5	44.2
F	6	53	F	PU	Stage 3	Left hip/thigh area	47	2	25.37	14.1	11.27	44.4
G	7	72	M	DFU	WG 3	Left distal plantar 4th toe	10	2	1	0	1	100
H	8	68	M	PU	Stage 3	Lateral right heel	8	6	33	0	33	100
I	9	74	F	DFU	WG 2	Right ankle, medial aspect	24	10	16.32	16.75	−0.43	−2.63
J	10	77	F	DFU	WG 2	Right foot	24	6	1.5	0.66	0.84	56
K	11	76	M	DFU	WG 2	Left foot plantar to the 1st metatarsal head	8	10	0.88	0.08	0.78	88.6
L	12	50	M	DFU	WG 2	Left plantar heel	16	4	3.5	0.2	3.3	94.3
M	13	38	M	PU	Stage 4	Sacrum/buttock, coccyx-left buttock	9	10	80.5	10.8	69.7	86.6
M	14	38	M	PU	Stage 4	Sacrum/buttock, gluteus, right-right buttock	9	10	70.4	24.18	46.22	65.76
M	15	38	M	PU	Stage 2	Sacrum/buttock, gluteus, left-left lower	4	4	4.95	0.04	4.95	100
N	16	65	F	PU	Stage 3	Right gluteus	33	3	45.6	40.04	5.56	12.2
N	17	65	F	PU	Stage 3	Sacrum	33	3	28.8	33.88	−5.08	−17.6

Table 3. Wound characteristics and clinical course (continued)

Patient	Wound	Age, years	Sex	Wound aetiology	Stage/Wagner grade/ partial- or full-thickness	Wound location	Time from wound onset to graft application, weeks	Duration of graft application, weeks	Initial surface area, cm^2	Surface area at final follow-up provided, cm^2	Surface area reduction cm^2	Surface area reduction %
O	18	65	F	PU	Stage 2	Left buttock	NR	4	12.42	0	12.42	100
O	19	65	F	PU	Stage 4	Sacrum/buttock coccyx	25	10	33.55	29.5	4.05	12.1
P	20	67	M	PU	Stage 4	Sacrum	19	10	35.75	2	33.75	94.4
Q	21	84	F	DFU	WG 3	Right plantar aspect of the great toe on right foot	7	6	2.4	0.5	1.9	79.2
R	22	72	F	NF	FT	Right thigh	25	10	89.28	38.6	50.42	56.5
S	23	78	F	Traumatic injury	FT	Right arm	NR	3	2.94	1.5	1.44	49.0
T	24	91	M	PU	Stage 4	Left hip	23	8	45.6	17.1	28.5	62.5
T	25	91	M	PU	Stage 4	Right hip	24	8	38.4	16.7	21.7	56.5
T	26	91	M	PU	Stage 3	Right ischial	24	8	16	3	13	81.3
U	27	71	F	PU	Stage 4	Mid-back	11	3	6.72	0	6.72	100
V	28	53	M	PU	Stage 4	Right buttocks	9	10	9.8	0	9.8	100
V	29	53	M	PU	Stage 3	Coccyx	11	5	0.88	0	0.88	100
W	30	95	F	VLU	FT	Left anterior lower leg	7	6	2.1	0	2.1	100
X	31	73	F	VLU	FT	Right lateral lower leg	33	9	1.26	1.2	0.06	4.8
Y	32	101	F	PU	Stage 3	Right medial heel	6	5	19.27	4.59	14.68	76.2
Y	33	101	F	PU	Stage 3	Right lateral hip	6	5	11.7	5.8	5.9	50.4
Y	34	101	F	PU	Stage 3	Right medial lower leg	7	4	5	0.36	4.64	92.8
Z	35	59	M	PU	Stage 4	Sacral region	7	7	9.8	0	9.8	100
AA	36	82	F	Non-pressure chronic ulcer	PT	Popliteal crease right leg	18	2	32.33	16.04	16.29	50.4

DFU—diabetic foot ulcer; F—female; FT—full-thickness; M—male; NF—necrotising fasciitis; NR—not reported; PT—partial-thickness; PU—pressure ulcer; VLU—venous leg ulcer; WG—Wagner grade

Fig 4. Patient K, wound #11: a 76-year-old male patient with a diabetic foot ulcer (DFU) Wagner Grade 2 of left plantar foot to the first metatarsal head. Patient had a documented haemoglobin A1c of 8%, with a wound duration of >8 weeks. First graft application and post debridement **(a)**. After 10 applications with DermaBind, a 88.6% surface area reduction was noted **(b)**

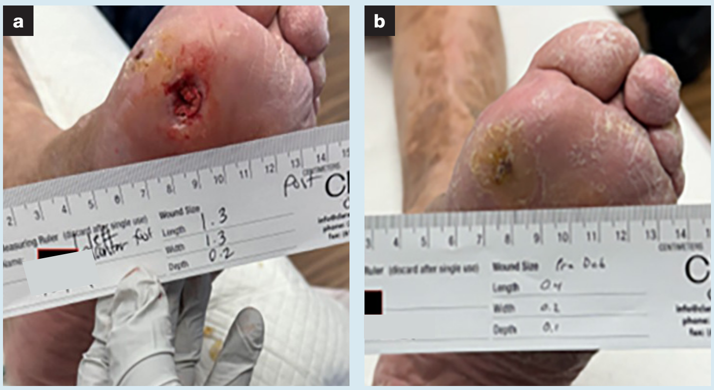
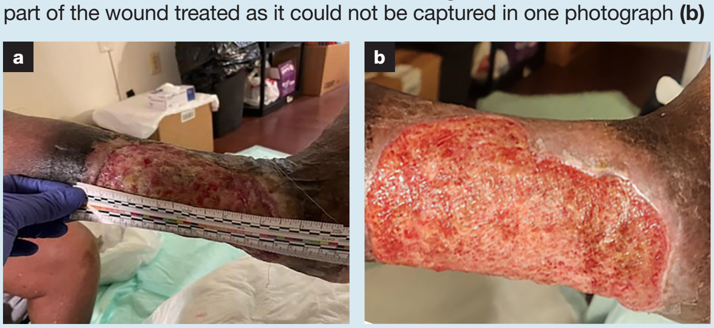


Fig 5. Patient V, wound #28: a 53-year-old male patient with a stage 4 pressure ulcer of the right buttock of nine weeks' duration. Initial visit prior to graft application **(a)**. After 10 applications with DermaBind, a 100% surface area reduction was observed **(b)**

Fig 6. Patient E, wound #5: a 74-year-old female patient with a full-thickness venous leg ulcer to right lower leg of 365 weeks' duration. Initial wound surface area was 460cm^2 **(a)**. After 10 applications with DermaBind, the surface area reduced to 256.5cm^2. This image is used as a reference for part of the wound treated as it could not be captured in one photograph **(b)**



the wound healing process.[4] These complexities are commonly seen in clinical practice and provide valuable perspective in the real-world management of hard-to-heal wounds. Interestingly, despite these important clinical considerations in wound management, there was no distinguishable impact of diabetes control among the patients included in this present case series. For example, Patient AA had an HbA1c of 9.7%; however, their corresponding wound (wound 36) demonstrated a 50.4% reduction in surface area. On the other hand, Patient I had an HbA1c of <8%, but their corresponding wound (wound 9) worsened by 2.63%.

Wound closure observations

Across the cohort, a variety of closure patterns were documented post use of the grafts as wound coverings. Some nine wounds had complete resolution, as reported by the clinician over the observation period, highlighting the complexity of managing hard-to-heal wounds to closure. Several wounds demonstrated progressive reduction in size during the observation, ultimately reaching full closure or a size reduction that no longer warranted the use of a graft as wound covering, as per Local Coverage Determination (LCD) guidelines. These guidelines are a vital resource for providers using skin substitute grafts, and cellular and tissue-based products.[23]

Other wounds remained stable without signs of deterioration and maintained a consistent wound surface without enlargement or breakdown. In certain cases, a striking reduction in wound size was observed. For example, wound 5 was a VLU with a surface area of 460cm^2 that had an onset of seven years prior to first graft application. DermaBind graft was initiated as part of a regimen to prevent lower limb amputation, as reported by the provider. The surface area was reduced to 256.5cm^2 after 10 graft applications, corresponding with a 44.2% surface area reduction.

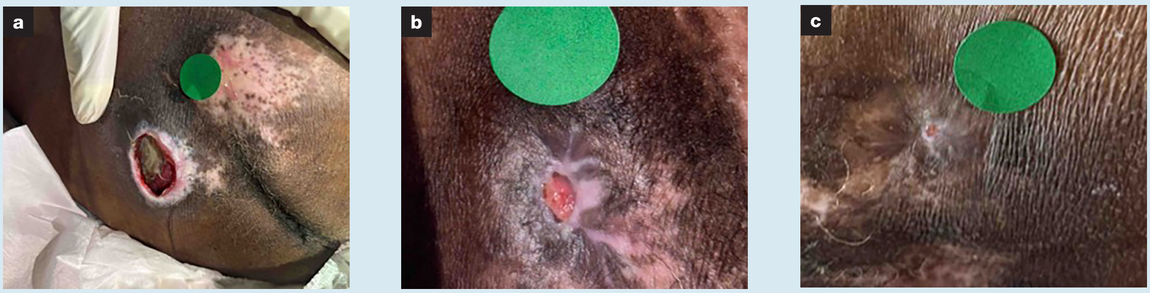
Pain

Pain scores reported by patients varied, with one patient (wound 20) moving from 9 to 0 on the pain scale. While these reports are anecdotal in nature, they illustrate the potential variability of patient experience under similar management strategies. Most cases report the stability of symptoms, with pain neither escalating nor declining significantly over the course of observation. It is important to note that all these observations are reported descriptively. They are not intended to imply a direct causal effect of the grafts but, rather, to provide a full account of clinical outcomes as observed. These accounts also highlight the heterogeneity of patient experience with wound coverings and reinforce the importance of individualised care.

Material utilisation and waste minimisation

An observation of practical importance was the low level of graft wastage documented throughout the series. In most cases, the selection of graft size was closely matched to the dimensions of the wound surface area, resulting in efficient utilisation. Minimal trimming was required and unused remnants were minimal. This careful matching not only reduced waste but also contributed to cost-conscious clinical practice. The

Fig 7. Patient Z, wound #35: a 59-year-old male patient with a Stage 4 pressure ulcer of the sacral region of seven weeks' duration. Initial visit prior to graft application **(a)**. Week 8, seven graft applications completed. Provider ceased graft application and proceeded with standard of care (SoC) **(b)** . Week 11, after three weeks of SoC, 100% re-epithelialisation was reported **(c)**



ability to use grafts efficiently is an important consideration for both providers and healthcare systems, particularly in the management of hard-to-heal wounds where resources are often applied repeatedly over extended periods. There are a variety of strategies that can be used to ensure appropriate use of grafts. It is vital to add that providers paid attention to the number of grafts used, and that they ceased to use placental membrane application as per LCD guidelines (e.g., when a wound size reduced to the point of not warranting further graft application) and continued with the SoC. The providers always chose treatments based on proper use, medical necessity and current LCD guidelines.[23] In this series, some cases (wounds 7, 8, 27, 29, 30 and 35) showed complete wound closure, post graft applications and return to SoC, after only a few visits, and in one case, after only one visit.

Adverse events

Throughout the observation, no adverse events were identified or reported in association with the application of the grafts by the providers. The absence of graft-related complications, such as infections, were consistent across all cases documented. This favourable safety profile is noteworthy given the inherent vulnerability of patients with hard-to-heal wounds, who are often at higher risk of complications due to comorbidities and impaired healing capacities. This reported finding is in line with the lack of significant adverse events reported in the post-marketing period of DermaBind. With >11,000 grafts shipped since June 2022, no adverse events have been reported. The lack of adverse events reporting suggests that, when used as wound coverings and as per manufacturer's instructions for use, the grafts were well-tolerated by patients. While causality cannot be inferred, the uniform absence of untoward outcomes provides reassurance about the acceptability of clinical use in the observed population. Continued vigilance and reporting will remain essential in broader clinical use.

Limitations

This series included a relatively low number of patients with wounds of diverse aetiology. Patients also had numerous comorbidities and were treated in different settings, such as outpatient clinics or at home via mobile care. Another confounding factor was the use of concomitant therapies. These interventions may have positively impacted wound healing and make it impossible to tease out the role played by these or by the graft as a wound covering—albeit this case series replicates what will be observed in real-world evidence and in practice, outside of registered clinical trials. These confounding factors limit comparability, generalisability and causality of the observations. Criteria for healing was not absolutely standardised and relied on the clinical judgement, experience and expertise of the providers in wound care. Complete re-epithelialisation was used to document complete wound closure by the providers. Confirmation of wound recurrence was not captured for this retrospective case series.

Data collection methods were diverse, mirroring real-world evidence capture of data. Cases were submitted using different tools, which introduces a risk of inconsistency, transcription errors and variability in data quality. To diminish these, data were entered then reviewed independently for accuracy as they were collated. Follow-up intervals were different between wounds, even within the same aetiology. Reported outcomes occurred at different timepoints (5, 8 and 11 weeks), without synchronisation across patients, as expected in wounds of varied aetiologies, size and severity, even if all wounds needed to be hard-to-heal in order to be included. This leads to variable exposure to the wound covering and to different numbers of graft applications, with an average of 6.7 weeks of treatment (range: 2–15 weeks).

There were no standardised tools to capture the pain measures across all sites, and the same is true for templates/questionnaires to assess wound tissue type, deepest exposed structure, exudate type and severity, and periwound description. Even though they were not standardised, the questionnaire and templates used by the providers not only shared similarities to validated tools, but they also shared similarities to each other.

Adverse events were collected if documented in the clinical chart; however, since they were not prospectively sought, this could lead to their being under-reported, and an over-estimation of the tolerability of the grafts.

No formal statistical analysis was performed, which is a weakness of the study. Further prospective studies powered to look at efficacy are warranted in the future.

Conclusion

These observations describe the clinical use of DermaBind as a wound covering material consistent with the placental membrane's natural homologous protective role. While complete closure was documented in some cases, stability was maintained in others, and two cases demonstrated worsening. The report of pain going from a level of 9 to 0 over the course of observation was reported in one case, whereas the broader cohort exhibited a more modest pattern of pain control. Minimal waste was observed due to appropriate graft-to-wound matching. The low wastage underscores the feasibility of tailoring graft selection to wound size in real-world practice. Finally, no adverse events were reported.

Importantly, these outcomes are presented descriptively, without inference of causation. The intent is to characterise the experience of a wound covering in practice while maintaining appropriate allograft stewardship to prevent overuse and waste. These findings may inform future protocol development, provide a foundation for future clinical observation, and highlight areas for research, particularly in pain outcomes, wound size progression and resource utilisation. JWC

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Reflective questions

- How is DermaBind TL/FM used and tolerated in real-world clinical practice as a wound covering?
- What complexities must clinicians navigate when managing hard-to-heal wounds?
- What characteristics and demographics that impact wound healing are observed in real-world clinical practice?

Application of a full-thickness placental allograft in complex wound management: a case series across diverse aetiologies

Objective: Management of complex hard-to-heal (chronic) wounds presents a substantial challenge in various healthcare settings where logistical constraints and patient-related factors can impede wound closure. This retrospective study evaluates outcomes associated with the use of a dehydrated, full-thickness placental allograft (CompleteFT; ExtremityCare, LLC, US) composed of the amnion, chorion and intermediate layers, when applied to complex hard-to-heal wounds in a mobile care environment.

Method: A retrospective analysis reviewed data collected between February 2024 and July 2025 from patients (aged ≥18 years) with complex hard-to-heal wounds. Data were retrieved from a single mobile wound care service provider team (Compassionate Care Concierge, US). Prior to allograft application, all wounds exhibited stalled healing for at least 30 days with standard of care (SoC). The allograft was applied to all wounds as an adjunct to SoC. Trend changes in wound surface area and percentage area reduction (PAR) across various wound aetiologies were assessed, with additional endpoints including the number of allograft applications and relevant patient parameters.

Results: The patient cohort (n=114, with a total of 184 hard-to-heal wounds), included 51 males and 63 females, with a mean age of 73.1 years. Analysis revealed statistically significant PAR values for various wound aetiologies, such that: $p<0.0001$ for diabetic foot ulcers (n=11); venous leg ulcers (n=48); pressure ulcers (n=73); and wounds classified as 'other' (n=39). Surgical wounds (n=13) demonstrated a $p<0.0007$. The study allograft was well-tolerated, with no adverse events directly attributable to the product.

Conclusion: Application of the full-thickness allograft as an adjunct to SoC presents a promising option for supporting wound size regression in complex, hard-to-heal wounds.

Declaration of interest: The author has no conflicts of interest to declare.

amniotic membrane • **chronic wounds** • **CompleteFT** • **complex wounds** • **full-thickness membrane** • **hard-to-heal** • **placental allograft** • **wound** • **wound care** • **wound closure** • **wound covering** • **wound dressing**

The global burden of complex, hard-to-heal (chronic) wounds, including diabetic foot ulcers (DFUs), venous leg ulcers (VLUs) and pressure ulcers (PUs), presents a significant challenge to healthcare systems.[1] Complex, hard-to-heal wounds are defined by a failure to predictably proceed through the established phases of physiological healing, classically arresting in a state of prolonged inflammation.[2] The challenges of hard-to-heal wounds are multifactorial, stemming from a combination of local wound considerations (e.g., infection, ischaemia, and repeated pressure) and patient comorbidities (e.g., high body mass index, diabetes and vascular disease).[2] Increasingly, hard-to-heal wounds are being recognised as a mortal disease associated with grave end-results on a scale similar to those observed for certain cancers.[3] For example, scientific literature indicates that the five-year mortality rate associated with patients with DFUs and ischaemic ulcers exceeds the rate observed with common malignancies, including prostate and breast cancer.[3,4] Additionally, when considering the mortality associated with hard-to-heal wounds, it should be recognised that the five-year mortality rate for patients who undergo diabetes-related limb amputations is approximately 50%.[5] Collectively, these concerns underscore the need to recognise hard-to-heal wound repair as a significant burden which necessitates early management.

Effective early management requires a comprehensive and multifaceted approach that adequately addresses all underlying impediments to wound closure.[2] Standard of care (SoC), which typically includes debridement, moisture balance and offloading, is foundational but often presents as insufficient for achieving closure.[2] This has catalysed the development and adoption of adjunct/supporting solutions including tissue-based products, such as placental tissue allografts.

Published literature has shown that the placenta provides a native extracellular matrix (ECM) scaffold that supports cellular migration and proliferation; delivers cytokines that promote angiogenesis and granulation; and exerts anti-inflammatory, anti-fibrotic, and immunomodulatory effects that may help facilitate transition of the wound from a hard-to-heal to a healing state.[6,7] Cellular, acellular and matrix-like products (CAMPs), including placental-derived allografts, are now widely used in wound care settings as a physical wound covering.[7–9] These membranes are often processed using proprietary or unique methods,

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resulting in a wide variety of available single- and multilayer constructs.[6,7]

Placental allografts that retain the amnion, chorion and intermediate spongy layers are considered full-thickness allografts. In these allografts, the amnion provides a basement membrane rich in collagens and laminin, the chorion offers a scaffold, and the intermediate layer consists of a non-fibrillar meshwork that connects the two.[6,10] Preserving this tripartite architecture is hypothesised to provide a more mechanically robust scaffold and a more complete biological payload compared to single-layer grafts.[8,11–14] Moreover, a previous study reported favourable outcomes associated with such full-thickness allografts.[11]

The present analysis was undertaken to improve understanding of this characterisation, through examining clinical outcomes observed in a larger, heterogenous cohort of patients receiving full-thickness allograft applications during their overall course of care. In addition to understanding the changes observed in wound size reduction via surface area (SA) and percentage area reduction (PAR) trends, further outcomes tracked included the incidence of adverse events (AEs) associated with use of the allograft and number of allograft applications.

Methods

Ethical approval and patient consent

This study was a retrospective cohort analysis of patient data collected from the electronic health records (EHR) of a mobile wound care provider servicing multiple locations in and around Denver, Colorado, US. Records were collected for patients with documented application of the allograft. The collection and evaluation of all protected patient health information was performed in a Health Insurance Portability and Accountability Act-compliant manner, and all patient data were fully deidentified to ensure patient confidentiality and privacy.

The study was reviewed and approved by Advarra Institutional Review Board (IRB). Using the [US] Department of Health and Human Services regulations 45 (Code of Federal Regulations) CFR 46.104(d)(4), the IRB determined that this study is exempt from IRB oversight. Research was conducted in full accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Declaration of Helsinki as amended in 2013.

General written informed patient consent (encompassing the use of data and images) was obtained at the start of care by the patient provider team.

Product compliance

The study allograft (CompleteFT; ExtremityCare, LLC, US) is a dehydrated, terminally sterilised, full-thickness placental tissue allograft that contains the amnion, chorion and intermediate (spongy) layer of the placenta. The product meets all criteria to be compliant with Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/P) that are regulated by the US Food and Drug Administration (FDA) under 21 CFR Part 1271 and Section 361 of the Public Health Service Act.

Patient eligibility and data collection

Patients who received the study allograft applications between February 2024 and July 2025 from a single mobile wound care service provider team were included in the study. Patients were identified through a query of the EHR database of the service provider, Compassionate Concierge Physicians, US. Inclusion criteria for the study were as follows:

- Patients aged ≥18 years
- Presence of a medically diagnosed complex, hard-to-heal wound
- Wound duration of at least four weeks prior to the first application of the allograft
- Documented failure to demonstrate signs of wound closure (per wound care regulations)
- There were no adjunct use of allografts other than the study allograft during the course of application.

Patient profile data were extracted from the provider group's EHR system. These included: demographic data (e.g., age, biological sex, race); smoking status; mobility classifications; diabetes diagnosis; and wound characterisation information. The latter encompassed: wound aetiology (e.g., VLU, DFU, PU, surgical, trauma, etc.); anatomical location; wound duration; and temporal wound measurements (including length, width and depth).

Wound assessment

Wound assessments were performed and recorded by the treating provider(s) at the initial care visit (prior to first allograft application) and at each subsequent visit. Wound dimensions were measured using a sterile, single-use ruler. Overall wound surface area was calculated as length×width when the ruler was positioned externally over the wound. Depth was measured by carefully inserting a sterile, cotton-tipped applicator into the wound, at its deepest point, after which the applicator was placed by a ruler to notate the value. Wound measurements were meticulously documented on standardised forms per application visit to ensure appropriate adherence to wound care and allograft use. Where applicable, the wound was also digitally assessed via a wound imaging device to verify size and bacterial bioburden.

Statistical analysis

Data were analysed via SAS Institute Inc., US, (Version 9.4). Descriptive statistics were used to summarise patient characteristics and outcomes, whereas categorical variables are presented as counts and percentages. Where possible, interquartile ranges are portrayed to illustrate the spread of the data, and to provide understanding of variability given the inherent heterogeneity within patient populations and wound aetiologies. The Wilcoxon signed-rank test was performed using the null hypothesis of no change from baseline to provide a clinically relevant comparator point for evaluating wound size changes as statistically significant. A p-value of ≤0.05 was deemed statistically significant.

Allograft application procedure

Wound site preparation

Prior to commencing allograft application procedures, patient documentation and history were comprehensively reviewed to confirm medical necessity. Additionally, appropriate insurance and consent details were also obtained and verified as needed. The application of the allograft was completed by trained wound care providers during mobile, in-home visits. At each visit, the wound was prepared according to standard clinical practice, following a sequence of steps grounded in best practice for wound bed preparation and allograft application. This included cleaning the wound site based on wound type, wound characteristics and patient needs. Duration of debridement and wound site cleaning could vary depending on wound type, severity and extent of necrotic tissue, as well as other site-specific or patient-specific factors. Typically, wounds were debrided for approximately 15 minutes by soaking with Vashe solution (Urgo Medical North America, US). Surrounding tissue and wound bed were scrubbed and cleansed with gauze soaked in Vashe solution to remove devitalised tissue.

Allograft application

The most appropriate size of allograft was selected to minimise wastage. The allograft was hydrated with sterile saline before it was applied directly to the prepared wound bed. It was positioned meticulously to ensure maximal coverage of the entire wound. The allograft was then secured in place with a non-adherent primary contact layer, followed by secondary dressing at the discretion of the provider. This composite dressing system was used to protect the allograft, control exudate and provide a conducive wound closure environment for the wound and the surrounding area. Weekly wound care and allograft applications were preformed based on the provider's assessment of wound progress.

Results

Patient and wound demographics

A total of 114 patients (51 male, 63 female) with 184 distinct hard-to-heal wounds met the retrospective assessment criteria and were included in the final analysis. The baseline patient characteristics are summarised in Table 1, whereas, wound type categorisations are detailed in Table 2. For the purposes of this study, wounds were categorised as: DFU (n=11); VLU (n=48); PU (n=73); surgical (n=13); and 'other' (n=39). 'Other' wounds included 10 wound subtypes (shown in Table 2), illustrating the heterogenous nature of the studied cohort. No AEs specific to the application of the placental allograft were observed within the patient records reviewed for this retrospective series.

Wound outcomes – percent area reduction (PAR)

PAR outcomes stratified by wound aetiology are presented in Table 3 along with their associated p-values.

Table 1. Patient demographics and baseline clinical characteristics (n=114)

Characteristics	n	%
Age, years, mean±standard deviation	73.11±11.83	—
Race		
White	47	41.2
American Indian or Alaskan Native	2	1.8
Other/mixed/unknown	65	57.0
Sex		
Male	51	44.7
Female	63	55.3
Diabetes history		
Yes	52	45.6
No	32	28.1
Not reported	30	26.3
Smoking history		
Non-smoker/no history	77	67.5
Previous history	17	14.9
Current	16	14.0
Other (vaping/chewing tobacco)	3	2.6
Not reported	1	0.9
Ambulatory status		
Assistive device/aid needed	86	75.4
Limited but mobile	13	11.4
Mobile	15	13.2

Table 2. Baseline wound type categorisation (n=184)

Wound type	n	%
Venous leg ulcer	48	26.1
Diabetic foot ulcer	11	6.0
Pressure ulcer	73	39.7
Surgical	13	7.1
Other*	39	21.2

*Includes: trauma; wounds secondary to calcinosis cutis; arteriovenous malformations; non-pressure hard-to-heal; abrasion; dehisced; laceration; vasculitis; arterial; stiff person syndrome

The Wilcoxon signed-rank test was used to evaluate whether the wound size change differed significantly from the null condition of no change from baseline. PAR was calculated as ((Initial SA – Final SA] / Initial SA) × 100, where SA is the surface area which was obtained using length and width measurements initially captured by the providers at the time of visit. Initial SA

Table 3. Percentage area reduction (PAR) outcomes stratified by wound aetiology

	DFU	VLU	PU	Surgical	Other
n	11	48	73	13	39
Mean PAR*	69.2	80.9	–157.9	70.1	46.1
Median PAR	75.8	98.1	82.8	98.3	78.3
p-value	<0.0001	<0.0001	<0.0001	<0.0007	<0.0001

*The observed mean, particularly the negative values, was influenced by a small number of outliers, which were retained for this table and statistical summary. For this reason, the median PAR values present a more robust measure of central tendency, as they are less affected by the extremes. DFU—diabetic foot ulcer; PU—pressure ulcer; VLU—venous leg ulcer

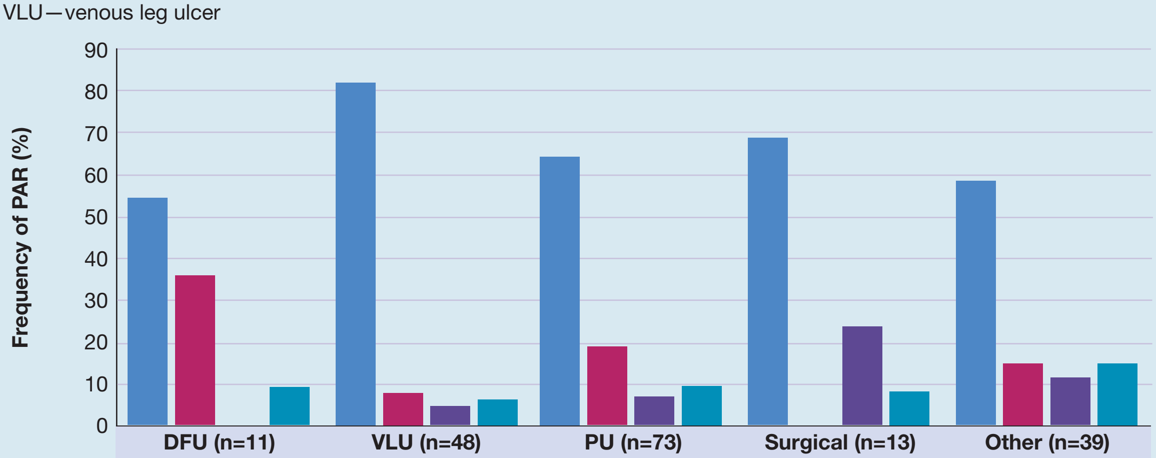
is the baseline measurement attained prior to allograft application, whereas Final SA is the measurement taken after final application of the allograft.

Wilcoxon signed-rank test revealed statistically significant p-values for PAR outcomes based upon wound aetiology, with a p-value of <0.0007 for surgical wounds and a p-value of <0.0001 for DFUs, VLUs, PUs and 'other' wounds (Table 3). The frequency of PAR is depicted in Fig 1. Within each wound type, the majority of the patient population achieved a PAR of ≥70% by the time the final allograft was applied. Of the 11 patients with DFUs, 54.5% (n=6) had a PAR of ≥70% and of the 48 patients with a VLU, 81.3% (n=39) fell into the high PAR ranges. This trend was consistent across PUs (64.4%; n=47), surgical wounds (69.2%; n=9), and 'other' wounds (59.0%; n=23). In each wound category, <15% of the patient population exhibited a negative PAR, indicating that increases in wound dimensions and poor response to allograft applications were minimal. The low incidence of negative PAR supports a favourable overall application effect for the study allograft across varying aetiologies.

Additionally, the box-and-whisker plots shown in Fig 2 demonstrate high central tendency values for both the DFU (median: 75.8) and VLU (median: 98.1) cohorts, regardless of the expected heterogeneity across patients, providing a reliable picture of how each wound type behaved when the study allograft was applied as an adjunct to SoC in the real-world, mobile wound care setting. Fig 3 depicts the PAR outcomes for all other wounds included in the study. The primary difference between Fig 3a and 3b is that 3a excludes one patient with a PU (n=72). The patient's extreme PAR obscured visualisation of the broader data distribution trends, therefore the patient case was excluded in Fig 3a for added data transparency and to facilitate clearer depiction of the trends to understand observed impacts of allograft applications. The overall retention of the central tendency values between Fig 3a and 3b shows that each of the wound aetiologies observed a PAR of >75%. To note, the outlier did not experience an AE related to the allograft application.

Fig 4 provides representative patient images at sequential timepoints (prior to initial allograft

Fig 1. Percentage area reduction (PAR) frequency by wound type. DFU—diabetic foot ulcer; PU—pressure ulcer; VLU—venous leg ulcer



	DFU (n=11)	VLU (n=48)	PU (n=73)	Surgical (n=13)	Other (n=39)
PAR >70%	6 (54.5%)	39 (81.3%)	47 (64.4%)	9 (69.2%)	23 (59.0%)
PAR 30–70%	4 (36.3%)	4 (8.3%)	14 (19.2%)	0 (0%)	6 (15.4%)
PAR 0–30%	0 (0%)	2 (4.2%)	5 (6.8%)	3 (23.1%)	4 (10.3%)
PAR <0%	1 (9.1%)	3 (6.3%)	7 (9.6%)	1 (7.7%)	6 (15.4%)

application, immediately prior to final application, and one week post final application), highlighting examples of wound progression which supplement the qualitative outcomes described above.

Wound outcomes – surface area reduction (SAR)

SA outcomes stratified by wound aetiology are presented in Table 4. Mean and median values are presented to demonstrate the overall trend towards wound size reduction. The table summarises data obtained prior to allograft application as compared to data obtained post allograft application. The difference between the two assessment timepoints consistently favours a reduction in wound SA, underscoring the net change trend of wound size regression across the different wound aetiologies.

Wound outcomes – number of allograft applications

Table 5 depicts that 31.5% of the wounds in this retrospective analysis received 1–5 applications, while 68.5% received 6–10 applications. When assessing PAR values based on the number of allograft applications stratified per wound aetiology (Table 6), it can be observed that wounds receiving 1–5 applications demonstrated relatively high PAR (median between 60.3–100.0%). Notably, for wounds requiring 6–10 placental allograft applications, the median PAR ranged between 71.4–98.3%. The comprehensive cumulative PAR ranged from 60.3–100.0% across varying allograft application counts. Overall, the favourable percentages suggest that application of the allografts supported positive wound size reduction trajectories across varying wound types.

Adverse effects and tolerability

The allograft applications were well tolerated across patients. There were no noted instances of AEs directly attributable to the placental allograft, such as allergic reaction, immune response or allograft rejection.

Discussion

The results of this retrospective analysis indicate that the adjunctive use of a full-thickness placental allograft was associated with positive wound regression trend outcomes in a patient population with complex/hard-to-heal wounds that had failed to respond to SoC alone. These findings are consistent with a growing body of evidence supporting the use of placental-derived tissues as wound coverings and suggest that this modality is a viable adjunct for supporting the process of addressing hard-to-heal wounds.

The observed benefit of including placental allografts during the care process is likely multifaceted, stemming

Fig 2. Percentage area reduction (PAR) for diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs). Max—maximum; Med—median; Min—minimum; Q—quarter

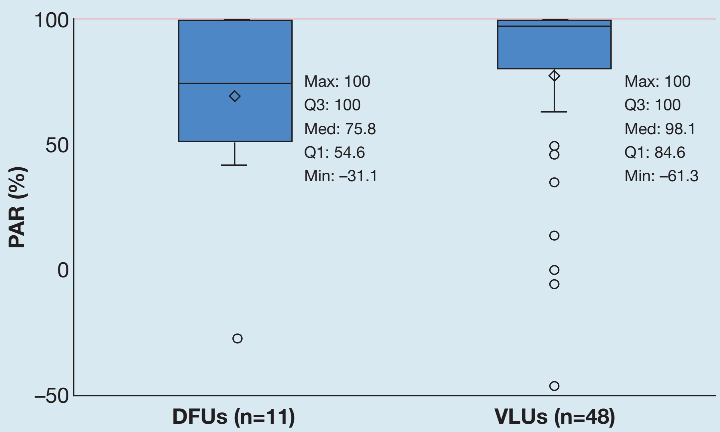


Fig 3. Percentage area reduction (PAR) for wounds other than diabetic foot ulcers and venous leg ulcers. Max—maximum; Med—median; Min—minimum; PU—pressure ulcer; Q—quarter. *(a) excludes an extreme patient outlier, while (b) includes this outlier for data transparency (wound measured 0.5×0.5cm at baseline but was 6.7×6cm at the final visit). However, the overall retention of the central tendency values (medians) between the sub-figures depicts that each of the wound aetiologies observed a PAR of >75%

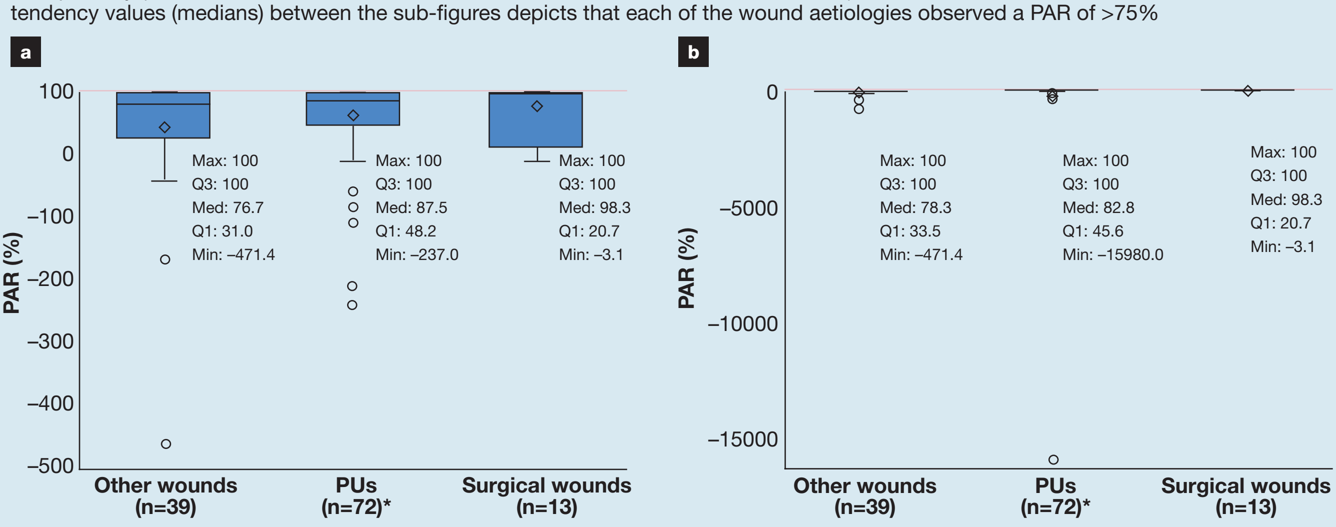
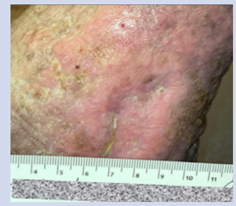
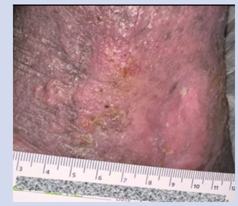
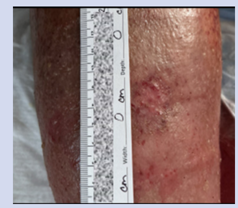
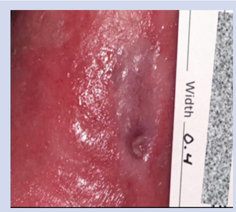
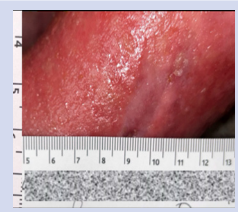


Fig 4. Patient case examples

	Prior to initial allograft application	Prior to final allograft application	One week post final allograft application
Venous wound, left lateral ankle: a 71-year-old male patient; former smoker; ambulatory with walker. Medical history indicated hypertension; PVD; ischaemic cardiomyopathy; atherosclerotic heart disease; type 2 diabetes. Before first allograft application, wound size 4.2×2.0×0.5cm. Before final application, wound size 0.8×0.2×0.1cm. One week after final allograft application, wound size 0.0×0.0×0.0cm			
Venous wound, right lower leg anterior extremity: a 76-year-old male patient; history of smoking; wheelchair ambulatory. Medical history indicated PVD; atherosclerotic heart disease; HLD; type 2 diabetes; venous stasis ulcerations; venous insufficiency; lymphoedema. Before first allograft application, wound size 4.5×4.0×0.3cm. Before final application, wound size 3.0×2.8×0.1cm. One week after final allograft application, wound size 0.0×0.0×0.0cm			
Venous wound, left lower extremity lower lateral: an 82-year-old female patient; non-smoker; ambulatory. Medical history indicated CHF; chronic venous HTN; venous insufficiency; rheumatism; LBBB; A-FIB; and multiple hard-to-heal venous ulcerations to the BLE. Before first allograft application, wound size 4.0×2.0×0.3cm. Before final application 56 days after initial application, wound size 0.5×0.5×0.1cm. One week after final allograft application, wound size 0.0×0.0×0.0cm			
Surgical wound, right groin: an 82-year-old female patient; current smoker; ambulatory with cane. Medical history indicated IDDM; atherosclerosis of coronary artery bypass graft(s); congenital hypothyroidism; enterocolitis due to *Clostridium difficile*. Before first allograft application, wound size 14.5×3.8×2.0cm. Before final application, wound size 0.1×0.1×0.1cm. One week after final allograft application, wound size 0.0×0.0×0.0cm			
Venous wound, right lateral lower leg: a 65-year-old female patient; history of smoking; bed/wheelchair dependency. Medical history indicated CAD; morbid obesity; PVD; type 2 diabetes; CHF; chronic pulmonary oedema; localised oedema; CKD3B; HTN; depression; muscle weakness. Before first allograft application, wound size 8.5×8.5×0.5cm. Before final application, wound size 4.5×1.0×0.2cm			
Trauma wound, right dorsal foot: a 66-year-old female patient; history of smoking; ambulatory. Medical history indicated muscle weakness; PVD; COPD; hypertension; tremor; cellulitis; sepsis. Before first allograft application, wound size 6.5×3.8×0.3cm. Before final application, wound size 3.2×1.5×0.1cm. One week after final allograft application, wound size 0.1×0.1×0.1cm			
Pressure wound, left heel: an 83-year-old male patient; non-smoker. Medical history indicated PAD and lymphoedema. Before first allograft application, wound size 3.4×0.2×0.2cm. Before final application, wound size 0.2×0.1×<0.1cm. One week after final allograft application, wound size 0.0×0.0×0.0cm			

A-FIB—atrial fibrillation; BLE—bilateral lower extremities; CAD—coronary artery disease; CHF—congestive heart failure; CKD3B—chronic kidney disease stage 3b; COPD—chronic obstructive pulmonary disease; HLD—hyperlipidaemia; HTN—hypertension; IDDM—insulin dependent diabetes mellitus (type 1); LBBB—left bundle branch block; PAD—peripheral arterial disease; PVD—peripheral vascular disease from their preserved native structure. Unlike single-layer amniotic membranes, the inclusion of the chorion and intermediate spongy layer provides a more conducive environment due to the native composition of these layers, retaining the inherent, basic characteristics of the placental tissue.[8,13] This is critically important, because hard-to-heal wounds are often stalled in a state of prolonged inflammation that is characterised by excessive levels of proteases and reactive oxygen species that degrade the native ECM, leading to cellular senescence and a failure to progress toward wound closure.[7] The rich composition provided by the full-thickness study allograft contributes to its integrity and utility to serve as a strong wound barrier; likely helping modulate the wound environment, including retaining moisture, thereby supporting the body to naturally transition toward the proliferative phase.

To contextualise this performance, it is useful to compare these outcomes with those associated with prior published tissue technologies. One such technology—assessed as part of a pivotal, multicentre, 12-week clinical trial—is a bilayered living cellular construct consisting of a bovine collagen matrix seeded with living human neonatal fibroblasts and a neonatal keratinocyte neoepidermis.[6,7,15–18] In this clinical trial, the construct showed a median time to wound closure of nine weeks, achieving what authors described as 'complete healing' in 56% of cases compared with 38% in the control group (p=0.0042). The study also portrayed that hard-to-heal DFUs in the allograft group reduced in size significantly faster than those wounds treated with SoC alone after an average of four applications (65 days versus 90 days, respectively; p=0.0026).[15]

While this current retrospective study does not incorporate all elements commonly seen in pivotal, prospective trials due to its retrospective nature, the findings nonetheless demonstrate favourable wound size regression trends. The results stratified per wound aetiology show positive outcomes with median PAR value ranging between 75.8–98.3%, with statistically meaningful p-values (ranging from p<0.0001 to p<0.0007) stressing clinical relevance. The results remain compelling even with a sample size of 11 DFUs (median PAR: 75.8%; p<0.0001) and 48 VLUs (median PAR: 98.1%; p<0.0001). Together, the findings highlight that the retrospective, real-world data effects measure up to the statistical expectations established from prior formalised clinical investigations.

Outcomes observed with other placental allografts

The findings from this study align with evidence from randomised controlled trials (RCTs) that have rigorously tested dehydrated amnion/chorion membranes to demonstrate the impact of placental allografts as adjuncts to SoC. DiDomenico et al.[19] published data for an 80-patient RCT assessing DFUs in which they found 85% of wounds managed with a minimally processed dehydrated human amnion/chorion membrane achieved closure by 12 weeks, compared to only 33% of those receiving SoC. The mean time to wound closure was also significantly faster: 37 days for the allograft group versus 67 days for the SoC group.[19]

Similarly, a 109-patient VLU RCT by Bianchi et al.[16] reported 60% of patients achieved wound closure at 12 weeks with weekly application of a dehydrated human amnion/chorion membrane, versus 35% with SoC alone; a Cox regression analysis revealed that patients who received the allograft were 2.26 times more likely to experience wound closure.

Additionally, a 218-patient DFU trial presented by Cazzell et al.[17] demonstrated a 48% greater probability of wound closure using a dehydrated full-thickness allograft, achieving a median time to closure of 84 days, while wounds in the SoC group failed to close by the 12-week endpoint. The consistency of these positive results across multiple trials, differing hard-to-heal wound aetiologies, and various full-thickness allograft products reinforces the effect observed in this present heterogeneous, real-world patient cohort.

Location and patient heterogeneity

The findings of this study were generated in a mobile, in-home clinical setting, demonstrating that effective wound care can be delivered in diverse locations. The successful deployment of the study allograft as part of the care regimen in this versatile environment highlights the clinical utility and adaptability of placental tissue technologies across various clinical care settings. The results support the notion that the stability

Table 4. Mean, median and net change in surface area reduction, stratified by wound aetiology

	Pre-allograft, cm^2	Post-allograft, cm^2	Net change trend	Net change, cm^2
Diabetic foot ulcer, n=11				
Mean	19.4	8.2	↓	11.2
Median	17.7	1.0	↓	16.7
Venous leg ulcer, n=48				
Mean	24.6	3.8	↓	20.8
Median	8.5	0.2	↓	8.3
Pressure ulcer, n=73				
Mean	9.0	5.9	↓	3.1
Median	5.5	0.3	↓	5.2
Surgical, n=13				
Mean	136.5	107.5	↓	29.0
Median	7.9	0.0	↓	7.9
Other, n=39				
Mean	14.4	13.1	↓	1.3
Median	7.5	0.5	↓	7.0

Table 5. Number of allograft applications stratified by wound aetiology

	DFU (n=11)	VLU (n=48)	PU (n=73)	Surgical (n=13)	Other (n=39)	Totals (n=184)
Median count	7	10	6	6	10	—
Categorical, n (%)						
1–5 applications	5 (45.0)	8 (17.0)	29 (39.7)	6 (46.2)	10 (25.6)	58 (31.5)
6–10 applications	6 (55.0)	40 (83.0)	44 (60.3)	7 (53.8)	29 (74.4)	126 (68.5)

DFU—diabetic foot ulcer; PU—pressure ulcer; VLU—venous leg ulcer

Table 6. Median percentage area reduction (PAR) values by number of allograft applications and wound aetiology

	DFU (n=11)	VLU (n=48)	PU (n=73)	Surgical (n=13)	Other (n=39)
1–5 applications					
Wound count, n	5	8	29	6	10
PAR, median %	68.0	100.0	91.5	60.3	100.0
6–10 applications					
Wound count, n	6	40	44	7	29
PAR, median %	87.0	96.0	79.1	98.3	71.4

DFU—diabetic foot ulcer; PU—pressure ulcer; VLU—venous leg ulcer

and ease of application features of such allografts are well-suited for a setting predisposed to varying logistical realities encountered during wound care.

Patient populations receiving mobile wound care, such as those in this study, are also often characterised by factors that impede the wound closure process, such as advanced age, limited mobility, behavioural considerations (such as patient adherence to wound care instructions), and complex comorbidities.[20] While previous assessments of placental allografts for hard-to-heal wounds in patients with such comorbidities have been promising, the available evidence is sparse. For example, a 2018 case series assessing allograft use in older patients with multiple comorbidities (diabetes, obesity, polymyalgia rheumatica, lymphoedema, peripheral vascular disease, steroid use and neuropathy) reported that all patients achieved complete wound closure.[21] The mean time to closure for the five wounds in the study was 4.8 weeks, with no complications, AEs, or wound recurrence reported.[21]

Other case series have likewise demonstrated positive outcomes using placental allografts as adjunct care modalities in highly complex cases including neuropathy, Charcot neuroarthropathy, hypertension, hyperlipidaemia, hypothyroidism, peripheral arterial disease, coronary artery disease, chronic kidney disease, chronic venous insufficiency, lymphoedema, chronic atrial fibrillation requiring anticoagulation, and chronic obstructive pulmonary disease.[22,23] The present study contributes to this body of evidence by providing data on the use of products, such as placental allografts, in real-world, heterogenous patient populations.

Potential implications for patient care

The observations of this study support several emerging considerations in contemporary wound care science. The data adds to the growing scientific knowledge which suggests an opportunity to reframe current approaches in the care paradigm of hard-to-heal wounds by incorporating tissue technology adjunct measures earlier on. Importantly, there is an opportunity to provide clinically meaningful benefits, such as reduction in amputations, hospitalisations, and in overall healthcare utilisation—ideally leading to cost-saving prospects for patients across various geographies and population demographics. Understanding there is a critical need to reduce the incidence of amputations and other grave outcomes associated with hard-to-heal wounds, serious consideration should be given to adoption of such allograft solutions into best practices and guidelines. The successful outcomes observed across this study's patient population exhibit the potential versatility and practical utility of placental allografts.

Limitations

As this study was conducted retrospectively, it provides valuable insight using real-world evidence derived and analysed using pre-existing data. Nonetheless, it is understood that prospective and randomised, controlled studies allow for more stringent standardisation and statistical power methodologies to be deployed. Given that analysis was constrained to using available patient data, this may also present survivorship bias. It is suggested that further multicentre studies with diverse patient demographics be conducted to further validate the shared results.

Conclusions

In this retrospective evaluation of complex hard-to-heal wounds managed in a mobile clinic setting, application of a full-thickness placental allograft as a wound barrier along with SoC found favourable wound closure trajectories, irrespective of wound aetiology. The observed results are consistent with the promising capabilities of placental allografts illustrated in other studies examining the potential role of such allografts in supporting wound care as adjuncts to SoC during the care of complex wounds. The data captures outcomes in the context of routine clinical practice, thereby alluding to the practical effectiveness of the placental allograft across heterogenous patient populations and mobile settings. These findings justify further investigation through additional large-scale retrospective and prospective trials, including RCTs. **JWC**

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The views expressed in the submitted article are of the author(s) and are not an official position of the organisation.

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Reflective questions

- What are the most vital properties of placental-derived allografts that you believe contribute to wound closure?
- Based on the current scientific literature and/or your clinical experiences, what patient populations benefit the most from placental allografts?
- Given the learnings from this manuscript and other published literature, what clinical scenarios have you found most promising for application of placental tissue allografts?

Real-world outcomes of a placenta-based tissue product versus standard of care for lower extremity diabetic ulcers: a Medicare cohort study

Objective: To review data from the Centers for Medicare and Medicaid Services (CMS) database in order to compare clinical outcomes of patients who were treated with Artacent Wound and Artacent AC (Tides Medical, US), a dual-layer amniotic membrane (DLAM), with patients who received debridement alone.
Method: A retrospective cohort study was conducted using a 1:1 matching procedure based on six pre-specified baseline covariates of Medicare patients who received DLAM or debridement alone for the treatment of lower extremity diabetic ulcers (LEDUs) between 2020 and 2023. LEDU episodes were constructed from claims data by linking sequential services until a 60-day clean period without LEDU-related claims was observed, which signified the end of an episode. Outcomes assessed within each completed episode included major and minor amputations, as well as emergency department (ED) visits, hospital readmissions, or care transitions to other sites of service, such as skilled nursing facilities.
Results: There were >2 million eligible episodes identified in the CMS database, of which 1244 LEDU episodes (622 in each cohort) met study eligibility and were analysed. Based on the analysis, approximately one major amputation was prevented for every 32 patients treated with DLAM as compared to debridement alone. Inpatient admissions, ED visits and skilled nursing facility visits were significantly reduced in the DLAM cohort.
Conclusion: Medicare patients treated with DLAM experienced significantly lower rates of major amputations and reduced healthcare use compared with those treated with debridement alone. Promising results from this study may provide another advanced wound care option to add to the treatment armamentarium.
Declaration of interest: Analysis of the Medicare database was funded by Tides Medical, Lafayette, LA, US. TT and KK serve as consultants to Tides Medical. WT has no conflicts of interest to declare.

debridement ● **diabetes** ● **diabetic ulcers** ● **Medicare** ● **lower extremity diabetic ulcer** ● **placental allograft** ● **real-world evidence** ● **wound** ● **wound care** ● **wound dressing** ● **wound healing**

Hard-to-heal wounds in patients with diabetes present a significant public health challenge and may be associated with substantial clinical burden to the patient, including reduced mobility, diminished quality of life, increased risk of infection and higher rates of amputation. As of 2020, for every 1000 adults diagnosed with diabetes, nearly seven were hospitalised for a lower-extremity amputation in the US.[1] Furthermore, lower extremity amputations in patients with diabetes have a five-year mortality rate of approximately 68%, similar to the rates of certain cancers.[2,3]

Imposition of major financial costs to the healthcare system is another growing concern. Among Medicare beneficiaries, the prevalence of hard-to-heal lower extremity diabetic ulcers (LEDUs) rose from 406,000 to 507,000 (an increase of 24.9%) between 2014–2019.[4] Treatment costs are expected to climb if the wound is considered recalcitrant or affects deeper tissue layers. Lifetime costs of amputations exceed $200,000 USD while costs of hospital admissions can exceed $14,500 USD per patient.[5,6] Advanced ulcers are estimated to cost around $50,000 USD per episode.[7]

Standard of care (SoC) for LEDUs encompasses the core, evidence-based principles of comprehensive wound management. SoC measures include: infection control; moisture balance; surgical debridement; revascularisation; offloading; and compression.[8,9] The guidelines on the treatment of LEDUs provided by the International Working Group on the Diabetic Foot (2023 update) and the Society for Vascular Surgery guidelines emphasise that early identification and treatment of ischaemia, infection and mechanical pressure are fundamental to promoting healing and preventing amputation.[10,11] The Cochrane systematic review by Santema et al.[12] and the Tissue, Inflammation and infection, Moisture balance, Edge, Repair and regeneration, and Social factors (TIMERS) wound healing framework[13] further reinforce that consistent

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debridement, moisture management and wound bed preparation are critical for achieving closure in hard-to-heal ulcers. Likewise, Armstrong et al.[14] demonstrated that adherence to evidence-based SoC interventions—particularly aggressive offloading and regular debridement—substantially reduces recurrence and major amputation rates.

In recent years, cellular, acellular and matrix-like products (CAMPs) have emerged as promising adjunctive therapies for hard-to-heal wounds.[15–17] These biologic, synthetic or biosynthetic materials are designed to mimic the structural and functional properties of native skin, thereby supporting and accelerating wound closure.[3] A growing body of evidence suggests that when used in conjunction with SoC, CAMPs—particularly dermal and multilayer products—may improve healing rates and reduce complications in hard-to-heal, persistent ulcers.[10,17–19]

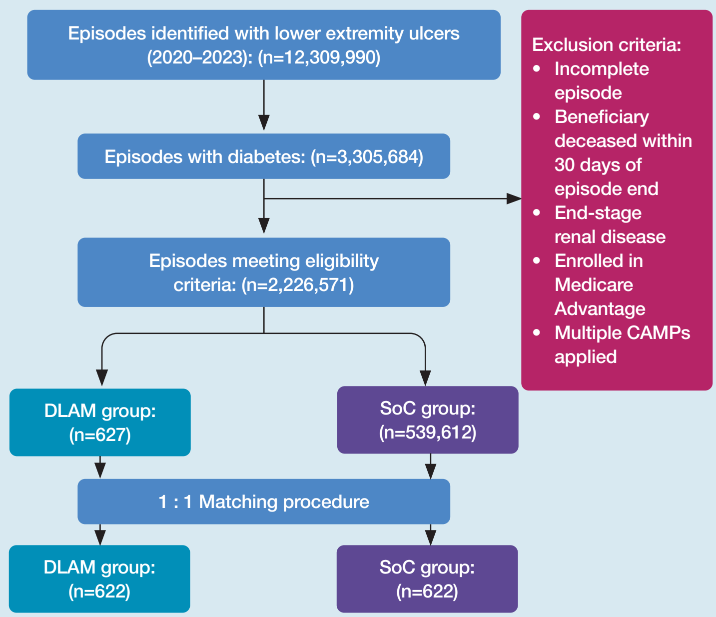
Among the various classes of CAMPs, placental allografts represent a biologically rich option, containing a matrix of extracellular components, growth factors and viable cells, such as fibroblasts, epithelial cells and stem cells.[19,20] Human placental membranes have been used historically for their regenerative properties, and studies suggest their adjunctive use may promote faster wound closure and mitigate long-term risks, including recurrence, amputation and mortality.[19–23] Artacent Wound (Q4169) and Artacent AC (Q4190) (both Tides Medical, US), are dual-layer amniotic membranes (DLAM) that are minimally manipulated and preserve the native characteristics of amniotic tissue. The purpose of this study is to retrospectively review the outcomes of Medicare patients treated with DLAM as compared to patients who received debridement alone. Similar outcomes to other covered CAMPs available on the market would be expected.

Methods

Ethical approval and patient consent

As this study involved secondary analysis of existing Centers for Medicare & Medicaid Services (CMS) claims data without direct patient contact, individual informed consent was not required. The Research Identifiable Files (RIFs) available through the Virtual Research Data Center (VRDC) do not include direct patient identifiers, such as name or Social Security number, as defined by the Health Insurance Portability and Accountability Act of 1996 privacy rule. However, since files contained beneficiary-level information in its dataset, including dates of service and geographic variables, access to this data required, as part of the access pathway, a CMS Data User Agreement. Therefore, WCG Institutional Review Board (IRB) reviewed the proposed study and granted an exemption in accordance with federal regulations (45 CFR 164.512)[24] governing research with existing data on 9 May 2025 (IRB#20251067). All analyses were performed within the secure VRDC environment under the CMS privacy and security safeguards.

Fig 1. Determination of the final patient cohort. CAMPs—cellular, acellular and matrix-like products; DLAM—dual-layer amniotic membrane; SoC—standard of care



Data source

A retrospective cohort study was conducted using the CMS RIFs accessed via the VRDC. Data included the Carrier, Outpatient, Inpatient, MedPAR, Home Health and Master Beneficiary Summary Files (MBSF). The determination of the final patient cohort for analysis followed the process outlined in Fig 1. The data were reviewed to analyse patients who received care for an LEDU between 2020 and 2023. Archived versions claims were reviewed using the International Statistical Classification of Disease and Related Health Problems (ICD)-10 diagnosis codes to ensure inclusion of patients with a confirmed LEDU who either received DLAM or SoC. Patients included in the study had to have a confirmed diagnosis of diabetes (type 1 or 2) during the episode of care (EOC). An EOC was defined by the presence of an initial claim for a LEDU that was preceded by a 60-day period without any LEDU-related claims. A new EOC was defined whenever a patient began treatment for a wound after at least 60 days without related claims. All subsequent wound-related claims were assigned to the same EOC until another 60-day claim-free interval was observed, at which point the EOC was closed. This framework enabled the identification of multiple, non-overlapping EOCs per patient and provided consistent EOC boundaries for outcome measurement. Treatment with DLAM was identified in claims data using its corresponding Healthcare Common Procedure Coding System (HCPCS) Level II Q-codes. SoC was defined by the presence of sharp debridement procedures, which were identified using Current Procedural Terminology (CPT) and HCPCS Level I codes.

A 30-day readmission was defined as any unplanned inpatient admission to an acute care hospital that occurred within 30 days of discharge from a prior index hospitalisation. Diagnosis for complications, such as major or minor amputation, end-stage renal disease and osteomyelitis, were defined using the appropriate CPT or ICD-10 diagnosis codes.

Retrospective cohort study

Eligible patients were identified in the CMS database if they had a confirmed diagnosis of diabetes documented during an EOC or within the 60 days preceding EOC initiation. Patients were excluded if they had end-stage renal disease, were enrolled in Medicare Advantage during the study period, initiated an EOC within the first 60 days or extended into the final 60 days of the observation window, or died within 30 days following EOC completion.

In the study, two treatment cohorts were evaluated: the DLAM cohort, which included beneficiaries with more than one claim for DLAM, and the SoC cohort, which included beneficiaries with at least one claim for wound debridement but no claims for CAMP products during the EOC. The two treatment groups were matched 1:1 across six baseline covariates: age (categorised); sex; frailty score (categorised) as defined by the Hospital Frailty Risk Score (HFRS); EOC start year; time to treatment initiation (defined as the interval between EOC start and the first claim for DLAM in the treatment group or debridement in the SoC group); and ulcer size, defined by debridement procedures exceeding $20cm^2$.

The approach to defining study eligibility criteria and constructing EOC was informed by prior Medicare claims-based analyses of skin substitutes in diabetic foot and venous leg ulcers, which used similar logic to identify eligible patients and define EOCs.[8,21–23,25] While the definitions used in this present analysis were not identical, they were conceptually aligned with these published methods to ensure comparability with existing real-world evidence.

To determine baseline patient comorbidity, two indices were used. The Hospital Frailty Risk Score uses 109 ICD-10 codes associated with frailty syndromes (e.g., falls, delirium, incontinence) to identify older adults at risk of poor health outcomes.[26] The Charlson Comorbidity Index (CCI) is a claims-based measure that summarises the overall comorbidity burden by assigning weighted scores to 17 major chronic conditions, with a higher score indicating greater risk of mortality.[27] The HFRS was chosen over CCI as it demonstrated a broader distribution of values for this cohort, allowing for finer stratification of risk (six versus three categories, respectively). In addition to assessing baseline comparability between groups, the CCI was incorporated into sensitivity analyses to evaluate the robustness of study findings under different assumptions regarding comorbidity burden.

Additional baseline variables analysed included dual-eligibility status (enrolment in both Medicare and Medicaid), presence of osteomyelitis, and ulcer depth involving the subcutaneous fat layer. Wound size and depth were approximated from claims using debridement CPT/HCPCS codes for procedures exceeding $20cm^2$ and ICD-10 diagnosis codes indicating fat layer involvement. The primary outcomes were rates of major and minor amputations.

Secondary outcomes included inpatient admissions, hospital readmissions, emergency department (ED) visits, skilled nursing facility (SNF) admissions, and intensive care unit (ICU) days. All outcomes were assessed over the full duration of each EOC and were required to be LEDU-related, as determined by the presence of corresponding ICD-10 diagnosis codes on claims.

Statistical analyses

Descriptive statistics were used when evaluating demographic and baseline characteristics. Between-group outcome comparisons were conducted using Chi-squared tests for categorical variables and t-tests for continuous variables. Sensitivity analyses evaluated the robustness of results by repeating matching with the CCI in place of frailty score. Statistical analyses were performed in SAS 9.4 (SAS Institute Inc., US) within the VRDC. Statistical significance was defined as $p<0.05$.

Results

Data reviewed from the CMS database between 2020–2023 revealed a total of 2,226,571 EOCs which met eligibility criteria and included a confirmed diagnosis of diabetes with a lower extremity ulcer. A total of 1244 LEDU EOCs were analysed (622 in each cohort). Prior to conducting the 1:1 matching procedure, the DLAM cohort exhibited higher comorbidity burden, HFRS and ulcer complexity, as shown in Table 1. Once matching was performed, all baseline covariates were balanced and no statistically significant differences between the groups were observed.

The mean age of patients was 72.5±10.6 years in the DLAM cohort and 73.2±11.0 years in the SoC cohort. The patient population was 58.8% male in each cohort. The HFRS was 21.3±15.3 and 21.7±16.1 points in the DLAM and SoC cohorts, respectively. Average days before treatment started were 90.1 days in the DLAM cohort and 87.8 days in the SoC cohort ($p=0.714$). The mean EOC length was 225.1 days for the DLAM cohort and 206.6 days for the SoC cohort ($p=0.336$).

As shown in Table 2, major amputations occurred in 2.6% of identified DLAM EOCs compared to 5.6% of patients in the SoC cohort (relative risk (RR): 0.46; 95% confidence interval (CI): 0.26, 0.82; risk difference: –3.1%; 95% CI: –5.3%, –0.9%; ^{2}=7.38; $p=0.0066$). This corresponds to approximately one major amputation prevented for every 32 patients treated with DLAM. Minor amputations occurred in 13.3% of DLAM EOCs compared with 15.4% of SoC EOCs (RR: 0.86; 95% CI:

0.66, 1.13; risk difference: –2.1%; 95% CI: –5.9%, 1.8%; ^{2}=1.10; p=0.29). Although the difference did not reach statistical significance, the effect direction favoured DLAM, suggesting a potential reduction in minor amputations. Inpatient admissions averaged 0.66 per EOC in the SoC group (662 per 1000 EOCs) compared with 0.48 per EOC in the DLAM group (479 per 1000 EOCs), a significant reduction (t=–3.29; p=0.0010). This corresponds to approximately 183 fewer admissions per 1000 EOCs, or one admission prevented for every six LEDU EOCs treated with DLAM.

ED visits and SNF admissions were significantly lower for the DLAM-treated cohort when compared to the SoC group. More specifically, DLAM-treated patients resulted in approximately 154 fewer ED visits per 1000 EOCs when compared with patients in the SoC cohort (p=0.011). This corresponds to one visit prevented for every seven LEDU EOCs treated with DLAM. Similarly, SNF admissions averaged 84 per 1000 EOCs in the DLAM cohort and 135 per 1000 EOCs in the SoC cohort (p=0.05). This equates to approximately 51 fewer SNF admissions per 1000 EOCs, or one admission prevented for every 19 LEDU EOCs treated with DLAM. Hospital readmissions occurred in 4.5% of DLAM EOCs compared with 6.8% of SoC EOCs (p=0.085), reflecting a non-significant trend toward fewer readmissions in the DLAM group. ICU use followed a similar pattern—an average of 0.68 ICU days in the DLAM group versus 0.83 ICU days in the SoC group (p=0.387).

Findings were consistent across frailty subgroups (high risk ≥15 versus low/medium risk <15). DLAM EOCs demonstrated significantly fewer inpatient admissions, ED visits and major amputations in both subgroups. Sensitivity analyses substituting CCI for frailty score yielded similar results, supporting the robustness of the findings.

Discussion

Results from this current study revealed that treatment with DLAM was associated with improved clinical outcomes compared with standard sharp debridement (SoC) alone. Most notably, DLAM episodes demonstrated a significantly lower rate of major amputation, corresponding to one major amputation prevented for every 32 treated patients. This finding is clinically meaningful given the high morbidity, mortality and healthcare costs associated with lower extremity amputations in patients with diabetes.

Reductions in inpatient admissions, ED visits and SNF admissions further suggest that the use of DLAM may help mitigate the downstream burden of hard-to-heal LEDUs. Given that each inpatient admission or SNF stay incurs substantial Medicare expenditures, these reductions are likely to translate into meaningful cost savings. Prior economic analyses of comparable placental allografts have shown that even modest decreases in hospitalisation or amputation rates yield significant reductions in total EOC costs. Based on contemporary Medicare cost benchmarks (average inpatient admission ≈ $14,500[5] USD and SNF admission ≈ $9,000 USD per stay[28]), the reductions observed in this analysis correspond to an estimated saving of >$2500 USD per EOC treated with DLAM.

Product cost comparisons were not included in the current study because the proposed CMS Local Coverage Determination (LCD) would shift all CAMPs to a fixed

Table 1. Baseline characteristics of standard of care (SoC) versus dual-layer amniotic membrane (DLAM) cohorts (pre- and post-matching). All baseline variables were balanced after matching, with no statistically significant differences

Baseline characteristic	Pre-matching			Post-matching		
	SoC (n=539,612)	DLAM (n=627)	p-value	SoC (n=622)	DLAM (n=622)	p-value
Age, years, mean±SD	73.2±11.0	72.5±10.6	0.089	72.2±11.3	72.5±10.6	0.609
Male sex, %	60.1	58.5	0.309	58.8	58.8	1.000
Dual-eligibility (Medicare and Medicaid), %	25.9	26.0	0.973	30.9	25.9	0.051
Hospital Frailty Risk Score, mean±SD	15.9±13.6	21.3±15.3	<0.001	21.7±16.1	21.3±15.3	0.649
Charlson Comorbidity Index, mean±SD	5.0±2.5	5.6±2.6	<0.001	5.8±2.7	5.6±2.6	0.139
Ulcer depth fat, % deep	58.9	75.8	<0.001	75.9	75.9	1.000
Osteomyelitis, %	16.3	27.9	<0.001	28.8	27.8	0.701
Number of ulcers per patient, mean±SD	1.29±0.53	1.48±0.52	<0.001	1.49±0.54	1.48±0.52	0.630
Debridement >20cm², %	9.2	13.1	<0.001	13.7	13.2	0.803
Days to treatment start, n, mean±SD	15.3±37.8	90.4±115.4	<0.001	87.8±110.1	90.1±114.1	0.714
Episode start year = 2020, %	25.6	25.0	0.732	25.1	25.1	1.000
Episode start year = 2021, %	30.5	36.2	0.002	36.2	36.2	1.000
Episode start year = 2022, %	27.8	31.1	0.072	31.0	31.0	1.000
Episode start year = 2023, %	16.0	7.7	<0.001	7.7	7.7	1.000

SD—standard deviation

Table 2. Clinical outcomes by cohort (post-matching)

Outcome	SoC (n=622)	DLAM (n=622)	Absolute Difference	RR (95% CI)	NNT (95% CI)	p-value
Major amputation, %	5.6	2.6	–31	0.46 (0.26, 0.82)	32 (19, 117)	0.0066
Minor amputation, %	15.4	13.3	–21	0.86 (0.66, 1.13)	ns	0.2900
Inpatient admissions (per 1000)	662	479	–183	0.72	6	0.0010
ED visits (per 1000)	690	535	–154	0.78	7	0.0110
ICU days (per 1000)	834	683	–151	0.82	ns	0.3870
SNF admissions (per 1000)	135	84	–51	0.62	19	0.0500
30-day readmission, %	6.8	4.5	–23	0.67 (0.42, 1.06)	ns	0.0850

DLAM—dual-layer amniotic membrane; ED—emergency department; ICU—intensive care unit; NNT—number needed to treat; ns—not significant; RR—relative risk; SNF—skilled nursing facility. RR for continuous outcomes (inpatient, ED, ICU, SNF) reflects relative rates (Artacent versus SoC). NNT is shown only when effects are statistically significant

reimbursement rate per cm², making current average sales price (ASP)-based prices less representative of future payment conditions. Although the ASPs for Artacent Wound and Artacent AC differ under current policy, these differences will not apply once the standardised reimbursement structure is implemented.

In the Medicare cohort, all patients were required to have at least one sharp debridement encounter prior to product application. Debridement frequency served as a proxy for wound bed preparation, with shorter intervals indicating more active management. A previous study showed that episodes treated with a CAMP and 1–7-day debridement intervals demonstrated markedly lower major amputation rates (2.1% versus 6.0% with SoC) and reduced acute care use ($p<0.0001$).[9] Earlier CAMP initiation was also observed with more frequent debridement (66 versus 98–117 days; $p<0.0001$).[9] These findings are consistent with previous evidence showing that adequate and frequent debridement optimises graft incorporation and improves healing outcomes.[9,29]

Amniotic membranes are biologically rich matrices that retain extracellular structure and signalling molecules with potential to accelerate wound healing and reduce complications. As a result, it has been integrated into treatment strategies for hard-to-heal wounds. While randomised controlled trials (RCTs) have demonstrated the clinical efficacy of several CAMPs, RCT data on the product under evaluation has yet to be published. However, the current analysis offers meaningful real-world evidence on its performance in the Medicare population, where variability and patient complexity are high, a condition often encountered in routine clinical practice. Previous evaluations of CAMPs and placental-derived allografts have demonstrated improved healing rates, and lower risks of major amputation and hospital use compared with SoC.[21,30] These results are consistent with foundational wound healing research showing that a 50% reduction in wound area within four weeks is a robust predictor of 12-week closure and subsequent limb preservation.[31–33] Furthermore, frequent and adequate debridement has been independently linked to accelerated closure and reduced amputation risk.[9,29] Taken together, this body of evidence and the present Medicare findings reinforce the biologic and clinical rationale for placenta-derived tissue products and illustrate how real-world data can complement, as well as validate, RCTs by capturing outcomes in broader, more complex patient populations.

Limitations

Several limitations of this study should be acknowledged. As with all claims-based studies, certain clinical details, such as wound size, ulcer depth and patient adherence, were not directly observable and were approximated using procedure and diagnosis codes. While proxies were applied where feasible, these remain indirect measures and may underestimate heterogeneity in wound severity. Centre-level information was available but was not included in the matching process due to inconsistent reporting and limited ability to characterise multidisciplinary wound care environments. As a result, potential variation related to provider experience or practice patterns could not be fully addressed, though matching on key patient and episode level variables helped reduce this bias.

The study cohort was restricted to Medicare fee-for-service beneficiaries, which may limit generalisability to younger or commercially insured patients; however, Medicare is the dominant payer for LEDU care, making this population clinically and policy relevant. While matching balanced observed covariates, unmeasured confounding cannot be fully excluded. Finally, as this was a retrospective analysis, the results show associations rather than direct cause-and-effect. Nonetheless, they build on previous trial evidence by showing how these therapies perform in everyday clinical practice and over longer follow-up among Medicare patients.

Despite these limitations, the findings provide important real-world evidence supporting the clinical effectiveness of DLAM in the management of LEDUs. By demonstrating reductions in major amputation and healthcare use relative to debridement alone, this study underscores the potential value of placental allografts as an adjunctive therapy in advanced wound care. These results have implications for both clinical practice and payer decision-making, highlighting the role of real-world evidence in evaluating therapies for complex hard-to-heal wounds.

Conclusion

In this retrospective Medicare analysis, treatment with DLAM was associated with significantly lower rates of major amputation and reduced healthcare use compared with sharp debridement (SoC) alone. These benefits were consistent across frailty subgroups and robust to sensitivity analyses. While claims-based data impose certain limitations, the findings provide real-world evidence supporting the role of DLAM as an adjunctive therapy for LEDUs. Broader adoption of DLAM may improve patient outcomes and lessen the clinical and economic burden of hard-to-heal LEDUs in the Medicare population. **JWC**

AI disclosure

ChatGPT was used solely to check for grammar and help maintain a consistent voice. No new content was generated and no sentences were rewritten so as to change their original meaning. The authors carefully reviewed and approved all text in full.

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The hidden costs of limiting access: clinical and economic risks of Medicare's future effective cellular, acellular and matrix-like products (CAMPs) Local Coverage Determination

Objective: To evaluate the impact of Medicare's future effective Local Coverage Determination (LCD) for cellular, acellular and matrix-like products (CAMPs), which, while informed by a literature review and expert input, was finalised without incorporating a detailed statistical or cost analysis of its projected clinical and economic impact across diverse wound care delivery settings (e.g., hospital-affiliated, private practice, and post-acute care). This analysis focuses on the clinical consequences for Medicare beneficiaries with chronic or hard-to-heal lower extremity diabetic ulcers (LEDUs) and venous leg ulcers (VLUs). Additionally, it aims to assess the economic implications of implementing a capitated or fixed-fee schedule on CAMPs' use, Medicare expenditures and associated medical outcomes.
Method: A review of retrospective analyses of Medicare claims (2015–2020) was conducted, comparing treatment outcomes for LEDUs and VLUs using CAMPs plus medically accepted standard of care (SoC) versus SoC without CAMPs. Clinical endpoints included rates of hard-to-heal ulcer healing, amputation rates, hospitalisations and healthcare resource use. Cost-effectiveness models evaluated the impact of CAMP reimbursement structures on overall Medicare costs. Analysing the impact of a fixed-fee schedule involved evaluating Medicare claims data from 2016–2023 to determine the number of commercially available CAMPs, along with the most up-to-date average sales price (ASP). A comparative cost analysis model using an activity-based costing approach and a prospective payment system comparison was applied to evaluate two distinct reimbursement structures: an ASP fee-for-service model versus a fixed-fee schedule model.
Results: Medicare beneficiaries receiving SoC plus CAMPs for stalled wounds demonstrated significantly lower amputation rates, reduced hospitalisations and improved wound healing times compared with those receiving SoC without a CAMP during the episode of care. Beneficiaries receiving CAMPs also realised annual cost savings of $3670 USD per patient and a five-year net benefit of $5003 USD per patient. When evaluating over a 12-month window, restricting CAMPs to eight applications in the treatment of hard-to-heal VLUs and LEDUs resulted in estimated treatment failure rates of 10.9% and >30%, depending on the area of investigation. Moreover, the non-real-world restriction of a 16-week treatment episode in the future effective CAMP LCD, which fails to account for care delays (e.g., cellulitis, hospital admissions), will likely drive treatment failure rates even higher. Among failed LEDU cases receiving a CAMP, 1% require an amputation at a reimbursement rate of $23,435 USD per case, 37% are readmitted at a rate of $2079 USD per admission, and 30% seek emergency care at a reimbursement rate of $8292 USD per visit. These complications could result in hundreds of millions of dollars in additional annual Medicare expenditures, eroding any expected savings from the future effective CAMP LCD. Implementing a fixed CAMPs fee schedule instead of the traditional ASP reporting system could potentially reduce Medicare expenditures on CAMPs by >51% while still enabling wound care providers to determine medical necessity on evidence-based decision-making.
Conclusion: The proposed CAMPs LCD could negatively impact outcomes for Medicare beneficiaries who experience adverse outcomes when treatment is prematurely limited to eight applications over a fixed 16-week episode of care. While this subset of patients represents a relatively small proportion, they are at high risk of costly complications, which are likely to escalate when effective and medically necessary CAMPs treatment, ordered, selected and applied by their healthcare provider, is denied. Implementing a fixed-fee schedule for CAMPs without an absolute eight-application cap could enhance access by allowing healthcare providers to treat a greater proportion of hard-to-heal ulcers to closure with the goal of limb preservation, while maintaining cost controls. Policy adjustments should incorporate real-world evidence demonstrating the effectiveness of CAMPs rather than relying solely on randomised controlled trials.
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CAMPs ● cellular, acellular and matrix-like products ● local coverage determination ● wound ● wound care ● wound dressing

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Hard-to-heal (chronic) wounds, particularly lower extremity diabetic ulcers (LEDUs) and venous leg ulcers (VLUs), pose a significant public health challenge, impacting millions of individuals and creating substantial economic and clinical burdens on healthcare systems. Between 2015–2019, >1.2 million Medicare beneficiaries were diagnosed with LEDUs.[1] An estimated 500,000–600,000 beneficiaries develop VLUs annually, with combined Medicare expenditures surpassing $1.1 billion USD.[2] These conditions are linked to prolonged healing times, recurrent hospitalisations and an increased risk of complications, including limb loss. LEDUs alone account for >100,000 amputations annually in the US, with VLUs further complicating the healthcare landscape due to high recurrence rates and increased morbidity.[1–3]

Advanced wound care strategies, including cellular, acellular and matrix-like products (CAMPs), have emerged as critical tools for limb salvage by improving healing rates and reducing infection risks, ultimately lowering healthcare costs. Previous retrospective analyses of Medicare claims data have demonstrated that CAMPs, when applied according to established clinical parameters (following parameters for use (FPFU)), can significantly improve patient outcomes by decreasing the incidence of major amputations, reducing emergency department visits and facilitating wound closure.[1,2] These benefits underscore the importance of ensuring continued access to proven, effective treatments for hard-to-heal wounds.

To date, the Center for Medicare & Medicaid Services (CMS) has been managing two separate payment models within the outpatient wound care arena: a bundled payment system for claims submitted in the hospital outpatient department (HOPD) wound care settings, and an average sales price (ASP) reimbursement model for claims submitted in the private office and post-acute wound care settings. While the bundled model has long been criticised for underfunding care for larger or more complex wounds, the ASP model, though more reflective of actual product costs, has led to significant variability in reimbursement due to wide disparities in product pricing.

The recent proposals made by the seven Medicare Administrative Contractors (MACs) for 2024 and 2025 to implement an updated Local Coverage Determination (LCD) for CAMPs represent a pivotal shift in reimbursement policies that could significantly impact access to and use of these essential treatments. Notably, the policy limits CAMP applications to a maximum of eight within a 16-week episode of care, regardless of wound complexity or clinical response, and does so without addressing the shortcomings of the current ASP payment model. Advocates assert that a capitated or fixed-fee schedule may enhance access to CAMPs, enabling providers to address hard-to-heal wounds more efficiently, provide a solution to the flawed bundled payment methodology, and address the MACs' desire to limit CAMP applications unnecessarily. However, valid concerns exist about potential restrictions on treatment frequency and the implications these may have on patient outcomes. This analysis is crucial as it aims to evaluate the clinical and economic consequences of the future-effective CAMPs LCD for Medicare beneficiaries, particularly those with chronic or hard-to-heal LEDUs and VLUs. Specifically, we assess:

- The real-world impact of restricting CAMP applications to a fixed number, such as the proposed eight-application limit, on patient outcomes and healthcare use
- The projected economic burden of treatment failure resulting from premature cessation of therapy
- The cost-saving potential and clinical viability of replacing the ASP-based reimbursement system with a fixed-fee schedule model.

By integrating Medicare claims data with cost-effectiveness modelling, we seek to inform policy revisions that preserve clinical flexibility, reduce preventable complications and support value-based care.

Methods

A review of cohort analyses was conducted using Medicare Limited Data Standard Analytic Files (2015–2020). The claims data originated from inpatient hospitals and HOPDs. Propensity-matched groups that received CAMPs were compared to standard of care (SoC) patients who did not receive a CAMP during their episode of care. Statistical analyses included logistic regression models for assessing amputation risks and hospital use, as well as Markov models for evaluating cost-effectiveness up to a five-year horizon. Analysing the impact of a fixed-fee schedule model involved evaluating a limited 2016–2023 Medicare claims database to determine the number of commercially reimbursed CAMPs, along with the most up-to-date ASP. This dataset included claims from inpatient hospitals, HOPDs, and a 5% sample from private offices and post-acute care settings. A comparative cost analysis model using an activity-based costing approach and a prospective payment system comparison was applied to evaluate two distinct reimbursement structures: an ASP fee-for-service model versus a fixed-fee schedule model.

Ethical standards and patient consent

The Medicare Limited Data Set (LDS) files (2015–2023) were acquired under a data use agreement with CMS. Medicare LDS files do not contain specific direct

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identifiers, as defined in the Health Insurance Portability and Accountability Act Privacy Rule. All analysis and reporting of Medicare data was performed in compliance with relevant laws and institutional guidelines approved by the CMS. Patient consent was not required for this study.

Results

Lower extremity diabetic ulcers

A favourable impact was observed when comparing propensity-matched Medicare beneficiaries, from 2015–2018, with hard-to-heal LEDUs and who received CAMPs during their episodes of care to those who did not receive such intervention:

- Clinical effectiveness
  - Decreased major amputation rates ($p<0.0001$), fewer emergency department visits ($p<0.0001$), decrease in readmission rates ($p<0.0001$) (Table 1)[1]
  - Propensity-matched groups revealed that applying CAMPs in alignment with FPFU resulted in lower minor amputation rates ($p=0.002$).[1] (FPFU is defined as initiating treatment with CAMPs within 30–45 days of diagnosis and re-applying new CAMPs at regular intervals within the specified 7–14 day range)
- Cost-effectiveness
  - A retrospective cohort study analysing Medicare beneficiaries (2015–2019) with hard-to-heal LEDUs, using a hybrid economic model that combined a one-year decision tree and a four-year Markov model, demonstrated that placental-derived CAMPs provided an additional 0.013 quality-adjusted life years (QALYs) while saving $3670 USD per patient in the first year alone. Over a five-year horizon, the net monetary benefit (NMB) was estimated at $5003 USD per patient, based on a willingness-to-pay threshold of $100,000 USD per QALY (Table 1).[4]

Venous leg ulcers

Some 42% of Medicare beneficiaries with chronic venous insufficiency, evaluated from 2015–2019, developed at least one VLU, and 79% had their episode claim resolved within one year. However, 59% of patients developed another VLU during the 12-month study period.[2] A favourable impact was observed when comparing propensity-matched Medicare enrolees with a hard-to-heal VLU who received CAMPs during their episodes of care.

- Clinical effectiveness
  - Faster healing time (by 21 days; $p=0.0027$), lower infection rates ($p=0.034$), and reduced hospital resource use (Table 2)[5]
  - Timely initiation and routine application of CAMPs reduced VLU recurrence rates[6]
- Cost-effectiveness:

Table 1. Real-world outcomes and cost savings of CAMPs versus SoC in Medicare patients with a LEDU

Outcomes (2015–2018)	LEDUs
QALY gain (versus SoC)	+0.013 QALYs (5-year model)[4]
Net monetary benefit	$5003 USD per patient (5-year horizon)[4]
Cost savings per patient	$3670 USD (year 1); $p<0.05$[4]
Reduction in major amputations	↓ 50.0% (3.2% → 1.6%); $p<0.0001$[1]
Reduction in emergency department visits	↓ 21.0% (23.1% → 18.3%); $p<0.0001$[1]
Reduction in hospital readmissions	↓ 38.0% (6.4% → 4.0%); $p<0.0001$[1]

CAMPs—cellular, acellular and matrix-like products; LEDU–lower extremity diabetic ulcer; QALY—quality-adjusted life year; SoC—standard of care

Table 2. Real-world outcomes and cost savings of CAMPs versus SoC in Medicare patients with a VLU

Outcomes (2015–2018)	VLUs
QALY gain (versus SoC)	+0.010 QALYs (3-year model)[6]
Net monetary benefit	$1178 USD per patient (3-year horizon)[6]
Cost savings per patient	$170 USD (3 years); $p<0.05$[6]
Reduction in cellulitis	↓ 28.8% (17.0% → 12.1%); $p=0.00398$
Reduction in sepsis	↓ 51.1% (4.5% → 2.2%); $p=0.00038$[2]
Reduction in emergency department visits	↓ 18.2% (56% → 45.8%); $p<0.00012$[2]
Reduction in hospital readmissions	↓ 56.4% (11.7% → 5.1%); $p<0.0018$[2]

CAMPs—cellular, acellular and matrix-like products; QALY—quality-adjusted life year; SoC—standard of care; VLU—venous leg ulcer

- A Markov model-based cost-effectiveness study on VLUs in Medicare enrolees revealed that a placental-derived CAMP, when following clinical guidelines, yielded a lower per-patient cost of $170 USD and an increase of 0.010 QALYs over three years. The resulting NMB was $1178 USD per patient, favouring treatment episodes that included a CAMP. The analysis also demonstrated that early and regular application of CAMPs reduced hospital readmissions and overall healthcare expenditure (Table 2).[6]

Economic impact of CAMP application limitations

A retrospective observational cohort study using real-world evidence from a Medicare LDS between 2016–2020 demonstrated that treating LEDUs and VLUs with placental-derived CAMPs resulted in a 26% reduction in one-year mortality, a 91% lower recurrence rate, and 71% fewer adverse outcomes compared with SoC.[7] Limiting beneficiaries with hard-to-heal LEDUs and VLUs to eight CAMP applications over a static 16-week episode of care will lead to significant adverse events and economic losses. When evaluating 2023 Medicare claims data over a 12-month period, restricting CAMPs to eight applications in the treatment of hard-to-heal LEDUs led to estimated treatment failure rates of 10.9% in the HOPD setting, 22.3% in the private office and post-acute care settings, reaching ≥30% in published comparative trials.[8–10] The prospective randomised controlled trials (RCTs) that had a ≥30% failure rate were designed and strictly controlled to evaluate the frequency of complete wound closure at 12 and 16 weeks compared to SoC, but included a cohort of non-Medicare patients.[9,10] Our analysis of Medicare enrolees demonstrated that 10.9% of patients in the HOPD setting and 22.3% in the private office and post-acute care settings had claims that remained open after eight applications.

The future CAMP LCD further exacerbates this issue by imposing a rigid 16-week episode-of-care limit, which fails to account for real-world care delays (e.g., cellulitis or inpatient admission) and prematurely discontinues therapy in wounds that are responding but have not yet achieved closure. As highlighted in recent analyses, complex VLUs, which were defined as hard-to-heal VLUs that develop an infection, required significantly more healthcare resources and CAMP applications.[2,6] The study found that when adding one standard deviation to the mean number of CAMP applications, the total exceeded eight, demonstrating that many patients, particularly those with infections or other complications, need extended treatment beyond the imposed limits of the future effective CAMPs LCD. This arbitrary restriction not only increases the likelihood of treatment failure but also forces a shift toward more aggressive and expensive healthcare interventions throughout the patient's wound care continuum. Unfortunately, all CAMP-related expenditures in these failed treatment episodes are wasted, undermining both clinical outcomes and healthcare resource efficiency.

To calculate the total number of Medicare patients at risk after reaching application limitations without closure of their LEDU (Table 3), an extrapolation was made from the 2022–2023 population,[11] among which 31.8% of the

Table 3. Annual demographic at risk of not reaching LEDU closure at eight applications of cellular, acellular and matrix-like products in the HOPD setting

Parameter description	Factor	Population size, n
US population on 31 December 2022		335,453,105[14]
US Medicare population 2023		68,300,000[11]
US Medicare population with diabetes in 2022	31.8%[12]	21,719,400
Medicare patients who developed a LEDU	8.0%[13]	1,737,552
Patients with a LEDU which did not close after eight applications	10.9%[8]	189,393

HOPD—hospital outpatient department; LEDU—lower extremity diabetic ulcer

Table 4. Economic burden of non-healing LEDU episodes after eight applications of cellular, acellular and matrix-like products in the HOPD setting, 2022

Complication	% of LEDU population[4]	Projected cost per event, $ USD[4]	Projected total cost for patients with failed episodes care, $ USD
Major amputations	1.0	23,435	44,384,289
Hospitalisations	37.0	2097	146,948,265
Emergency department visits	30.0	8292	471,134,445
			662,466,999

HOPD—hospital outpatient department; LEDU—lower extremity diabetic ulcer

Medicare beneficiaries were projected to have diabetes.[12] An 8% subset was assumed to develop an LEDU,[13] and in the HOPD setting, 10.9% were expected to reach the eight application limit without ulcer closure, resulting in an annual at-risk Medicare population of 189,393.

Estimates were previously derived for patients whose ulcers may or may not close as part of a 2023 Markov model.[4] These values differed from clinical trial data and likely underestimated the number of patients who were slow responders to CAMP treatment (Table 4). Nearly 70% of patients are expected to have significant events if CAMP applications are halted at eight applications. The estimated cost of these events for 2022 is an astounding $662 million USD (Table 4).

For comparison, allowing medical necessity to determine whether additional applications are required, even two further applications for all 189,393 patients would cost $167 million USD less than the $662 million USD in complications at a reimbursement rate of $1307 USD per application.

This financial impact may be even more substantial if the estimates account for patients with VLUs, which are less prevalent but tend to require longer healing times. Medicare claims data from 2015–2020 indicate that approximately 20% of VLU episodes failed to close after eight CAMP applications.[6] Among those failed episodes that continued with the SoC alone, up to 2% underwent an amputation,[2] 12.2% were treated in the hospital setting,[7] and nearly 55% developed cellulitis.[2] When the costs associated with VLU-related complications are combined with the projected economic burden of LEDU complications, the financial impact of an eight-application limit is likely to exceed $1 billion USD annually.

Impact of the current CAMPs ASP reimbursement model versus a fixed-fee schedule

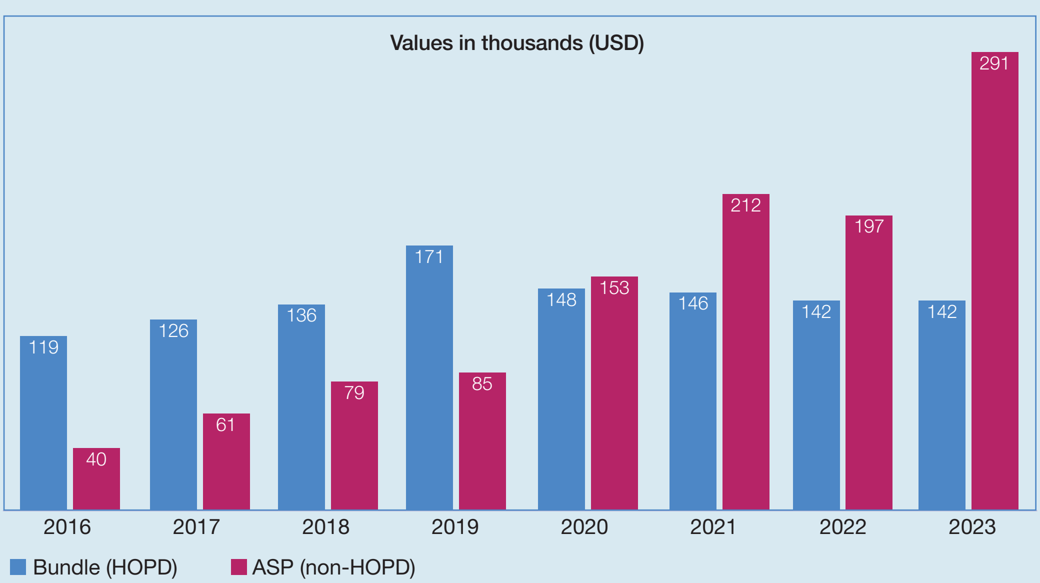
In 2025, there were calculated to be 221 CAMPs with Healthcare Common Procedure Coding System codes assigned by CMS: 23 with an A code; and 198 with a Q code. CAMPs scheduled for reimbursement by CMS can be found in CMS's ASP pricing file (https://www.cms.gov/medicare/payment/part-b-drugs/asp-pricing-files).

Based on 2023 Medicare claims data, 432,450 CAMP applications, excluding powders and flowables, were performed on hard-to-heal wounds, with 67.3% occurring outside the HOPD setting (Fig 1). Once the future effective CAMPs LCD is fully implemented in its current form, approximately 64% of CAMP technologies (275,471 applications based on 2023 HOPD, private office and post-acute care Medicare claims data) will be eliminated as a treatment option. This includes the loss of 72% of CAMP applications in private office and post-acute care settings (non-HOPD) and 28% in the HOPD setting, resulting in a significantly skewed delivery of care (Fig 2).

In the short-term, a reduction in reimbursed CAMPS will lead to product shortages, such as placental-derived human allografts, primarily due to the need to scale up manufacturing capacity for the remaining 17 of the 221 commercially available CAMPs listed as covered in the future effective CAMPs LCD. These shortages are yet another example of the unintended consequences of a poorly designed future effective CAMPS LCD, which is likely to create additional barriers to patient access and negatively affect outcomes for this at-risk population.

Given the current concerns of wound care providers in private offices and post-acute care settings that use

Fig 1. Cellular, acellular and matrix-like product (CAMP) applications by place of service and year, derived from 2016–2023 Medicare claims data. ASP—average sales price; Bundle—reimbursement is provided as a lump sum to the HOPD for a particular procedure, rather than a separate reimbursement for the CAMP product itself. HOPD—hospital outpatient departments



CAMPs with high ASPs, a comparison was performed using a weighted average ASP based on the 2023 Medicare claims data. The average weighted reported ASP in the non-HOPD setting for 2023 was \$828 USD/cm^2, ranging from an ASP of \$7.39 USD/cm^2 to \$13,116.92 USD/cm^2. This represents a total spend of \$3,883,091,207 USD on CAMPs by CMS in 2023.

Reimbursement for CAMPS should be guided by a multifactorial approach that encourages innovation while ensuring cost containment across the industry. A tiered reimbursement system may be necessary to balance these goals. For example, adopting a fixed-fee schedule model at \$828 USD/cm^2 would represent a break-even point in expenditures relative to CMS's total spending on CAMPs in 2023. While setting an ASP of \$400 USD/cm^2 may be considered a reasonable benchmark, as approximately 50% of CAMPs reimbursed by CMS in 2023 were priced close to or below this level. At this rate, a \$400 USD/cm^2 capitated cost would lead to substantial savings for CMS, with an estimated annual saving of \$2.01 billion USD in Medicare expenditures, representing a reduction of >51% in Medicare spending on CAMPs (Fig 3).

Compared to the reported ASP system, bundled payment models, which assign a fixed cost regardless of wound size or complexity, have faced criticism, including from CMS (calendar year 2023 payment rules). These models have been found to discourage HOPD-based providers from treating more extensive wounds (≥26cm^2, especially those exceeding 100cm^2) due to financial losses. Expressly, when the cost of CAMPs required for adequate surface area coverage exceeds the fixed bundled reimbursement, the HOPD wound clinic itself incurs a financial loss, leading to reluctance to treat such cases.

One consideration is that a fixed-fee solution could be implemented by generating temporary per cm^2 G-codes to replace the current procedural terminology (CPT) codes for CAMPs application procedures. The 'G' in

Fig 2. Total cellular, acellular and matrix-like products (CAMPs) applications in 2023 subjected to proposed Local Coverage Determination restrictions. CAMPs that remain covered (red) represent only 36% of ASP in the non-hospital outpatient department (HOPD) setting for 2023. CAMPs that are proposed to be eliminated (blue) represent 64% of all 2023 applications, of which 72% were provided in non-HOPDs. Non-HOPD settings include Medicare private office and post-acute care settings

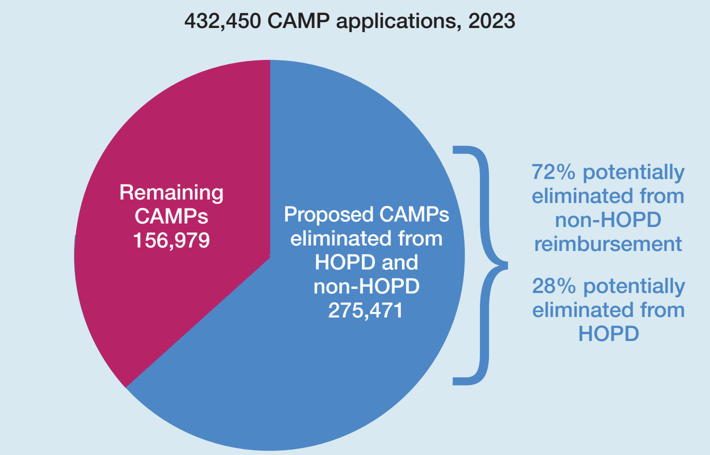
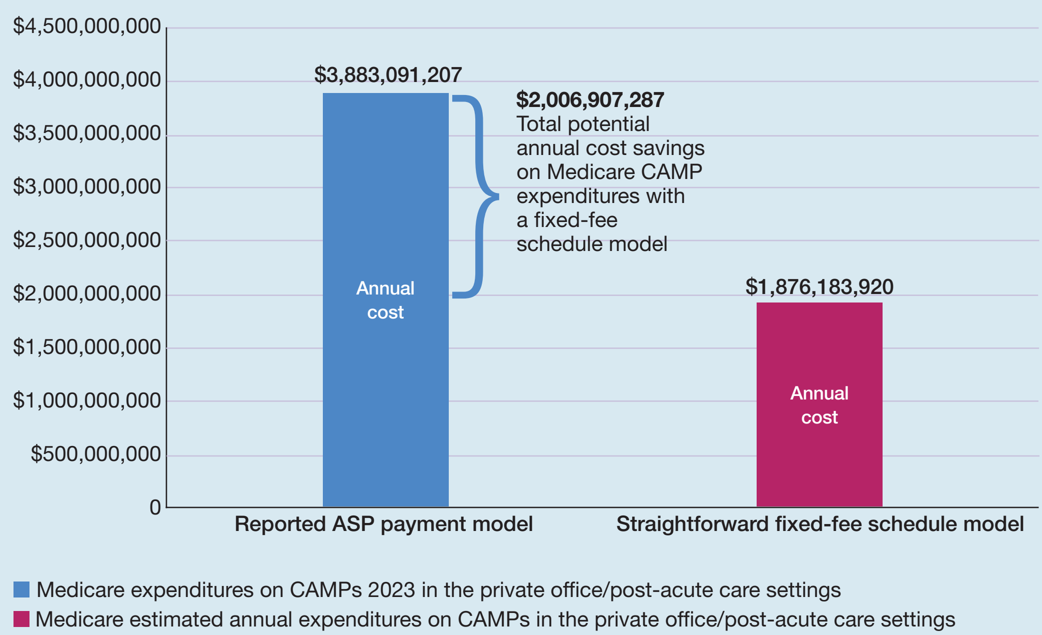


Fig 3. Cost comparison of Medicare cellular, acellular and matrix-like product (CAMP) expenditures (in USD): reported average sales price versus fixed-fee schedule model (2023 Medicare claim data). ASP—average sales price



G-codes, part of the Healthcare Common Procedure Coding System, signifies temporary codes used by Medicare to report and reimburse specific procedures, services and quality measures that do not have equivalent CPT codes. Q-codes for individual products would remain for data tracking purposes but would be billed at a zero-dollar amount. G-codes could be billed in 1cm² increments to match the wound size, ensuring appropriate reimbursement.[15] This approach would enable CAMPs to be categorised into specific classifications, allowing products to be compared to similar ones and priced accordingly. Compared to the current ASP fee structure, a fixed reimbursement per cm² for each G-code, calculated based on the average of all reported ASPs within comparable classifications, could save CMS hundreds of millions of dollars annually, and eliminate the inefficiencies of both the ASP and bundled payment processes, yet allowing access to CAMPs to beneficiaries requiring this advanced modality.

These approaches highlight the dramatic potential for cost containment in Medicare CAMP-related expenditures by transitioning to a fixed-fee schedule model without having to implement restrictive policies that have the potential to impact Medicare beneficiaries unfavourably.

Discussion

The economic impact of limiting CAMPs applications to eight per 16-week episode of care for patients with either a LEDU or VLU is substantial.[16,17] With up to 30% of patients experiencing treatment failure due to these restrictions, additional healthcare interventions, including costly amputations and hospitalisations, will become necessary. A comparative analysis of the current reported ASP reimbursement system versus a fixed-fee schedule model demonstrates the need for policy adjustments. Under the current ASP reporting structure, Medicare expenditures for CAMPs in 2023 totalled >$3.8 billion USD, which was further exacerbated by inconsistent manufacturer-reported pricing. In contrast, a fixed-fee schedule model (i.e., $400 USD/cm^2) would have reduced these expenditures to $1.9 billion USD, achieving an annual cost saving of >$2.0 billion USD, an overall 51.7% reduction. A fixed-fee schedule model offers predictable, controlled costs while preserving access to essential wound care treatments. Moreover, it would enable providers to treat multiple ulcers and more extensive wounds concurrently rather than adhering to a rigid and inflexible 'one-size-fits-all' reimbursement policy. Expanding coverage to permit ongoing CAMP applications based on clinical response and medical necessity is a logical step towards balancing cost containment with effective patient care.

Treatment limitations invariably induce disparities, particularly for high-risk populations. For example, a retrospective analysis of VLU outcomes revealed that Medicare/Medicaid dual enrolees frequently encounter more substantial socioeconomic barriers and experience significantly poorer clinical outcomes, including lower ulcer healing rates, higher infection rates and increased overall healthcare use.[5] Restricting the number of CAMPs applications under the future effective CAMPs LCD will disproportionately impact vulnerable patients, leading to increased numbers of amputations, hospitalisations and emergency department visits. Given that those dual enrolees required an average of 21 additional days for VLU closure and experienced higher complication rates,[5] similar adverse outcomes can be anticipated under the proposed CAMPs restrictions. The financial burden of delayed healing and increased complications would likely offset any intended cost savings of the LCD, ultimately driving up overall Medicare expenditures.

The proposed LCD's restrictions also fail to align with evidence-based best practices and create avoidable complications by prematurely terminating treatment, solely in the name of cost savings, for patients whose wounds are responding but not yet fully healed.[16,17] The policy allows for up to eight applications within the 16-week episode of care, with a KX modifier (a claim description indicating medical necessity and the justification for continued care) after the fourth application. However, it provides no option to continue treatment beyond the specified eight applications, even for complex wounds that demonstrate slow but progressive healing or when a healthcare provider determines it is medically necessary to avoid further complications. Wound care experts widely support an individualised approach, as highlighted during a townhall session at the CAMPs Wound Care Summit 2025 (28 February–2 March, 2025, Fort Lauderdale, FL, US) where both wound care providers and industry leaders advocated for the removal of rigid application limits in favour of evidence-based, patient-specific treatment pathways. Moreover, the proposed fixed-fee schedule model would eliminate the administrative burden associated with calculating and enforcing a rigid 16-week episode of care. This change would streamline reimbursement processes, reduce provider confusion and align payment models more closely with real-world clinical care timelines.

Achieving optimal clinical outcomes with CAMP therapy will not be possible unless the CAMPs LCD, entitled *Skin Substitute Grafts/Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers*,[18] is rescinded. In concert, CMS should convene a panel of clinically active wound care experts who have produced peer-reviewed publications in advanced wound care to develop a new National Coverage Determination (NCD) focused exclusively on CAMPs, accompanied by a separate coverage determination addressing general wound and ulcer care. A model similar to the LCD published by Medicare Administrator Contractor, Noridian, *Wound and Ulcer Care* (L38904), should be considered.[18] The revised framework for wound and ulcer care should prioritise evidence-based best practices to drive wound bed preparation, including the incorporation of endorsed screening techniques for haemodynamic and tissue perfusion assessments. In parallel, the CAMPs coverage determination should focus more specifically on contraindications for CAMPs use, treatment initiation criteria, timely initiation of CAMPs,[19] routine application following initiation[19] and clear parameters for discontinuing CAMPs in non-responsive cases.

A strong foundation in wound bed preparation is essential for optimising treatment outcomes with CAMPs. A retrospective study analysing Medicare claims data (2015–2019) and multicentre prospective RCTs found that ulcers receiving frequent debridement at intervals of ≤7 days had significantly improved healing rates, lowered amputation risks and reduced hospital resource use.[20] Among LEDUs, routine debridement combined with CAMP therapy resulted in 65% fewer major amputations ($p<0.0001$) and 42% fewer emergency department visits ($p<0.0001$).[21] Additionally, a standardised, evidence-based debridement protocol increased wound closure rates to 74%, compared to only 21% in ulcers with inadequate debridement.[20] Advanced imaging technologies can further enhance wound bed preparation by guiding clinicians in optimising bioburden removal and ensuring adequate perfusion.[20] Standardising debridement practices as a prerequisite to CAMPs therapy could improve healing outcomes and reduce overall Medicare expenditures by preventing complications. The widely accepted principle that clinical outcomes improve with provider education and training is particularly relevant to the use of CAMPs. Demonstrating competency in CAMPs-specific knowledge and skills can be achieved through certification, such as a Certificate of Added Qualification offered by a recognised certifying organisation.

Despite the critical role that CAMPs play in treating complex wounds, the current future effective CAMPs LCD neglects to address a significant patient population, those with hard-to-heal pressure injury ulcers. Each year, an estimated 2.5 million individuals in the US develop pressure injury ulcers, leading to substantial morbidity and healthcare costs.[22] The potential exclusion of credentialled wound care professionals from determining the medical necessity of CAMPs for hard-to-heal pressure injury ulcers is especially troubling. Without a clear medical necessity provision, clinicians lack the guidance needed to determine appropriate use beyond non-LEDUs and VLUs. This ambiguity, coupled with uncertainty about future CMS audits, effectively restricts access for the patients who need treatment the most. In post-acute care settings, where hard-to-heal pressure injury ulcers are frequently encountered, the absence of policy guidance is likely to delay healing, increase hospital readmissions and drive up overall healthcare costs.

A comprehensive, evidence-based approach to wound care should drive Medicare policy. Policy development should incorporate the findings of large retrospective analysis of Medicare enrolees and real-world registries in addition to RCTs. Real-world data provides important perspectives on patient outcomes, costs and point-of-service issues that are often overlooked in an RCT. Establishing a separate, revised NCD for CAMPs, distinct from a broader wound and ulcer coverage determination, would provide a framework for determining when CAMP therapy is appropriate, when it should be discontinued, and how to ensure just access for complex, non-healing wounds. The establishment of an NCD, rather than multiple LCDs, will promote socially equitable, uniform coverage across the US. An example occurred previously with hyperbaric access under an NCD implemented on 18 December 2017.[23] Without these critical updates, the future effective CAMPs LCD will fail to achieve cost savings and worsen clinical outcomes for some of the most vulnerable patient populations.

Conclusion

The future effective CAMPs LCD represents a fundamental shift in Medicare reimbursement that could significantly undermine patient care and increase long-term healthcare costs. By limiting CAMPs applications to eight per 16-week episode of care, the policy eliminates the ability of treating providers to determine medical necessity for patients who require continued treatment. The present one-size-fits-all approach disregards clinical evidence demonstrating that many hard-to-heal wounds require extended therapy to achieve closure, prevent complications, and reduce costly interventions, such as amputations and hospitalisations.

Policy adjustments should prioritise real-world clinical evidence supporting the effectiveness of CAMPs in improving patient outcomes. Implementing a fixed-fee schedule model, rather than restricting treatment options, would allow for cost control while maintaining access to necessary interventions. This framework would empower providers to tailor treatment plans based on patient-specific needs, ensuring optimal healing trajectories and reducing the economic burden of wound care on the Medicare system. Ultimately, the forthcoming CAMPs LCD does not offer a long-term solution to the issue of high-ASP CAMPs. A solution is necessary since a new wave of ‘me-too’ products will enter the market as manufacturers complete required RCTs for CAMPs projected as non-covered CAMPs. Thus, CMS may see a resurgence in elevated ASPs in the coming 2–4 years, recreating the cost challenges we currently face.

Another consideration regarding the future effective CAMPS LCD is the exclusion of allowing frontline wound care providers to determine ‘medical necessity’. This will most likely create a critical gap in the treatment of pressure injury ulcers due to uncertainty in the proposed policy and stance on future audits. With 2.5 million patients developing pressure injury ulcers annually,[22] failure to provide access to a clinically proven therapy, particularly in the post-acute care settings, will likely result in delayed healing, increased hospital readmissions and higher Medicare expenditures. The policy should be revised to reflect the medical necessity of CAMPs for pressure injury ulcers and other hard-to-heal wounds that extend beyond LEDUs and VLUs.

To ensure an effective, evidence-based wound care policy, CMS must retire the current CAMPs LCD and engage wound care experts with clinical and research expertise in developing an NCD that aligns with best practices. A comprehensive, patient-centred approach will preserve limb function, prevent unnecessary hospitalisations, and ultimately reduce overall healthcare costs, while ensuring that Medicare beneficiaries receive the highest standard of wound care available. **JWC**

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The impact of dual-enrolee (Medicare/ Medicaid) status on venous leg ulcer outcomes: a retrospective study

Objective: To quantify race, sex, comorbidities, Medicaid status, and compare health outcomes for Medicare-only versus Medicare/Medicaid dual-enrolees who developed a hard-to-heal venous leg ulcer (VLU).
Method: Medicare Limited Data Standard analytic hospital inpatient and outpatient department files were used to follow episodes of medical care for a VLU from 1 October 2015–2 October 2019. In an earlier study, patients diagnosed concurrently with chronic venous insufficiency and a VLU were propensity-matched. In this current work, cohorts were split into patients enrolled in Medicare-only and those enrolled in Medicare and Medicaid (dual-enrolees). Treatment methods were compared and the most commonly used cellular, acellular and matrix-like product (CAMP) among Medicare beneficiaries—dehydrated human amnion chorion membrane (DHACM)—was evaluated. Episode claims were used to document demographics, comorbidities and treatments of Medicare enrolees who developed VLUs and outcomes such as time to ulcer closure, rates of complications and hospital usage rates. Quality of life (QoL) metrics, such as pain and time to VLU closure, were compared across the groups.
Results: Of the 555,284 Medicare beneficiaries evaluated in this analysis, 27% were Medicare/Medicaid dual-enrolees and 73% were Medicare-only enrolees. To qualify for Medicaid, patient income had to be ≤133% of the federal poverty level. Only 3% of Medicare-only patients and 6% of dual-enrolees had an Advantage plan, a lower rate than the general Medicare population. Dual-enrolees, compared to those covered by Medicare-only, demonstrated: a Charlson Comorbidity Index (CCI) score one point greater (p<0.0001); a higher percentage (16%) of patients from minority ethnic backgrounds; and significantly higher rates of emergency department visits (p<0.0001) and cellulitis (p=0.034). Dual-enrolees who received early and regularly applied CAMPs also reduced their treatment time by 21 days (p=0.0027), all of which can impact costs.
Conclusion: The socioeconomic status of dual-enrolees included near poverty status, a higher percentage of patients from a minority ethnic background, and high rates of comorbidities compared to their Medicare-only counterparts. The VLUs of dual-enrolees took longer to close, developed more complications, and used significantly more hospital resources and expenses. Outcomes significantly improved when VLU episodes were treated with a CAMP, such as DHACM, while following parameters for use. Socioeconomic variables are associated with poor outcomes for patients with hard-to-heal (chronic) wounds. This should be tracked to find cost-effective interventions throughout their journey to provide equitable care and ensure they are not left behind. Greater access for dual-enrolees to CAMPs has the potential to improve clinical outcomes and patient QoL, while concomitantly reducing overall healthcare expenditure.
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CAMP • cellular, acellular and matrix-like product • dehydrated human amnion chorion membrane • Medicaid • Medicare • skin substitutes • social determinants of health • wound • wound care • wound dressing • wound healing

Social determinants of health (SDOH) have risen to the forefront as an important key to improving healthcare for all recipients. The impact of race, ethnicity, sex, socioeconomic status, disability status, accessibility to healthcare, literacy and cultural language used to access care providers, as well as economic resources, significantly impact personal vitality.[1] With every innovative technology, treatment or change to the healthcare system, there may be a group of patients for whom access becomes more challenging. Patients with hard-to-heal (chronic) wounds are a particularly vulnerable group who face physical limitations of mobility, social support and often emotional withdrawal,[2] which reduces their motivation to engage with the healthcare system. This study builds on analyses of the health outcomes[3] and cost-effective treatments for Medicare enrolees,[4] examining how key SDOH among 500,000 Medicare enrolees who developed a venous leg ulcer (VLU) impacted treatment outcomes.

It is estimated that 500,000–600,000 people develop a VLU annually in the US.[5] Wound cases increased from 8.2 million to 10.5 million Medicare beneficiaries during 2014–2019, while costs decreased from $102.6 billion USD to $67.2 billion USD during the same time period. However, beneficiaries with VLUs and associated infections were an outlier to this trend, increasing in frequency and cost during this five-year period.[6]

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Patients with venous insufficiency enter an episodic cycle of ulceration, infections, hospitalisations and additional VLUs,[3] which dramatically affects their quality of life (QoL). Dual-enrolees have several documented SDOHs that negatively affect their QoL. Specifically, in terms of socioeconomics, they have an average income of ≤133% of the federal poverty level, which is further compounded by coinciding medical comorbidities. The recent publication of 854,266 VLU episodes among Medicare beneficiaries provided an opportunity to compare dual-enrolees with those covered by Medicare only.[3,4] Previously, propensity-matched groups were split into Medicare-only and dual-enrolee groups,[3,4] allowing for a quantitative comparison of health outcomes and a discussion of patient QoL.

The effects of VLUs on patients' QoL have been studied. UK researchers used European Quality 5-Dimensions (EQ-5D) surveys to evaluate patients with VLUs (n=80). They measured five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) on a scale between 0 (death) and 1 (perfect health) and calculated a score of 0.62 associated with VLUs.[7] One study has shown that QoL can be significantly predicted based on patient activities, psychology and symptoms.[8] Important variables included: venous clinical severity score; pain; fatigue; marital status; and depression, and these predictors were able to serve as the basis of interventions for patients with VLUs (n=167).[8] Significant relationships were found between delayed ulcer healing, decreased QoL, moderate-to-severe pain, depressive symptoms, and fatigue or sleep disturbance (n=247).[9] Australian researchers have shown that QoL scores were significantly higher when patients with a VLU received optimal care (consisting of guideline-based compression stocking use and specialist intervention as warranted) compared with usual standard of care (n=80). Optimal care also improved the time spent healing and reduced the costs.[7] Thus, researchers have shown significant links between patients developing VLUs and poor outcomes. Despite these analyses, a large US study has not been undertaken to examine the impact of dual-enrolee status on VLUs.

This study evaluated an efficacious treatment for VLUs using a placental allograft.[3,10] Large retrospective Medicare studies demonstrated superior diabetic foot ulcer (DFU) and VLU clinical outcomes when using a placental-derived cellular, acellular and matrix-like product (CAMP), such as dehydrated human amnion/chorion membrane (DHACM), compared with enrolees who did not receive a CAMP during the observed treatment episode,[3,11] and concluded that DHACM was cost-effective at any willingness to pay level for patients with DFUs,[10] and should be a dominant treatment for those with either DFUs or VLUs.[4,10]

Methods

Product statement

This study evaluated an efficacious treatment for VLUs using DHACM (EPIFIX; MIMEDX Group Inc., US), the single most widely used high-reimbursement group CAMP in Medicare for DFUs and VLUs during 2015–2019.[3,10]

Ethical approval and patient consent

This retrospective Health Insurance Portability and Accountability Act (HIPAA)-compliant study was exempted from internal review board, as the Medicare LDS was previously collected, deidentified, and is available from the Centers for Medicare and Medicaid Services (CMS). All analysis and reporting of Medicare data was performed in compliance with relevant laws and institutional guidelines approved by the CMS. Consequently, no ethical approval or patient consent was necessary.

Data source and study design

The Medicare Limited Data Set (LDS) files (1 October 2015–2 October 2019) were acquired under a Data Use Agreement.

Medicare LDS analytic hospital inpatient and outpatient department files were used to retrospectively analyse patients with chronic venous insufficiency (CVI) who received medical care for a VLU between 1 October 2015–2 October 2019, as previously published.[3] Patients diagnosed with CVI and a VLU for 90 days from the initial claim submission were identified as having hard-to-heal VLUs. Episodes remaining after exclusions were referred to as the eligible hard-to-heal VLU group and were propensity-matched into four groups:[3]

- Group 1: those provided with an advanced treatment (AT) (n=30,547) matched to those who received no AT
- Group 2: those provided with DHACM (n=7567) matched to other ATs
- Group 3: those following parameters for use (FPFU) (n=6546) matched to those who did not
- Group 4: those provided DHACM FPFU (n=1946) matched to those who did not.

Each propensity-matched group was then split into those covered by Medicare-only or dual-enrolees. Episode claims were used to document demographics; the recorded International Classification of Diseases, 10th Revision/Diagnostic Related Groups (ICD-10/DRG) codes identifying comorbidities and Current Procedural Terminology/Healthcare Common Procedure Coding System (CPT/HCPCS) codes were

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Fig 1. Medicare patients with venous insufficiency enter a downward cycle of ulceration, infections, hospitalisations and recurrence.[3] Claims data were used to determine the demographics of patients with venous insufficiency and the complications for the 42–49% who develop venous leg ulcers. CCI—Charlson Comorbidity Index; ED—emergency department; VLU—venous leg ulcer. *Medicare rates in VLU metagroup=555,284 patients. †Medicare rates in propensity matched group 1=30,547 episodes

2015–2019
1,255,278 Medicare patients with venous insufficiency

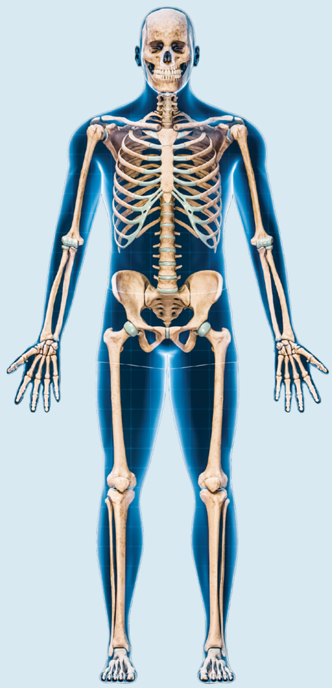
Medicare-only 948,282

43% develop a VLU*

404,834 patients*
Mean age of 75 years
89% white
50% female
Mean CCI=2.7
44% with diabetes
3% with Advantage plan

Mean 2.1 VLU episodes
2.6% amputation†
16% pain†
27% complication†
50% ED visits†
1.3 hospital visits each†

75% wound closure at 1 year†
51.6% developed another VLU*



Dual-enrolee 306,996

49% develop a VLU*

150,450 patients*
Mean age of 67 years
73% white
51% female
Mean CCI=3.7
59% with diabetes
6% with Advantage plan

Mean 2.3 VLU episodes
4.8% amputation†
22% pain†
44% complication†
84% ED visits†
1.6 hospital visits each†

69% wound closure at 1 year†
59.6% developed another VLU*

Fig 2. Infection and complication rates were statistically highest for venous leg ulcer episodes covered by Medicare and Medicaid (dual-enrolees in dark coloured bars) compared to Medicare-only covered episodes (light coloured bars, p-values provided above bar). When episodes were treated with dehydrated human amnion/chorion membrane (DHACM) following parameters for use (pink bars), complication rates were lower than those provided with no advanced treatment (NAT) (blue bars). Total complications included every measured event across all episodes and revealed a difference between dual-enrolees who received NAT or DHACM (p=0.08364) or Medicare-only patients who received NAT or DHACM (p=0.00252)

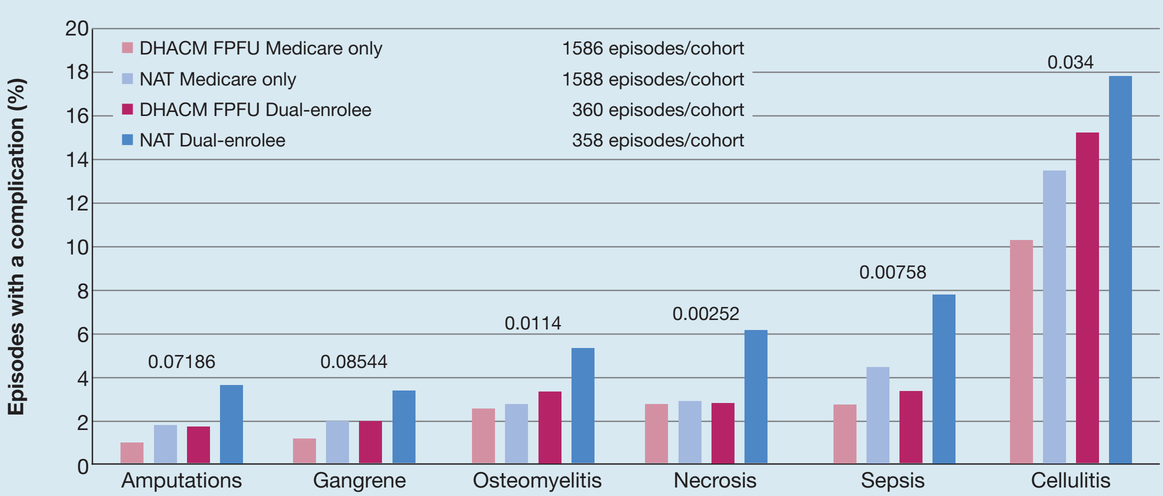


Table 1. Venous leg ulcer treatments for Medicare enrolee subgroups

Adjunct treatments	Metagroup		NAT		DHACM FPFU	
	614,102 episodes	240,164 episodes	1588 episodes	358 episodes	1586 episodes	360 episodes
	Medicare-only	Dual-enrolee	Medicare-only	Dual-enrolee	Medicare-only	Dual-enrolee
Debridement	17.3%	18.5%	71.5%	74.9%	75.7%	75.8%
Combination treatments	16.7%	17.8%	58.4%	65.1%	65.6%	65.3%
High compression bandage	16.4%	17.6%	57.6%	64.2%	65.2%	64.4%
Axial venous closure	0.5%	0.5%	2.0%	0.8%	1.6%	1.4%
Compression stockings	0.0%	0.0%	0.1%	0.0%	0.2%	0.6%
Advanced treatment	5.8%	5.1%	0.0%	0.0%	100.0%	100.0%
Negative pressure wound therapy	0.5%	0.5%	1.1%	1.7%	1.6%	0.6%
Mean Charlson Comorbidity Index Score	2.7	3.7	2.1	2.5	2.0	2.7

Metagroup (n= 555,284 patients with 854,256 episodes). DHACM—dehydrated human amnion/chorion membrane; NAT—no advanced treatment; Current Procedural Terminology codes: Debridement: 11042–11047, 15002–15005, 97597, 97598, 97602; Compression: A4490–A4510, A6530–A6541, A6544, A6545, A6549; Axial venous closure: 36465–36466, 36473–36479, 36482, 36483, 37700, 37718, 37722, 37735, 37760, 37761, 37780; High compression bandage: 29580, 29581; Negative pressure wound therapy: A9272, 97605–97608

used to list treatments for Medicare enrolees who developed VLUs. Outcomes, such as length of VLU treatment, rates of complications, hospital usage rates, and QoL metrics (i.e., pain) were compared across propensity-matched groups.

The income level of dual-enrolees was assumed to follow Medicaid financial eligibility guidelines determined by the Affordable Care Act threshold of ≤133% of the federal poverty level, with a few exceptions for disability and age.[12] States were able to extend coverage below the federal poverty level, which was set to a low of $11,770 USD for an individual in 2015 and a high of $25,750 USD for a family of four in 2019.[13]

Results

Financial status, demographics, ulcer progression

In the VLU-metagroup (555,284 patients who developed a VLU), 150,450 (27%) patients were dual-enrolees (Medicaid and Medicare), and only 6% of dual-enrolees had an Advantage plan (Fig 1). Medicaid eligibility rules require the enrolee to earn ≤133% of the federal poverty level.[12] In 2015, this equated to an income no higher than $16,243 USD for an individual in comparison to the US census median household income of $56,516 USD[14] at that time. At the higher end, 133% of the federal poverty level for a family of four was $34,248 USD in 2019, compared to that year's median household income of $68,703 USD.[15]

Fig 3. Dual-enrolees had the highest hospital usage rates among the studied cohorts. The lowest hospital use (20–60% less) was observed among episodes covered by Medicare only using dehydrated human amnion/chorion membrane (DHACM) following parameters for use (FPFU). Total hospitalisation included all intensive care unit (ICU) stays, readmissions, admissions and emergency department (ED) visits from all episodes, which exceeded an average of once per episode. dual-enrolee—Medicare+Medicaid; NAT—no advanced treatment

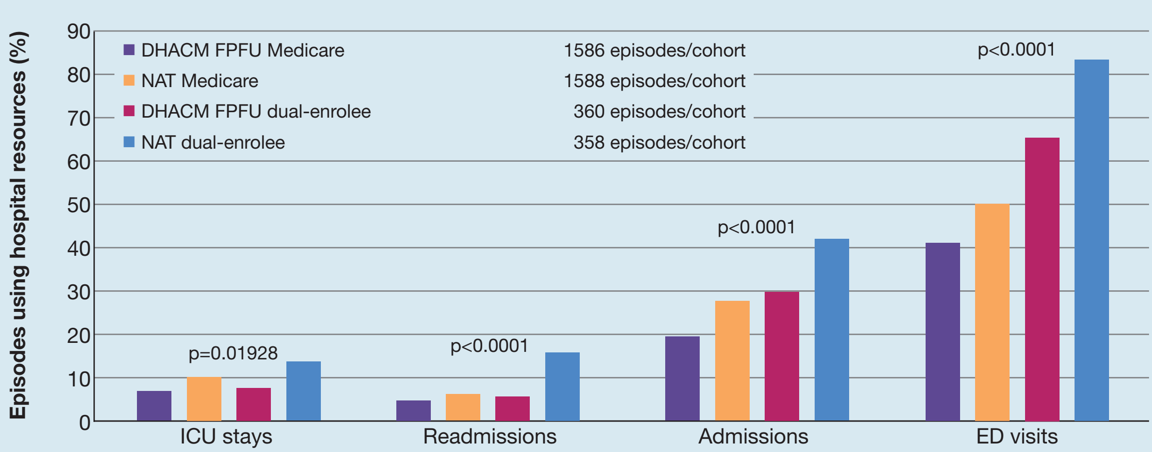


Table 2. Length of treatment and application patterns

Study group	Medicare-only		Dual-enrolee		Medicare-only		Dual-enrolee	
Coverage	NAT	All CAMPs FPFU	NAT	All CAMPs FPFU	NAT	DHACM FPFU	NAT	DHACM FPFU
Patients, n	5267	5145	1214	1219	1582	1557	358	350
Episodes, n	5325	5286	1221	1260	1588	1586	358	360
Mean applications, n	–	5.2	–	5.9	–	4.7	–	5.6
ALOT, days	107.9	99.4	150.2	128.9	109.8	95.1	138.7	125.5
p-value	0.0008		0.0027		0.0013		0.2683	

ALOT—average length of treatment; CAMPs—cellular acellular, matrix-like products; DHACM—dehydrated amnion/chorion membrane; dual-enrolee—Medicare+Medicaid; FPFU—following parameters for use; NAT—no advanced treatment

Among all eligible Medicare beneficiaries, 11% were from ethnic groups other than white, which increased to 27% among dual-enrolees. A higher proportion of patients who were dual-enrolees were of Hispanic (9.75-fold) or North American Native (5.3-fold) ethnicity. These findings alone underscore how socioeconomic status can disproportionately affect access to healthcare resources in various ethnic groups. The health status of all enrolees was evaluated by their average CCI. The CCI can be used to predict the 10-year mortality for a patient who may have a range of comorbid conditions. The mean CCI score for dual-enrolees was 3.7 compared to a significantly lower mean CCI score of 2.7 for those covered by Medicare-only (p<0.0001, Table 1).

The Medicare claims data also revealed that from 2015–2019, 42% of patients diagnosed with CVI developed a VLU (n=555,284). Within propensity-matched group 1 (n=30,547 episodes), wound closure rates after one year were 75% for the Medicare-only group and fell to 69% for the Medicare/Medicaid dual-enrolee cohort (p<0.0001) (Fig 1).

Cohort analysis and treatments received

This study analysed metagroup episodes (n=854,256), which were separated into those with only Medicare coverage (73%) or those with Medicare and Medicaid coverage (dual-enrolees, 27%). Further cohort divisions were based on the VLU treatment provided (full details of inclusion/exclusions, propensity-matching and pre-existing conditions were previously published).[3] VLU treatment of any type was substantially lower in the metagroup, as it was previously determined that approximately half of the episodes treated under standard of care resolved within 90 days of diagnosis without substantial intervention.[3] This analysis focused on episodes in which a CAMP, such as DHACM, was applied while FPFU and propensity-matched with a cohort in which no CAMP was used during the episode of care. DHACM was previously identified as the most commonly used CAMP among Medicare beneficiaries.

We initially validated 112,400 episodes for further analysis. Of these, 30,547 (27%) episodes were treated with an AT or CAMP, with 21.4% of the CAMP applications FPFU. DHACM FPFU was used in 1946 (1.7%) episodes. Patients who did not receive AT were assigned to the No AT (NAT) cohort. Other treatments for VLUs included debridement, combinations of compression, and axial venous closure (Table 1).

During VLU episodes of care, dual-enrolees were found to have statistically higher complication rates, such as cellulitis (p=0.034), sepsis (p=0.00758), and necrosis (p=0.00252), compared with the Medicare-only cohort (Fig 2, p-values above bars). The highest rates of complications occurred among dual-enrolees when episodes received NAT. Complication rates were lowest when patients received DHACM FPFU compared with NAT.

Episodes of care for dual-enrolees used more healthcare resources, statistically, than episodes covered by Medicare-only (Fig 3). For example, during episodes of care that did not use a CAMP, 84% of dual-enrolees, compared to 50% of Medicare-only covered patients, visited the emergency department (ED) (p<0001). ED use dropped even further to 41% when Medicare-only patients were treated with DHACM FPFU. When accounting for admissions, readmissions, ICU stays and ED visits, the average dual-enrolee episode not receiving CAMPs required 1.5 hospital visits compared to only 0.9 visits within Medicare-only episodes. For comparison, only 0.7 hospital visits were required when covered by Medicare-only and treated with DHACM FPFU.

Dual-enrolee episodes had the longest durations of VLU treatment compared with those covered by Medicare-only (Table 2). Dual-enrolee episodes were the longest when no CAMPs were used. Conversely, when CAMP applications FPFU were integrated into the VLU treatment episode, a reduction of 21.3 days to a total length of treatment of 128.9 days was observed (p=0.0027). When specifically provided DHACM FPFU (the smallest cohort), the treatment length was shortened to 125.5 days (p=0.2683). Episodes covered by Medicare-only were longest when not treated with a CAMP but dropped significantly to the shortest averages measured in the study when treated with DHACM FPFU (95.1 days versus 109.8 days, respectively, p=0.0013).

Discussion

The consensus approach to VLU treatment is routine wound cleaning, debridement and compression. If an open VLU does not close by 40% after three weeks, transitioning the patient to an AT, such as a CAMP, is warranted.[16] However, this only occurs in approximately one-in-five episodes among Medicare patients. Additionally, established practices, such as axial closure and compression stockings, are underused in VLU episodes (Table 1). Best practice and prophylactic treatments have proven cost-effective in the Medicare population. Any reduction of best practice among vulnerable populations perpetuates disparities in healthcare access issues. Policies that offer more substantial support for best practice could go far in improving wound care for all.

Dual-enrolees are generally a low-income group with an increased proportion of patients from ethnic minority groups. When dual-enrolees develop a VLU, their outcomes, including length of treatment, complications and use of hospital resources, are significantly worse than their Medicare-only counterparts. Patients with CVI experience cycles of ulceration, healing and recurrence (Fig 1), which can lead to increased pain,[3] odour, reduced mobility, social isolation, job loss, economic hardship and dependency on caregivers for activities of daily living.[17–19] Given the greater toll on outcomes for dual-enrolees (Fig 1), there are likely increased impacts beyond health outcomes—emotional, social, employment and overall health-related QoL.

Medicaid is intended to provide ‘safety net’ resources to US citizens with low incomes or certain disabilities. A national survey showed that while 75.6% of Medicaid beneficiaries <65 years were employed, 14.1% lost their employment before enrolment,[20] suggesting pressure on beneficiary working capabilities. Medicare Advantage plans can reduce costs and were present for 39% of the general Medicare beneficiaries in 2019,[21] but Advantage enrolment is 13-times lower for those who develop a VLU (Fig 1). Out-of-pocket copayments will vary depending on the presence of an Advantage plan, but payments are low or non-existent for Medicaid patients seeking wound care. Despite this benefit, the poor outcomes of dual-enrolees suggest other social determinants, such as greater disparities in care or access to care, also impact their health. It is also true that dual-enrolees have a higher number of comorbidities than the average Medicare-only beneficiary (Fig 1, Table 1), but poor outcomes are not inevitable.

Economics and comorbidities combined with other social determinants to impact the outcomes for the 150,450 dual-enrolees studied in this work. When dual-enrolees developed a VLU, they experienced longer periods of treatment (Table 2), higher rates of infection (Fig 2) and reported pain (Fig 1) more frequently on their claims. In comparison to their Medicare-only counterparts, dual-enrolee VLU closure rates were about 7% lower, and they were more likely to have another VLU despite being, on average, eight years younger (Fig 1). The improved outcomes demonstrated with the use of DHACM FPFU are not assumed to have ‘cured’ the social determinants that establish the status of a dual-enrolee. Rather, it reflects using an AT, such as a CAMP, applied by a knowledgeable provider, using good wound practices, and taking a genuine interest in their patient’s overall health.

The aspects of Medicaid enrolment that lead to poorer health outcomes push patients downward in the cycle. When a person with low income qualifies for Medicaid and requires time off work for a painful VLU, their treatment time is longer than for their propensity-matched Medicaid-only counterparts, resulting in greater impact to their income. Sitting at home leaves them focused on their situation. The odour and exudate of the wound can discourage them from socialising, yet they are increasingly dependent on family or caregivers for assistance. Once the wound closes, they are more likely to develop another VLU, and so the cycle continues.

There are likely many inflection points within prevention and treatment where the cycle can be alleviated. The most obvious is treatment for the VLU. Identifying that DHACM FPFU is associated with better outcomes for both Medicare-only and dual-enrolees suggests that the increased comorbidities, lower income, and higher rates of ethnic minority groups observed among dual-enrolees do not have to equate to poorer outcomes for this population. Indeed, while dual-enrolees who did not receive a CAMP had the longest length of treatment for closure of their VLU, the propensity-matched episodes using any AT were 21 days shorter ($p=0.0027$, Table 2). Closing wounds quickly reduced the opportunities for infections, as observed (Fig 2). Considering that patients treated with DHACM FPFU had the shortest average length of treatment among studied dual-enrolees and this has been shown to be cost-effective for the entire 112,400-episode cohort that included Medicaid patients,[4] the dual-enrolee subgroup objectively benefits most from DHACM FPFU. We note that the recent cost-effectiveness analysis only examined the costs of treating patients,[4] and not their loss of productivity or the costs to their family and care providers, which certainly bolsters the case for providing patients with advanced wound treatment.

Intervention in the VLU cycle may also be alleviated by other physical, psychological and social impacts, as well as alternative treatments.[17] Efforts on multiple fronts will likely be necessary to achieve health equity among Medicare enrolees: innovative policy development, especially related to coverage; geographical access to care; health workforce diversity; health literacy and education; community engagement; data collection; and monitoring. When VLU healing stalls, closing the wound as quickly as possible is important,[22] and DHACM FPFU generates significant improvements in wound closure times.

Limitations

All research based on claims data is sensitive to the accuracy of medical coding and while some reporting errors are certainly in the dataset, they are not likely to have a substantive impact on the outcomes.[23] Additionally, retrospective data is not appropriate for identifying causal relationships, but such large datasets are useful for generating hypotheses, as presented here. Assumptions are made on the qualifying factors of dual-enrolees, e.g., income levels and comorbidities. We note that various states have exceptions for income and disability; however, in general, the projected incomes are the highest to be expected for all but a minority of dual-enrolees.

Conclusions

Patients with dual-enrolee status have incomes ranging from slightly above, at, or below the poverty level, greater numbers of comorbidities, and are more than twice as likely to be from an ethnic minority group compared with Medicare-only enrolees. Their socioeconomic status is associated with VLU treatments that take longer to close, develop higher numbers of complications, and use significantly more hospital resources, resulting in greater expense. Many SDOHs impact their outcomes and are differentiated from patients covered only by Medicare. Outcomes improved when dual-enrolees were treated with a CAMP, such as DHACM, while FPFU. Socioeconomic variables are associated with poor outcomes for patients with VLUs and should be tracked to find opportunities, such as DHACM treatments FPFU, to improve health outcomes and QoL. SDOH deserves increased attention to improve patient outcomes. JWC

Reflective questions

- Compare the differences in the age, ethnic status and number of comorbidities of dual-enrolees to their Medicare-only covered counterparts?
- Are Medicare enrolees with venous leg ulcers (VLUs) missing opportunities for advanced treatments due to their eligibility or access to a specialist? And if so, how?
- What are common complications of VLUs among Medicare patients? How does this change for those covered by Medicaid? Why?
- Why are treatment lengths longer for dual-enrolees with VLUs?

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Bovine-derived collagen matrix as an adjunct in stage 3 pressure injuries: a case series of lower extremity wounds

Objective: Hard-to-heal (chronic) stage 3 pressure injuries (PIs) in medically complex patients are often refractory to standard treatments, and pose significant risks of infection, limb loss and diminished quality of life. Adjunctive use of advanced biologic materials, such as bovine-derived collagen matrices, may support more efficient wound resolution in these high-risk populations.
Method: In this retrospective case series, patients with hard-to-heal stage 3 PIs of the lower extremity were treated with a single application of a bovine-derived collagen matrix as part of a multidisciplinary wound care protocol. All patients had significant comorbidities, including diabetes and dementia, as well as mobility impairments, such as peripheral neuropathy and multiple sclerosis with paraplegia. Interventions included debridement, a single application of a bovine-derived collagen matrix, appropriate wound dressings and pressure offloading.
Results: All three patients (each with one PI) had failed to respond to prior standard wound care and their PIs had persisted from four weeks to approximately three years before treatment. Following a single application of the collagen matrix, complete wound closure was achieved within 27–52 days. Early wound responses were notable: one PI showed a 98% area reduction by day 14, another reduced by 76% by day 6, and in Case 2, closed by primary intention, stable closure was observed as early as day 3. No repeat applications of the bovine-derived collagen matrix were required, and no complications or recurrences were observed at follow-up.
Conclusion: This case series highlights the potential of bovine-derived collagen matrix as an effective adjunct to comprehensive wound care in medically complex patients with stage 3 PIs that have persisted for several months to years, despite prior standard treatments. In all cases, complete wound closure was achieved following a single application of collagen matrix, highlighting its potential utility in the management of hard-to-heal PIs. Further prospective studies are warranted to validate these outcomes.
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adjunctive wound therapy • bovine-derived extracellular matrix • collagen-based matrix • complex comorbidities • hard-to-heal wound • lower extremity ulcer • stage 3 pressure injury • wound • wound care • wound dressing • wound healing

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Pressure injuries (PIs), also referred to as bedsores, decubitus ulcers or pressure ulcers (PUs), are localised injuries to the skin and underlying soft tissue resulting from prolonged pressure and shear forces, predominantly over bony prominences.[1] In 2016, the National Pressure Injury Advisory Panel (NPIAP) introduced updated terminology, recommending the term ‘pressure injury’ to better reflect the full spectrum of tissue damage, including stages that occur before visible skin breakdown.[2] Although the term ‘pressure ulcer’ remains in common use, it is important to note that incidences of non-uniform loading, not just direct pressure, can cause reduced blood flow to the affected area and shear deformation of tissue, potentially leading to injury.[3] Symptoms include redness, pain and open sores, which can progress to deep wounds exposing muscle and bone.[4]

The development of PIs is complex and multifactorial, involving the interplay of intrinsic and extrinsic factors. Extrinsically, prolonged pressure, friction, shear forces and moisture contribute to tissue deformation and ischaemia.[1] Internally, a range of factors, including comorbidities such as diabetes, vascular and cardiovascular disease, neurologic disorders (e.g., multiple sclerosis (MS), peripheral neuropathy), malnutrition, anaemia, dehydration and impaired perfusion compromise tissue integrity and accelerate breakdown.[1] PIs result from sustained mechanical loading, including compression, tension and shear, that induce cellular deformation, ischaemia and soft tissue necrosis.[5] The risk is particularly high in individuals with limited mobility, such as older people, patients who are bedbound or individuals who are wheelchair-dependent. Additional contributors include hypotension, prolonged anaesthesia, recent surgery, and the use of medications (e.g., sedatives, vasopressors, corticosteroids and analgesics) that impair mobility, sensory feedback and circulation.[4,6,7] In healthcare settings, especially nursing

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homes, PIs remain a significant concern due to the high prevalence of frailty, immobility and chronic disease.

There are four recognised stages of PIs, classified by the NPIAP, based on the depth of tissue involvement.[1]

1. Stage 1 is characterised by intact skin with non-blanchable erythema
2. Stage 2 involves partial-thickness skin loss affecting the epidermis and dermis
3. Stage 3 involves full-thickness tissue loss that extends into the subcutaneous layer, without exposing muscle or bone
4. Stage 4 includes deeper tissue loss with visible exposure of muscle, bone or supporting structures.[1]

In addition to these, unstageable injuries involve full-thickness tissue loss where the wound bed is obscured by slough or eschar. Deep tissue PI is a separate category marked by persistent, non-blanchable, deep red, maroon or purple discolouration, typically resulting from pressure and shear at the bone–muscle interface.[1]

In patients with comorbidities or mobility impairments, these wounds often resist standard therapies due to impaired perfusion, repeated pressure, delayed immune response, poor tissue regeneration, and reduced ability of the patient to manage their care effectively. In the absence of timely and appropriate intervention, hard-to-heal PIs may undergo progressive staging, resulting in high healthcare costs, prolonged hospitalisation, deterioration in physical and psychological health, increased risk of infection and sepsis, and, in severe cases, extensive tissue destruction, limb loss or death.[8–11]

An estimated 2.5 million new cases of PIs occur annually in the US, representing the second-most common diagnosis across the national healthcare system.[11] The clinical and economic burden of PI management is substantial. Treatment costs per case vary widely—from approximately \$20,900 to \$151,700 USD, depending on severity. The annual national expenditure is estimated at around \$26.8 billion USD.[11,12] Stage 4 PIs, in particular, are associated with average hospital costs exceeding \$124,000 USD per episode and add more than \$11 billion USD to healthcare expenditures each year.[13] Healing trajectories are often prolonged; approximately 50% of stage 2 PIs and up to 95% of stage 3 and 4 PIs fail to achieve closure within eight weeks.[13] Moreover, stage 3 and 4 ulcers are frequently complicated by deep tissue infections, such as bacteraemia and osteomyelitis, which may become life-threatening without timely and advanced intervention.[13] Patients with PIs have increased healthcare use, including significantly higher 30-day hospital readmission rates, and experience a 2.81-fold increase in in-hospital mortality.[14,15] According to US Centers for Disease Control and Prevention estimates, approximately 60,000 deaths annually in the US are attributable to PI-related complications, underscoring their critical impact on morbidity and mortality within vulnerable populations.[11]

PIs most commonly develop over bony prominences subjected to prolonged pressure, such as the hips, sacrum, coccyx and heels, but can also occur on the feet and ankles.[16] When present in these locations, they may cause significant discomfort, pain and functional impairment. Foot-related PIs are particularly concerning due to their tendency to progress quickly and their impact on ambulation and quality of life (QoL). The heel is recognised as the second-most common site for PI development, but ulcers can form on any part of the foot. Contributing factors include poorly fitted footwear, prolonged pressure from bed sheets or mattresses, and limited offloading.[17] As discussed earlier, underlying chronic conditions, such as diabetes, peripheral artery disease and autoimmune diseases, can further compromise skin integrity and increase the risk of ulcer development.

Current standards of care (SoC) for PI management include cleaning, debridement to remove the necrotic tissues, and dressings to provide a moist wound environment. Addressing underlying aetiologies—such as correcting nutritional deficiencies and implementing frequent repositioning to offload pressure—is equally important to promoting tissue repair and preventing progression.[18] Advanced treatments, such as negative pressure wound therapy, cellular and tissue-based products, and surgical intervention, are often required for patients with stage 3 or 4 PIs, hard-to-heal wounds, or those with complicating factors, such as infection, extensive tissue loss or underlying comorbidities, that impair healing.[18,19] As the stage of a PI advances, achieving wound closure and meeting clinical goals become increasingly challenging. The presence of chronic conditions can further complicate treatment by interfering with the body's natural healing processes, impairing circulation, reducing immune response, and compromising tissue regeneration. Management becomes challenging in cases involving deep or tunnelling wounds, infection, heavy exudate, persistent inflammation, elevated proteolytic enzyme activity, and exposure of bone or muscle tissue.[18,19]

Bovine-derived collagen matrices have demonstrated efficacy as biological scaffolds in the treatment of hard-to-heal wounds, including PIs.[20,21] These matrices provide a structural framework that supports cellular infiltration, angiogenesis and extracellular matrix remodelling. By facilitating the body's natural fibroblast migration and deposition of new granulation tissue, collagen-based products contribute to the re-establishment of a functional dermal layer.[20,21] Their low immunogenicity, biocompatibility and ability to sequester proteases make them particularly useful in wounds that are stalled in the inflammatory phase or exhibit high proteolytic burden.[20,21] Several studies have evaluated the clinical efficacy of collagen dressings in hard-to-heal wound management.[22–26] A systematic review and meta-analysis encompassing 11 randomised controlled trials (RCTs) with a total of 961 patients found that the addition of collagen dressings to SoC significantly improved wound closure rates and reduced time to closure compared with SoC alone.[27]

More recently introduced for clinical use, the advanced bovine-derived collagen matrix HELIOGEN (MIMEDX Group Inc., US) is indicated for the management of moderately to heavily exudating wounds and to control minor bleeding. HELIOGEN may be used for the management of exudating wounds such as PUs, venous stasis ulcers, diabetic ulcers, acute wounds (such as traumatic and surgical wounds) and partial-thickness burns. It contains type I and type III collagen, providing a matrix that supports cell adhesion and migration into the wound site, thereby promoting re-epithelialisation and wound closure.[28] The matrix also possesses intrinsic haemostatic properties that assist in controlling minor bleeding. Its absorbent nature allows for effective management of wound exudate while maintaining a moist environment, optimal for closure. The matrix may be applied dry or in a hydrated paste form, depending on the clinical need.[28]

This case series evaluates the effectiveness of a single application of bovine collagen matrices for hard-to-heal stage 3 PIs in medically complex patients with multiple comorbidities and significant mobility impairments, where the extent of full-thickness tissue loss conferred a high risk for secondary infection, delayed wound closure, and progression to more severe tissue damage and escalation of wound severity.

Method

Patient selection

Patients with hard-to-heal stage 3 PIs on the foot or lower extremity were retrospectively identified from a single physician practice in the US, with all procedures performed by the same attending surgeon. All patients exhibited profound mobility impairments and multiple comorbidities known to impair wound healing. The inclusion criteria were as follows:

- Stage 3 PIs, classified according to NPIAP guidelines, characterised by full-thickness tissue loss
- Hard-to-heal ulcers refractory to SoC therapies
- Underlying conditions impairing wound healing, e.g., MS, diabetes, neuropathy, dementia or prior amputations
- Wounds located on high-pressure areas of the foot or lower extremity, including metatarsal heads and amputation stumps.

Ethical statement and patient consent

All procedures were performed in accordance with the ethical standards of the respective institutions involved and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Institutional review board (IRB) approval was not applicable, as the study involved a retrospective review of data from three deidentified patients. This meets common criteria for exemption from IRB review, as such small case series are not considered human subjects under U.S. federal regulations (45 CFR 46.102).[29]

Written informed consent was gained from the patients for the publication of photographs and use of their data with the understanding that this information may be made publicly available.

Treatment protocol

All patients underwent initial surgical preparation, which included sharp debridement of devitalised tissue. In two cases, additional offloading surgical procedures were performed (fifth metatarsal head resection or exostectomy) to relieve localised pressure. After achieving a clean, viable wound bed with evidence of active bleeding, a single application of dry bovine-derived collagen matrix (500mg, single-use unit) was made to the wound surface. Following collagen matrix application, the wounds were dressed with a non-adherent layer (e.g., Adaptic (CURITY; Cardinal Health, US)), sterile gauze, and secured with a Kerlix (Bulkee II; Medline Industries, China) gauze wrap to maintain a moist wound environment. In one patient, wound edges were re-approximated with sutures to facilitate closure.

Postoperatively, all patients were maintained on strict non-weight-bearing protocols using wheelchairs, controlled ankle motion (CAM) boots or diabetic healing footwear, as appropriate, to ensure pressure offloading at the wound site. Patients were instructed on offloading strategies and monitored regularly with serial wound assessments to evaluate closure progression. No additional applications of extracellular matrix were performed.

Outcome measures

The primary outcome was the time to complete wound closure, defined as full re-epithelialisation with no drainage and no need for further surgical intervention. The secondary outcomes included the presence or absence of wound-related complications, such as secondary infection, wound dehiscence, or the need for additional surgical procedures (e.g., amputation), as well as the durability of closure observed during follow-up when available.

Statistical analysis

Descriptive statistics were used to summarise patient and wound characteristics, time to wound closure, and the absence of complications. No inferential statistical analyses were performed due to the small sample size.

Results

Demographics and wound characteristics of the three included patients are outlined in Table 1. The patients, with hard-to-heal stage 3 PIs of the foot or lower extremity, were treated with a single application of collagen matrix following wound bed preparation. All patients had significant comorbidities, including MS, diabetes, peripheral neuropathy and dementia, as well as profound mobility impairments.

Initial wound sizes ranged from 2.0×1.5×0.5cm to 4.5×4.5×1.0cm. Wound locations included the lateral plantar aspect of a transmetatarsal amputation (TMA) stump and the sub-fifth metatarsal head. Two patients

Table 1. Patient profiles, wound characteristics and outcomes following collagen matrix application

Case	Age, years	Sex	Initial wound size, cm	Comorbidities	Pre-application wound duration	Contributing factors	Days to full closure	Early wound response	Follow-up outcome
1	54	F	2.0×1.5×0.5	Multiple sclerosis, paraplegia	3 months	Immobility, sensory loss	27	Significant improvement by day 14 (~98% reduction)	Wound remained closed at day 69
2	68	M	1.0×1.5×0.4	Type 2 diabetes, hard-to-heal foot ulcers	~3 years intermittent, 4 months continuous	Neuropathy, tailor's bunion	52	Progressive closure, no complications	Closure stable at day 131
3	60	M	4.5×4.5×1.0	Type 2 diabetes, peripheral neuropathy, dementia	4 weeks	Post-TMA pressure point, sensory loss	41	76% size reduction by day 6	Wound remained closed; amputation avoided

F—female; M—male; TMA—transmetatarsal amputation

underwent surgical offloading procedures (exostectomy or metatarsal head resection) in addition to debridement; one patient received sharp debridement for a deep tunnelling wound.

Complete wound closure was achieved in all three patients following a single application of collagen matrix. Time to closure ranged from 27–52 days. No complications, such as secondary infection, dehiscence, or need for further surgical intervention, were reported. At follow-up evaluations (ranging from 41–131 days after treatment), all wounds remained closed without recurrence.

Fig 1 shows the duration of chronicity before treatment with collagen matrix and time to wound closure following application of a bovine-derived collagen matrix. Pre-treatment wound duration ranged from 28 days (Case 3) to approximately three years (Case 2). Despite the prolonged chronic phase, all three patients achieved complete wound closure within 27–52 days after collagen matrix application. The mirrored timeline illustrates the contrast between prolonged wound chronicity and relatively rapid post-treatment wound closure.

Fig 2 illustrates the percentage of wound area reduction over time in two patients treated with the bovine-derived collagen matrix. Case 3 demonstrated a 76.3% reduction by day 6 and achieved full closure by

Fig 1. Wound duration before and after collagen matrix application

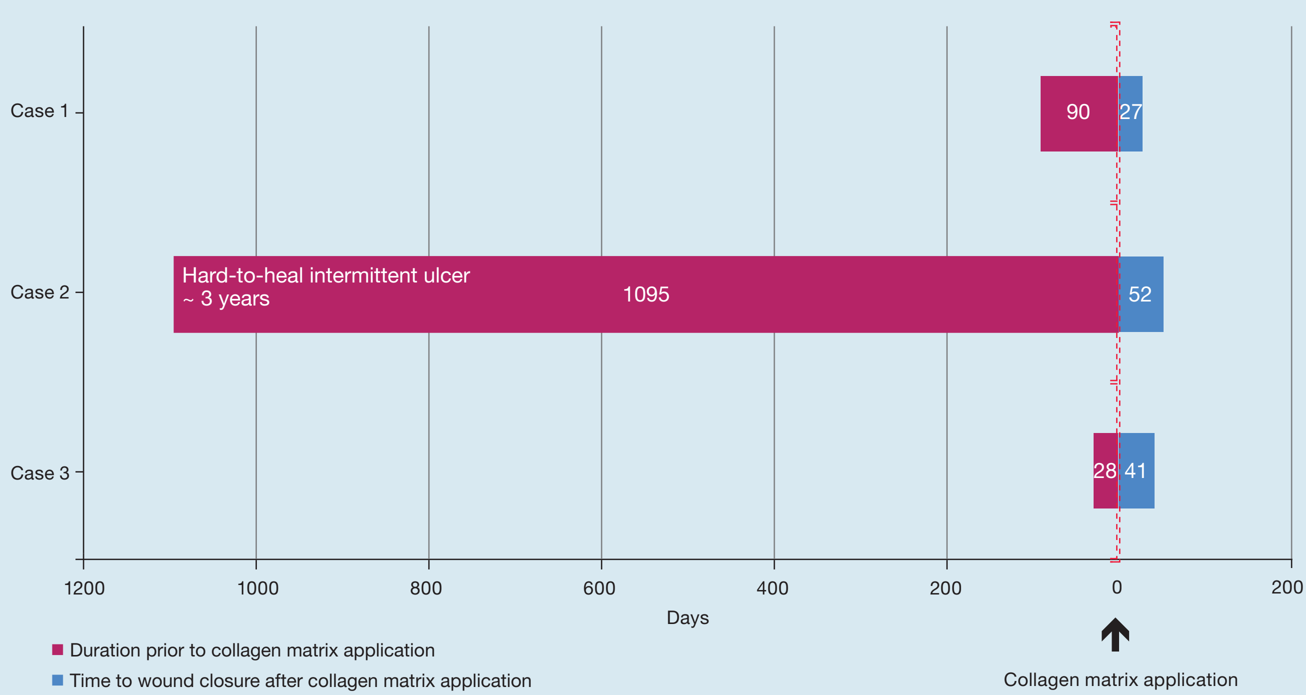
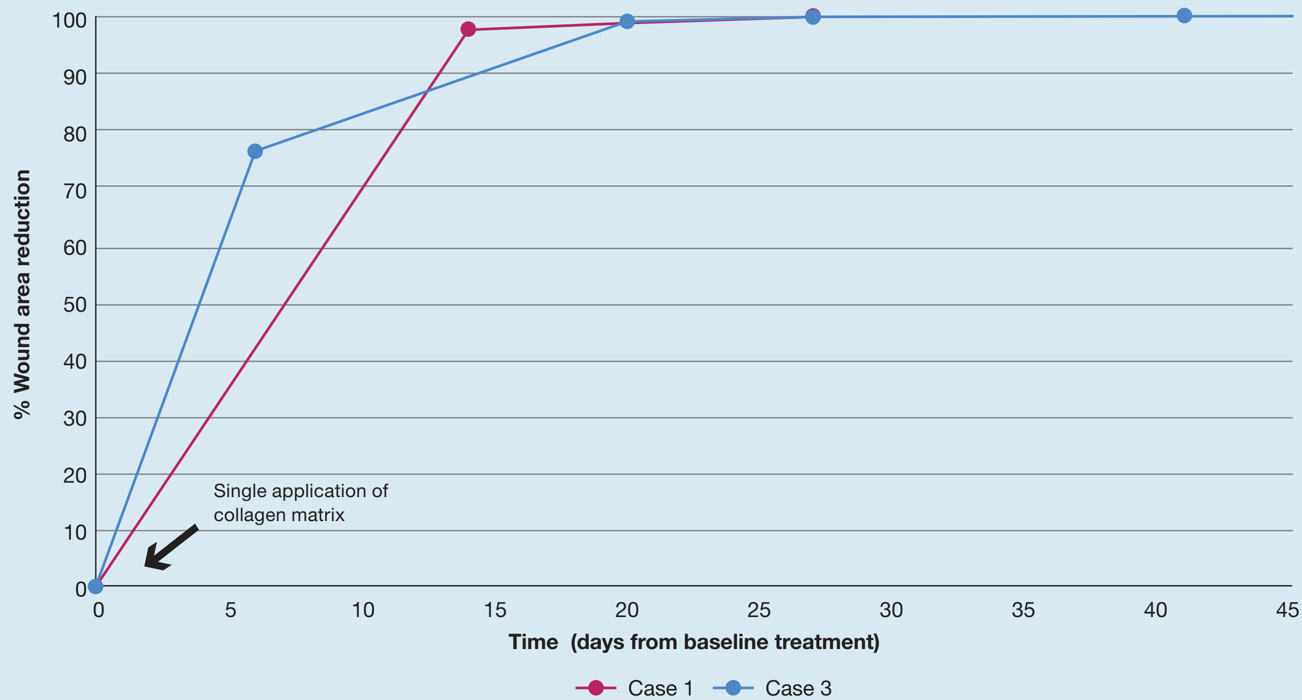
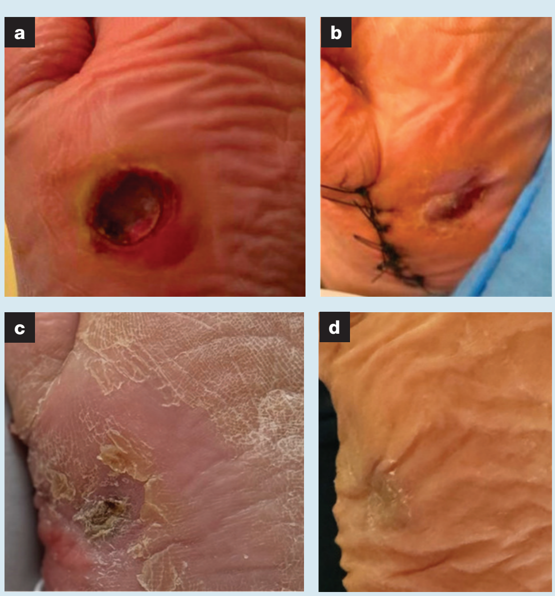


Fig 2. Percentage wound area reduction over time after collagen matrix application. Case 2 was managed with primary closure and wound edge approximation, preventing accurate measurement of wound size during the early closure phase. As a result, this case is not included



day 27. Case 1 showed a 97.6% reduction by day 14, progressing to complete closure by day 27. The figure highlights the rapid and substantial wound responses observed following a single collagen matrix application.

Fig 3. Case 1. A 54-year-old female patient with multiple sclerosis and paraplegia presented with a hard-to-heal stage 3 pressure injury on the right foot. The ulcer was located at the sub-fifth metatarsal head. At day 0, when the matrix was applied **(a)**; at day 14 **(b)**; at day 27**(c)**; and at day 69 **(d)**



Case presentations

Case 1

A 54-year-old female patient with MS and paraplegia presented with a hard-to-heal stage 3 PI on the right foot, measuring 2.0×1.5×0.5cm, located at the sub-fifth metatarsal head. The ulcer had persisted for three months despite multiple advanced wound care treatments, including silver alginate, Prisma (Promogran Prisma Matrix; Systagenix, UK), Hydrofera Blue (Hydrofera, LLC., US), and cadexomer iodine, none of which promoted closure. Her impaired mobility due to MS and paraplegia contributed significantly to the ulcer's chronicity and presented challenges to effective treatment.

Given the ulcer's hard-to-heal nature, its location over a pressure-prone bony prominence and the presence of devitalised tissue, the patient underwent fifth metatarsal head resection and surgical debridement. These procedures were performed to remove necrotic tissue and structurally offload the area, thereby eliminating the mechanical pressure and potential osseous involvement that hindered healing. Following the procedure, a single application of dry bovine-derived collagen matrix (500mg, single-use unit) was made to the wound bed to support granulation and re-epithelialisation. The wound was dressed with a non-adherent layer, gauze and a Kerlix wrap to maintain a moist environment. The patient was instructed to remain non-weight-bearing in a wheelchair to prevent additional pressure and was temporarily unable to participate in physical therapy for gait training.

By day 14, the wound area had reduced by approximately 97.6%, with complete closure observed by day 27 with a single collagen matrix application. At follow-up on day 69, the wound remained closed with no evidence of recurrence. The patient resumed her normal activities.

Fig 4. Case 2. A 68-year-old male patient with type 2 diabetes and peripheral neuropathy presented with a hard-to-heal stage 3 pressure injury at the left fifth metatarsal head. At day 0 **(a)**; at day 0, with a single-use unit of dry HELIOGEN (500mg) **(b)**; at day 0, skin edges re-approximated and closed primarily **(c)**; at day 3 **(d)**; and at day 131 **(e)**

Case 2

A 68-year-old male patient presented with a hard-to-heal stage 3 PI measuring 1.0×1.5×0.4cm at the left fifth metatarsal head. His medical history included type 2 diabetes, peripheral neuropathy, a tailor's bunion and bilateral chronic foot ulcerations. The wound had recurred intermittently over the previous three years and had remained continuously open for approximately four months, qualifying it as a hard-to-heal ulcer. This classification was based on its prolonged duration, repeated recurrence, and the presence of comorbid conditions known to impair wound healing. A few weeks before the most recent exacerbation, the patient had undergone a left first metatarsal phalangeal joint fusion.

On initial evaluation, the wound showed necrosis and pressure-related changes. The patient underwent surgical debridement and exostectomy to prepare the wound bed and offload the affected area. Dry bovine-derived collagen matrix (500mg, single-use unit) was placed into the wound bed as a single application. The skin edges were re-approximated and sutured to promote primary closure. The wound was dressed with a non-adherent layer, a 4×4cm gauze pad and a Kerlix wrap. The patient was advised on pressure offloading using a CAM boot and diabetic healing shoe. Regular wound assessments were scheduled to monitor closure.

The wound achieved complete closure within 52 days following a single collagen matrix application, with stable primary closure noted as early as day 3. At follow-up on day 131, the wound remained fully closed, with no evidence of complications or recurrence. Due to surgical approximation and early primary closure, serial wound measurements were not feasible and were therefore not recorded.

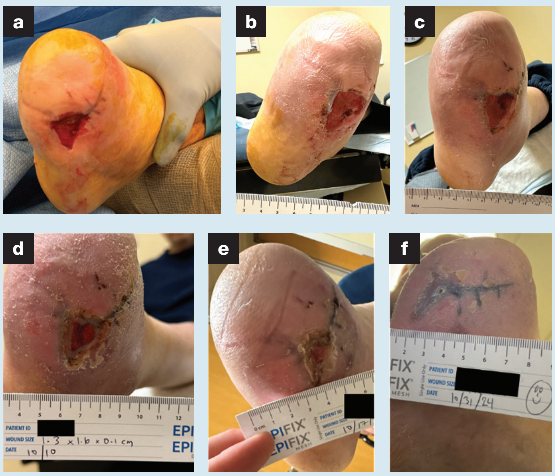
Case 3

A 60-year-old male patient with a history of type 2 diabetes, peripheral neuropathy and dementia presented with a hard-to-heal stage 3 PI measuring 4.5×4.5×1.0cm on the plantar lateral aspect of his left TMA stump. The ulcer demonstrated extensive tissue loss with visible subcutaneous involvement and had been open for four weeks with minimal signs of healing. The patient's comorbidities significantly impaired his ability to perform self-care, contributing to the persistence of the wound. He had previously undergone a partial fifth toe amputation and a partial fourth ray amputation due to osteomyelitis, both of which healed without complication. These procedures ultimately led to a left TMA. Following the TMA, pressure redistribution and loss of lateral forefoot support made the plantar lateral aspect of the stump particularly prone to ulceration. This region often becomes a weight-bearing focal point, especially in patients with prior lateral ray loss, due to altered biomechanics, reduced soft tissue padding, and shear forces during transfers or residual ambulation. At six months following the TMA, he developed a PI at the lateral stump, raising concern for the need for a more proximal amputation, which would have significantly impacted his mobility and QoL.

On initial evaluation, the wound exhibited deep tunnelling and necrotic tissue, requiring aggressive debridement. Active bleeding was noted, indicating adequate perfusion and a favourable wound environment. A single-use 500mg unit of dry bovine-derived collagen matrix was applied to the wound bed as a single application, and the wound was dressed with a non-adherent layer. The patient was instructed to remain non-weight-bearing in a wheelchair to offload pressure from the ulcerated area.

By day 6, the wound area had reduced by 76%, with healthy granulation tissue forming and the tunnelling beginning to resolve. Complete closure was achieved by day 41 following a single application of the collagen matrix, preventing the need for further amputation. This notably improved the patient's mobility and overall QoL.

Fig 5. Case 3. A 60-year-old male patient with a history of type 2 diabetes, peripheral neuropathy and dementia presented with a hard-to-heal stage 3 pressure injury on the plantar lateral aspect of his left transmetatarsal amputation stump. At day 0 **(a)**; at day 6 **(b)**; at day 13 **(c)**; at day 20 **(d)**; at day 27**(e)**; and at day 41 **(f)**



Discussion

Hard-to-heal PIs in patients with complex comorbidities remain a persistent challenge in wound management, often requiring prolonged care and carrying a high risk of complications, such as infection, limb loss and diminished QoL.[9–12] This risk is further amplified in higher-stage ulcers, which involve deeper tissue structures and typically demand more aggressive interventions than stage 1 or stage 2 PIs.[1]

The three cases in this series illustrate the potential of a single application of the collagen matrix to facilitate rapid and complete wound closure in medically complicated patients. All ulcers were classified as stage 3, involving full-thickness skin and soft tissue loss with a significant risk of deterioration. Each patient presented with a hard-to-heal PI that was unresponsive to SoC. Importantly, all patients in this series exhibited significant healing impairments due to comorbidities such as MS with paraplegia, type 2 diabetes, peripheral neuropathy and dementia. These conditions are well-documented risk factors for delayed wound closure, associated with impaired circulation, reduced immune response, and limited ability of the patient to adhere to pressure offloading and self-care regimens. Despite these barriers, all wounds achieved complete closure within 27–52 days following a single bovine-derived collagen matrix application, substantially shorter than the duration of chronicity before treatment, which ranged from four weeks to approximately three years. This contrast underscores the potential of collagen matrix in managing high-risk, treatment-refractory PIs. The duration of chronicity prior to treatment with collagen matrix highlights the burden these wounds can impose when left unresolved. Achieving full closure within a markedly shorter timeframe suggests not only clinical efficacy, but also a potential for greater cost-effectiveness. By reducing the need for prolonged care, repeat interventions and complication-related procedures, single-application collagen matrix treatment may help lower healthcare use in high-risk clinical scenarios. This potential was observed consistently across the three cases, despite differences in ulcer location and complexity. Early wound responses were also notable: one wound reduced in area by 98% by day 14, and another by 76% by day 6. In Case 2, where the wound was closed by primary intention, stable closure was observed as early as day 3. These findings highlight not only the effectiveness of the collagen matrix when combined with SoC but also the speed of tissue response in a population where wound closure is typically delayed.

Wounds varied in location, size and depth—from sub-metatarsal head ulcers to complex post-amputation stump ulcers—yet all responded favourably to the same treatment protocol. This consistency suggests broad applicability of the bovine-derived collagen matrix across different anatomical sites and levels of tissue involvement. Additionally, none of the cases required repeat application, indicating a potentially cost-effective approach that minimises patient burden and optimises healthcare resource use. A particularly compelling example is Case 3, in which the collagen matrix application directly contributed to limb preservation as part of the continuum of care. This reinforces the broader implications of timely wound closure: restoring tissue integrity, preserving mobility and independence, and improving overall QoL. These cases also emphasise the importance of comprehensive wound care. Surgical debridement, pressure offloading and appropriate dressing techniques were integral to management. The bovine-derived collagen matrix functioned as an effective adjunct within this multidisciplinary framework, enhancing rather than replacing SoC protocols.

The outcomes observed in this case series are consistent with prior studies demonstrating the clinical benefits of collagen-based matrices in hard-to-heal wound care. Previous RCTs and meta-analyses have reported improved wound closure rates, accelerated time to closure, and reduced the need for repeat interventions when collagen dressings or matrices are used as adjuncts to SoC.[24,25,27,30] However, many of these studies involved multiple applications over extended periods. In contrast, the present series demonstrates that a single application of a bovine-derived collagen matrix, when integrated into a comprehensive treatment protocol, may achieve comparable or superior outcomes in high-risk patients with stage 3 PIs. This suggests a potentially more efficient and resource-conscious therapeutic approach for managing complex wounds.

Limitations

While these results are promising, they are limited by the small sample size and lack of a control group. Further studies, including RCTs, are needed to confirm

Reflective questions

- What patient-specific or wound-related factors may influence responsiveness to bovine-derived collagen matrix in the treatment of hard-to-heal stage 3 pressure injuries (PIs)?
- In what ways can bovine-derived collagen matrices be effectively integrated into comprehensive wound care protocols for patients with significant comorbidities or impaired healing capacity?
- What types of clinical studies are most needed to evaluate long-term outcomes, application frequency and patient selection criteria for collagen matrix use in PI management?

these findings, determine optimal patient selection criteria, and evaluate long-term outcomes. Nonetheless, the rapid and complete wound closure observed in the medically complex patients in this study suggests that collagen matrix application may offer meaningful therapeutic value in hard-to-heal wound care.

Conclusion

These findings highlight the potential value of bovine-derived collagen matrix as an effective adjunct to established wound care protocols, particularly in high-risk, treatment-refractory cases. The consistency of outcomes across different anatomical locations and patient profiles suggests broad clinical applicability. Moreover, the ability to achieve full closure with a single application may reduce treatment burden, improve compliance and optimise resource use. While further research is needed, this series supports the integration of collagen matrix as a valuable component of multidisciplinary wound care strategies. JWC

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Clinical outcomes of lyophilised human amnion/chorion membrane in treatment of hard-to-heal diabetic foot ulcers in complex cases: a case series

Objective: Diabetic foot ulcers (DFUs) are a common and severe complication of diabetes, characterised by high morbidity, recurrence and risk of amputation. Hard-to-heal (chronic) DFUs often fail to respond to standard of care (SoC), necessitating advanced interventions. Lyophilised human amnion/chorion membrane (LHACM) is a trilayer placental allograft that provides extracellular matrix support, growth factors and anti-inflammatory properties to promote wound closure. This case series evaluates the effectiveness of LHACM as an adjunct to SoC in treating hard-to-heal DFUs unresponsive to conventional treatments.
Method: Patients with Wagner Grade 2 or 3 DFUs (each of which had been hard-to-heal and unresponsive to SoC for 1–3 years) and multiple comorbidities were treated with LHACM following thorough wound debridement, customised dressings and offloading strategies. Wound closure, infection control and functional outcomes were assessed.
Results: This was a case series of three male patients, aged 65–66 years. All wounds demonstrated significant size reduction within three weeks of treatment, achieving complete closure within a mean of 47 days (range: 35–56 days). No infection recurrences or complications were observed and patients resumed daily activities. LHACM's ease of application and compatibility with SoC facilitated integration into the treatment protocol.
Conclusion: LHACM demonstrated effectiveness in accelerating wound closure in complex hard-to-heal DFUs resistant to SoC, highlighting its potential to mitigate complications, reduce healthcare costs and improve patient quality of life. Further large scale studies are warranted to confirm these findings and explore broader applications in advanced wound care.
Declaration of interest: This study was sponsored by MIMEDX Group Inc., Marietta, GA, US. MO and DK serve on a MIMEDX speakers bureau. MO serves as a consultant to MIMEDX Group Inc. TG has no conflicts of interest to declare. SS, CD and RAF are employees of MIMEDX.

diabetic foot ulcer • hard-to-heal • LHACM placental allograft • lyophilised human amnion/chorion membrane • standard wound care • wound • wound care • wound dressing • wound healing

Diabetes is a significant healthcare concern due to its increasing prevalence and significant impact on individuals and healthcare systems. According to the 2021 International Diabetes Federation report, approximately 537 million people worldwide were living with diabetes, representing about 10.5% of the global population. The prevalence is estimated to rise to 11.3% (578 million) by 2030, and 12.2% (700 million) by 2045.[1] Diabetic foot ulcers (DFUs) are a severe complication of diabetes, and pose a substantial health risk, including high rates of disability and mortality. With a lifetime risk of 15–25% for developing DFUs in adults with diabetes, these ulcers impose a significant burden on both public health and the economy; in the US alone, the annual direct cost of diabetes care is estimated at $176 billion USD, with one-third of the cost related to lower extremity care, including DFUs.[2] The longer an ulcer is open, the more likely it will develop infections, gangrene, necrosis and skin defects affecting all layers of tissue, from distal to proximal areas of the body.[3] Patients with DFUs may experience pain that disrupts daily activities and sleep, significantly impacting their quality of life (QoL). In addition, many DFUs have a high recurrence rate, with 65% of the ulcers returning within five years.[4]

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DFUs are primarily caused by chronic hyperglycaemia, which leads to endothelial dysfunction, resulting in vascular insufficiency and peripheral nerve damage (neuropathy).[5] Individual factors, such as obesity, alcohol consumption and tobacco use, can accelerate the development of foot ulcers.[6] Additionally, vascular disease may complicate these ulcers by impairing the body's healing ability and increasing infection risk. Consistently high blood glucose levels diminish the body's capacity to combat infections and delays the closure of wounds. Social and cultural practices, such as walking barefoot and prolonged squatting—common in occupations such as tailoring, farming, construction and domestic work—are also risk factors for DFU.[7] Furthermore, inadequate access to diabetes screening, blood sugar monitoring and management, and foot care, combined with poor socioeconomic conditions, are associated with DFUs.[6,8]

With a median wound closure time of 12 weeks,[9] about 20% of moderate-to-severe[10] DFUs may eventually result in foot amputation.[11] Over the past decade, the annual rate of DFU-related amputations in the US has risen from 1.5 to 3.5 cases per 1000 patients with diabetes.[12] Lower limb amputations can lead to disability, extended hospital stays and increased mortality.[13–15] Furthermore, the five-year mortality rate after a major lower extremity amputation (above the level of the ankle) is 56.6%, and, when compared with mortality rates for cancer, is second only to that of lung cancer (80%).[16] Following a diabetic amputation, 19% of patients within one year and 37% within five years will undergo another amputation.[17] Thus, given the substantial cost and morbidity associated with diabetic foot complications, the need to accelerate wound closure in hard-to-heal DFUs is critical.

Identifying and implementing an effective treatment regimen for patients with a DFU is a growing challenge for clinicians worldwide. The current standard of care (SoC) for DFUs is debridement, followed by a moist dressing covering, wound offloading and a vascular assessment.[18] However, in some cases, the SoC is insufficient for effectively managing DFUs. In addition, due to a myriad of other potential intrinsic and extrinsic factors, such as peripheral vascular disease, neuropathy and poor blood glucose control, DFUs are slow to heal. Advanced treatments are needed when a wound fails to close by 50% at four weeks.

Advanced wound care for DFUs

The use of amnion in medical applications dates back over a century, with its first recorded use in skin transplants at Johns Hopkins Hospital in 1910.[19] Amniotic grafts, derived from placental membranes, possess extracellular matrix (ECM) proteins, growth factors and anti-inflammatory cytokines that support wound closure processes. These properties contribute to promoting angiogenesis, enhancing dermal fibroblast activity and facilitating the recruitment of mesenchymal stem cells. A key advantage of amnion is its lack of immunogenic markers, making it 'immunologically privileged' thus minimising the risk of an immune response when applied to a host.[20,21]

The amniotic membrane comprises a thin epithelial layer, a thick basement membrane and an avascular stroma, providing structural collagen and various bioactive molecules. Collagen types IV, V and VII contribute to the membrane's structural integrity and facilitate wound closure. This natural amniotic membrane has been reported to exhibit antimicrobial properties that reduce the risk of infection and create an environment conducive to effective wound closure.[22] Its application has also been reported to alleviate pain by minimising inflammation and scar tissue formation at the site, thereby supporting the wound closure process.[22–24]

Over the past decade, human placental membranes have become a prominent component of wound care protocols in the US,[25,26] accounting for a substantial proportion of the cellular, acellular and matrix-based products (CAMPs) used to manage hard-to-heal DFUs. Amnion with chorion (AC), in various formulations, has been used for wound management and has demonstrated significantly improved closure rates compared to SoC alone.[20] A related product, dehydrated human amnion/chorion membrane (DHACM) (EPIFIX, MIMEDX Group Inc., US), was the most widely used high reimbursement group CAMP in Medicare for DFUs and venous leg ulcers (VLUs) during 2015–2019.[27] Real-world Medicare data demonstrated superior clinical outcomes for DFUs and VLUs in patients treated with DHACM compared to those who did not receive this treatment.[27,28] DHACM has been shown to be cost-effective for VLUs[28] and remains cost-effective at any willingness-to-pay threshold for patients with DFUs.[27]

More recently available for clinical use, the lyophilised human amnion chorion membrane (LHACM) (EpiEffect, MIMEDX Group Inc., US) is designed for both acute and hard-to-heal wounds.[29] It is a trilayer allograft composed of placental amnion, intermediate and chorion layers, >300 regulatory proteins, and a biocompatible ECM forming a protective barrier that supports the natural healing cascade. The allograft thickness simplifies application and repositioning after hydration.[29] Its five-year shelf-life and terminal sterilisation process enhance both safety and convenience (in terms of ease of application) for health professionals treating wounds.[29]

The aim of this case series was to evaluate the effectiveness of LHACM in combination with tailored wound care strategies, including debridement, offloading and dressings, for treating hard-to-heal DFUs in patients with comorbidities.

Methods

This retrospective, multicentre and multiprovider case series examined the management and outcomes of patients with hard-to-heal DFUs that were unresponsive to SoC.

Patient selection

Patients were selected for inclusion in this case series based on the presence of hard-to-heal DFUs (Wagner Grades 2 or 3) that had not responded to SoC. Selection was based on clinical characteristics relevant to study the objective; specifically, due to complicating factors such as peripheral neuropathy, Charcot foot deformity or osteomyelitis, rather than demographic factors. The sample was representative of cases where the diagnosis was comprehensive, treatment was completed with

LHACM and the representative photographs of different wound closure time intervals were sufficiently clear. Patients were non-randomly selected from the medical records of three physician practices, ensuring a diverse range of clinical settings was represented.

Ethics statement and patient consent

All procedures were performed in accordance with the ethical standards of the respective institutions involved, and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Institutional review board (IRB) approval was not applicable for a study involving ≤3 patients. Written informed consent for the publication of patient photographs or use of their identified data was obtained by the authors and included at the time of article submission to the journal stating that all patients gave consent with the understanding that this information may be publicly available.

Treatment protocol

All patients received a combination of LHACM, debridement, appropriate wound dressings and offloading at each visit, with variations in the specific methods tailored to each patient's needs. Patients underwent thorough wound debridement at each visit to remove necrotic tissue and create a clean wound bed. This procedure was performed under sterile conditions to reduce the bacterial load. Following debridement, LHACM was applied to the wound bed according to the manufacturer's guidelines. LHACM application was followed by a non-adherent contact layer, such as Mepitel (Mölnlycke Health Care, Sweden) and Adaptic (Johnson & Johnson, US) to prevent the dressing from adhering to the wound, and to facilitate easy removal. Weekly follow-up visits were scheduled to monitor the progress of wound closure, reassess for signs of infection and perform dressing changes. LHACM was applied at each follow-up visit and additional debridement was carried out when necessary to maintain a healthy wound bed.

Education was provided to each patient on the importance of offloading techniques, appropriate footwear and daily footcare to prevent further complications. Patients were educated on using skin protectants over re-epithelialised areas and advised on lifestyle modifications, such as smoking cessation (where applicable), to optimise wound closure.

Outcome measures

The primary outcome measure for this case series was time to complete wound closure, characterised by re-epithelialisation and cessation of drainage. Secondary outcomes included infection control and the patient's ability to resume daily activities, such as walking or driving. Infection was monitored based on clinical signs and laboratory tests (e.g., wound cultures when indicated).

Statistical analysis

Descriptive statistics were used to summarise patient demographics, treatment regimens and outcomes. Wound closure times and infection rates were reported for each patient. Due to the small sample size, no inferential statistical analyses were conducted.

Results

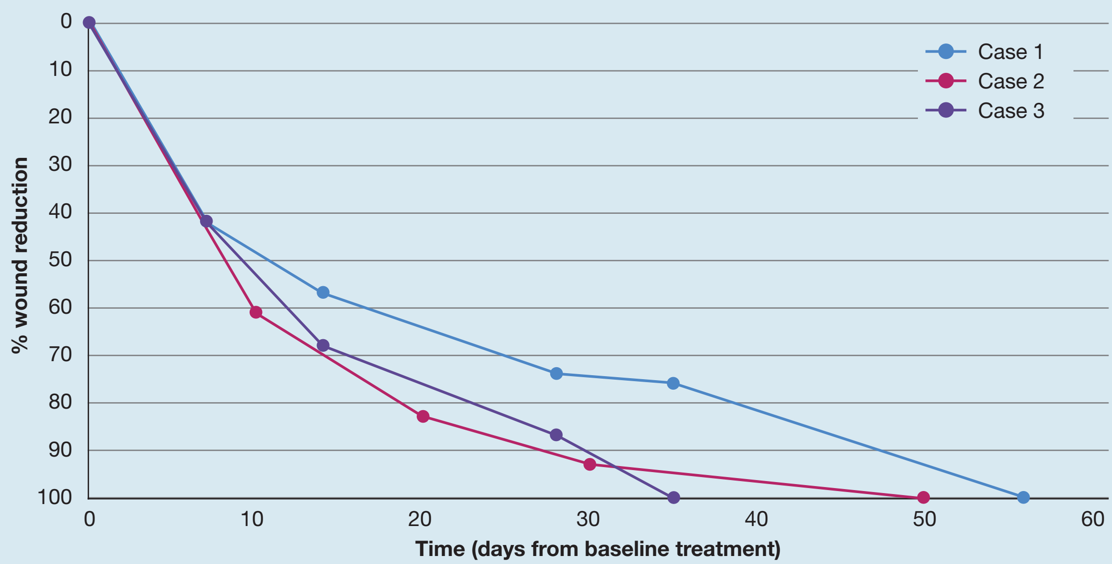
Patient demographics and wound characteristics are outlined in Table 1. The case series included three male patients, aged 65–66 years, with multiple comorbidities, including diabetes and hypertension. All wounds had failed to close for 1–3 years with prior treatments and dressings before the application of LHACM. The mean wound size reduction of the three wounds was 69.33% and a median reduction of 68% by three weeks of treatment, and all LHACM-treated wounds closed with a mean time to closure of 47±10.82 days (Fig 1). Individual cases are described below.

Table 1. Patient demographics and wound characteristics for three DFU cases

Case number	Age, years	Sex	Comorbidities	Wagner grade	DFU location	Initial wound size	Time to wound closure, days
1	65	Male	Type 2 diabetes, neuropathy, CNA, HTN, HLD	3	Left plantar foot	1.0×2.5cm Exposed fat layer Present for >1 year	56
2	66	Male	Type 2 diabetes, Charcot foot deformity, PAD, obesity, HTN, dyslipidaemia, hypothyroidism, neuropathy, smoking, polypharmacy (16 medications)	2	Right foot	3.8×1.1×0.3cm Present for three years	50
3	66	Male	Type 2 diabetes, neuropathy, HTN, CAD, chronic kidney disease (post-renal transplant), obesity, former smoker, polypharmacy (13 medications)	3	Left first metatarsal head	2.5×3cm Full-thickness, Present for >2 years	35

CAD—coronary artery disease; CNA—Charcot neuroarthropathy, DFU—diabetic foot ulcer; HLD—hyperlipidaemia; HTN—hypertension; PAD—peripheral arterial disease

Fig 1. Percentage of wound area reduction by time



Case presentations

Case 1

A 65-year-old male patient with a history of diabetes, Charcot neuroarthropathy, hypertension and hyperlipidaemia, presented with a hard-to-heal non-pressure DFU on the left plantar foot that had been present for over a year. The wound showed minimal improvement despite previous SoC, other allografts, alginate dressings, compression wraps, and offloading with a PegAssist shoe (Darco international, US). Upon referral to a specialist, the DFU was classified as Wagner Grade 3, a deep ulcer with exposed fat.

After debridement to remove necrotic tissue, the wound was treated with LHACM to promote wound closure (Fig 1), followed by Aquacel Extra Hydrofiber (ConvaTec, US) and Mepitel to maintain a moist wound environment. Steri-Strips (3M, US) were used to secure the dressings, and compression therapy (30–40mmHg) was used to manage swelling. Offloading was achieved with a PegAssist shoe due to balance issues that prevented the use of more

Fig 2. Case 1: A 65-year-old male patient with a hard-to-heal non-pressure diabetic foot ulcer (Wagner Grade 3). At day 0 **(a)**; at day 7 **(b)**; at day 14 **(c)**; at day 35 **(d)**; wound had closed by day 56 **(e)**

Fig 3. Case 2: A 66-year-old male patient with a hard-to-heal diabetic foot ulcer (Wagner Grade 2). At day 0 **(a)**; at day 10 **(b)**; at day 20 **(c)**; at day 30 **(d)**; wound had closed by day 50 **(e)**

restrictive offloading methods. The shoe allowed for partial offloading while providing adequate support and protection to the ulcer site. During five visits, the wound was regularly assessed, debrided and treated with LHACM, with dressings and compression wraps continued.

Despite some scheduling delays, the wound gradually reduced in size and began to show healthy granulation tissue. The DFU closed completely in 56 days with no complications or signs of infection. The patient resumed normal activities, including driving, and was fitted for new diabetic shoes and inserts to prevent future ulcers. The patient was also advised to use Cavilon skin prep (3M, US) for additional protection over the re-epithelialised area (Fig 2).

Case 2

A 66-year-old male patient with well-controlled insulin-dependent type 2 diabetes (glycated haemoglobin A1c: 6.1%) and a history of Charcot foot deformity presented with a hard-to-heal DFU on his right foot. The ulcer had persisted for three years despite previous treatments. His medical history included moderate obesity (body mass index: 36.6kg/m^2), hypertension, dyslipidaemia, hypothyroidism, peripheral neuropathy and peripheral arterial disease. The patient was a current smoker (0.5–1 pack/day), was on polypharmacy (16 medications), and was using an ankle foot orthosis brace due to foot instability. On evaluation, the patient had a Wagner Grade 2 DFU measuring 3.8×1.1×0.3cm, with sloughy tissue, moderate drainage and pain rated at 5–6/10. Despite prior wound management, the DFU showed no significant improvement and the patient experienced increased pressure from altered foot biomechanics.

Given the chronic nature and resistance to SoC, LHACM was introduced to promote granulation tissue formation and expedite wound closure (Fig 1). The treatment plan included regular wound debridement followed by the application of LHACM, which was covered with Adaptic, followed by Coban compression wrap (3M, US) and sterile strips. Given the patient's Charcot foot deformity, offloading felt pads inside custom made shoes were used to alleviate pressure on the DFU and redistribute weight, preventing further mechanical stress and promoting wound closure. The treatment protocol was performed over four applications.

Within 50 days, the wound showed significant improvement and complete closure. Pain was reduced to 0–1/10, with a noticeable reduction even after the first application. There was no sign of infection or drainage and the DFU ulcer had fully re-epithelialised (Fig 3).

Case 3

A 66-year-old male patient with type 2 diabetes, chronic kidney disease (post-renal transplant), hypertension, coronary artery disease and peripheral neuropathy, presented with a Wagner Grade 3 DFU on the left first metatarsal head that had persisted for >2 years. The ulcer, complicated by osteomyelitis, was a full-thickness wound, increasing the risk of infection and delayed wound closure. The patient's medical history was further complicated by obesity, a history of smoking and polypharmacy (13 medications) (Fig 1).

Given the DFU's hard-to-heal nature and the patient's complex comorbidities, the treatment plan focused on optimising the wound healing environment, managing infection risk and supporting systemic health. The DFU was cleansed and debrided, including bone debridement, to address the complications of osteomyelitis. A moist wound environment was maintained using Hydrofera Blue (Hollister Wound Care, US), an antimicrobial dressing and a contact layer dressing, followed by the application of LHACM. In addition, the patient was fitted with a total contact cast (TCC) to offload pressure from the ulcer site, providing more even weight distribution across the foot and preventing further trauma to the wound site, which was essential due to the patient's peripheral neuropathy.

The patient underwent four applications of LHACM over 35 days, with significant progress noted at each stage. The combination of wound debridement, advanced dressing and pressure offloading led to 100% wound closure in 35 days with no complications. This approach supported the rapid formation of granulation tissue and re-epithelialisation, despite the challenges posed by osteomyelitis and diabetes. The presence of osteomyelitis, along with complex comorbidities, made treatment particularly challenging. However, the diligent and regular care provided, including consistent treatment and pressure offloading, led to fast wound closure, highlighting the effectiveness of comprehensive, frequent care (Fig 4).

Fig 4. Case 3: A 66-year-old male patient with a diabetic foot ulcer (Wagner Grade 3). At day 0 **(a)**; at day 7 **(b)**; at day 14 **(c)**; wound had closed by day 35 **(d)**

Discussion

This case series demonstrates the efficacy of LHACM as part of a structured wound care protocol for treating hard-to-heal DFUs unresponsive to SoC.[30] DFUs represent a significant challenge in clinical practice due to their multifactorial aetiology, which includes peripheral neuropathy, vascular insufficiency, and impaired immune function associated with hyperglycaemia. Hard-to-heal wounds, particularly those with complications such as infection, Charcot deformities and osteomyelitis, require advanced interventions beyond SoC to achieve closure and prevent recurrence.[31]

All three patients in this series presented with Wagner Grade 2 or 3 DFUs and multiple comorbidities, including peripheral neuropathy, hypertension and osteomyelitis, that contributed to delayed wound closure, despite 1–3 years of SoC. Despite such complex factors, complete wound closure was achieved in all patients within a mean of 47 days, demonstrating the effectiveness of LHACM in combination with SoC, including debridement, appropriate dressings and offloading strategies. Furthermore, the mean wound size reduction observed in this complex series was 69.33% by three weeks of treatment.

The biological properties of LHACM support wound management by addressing impediments to wound closure. Its ECM provides a scaffold for cellular migration and tissue regeneration, while its growth factors and cytokines promote angiogenesis, granulation tissue formation and re-epithelialisation. Additionally, its lack of immunogenicity minimises inflammation and supports wound closure in challenging conditions.[32] The rapid formation of granulation tissue observed in these cases aligns with the established mechanisms of action of LHACM, particularly in hard-to-heal wounds.[33] Additionally, LHACM's design features, including its trilayer structure, simplify positioning, hydration and reapplication, and offer a practical and efficient option for clinicians managing complex wounds. The terminal sterilisation process ensures product safety, and its five-year shelf-life supports efficient clinical inventory management. These characteristics make LHACM a practical option for incorporation into comprehensive wound care protocols.

The multifaceted approach used in the treatment of patients in this case series, tailored to each individual, was pivotal in optimising outcomes. Effective offloading techniques, such as TCC and custom offloading pads, redistributed mechanical stress away from the ulcer sites, complementing the biological effects of LHACM.

Moreover, regular debridement and vigilant infection control ensured a healthy wound bed conducive to closure. The lack of infection recurrence in the patients is noteworthy, given the high susceptibility of hard-to-heal DFUs to secondary infections that often necessitate surgical interventions or lead to amputation. Regular and frequent visits were essential in reducing the overall length of treatment, highlighting the importance of continuous care in promoting faster wound closure and recovery.

Comparison with existing literature demonstrates consistency in the efficacy of amniotic membrane-based products for wound management.[34–36] However, LHACM offers unique advantages, including enhanced structural durability and ease of handling.[30] These features may expand its applicability across diverse clinical scenarios. The potential of LHACM to support wound closure is particularly significant from a cost-effectiveness perspective. In this series, the average 50-day treatment period to achieve wound closure compared favourably with prolonged durations under SoC, such as the one-year timeline for Case 1 and the three-year timeline for Case 2. These findings suggest an opportunity for substantial healthcare savings by reducing the duration of care, lowering the risk of complications, and preventing extended hospital stays or amputations. The potential cost benefits of LHACM align with observations from studies on DHACM, which demonstrated both clinical efficacy and cost-effectiveness in DFU management.[27,37,38] The shorter treatment duration also enhances patients' QoL by allowing them to resume daily activities sooner and reducing the psychosocial burden associated with hard-to-heal wounds.[39]

Limitations

Despite the promising results, this case series is limited by its small sample size and retrospective design. Future research will be critical in further substantiating these findings. An ongoing multicentre, randomised controlled trial evaluating LHACM for hard-to-heal wounds (registered on clinicaltrials.gov (NCT06600724)), aims to provide high-quality evidence for its comparative effectiveness. This study will address key questions regarding optimal usage patterns, long-term outcomes, and QoL measures. Additionally, investigations into the molecular mechanisms of LHACM may uncover new insights into its regenerative capabilities, enabling broader applications in wound care and other tissue repair contexts.

Conclusion

In conclusion, this case series provides evidence for the role of LHACM as an adjunctive therapy in managing complex DFUs. Its integration into a comprehensive wound care protocol accelerated wound closure, mitigated complications, and addressed a critical need in the treatment of hard-to-heal wounds in the patients in this case series. LHACM's ease of application and its support for the wound healing cascade position it as a valuable tool in advanced wound management. These findings support the broader adoption of LHACM in clinical practice to improve outcomes and QoL for patients with hard-to-heal DFUs. LHACM has the potential to reduce complications, prevent amputations, and significantly improve outcomes for patients with hard-to-heal wounds, such as DFUs. JWC

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Reflective questions

- In what circumstances are hard-to-heal diabetic foot ulcers (Wagner Grade 2–3) good candidates for lyophilised human amnion/chorion membrane (LHACM) application?
- What features of LHACM are good handling characteristics?
- Why are customised treatment plans important for patients?

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Dehydrated human amnion/chorion membrane to treat venous leg ulcers: a cost-effectiveness analysis

Objective: To evaluate the cost-effectiveness of dehydrated human amnion/chorion membrane (DHACM) in Medicare enrolees who developed a venous leg ulcer (VLU).
Method: This economic evaluation used a four-state Markov model to simulate the disease progression of VLUs for patients receiving advanced treatment (AT) with DHACM or no advanced treatment (NAT) over a three-year time horizon from a US Medicare perspective. DHACM treatments were assessed when following parameters for use (FPFU), whereby applications were initiated 30–45 days after the initial VLU diagnosis claim, and reapplications occurred on a weekly to biweekly basis until completion of the treatment episode. The cohort was modelled on the claims of 530,220 Medicare enrolees who developed a VLU between 2015–2019. Direct medical costs, quality-adjusted life years (QALYs), and the net monetary benefit (NMB) at a willingness-to-pay threshold of $100,000/QALY were applied. Univariate and probabilistic sensitivity analyses (PSA) were performed to test the uncertainty of model results.
Results: DHACM applied FPFU dominated NAT, yielding a lower per-patient cost of $170 and an increase of 0.010 QALYs over three years. The resulting NMB was $1178 per patient in favour of DHACM FPFU over the same time horizon. The rate of VLU recurrence had a notable impact on model uncertainty. In the PSA, DHACM FPFU was cost-effective in 63.01% of simulations at the $100,000/QALY threshold.
Conclusion: In this analysis, DHACM FPFU was the dominant strategy compared to NAT, as it was cost-saving and generated a greater number of QALYs over three years from the US Medicare perspective. A companion VLU Medicare outcomes analysis revealed that patients who received AT with a cellular, acellular and matrix-like product (CAMP) compared to patients who received NAT had the best outcomes. Given the added clinical benefits to patients at lower cost, providers should recommend DHACM FPFU to patients with VLU who qualify. Decision-makers for public insurers (e.g., Medicare and Medicaid) and commercial payers should establish preferential formulary placement for reimbursement of DHACM to reduce budget impact and improve the long-term health of their patient populations dealing with these chronic wounds.
Declaration of interest: Support for this analysis was provided by MiMedx Group, Inc., US. JLD, and RAF are employees of MiMedx Group, Inc. WHT, BH, PS, BGC and WVP were consultants to MiMedx Group, Inc. VD, AO, MRK, JAN, NW and GAM served on the MiMedx Group, Inc. Advisory Board. MRK and JAN served on a speaker's bureau. WVP declares personal fees and equity holdings from Stage Analytics, US.

CAMPs • cellular, acellular and matrix-like products • cost-effectiveness • dehydrated human amnion/chorion membrane • Medicaid • Medicare • venous leg ulcer • wound • wound care • wound dressing • wound healing

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Approximately 1–3% of total healthcare expenditures are devoted to hard-to-heal wounds in high-income countries, and these rates are likely to increase as the population ages.[1] In 2021, the US Medicare programme covered over 63.8 million lives, at a cost of $839 billion USD or 3.9% of the US gross domestic product (GDP), and is projected to increase to 6.5% of GDP by 2096.[2] Hard-to-heal or chronic wounds, defined as wounds which have failed to close by 40–50% after four weeks of good standard care,[3] affected about 10.5 million US Medicare beneficiaries in 2019 and cost projections for all wounds ranged from $22.5–67.0 billion USD.[4] In the US, it has been estimated that 500,000–600,000 people experience a venous leg ulcer (VLU) annually,[5] accounting for approximately 2% of total US healthcare costs.[6] A retrospective analysis highlighted Medicare spending for wound care per beneficiary with the principal diagnosis of VLU increased from a mean value of $1206 USD in 2014 to $1803 USD in 2019.[4] If medical resources and work absenteeism are taken into account, the annual US payor burden was estimated at $14.9 billion USD in 2014 for Medicare and private insurers, excluding generic payors.[7]

Payroll taxes, beneficiary premiums, surtaxes from beneficiaries, copayments, deductibles and general US Treasury revenue fund Medicare.[1] Revenue is used to create two funds:

1. The Hospital Insurance (HI) trust fund or Medicare Part A
2. The Supplementary Medical Insurance (SMI) trust fund or Medicare Parts B and D (Table 1).

The HI trust fund will likely be <90% funded beginning in 2028, as the ratio of working contributors to the programme relative to beneficiaries decreases from 4:1 in 2000 to about 2.5:1 in 2030.[2] The SMI trust fund is adequately financed for several decades because general revenues are reset annually.[2]

To maintain Medicare enrolee health, continued improvements in healthcare must be accompanied by policies that promote cost efficiency, economies of scale, cost-containment measures, or increases in taxes and fees. These issues are acutely evident in wound care, where new and innovative methods of wound care management have improved healthcare outcomes,[8,9] but which, in some instances, have resulted in steeply rising costs.[10]

Patients with VLUs often enter a cycle of infection and remission followed by recurrence.[11] Studies on patients with VLUs reveal significant variations in the duration of ulcers and recurrence rates.[12–14] When compression therapy, the consensus standard of care,[15] is provided in conjunction with surgical correction of superficial venous reflux, VLU recurrence rates decrease; however, trends in closure rates have not improved.[16,17] The Early Venous Reflux Ablation randomised controlled trials (RCT) conducted in the UK demonstrated greater VLU-free time for patients treated early with an endovenous intervention,[18,19] in addition to faster VLU closure. The study concluded that venous intervention is cost-effective in the long term.[18] A cost-effectiveness analysis of this RCT from the US Medicare perspective, comparing compression therapy to early endovenous ablation, found that early intervention was 90.8% likely at a threshold of $45,995 USD per quality-adjusted life year (QALY) over three years. Zheng et al.[20] concluded that payors should cover early ablation to prevent costly VLU complications and improve patient wellbeing. Unfortunately for patients, despite the favourable medical evidence, most providers do not follow parameters for use established for advanced therapy (AT), a situation which may be remedied with additional education.[21]

To address the economic impact of hard-to-heal wounds on the Medicare programme, cost-effective strategies for prevention, early intervention and effective wound care management are essential and need to be taken into consideration by policy decision-makers. Efforts on patient education on wound prevention and self-care,[20] the use of multidisciplinary wound care teams[22] and, ultimately, the continued promotion of evidence-based practices that improve wound closure while reducing use of healthcare resources and costs are ongoing goals among thought leaders in the field. The present study retrospectively examined the cost-effectiveness of using an AT with dehydrated human amnion/chorion membrane (DHACM) compared with no advanced therapy (NAT) among Medicare enrolees who developed a VLU.[11] Studies of Medicare enrolees suggest that when wounds fail to close in a timely fashion (40–50% by four weeks), only 9.8% of patients with a lower extremity diabetic ulcer[9,23] and 21% of patients with a VLU[19] receive an AT at weekly to biweekly intervals as consensus experts suggest.[24–26]

DHACM (EPIFIX, MiMedx Group, Inc., US) has been identified as the most widely applied AT among Medicare patients with VLUs[11] within the increasingly expanding selection of over 100 that are commercially available.[27] ATs, or high reimbursement skin substitutes, have recently been categorised in a peer-reviewed publication as cellular, acellular and matrix-like products (CAMPs).[24–26] DHACM allografts are immune-privileged, minimally manipulated, non-viable cellular human placental-derived tissue that provides a collagen scaffold to support the development of granulation tissue. In vitro[28–31] and in animal models,[31,32] DHACM has been shown to influence inflammation, cell proliferation, metalloproteinase activity and recruitment of stem cells, all of which play a role in the wound healing cascade.[31–33] Additionally, DHACM is known to contain >300 preserved regulatory factors, which, in utero, are essential to tissue generation.[29,31]

Closure rates of 50–60% when DHACM was an adjuvant for standard comprehensive VLU therapy with either intent-to-treat (p=0.0473) or per protocol (p=0.0128) calculations were demonstrated by two prospective RCTs.[34,35] At four weeks, wound area reductions were 63% for DHACM-treated cohorts combined with multilayer compression therapy versus 32% for multilayer compression therapy cohorts treated without DHACM (p=0.005).[36] The use of CAMPs in

Table 1. Medicare is divided into four parts[2]

- **Part A:** covers hospital (inpatient, formally admitted only), skilled nursing (only after being formally admitted to a hospital for three days and not for custodial care), home healthcare and hospice services
- **Part B:** covers outpatient services, including some providers' services while inpatient at a hospital, outpatient hospital charges, most provider office visits, even if the office is 'in a hospital', durable medical equipment, and most professionally administered prescription drugs
- **Part C:** after enrolling in Parts A and B, Managed Medicare or Medicare Advantage gives choice of health plans with at least the same service coverage as Parts A and B (and most often more), with the benefits of Part D, and always an annual out-of-pocket expense limit which A and B lack
- **Part D:** covers mostly self-administered prescription drugs.

Table 2. Markov model health states (modified from Cheng et al.[48])

Health state	Description
Chronic or recurrent VLU	Patients receive treatment and have a chronic wound that is not initially infected. This health state has higher costs, higher hospital use and lower QoL than the healed state, but lower costs, lower hospital use and higher QoL than the complex state. This state subsumes previously closed wounds that remain unresolved and wounds that are no longer complex but require treatment and costs
Post-VLU (healed)	Patients no longer have an active wound. Patients in this health state have the lowest costs, lowest hospital use and highest QoL. Patients are susceptible to recurrent VLUs
Complex VLU	An unresolved VLU develops an infection. Patients in this health state have the highest costs, highest hospital use and lowest QoL. Added costs include hospitalisations, amputations, etc.
Death	Patients die related or unrelated to the VLU. There are no additional costs or benefits accrued

QoL—quality of life; VLU—venous leg ulcer

wounds that have stalled along the healing cascade is considered best practice among consensus experts as well as being supported by level one data.[24,25,35] Appropriate usage and integration of CAMPs into wound care practices have been shown to improve outcomes and reduce costs for Medicare patients with lower extremity diabetic ulcers.[9,23]

The Ontario Health Technology Assessment (OHTA)[37] found that adjunctive CAMP usage was more effective than standard care alone in hard-to-heal diabetic foot ulcers and VLUs. Additionally, patients were open to using CAMPs as a treatment option. However, within the parameter limits of the OHTA study, CAMPs were highly unlikely to be cost-effective compared with standard care for adults with VLUs. The OHTA used a three-state Markov model to evaluate cost-effectiveness,[37] and input parameters from only a single 128-patient intent-to-treat RCT with common inclusion/exclusion criteria.[35] Markov models are a mathematical stochastic process to predict possible health events in which the probability of each outcome depends only on the current state of the patient.

In contrast, the research presented in the present study builds upon the analysis of 530,220 Medicare enrolees with VLUs from 2015–2019, detailing their comorbidities, treatments, health outcomes and hospital use.[20] Patients with hard-to-heal VLUs, determined at 90 days and of any ulcer size and location below the knee, were evaluated over four years and labelled as 'chronic' in this article. Notably, patients with multiple comorbidities and other complications were included in a four-state Markov cost-effectiveness model. A complex VLU is one of the Markov states, and occurs when a patient develops an infection, leading to a health state of higher risk, cost and significance to patients, providers and payors. The model was developed from the US healthcare perspective and reflects real-world scenarios. The resulting economic analysis can be used by providers and payors participating in Medicare programmes or those with insured lives of comparable demographics to evaluate population applicability for coverage of CAMPs, specifically DHACM, compared with alternatives.

Methods

Ethical statement

The Medicare Limited Data Set (LDS) Files (1 October 2015–2 October 2019) were acquired under a Data Use Agreement (DUA) between the Center for Medicare and Medicaid Studies (CMS) and MiMedx Group, Inc. The Medicare LDS was previously collected, deidentified and available from CMS. LDS files do not contain specific direct identifiers as defined in the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. All analysis and reporting of Medicare data was performed in compliance with relevant laws and institutional guidelines approved by the CMS.

Retrospective cohort design and clinical definitions

This retrospective study design was developed as previously described.[8,19] ATs were high-cost CAMPs reported under Current Procedural Terminology (CPT) codes 15271–15278 and the applicable Healthcare Common Procedure Coding System (HCPCS) Q codes.[38] In this research, all DHACM applications were assumed to be FPFU, defined as the initiation of DHACM within 30–45 days of the first clinic visit or submitted claim date and, once started, DHACM was applied routinely within the range of every 7–14 days during the episode of care.[9,11,23] NAT referred to episodes treated without high- or low-cost CAMPs.[38] Clinical health states for the Markov model included chronic (hard-to-heal) or recurrent, complex, post-VLU, and death states (Table 2). A chronic VLU was defined as an ulcer that had not resolved within 90 days of the first claim. During this time, the patient received NAT, or if a VLU transitioned to AT, the VLU was also considered chronic. A complex VLU was defined as any chronic wound that developed an infection.

Cost-effectiveness analysis study design

We developed a Markov model from the US Medicare perspective to analyse the cost-effectiveness of DHACM FPFU in treating chronic VLUs in accordance with the Second Panel on Cost-Effectiveness in Health and Medicine.[39] The model compared DHACM FPFU to NAT in a Medicare cohort with chronic VLUs (that were currently uninfected). The model projected health outcomes over a three-year time horizon, using monthly cycles and roll-back periods at years one and two. Costs were adjusted to 2023 USD values, and clinical effectiveness was measured in units of QALYs. All parameters were discounted at 3% where appropriate. Results were reported using an incremental cost-effectiveness ratio (ICER), net monetary benefit

(NMB) and one-year budget impact. The cost-effectiveness of DHACM FPFU was measured at a \$100,000 USD/QALY willingness-to-pay (WTP) threshold. All modelling and analyses were conducted in 2023 using Microsoft Excel (Microsoft Inc., US).

Markov model structure

Medicare patients with a chronic uninfected VLU began the model in a chronic VLU health state (Fig 1). Patients were then treated with DHACM FPFU or NAT. Following treatment, VLUs either healed (Post-VLU), developed complications (Complex VLU), or remained unhealed. Individuals with healed VLUs either remained healed or regressed into a recurrent VLU (Recurrent VLU). Patients with complex VLUs either had their complications resolved and returned to a chronic VLU or transitioned to death. Recurrent VLUs followed the transition pathways of the original chronic VLU. Patients could transition to death from any health state.

Clinical inputs and transition probabilities

The initial transition probabilities from chronic VLUs were derived from a Medicare retrospective claims analysis.[11] The Medicare analysis provided complication rates, healing rates, and time to complication and healing (in days) for the DHACM FPFU and NAT arms (Table 3). These parameters were transformed into monthly transition probabilities. VLU recurrence and background mortality rates were derived from peer-reviewed literature and national databases.[40,41] Based on clinical opinion, the recurrence and mortality rates did not differ across treatment arms.

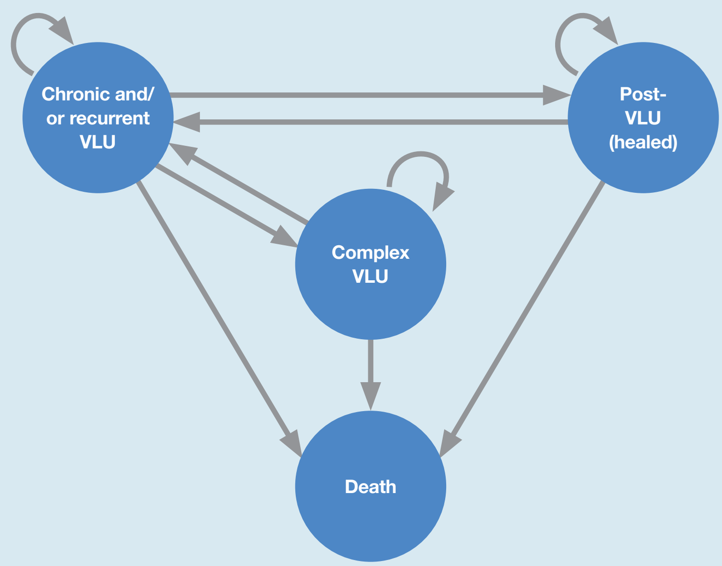
Costs

Monthly, health-state-specific costs were calculated by treatment arm. The Medicare analysis informed healthcare resource use and costs for inpatient admissions, readmissions, emergency department (ED) visits, outpatient observations, intensive care unit (ICU) stays, and amputations during treatment for a chronic, recurrent and complicated VLU (Table 3). The costs of DHACM treatment were calculated from 37,619 VLU episodes (34,698 patients), encompassing 166,227 outpatient claims that did not include any confounding ED visit, ICU or amputation charges. Other cost components of VLU chronic, recurrent and complicated care, such as home health visits, compression therapy and analgesics, were unavailable in the Medicare analysis and were derived from the literature.[20] AT costs were only applied to the DHACM FPFU arm. Recurrent VLUs were assumed to have the same treatment cost in both arms.

Health utility

Health utility weights, which measure effects on health, with a value between 0 (death) and 1 (perfect health), were used to estimate the quality of life (QoL) in each health state and were summed to calculate QALYs across the time horizon. A single QALY was equal to a year of perfect health. All utility weights were derived from the literature (Table 3). The baseline score for a healed skin ulcer was derived from a health-related QoL study on VLUs.[42] Baseline scores for chronic skin ulcers, venous insufficiency and additional conditions were estimated from a publication that used the US Medical Expenditure Panel Survey.[43] Patients in the chronic VLU health state were assumed to have venous insufficiency along with their chronic skin ulcer. The disutility associated with additional conditions was applied to individuals in the complex VLU health state. Patients with healed VLUs were assumed to have the baseline score, and those with recurrent VLUs were considered to have the same utility score as those with the original chronic VLU.

Fig 1. Markov model diagram. Four-state Markov model. Treatment arm 1: intervention with dehydrated human amnion/chorion membrane (DHACM) following parameters for use (FPFU) or treatment arm 2: no advanced therapy (NAT). Venous leg ulcers (VLUs) can remain chronic, become healed (Post-VLU), or develop complications (Complex VLU) after receiving treatment. Healed VLUs can remain healed or recur (Recurrent VLU). Complex VLUs can remain complex or return to chronic. All health states transition to death throughout the time horizon. Health states are defined in Table 2. Model parameters are provided in Table 3, and the outcomes of the Markov model are shown in Table 6



Sensitivity analyses

Univariate and probabilistic sensitivity analyses (PSA) were conducted to test the uncertainty of the base case results for the three-year time horizon. The univariate sensitivity analysis individually adjusted each base case parameter to an upper and lower bound value, while all other parameters were constant. The upper and lower bounds were based on reported standard error (SE) and a chosen statistical distribution.

For the PSA, all variables (both cost and QALYs) were simultaneously varied based on their point estimate, a measure of uncertainty and statistical distribution. The PSA was conducted over 10,000 Monte Carlo simulations. An assumed SE of ±10% of the base-case

Table 3. Model parameters

Parameter	Base case	Lower bound	Upper bound	Distribution	Source
Clinical					
DHACM					
Time from chronic to healing, months, 75th percentile	3.25	3.14	3.37	Gamma	11
Chronic to complex percentage	15.83	12.85	19.05	Beta	11
Time from chronic to complex, months	3.20	3.04	3.36	Gamma	11
Time from chronic after complex to healed, months, 75th percentile	4.12	3.93	4.32	Gamma	11
NAT					
Time from chronic to healing, months, 75th percentile	5.52	5.38	5.67	Gamma	11
Chronic to complex percentage	19.84	16.09	23.86	Beta	11
Time from chronic to complex, months	5.18	4.98	5.38	Gamma	11
Time from chronic after complex to healed, months, 75th percentile	6.48	6.26	6.70	Gamma	11
Treatment independent					
Chronic to death percentage	2.15	1.75	2.59	Beta	41
History of ulcer, hazard ratio	1.47	1.20	1.77	Gamma	44
Costs and healthcare use					
DHACM use – chronic					
Treatments, n	4.80	4.63	4.97	Gamma	11
OP visits, n	12.64	11.86	13.44	Gamma	11
OP observations, n	0.03	0.03	0.03	Gamma	11
Average length of treatment, months	2.71	2.56	2.87	Gamma	11
NAT use – chronic					
Treatments, n	0.00	-	-	-	11
OP visits, n	16.39	15.25	17.56	Gamma	11
OP observations, n	0.05	0.05	0.06	Gamma	11
Average length of treatment, months	2.81	2.61	3.02	Gamma	11
Treatment independent use – chronic					
Home health visits, n	1.00	-	-	-	18
Amitriptyline usage (rate), %	40.00	-	-	-	18
Gabapentin usage (rate), %	10.00	-	-	-	18
Hydrocodone usage (rate), %	5.00	-	-	-	18
DHACM use – complex					
IP admission, days	8.44	7.83	9.08	Gamma	11
Readmission, days	2.99	2.75	3.25	Gamma	11
ICU, days	2.38	2.20	2.56	Gamma	11
Readmission ICU, days	0.96	0.88	1.05	Gamma	11
ED visits, n	1.70	1.50	1.93	Gamma	11
OP amputations, n	0.02	0.01	0.02	Gamma	11
IP amputations, n	0.05	0.04	0.06	Gamma	11

Table 3. Model parameters (continued)

Parameter	Base case	Lower bound	Upper bound	Distribution	Source
Clinical					
NAT use – complex					
IP admission, days	11.65	10.62	12.71	Gamma	11
Readmission, days	4.53	4.11	4.97	Gamma	11
ICU, days	4.00	3.64	4.37	Gamma	11
Readmission ICU, days	0.98	0.91	1.05	Gamma	11
ED visits, n	1.48	1.37	1.60	Gamma	11
OP amputations, n	0.05	0.04	0.06	Gamma	11
IP amputations, n	0.08	0.07	0.10	Gamma	11
Utilisation costs (2023 USD)					
DHACM treatment	1700	1620	1782	Gamma	This work
OP visits	236	206	267	Gamma	11
OP observations	2034	1892	2180	Gamma	11
Home health visits	2979	2454	3554	Gamma	20
Amitriptyline	5.99	4.88	7.22	Gamma	45
Gabapentin	1.77	1.44	2.13	Gamma	45
Hydrocodone	2.26	1.84	2.72	Gamma	45
IP admissions days	1779	1664	1898	Gamma	11
Readmission days	1605	1420	1801	Gamma	11
ICU days	2054	1807	2316	Gamma	11
Readmission ICU days	1854	1478	2272	Gamma	11
ED visits	509	480	538	Gamma	11
OP amputations	2113	1687	2585	Gamma	11
IP amputations	22,742	18,553	27,352	Gamma	11
Compression therapy	76	63	91	Gamma	11
Health utilities					
Healed skin ulcer (utility)	0.7500	0.7444	0.7556	Beta	42
Chronic skin ulcer (utility)	0.6940	0.5503	0.8206	Beta	43
Venous insufficiency (disutility)	0.0380	0.0376	0.0384	Beta	43
2nd chronic condition (disutility)	0.0942	0.0940	0.0944	Beta	43

DHACM—dehydrated human amnion/chorion membrane; ED—emergency department; ICU—intensive care unit; IP—inpatient; NAT—no advanced treatment; OP—outpatient; USD—US dollars; VLU—venous leg ulcer

estimate was used for parameters without a reported SE or other measure of uncertainty. Parameters reported in percentages and utility scores (i.e., 0<x<1) followed a Beta distribution, while all other parameters (i.e., 0<x<∞) followed a Gamma distribution.

A threshold analysis was conducted for three variables based on the model's relative sensitivity to each. The 12-month recurrence rate (the same for each arm), DHACM FPFU complication rate and NAT complication rate were adjusted to the point that they provided a value that yielded an NMB of $0 USD.

Budget impact analysis

Compared to NAT, a hypothetical one-million-member health plan was used to assess the one-year budget impact of treating patients with a hard-to-heal

Fig 2. Hospital use increases when patients have a complex venous leg ulcer (VLU). Comparisons of episodes with a VLU (blue bars) or complex VLU (red bars) treated with DHACM FPFU (light colours) or NAT (dark colours) were tracked for their use of hospital resources (readmissions, ICU stays, admissions and ED visits). Significance was observed when comparing all DHACM FPFU (light bars) to all NAT (dark bars) for readmissions (p=0.03575), ICU stays (p=0.00062), admissions (p=0.00001), or ED visits (p=0.00036). DHACM—dehydrated human amnion/chorion membrane; ED—emergency department; FPFU—following parameters for use; ICU—intensive care unit; NAT—no advanced treatment

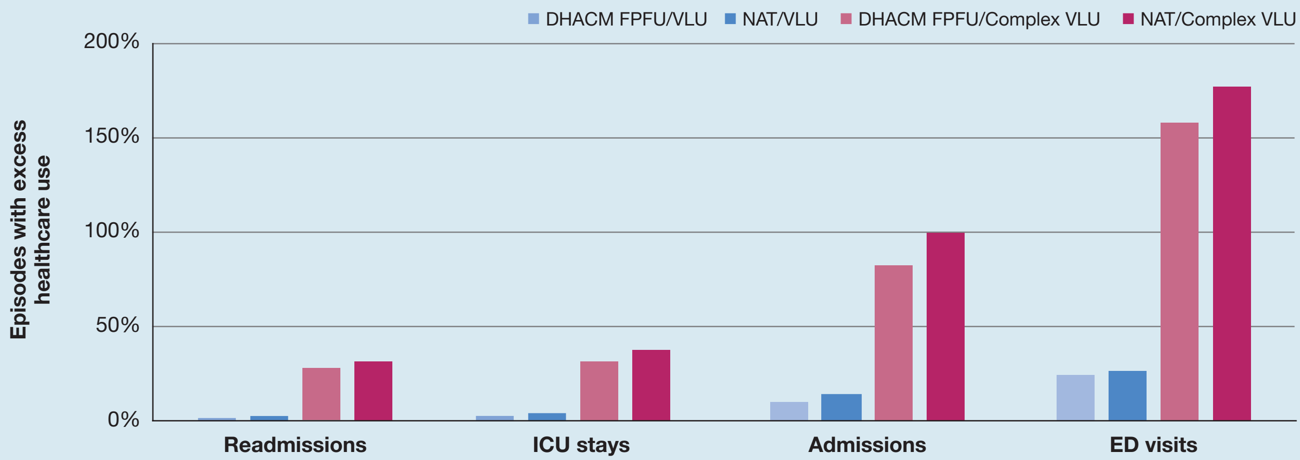
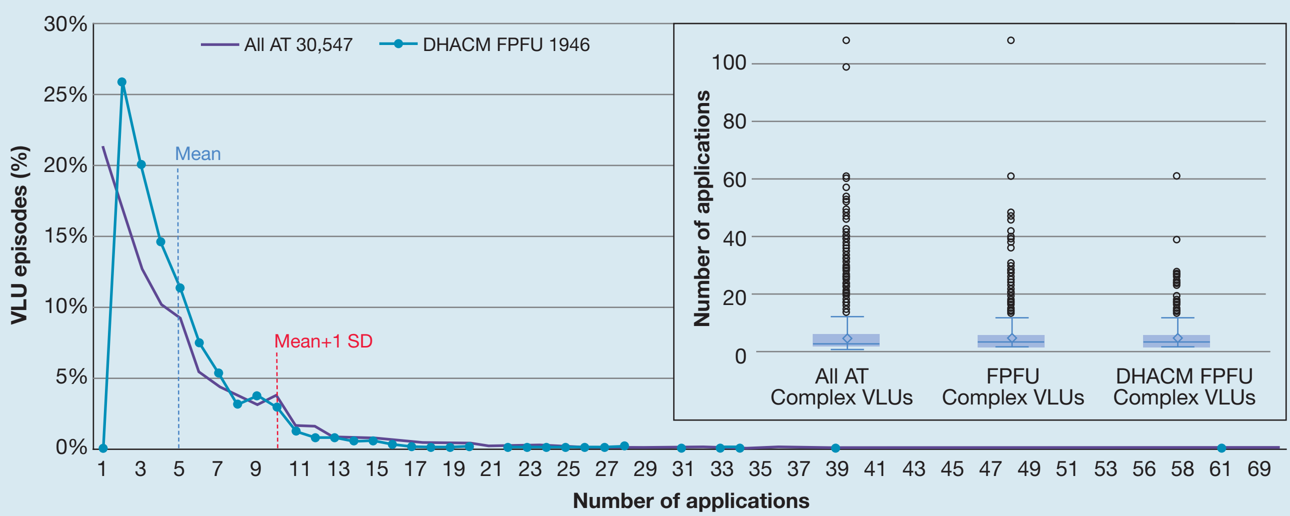


Fig 3. The number of AT applications required for claim closure (horizontal axis) versus the percentage of 2015–2019 Medicare episodes with a venous leg ulcer (VLU, vertical axis). All AT applications (purple line, 30,547 episodes) and enrolees receiving dehydrated amnion/chorion membrane applied following parameters for use (DHACM FPFU, blue line, 1946 episodes) were plotted. The mean CAMPs applications for all VLUs (dotted blue line, (area under the curve is 65% of the population)), plus one standard deviation (dotted red line, (area under the curve is 86% of the population)) are shown. Insert graph is the subset of complex VLU cohorts as box and whisker plots. DHACM—dehydrated human amnion/chorion membrane; FPFU—following parameters for use

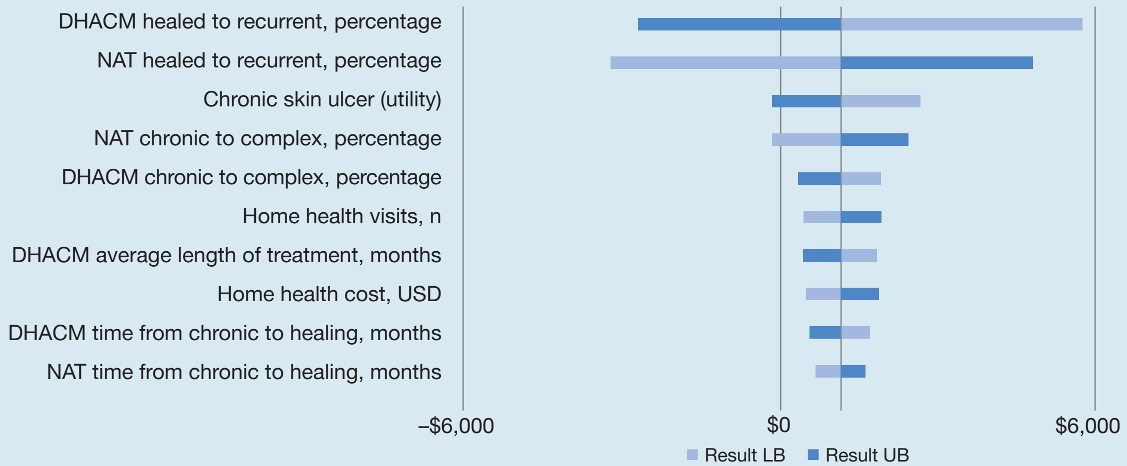


(chronic) VLU with DHACM FPFU. The incidence rate of VLUs was estimated to be 251/100,000 patients annually, of which 30% become chronic. The market share of DHACM was calculated to be 28.6%, all based on the Medicare analysis. The treatment cost difference per patient was calculated over the first year and multiplied by the risk pool to determine the overall cost difference for all at-risk patients. The year-one cost difference per covered member and per member per month (PMPM) was then calculated.

Results

Cohorts were evaluated for the frequency of comorbidities in the chronic and complex health states (Table 4). Notably, all of the top comorbidities increased in the complex VLU state. The symptom frequency of pain increased more than threefold (9.5% to 31.9%). The overall Charlson Comorbidity Index score (CCI, a 10-year mortality prediction for a patient based on their comorbidities)[46] between the chronic and complex health states increased by 29% (+0.6 CCI) for patients

Fig 4. Tornado diagram: univariate sensitivity results. Three-year net monetary benefit (NMB). The threshold analysis identified the break-even values (where the NMB=$0) for the following parameters: 12-month VLU recurrence rate (78.17%), NAT complication rate (16.37%) and DHACM complication rate (20.41%). DHACM—dehydrated human amnion/chorion membrane; NAT—no advanced therapy; USD—US dollars; LB—lower bound; UB—upper bound



receiving NAT, while patients receiving DHACM FPFU had an increase in their CCI score of 68% (+1.3 CCI).

Hospital resource usage increased by 6–10-fold in the complex VLU state compared to chronic VLUs without an infection. The use of DHACM FPFU demonstrated further reductions in hospital use in relation to NAT. Hospital use (readmissions, ICU stays, admissions and ED visits) was observed to add to the cost of a complex VLU.

Across the 30,547 episodes that received a CAMP in this study, a mean of 4.98±5.16 applications were required per completed claim (Fig 3, Table 5). The majority of episodes (n=23,486) were chronic VLUs with a slightly lower mean. However, the mean rose to 6.65±6.8 applications for those with a complex VLU (n=7061). Complex VLUs comprised 23% of the ulcers studied, requiring a statistically significant 2.2 further applications on average (p<0.0001, Table 5). Graphing the number of AT applications for the studied cohorts and those with complex VLUs revealed differential distributions (Fig 3).

Cost-effectiveness analysis base-case results

Over the three-year time horizon, DHACM FPFU was dominant over NAT, providing an additional 0.010 QALYs, while saving $170 USD per patient. The dominant result suggests that DHACM FPFU would be cost-effective compared to NAT in treating chronic VLUs at any WTP threshold over a three-year time horizon. The NMB at a $100,000 USD/QALY WTP threshold was $1178 USD (Table 6).

The advantage of DHACM FPFU over NAT increased throughout the time horizon. Over a one-year time horizon, DHACM FPFU was cost-effective compared to NAT before becoming dominant over the two- and three-year time horizons. The individual breakdown by time horizon is provided in Table 6.

Sensitivity analyses

The univariate sensitivity analysis identified only four scenarios in which DHACM FPFU would not be cost-effective compared to NAT at a $100,000 USD/QALY WTP threshold over a three-year time horizon. The most sensitive parameters were the VLU recurrence rates for DHACM and NAT, the utility score for a chronic skin ulcer, and the NAT complication rate (Fig 4).

Compared to NAT, over the three-year time horizon, the PSA estimated that DHACM FPFU had a 48.26% likelihood of being dominant and a 63.01% likelihood of cost-effectiveness at a $100,000 USD/QALY WTP threshold. DHACM FPFU had a >50% likelihood of cost-effectiveness at any WTP threshold (Figs 5, 6).

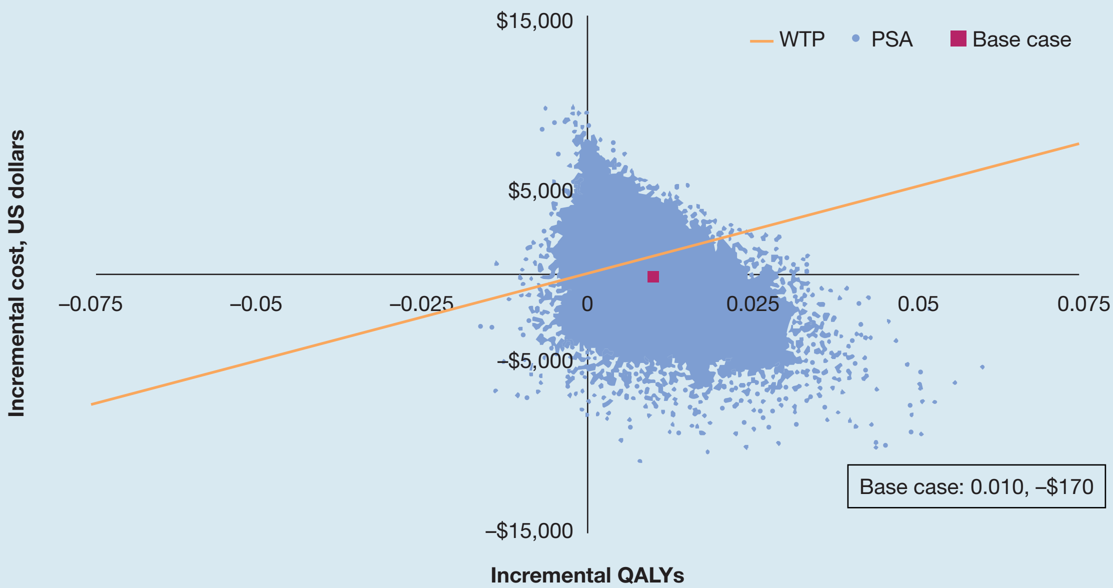
Budget impact results

The one-year budget impact of DHACM FPFU represented a <1 cent increase in PMPM spending in a hypothetical one-million-member plan. The $0.008 USD PMPM increase in spending represents a low barrier to treatment (Table 6). These results were estimated assuming 2510 patients of the one-million-member plan had a chronic VLU, of which 28.6% were treated with DHACM FPFU.

Discussion

This study addressed the cost-effectiveness of DHACM as an early treatment for patients with a VLU. Previous analysis of 854,266 VLU episodes demonstrated that using a CAMP reduces the time to VLU closure, results in fewer complications and decreases hospital usage.[11] When a CAMP, such as DHACM, was applied according to parameters for use, it provided the best outcomes.[11] This analysis determined that DHACM FPFU was a dominant treatment over NAT over a three-year time horizon. The upfront cost of DHACM FPFU for VLUs was offset by the significant reductions in hospital use,

Fig 5. Probabilistic sensitivity analysis. Results: three-year scatterplot. WTP—willingness to pay; PSA—probabilistic sensitivity analysis; QALYs—quality-adjusted life years



infections, and improved patient QALYs over a three-year period from the Medicare perspective. The PSA highlights the robustness of these results.

Table 4. Percentage of comorbidities within study group episodes

	NAT		DHACM FPFU	
Patients	1558	386	1607	307
Episodes	1560	386	1638	308
Comorbidity/symptom	**VLU**	**Complex VLU**	**VLU**	**Complex VLU**
Venous insufficiency	100.0%	100.0%	100.0%	100.0%
Deep vein thrombosis	74.7%	81.6%	79.1%	85.1%
Hypertension	46.3%	77.7%	49.6%	77.3%
Diabetes	37.8%	52.6%	38.6%	53.6%
Varicose veins, oedema	32.9%	45.6%	37.8%	42.9%
Peripheral vascular disease	26.8%	52.1%	23.4%	53.9%
VLU Inflammation	20.6%	25.4%	21.2%	23.4%
Neuropathy	14.7%	37.3%	15.7%	42.9%
Lymphoedema	14.2%	26.9%	9.4%	23.1%
Renal insufficiency	12.9%	33.7%	10.4%	36.4%
Polyneuropathy	10.3%	26.9%	11.3%	31.5%
Pain	9.5%	31.9%	11.1%	25.6%
Atherosclerosis	8.9%	23.6%	7.9%	23.4%
Charlson Comorbidity Index	2.1	2.7	1.9	3.2

DHACM—dehydrated amnion/chorion membrane; NAT—no advanced therapy; VLU—venous leg ulcer

Several cost-effectiveness models have been used to analyse patients with a VLU in the last 10 years, from the perspective of Europe,[47,48] Australia[49] and the US,[20,50,51] each of which found that intervention was cost-neutral-to-dominant. Studies supportive of intervention treatments analysed hydration response technology dressings,[47] single-use negative pressure wound therapy (NPWT) or traditional NPWT,[51] use of an antimicrobial wound dressing,[48] guideline-based use of compression therapy,[49] early endovenous ablation with compression therapy[18] and adjunctive use of CAMPs.[50] Most of the Markov models had three states, while, interestingly, guideline-based use of compression therapy required a five-health-state model to account for the high recurrence rate of VLUs and the excess costs of hospitalisations.[49] A review of the complex nature of patients with chronic venous insufficiency (CVI)[11] supports the concept that guidelines can stratify patients for intervention or best treatment modality upon the development of a VLU.

The two studies that examined adjunctive use of skin substitutes or CAMPs[37,50] used three-health-state Markov models and developed their data from four published studies[35,52–55] and a UK trial, which collectively enrolled approximately 1000 people across several countries after a run-in period of 14 days and typically strict run-in criteria, which included wound size.[37,50] Our model was informed by 530,220 Medicare patients with a VLU followed for four years. Study criteria included all VLU sizes below the knee and a broader range of comorbidities, providing direct relevancy of transition rates and cost efficiency to Medicare enrolees.

Running prospective studies with >500,000 patients,

Table 5. Number of CAMP applications in VLU cohorts

	Cost-effectiveness results (per patient)								
	Cohort name	**Cohort, n**	**Mean**	**SD**	**Min**	**Med**	**Max**	**Lower 95%**	**Upper 95%**
All	All VLU CAMPs	30,547	4.98	5.16	1	3	108	4.92	5.03
	VLU CAMPs FPFU	6546	5.32	4.75	2	4	108	5.21	5.44
	VLU DHACM FPFU	1946	4.84	3.81	2	4	61	4.67	5.01
Chronic	All VLU CAMPs	23,486	4.47	4.44	1	3	108	4.42	4.53
	VLU CAMPs FPFU	5423	5.00	4.14	2	4	108	4.89	5.11
	VLU DHACM FPFU	1638	4.62	3.56	2	4	61	4.45	4.79
Complex	All VLU CAMPs	7061	6.65	6.80	1	5	95	6.49	6.80
	VLU CAMPs FPFU	1123	6.87	6.78	2	5	95	6.48	7.27
	VLU DHACM FPFU	308	6.03	4.74	2	5	34	5.50	6.56

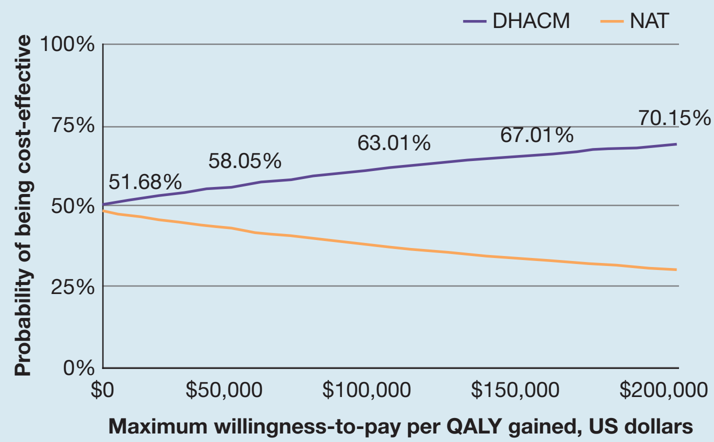
CAMPs—cellular, acellular and matrix-like products; DHACM—dehydrated amnion chorion membrane; FPFU—following parameters for use; Max—maximum; Med—median (the value separating the higher half from the lower half of the population); Min—minimum; VLU—venous leg ulcer; SD—standard deviation

with extended run-in, treatment and follow-up periods, is prohibitively expensive. This work highlights the value of extensive retrospective studies to identify population trends, generate data-backed hypotheses, and propose evidence-based best practices for achieving cost-efficient, positive patient outcomes in a resource-constrained system. The current study also supports previous work that suggests that most patients will benefit from early intervention in cases of a VLU,[20,47–49,51] using several other treatments and specifically with a CAMP, such as DHACM.[11,50]

Patients with CVI typically have multiple comorbidities, which complicate their treatment course. In this study, patients with a complex VLU treated with NAT had lower CCI scores than their DHACM FPFU counterparts (Table 4), yet still had worse outcomes. The Complex VLU state results in up to tenfold increases in hospital use compared to chronic VLU episodes from the NAT cohort (Fig 2), leading to cost increases, which will be the focus of future work. A 2.5-fold cost increase was calculated by comparing all chronic VLU episodes to the DHACM FPFU cohort. The benefits of treating patients with DHACM FPFU were observed across several outcomes (Fig 2). Other subgroup analyses, such as dual enrolee patients with Medicaid, saw substantial improvements and will be evaluated in future research.

Each patient may benefit from various prophylactic treatments (e.g., compression stockings, venous ablation). However, as long as a chronic ulcer remains open, infections increase hospital visits and potentially life-threatening complications. Of patients treated with DHACM, 24% use the ED (Fig 2), but this number rose to >175% when patients developed an infection and received NAT. A prospective RCT published in 2024 on patients in Asia concluded that closure of a VLU was vital to improving patient QoL and reducing costs. Patients with an open VLU at the six-month follow-up had costs that were 162% higher than those with a closed ulcer.[56] Shortening the time to ulcer closure and reducing recurrence rates are essential to ending the cycle and reducing healthcare expenditures.

Fig 6. Cost-effectiveness acceptability curve. Likelihood of DHACM cost-effectiveness at different willingness to pay thresholds. DHACM—dehydrated human amnion/chorion membrane; NAT—no advanced therapy; QALY—quality-adjusted life years



We note that of the 530,220 patients with a VLU during 2015–2019, only those who transitioned to DHACM FPFU or whose VLUs were labelled as chronic entered the model. Indeed, 28% of all enrolees still had an open wound after six months. Previous models were not based on studies that evaluated patients with wounds of such duration or multimorbid state. Yet, they make up three to nearly four of every 10 Medicare enrolees with a VLU. We anticipate this model to be relevant to populations of similar demographics within the US.

Medicare spends >$1.0 billion USD per year on the management of chronic VLUs.[4,57] The findings of this current study suggest that funds could be conserved if early interventional procedures, such as DHACM, were

Table 6. Cost-effectiveness and budget impact results

Cost-effectiveness results (per patient)			
	Year 1	Years 1–2 cumulative	Years 1–3 cumulative
Cost of DHACM, $USD	31,338	44,279	56,595
Cost of NAT, $USD	30,872	44,418	56,764
Cost difference, $USD	466	–139	–170
QALYs of DHACM	0.708	1.395	2.048
QALYS of NAT	0.699	1.385	2.038
QALYs difference	0.009	0.010	0.010
ICER ($/QALY)	51,059	Dominant	Dominant
NMB at $100,000/QALY WTP threshold, $USD	446	1142	1178
Budget impact for one million members in year one, $USD			
Cost difference for 753 people at risk			100,268
Cost difference per one-million-member health plan			0.10
Difference per member per month			0.008

DHACM—dehydrated amnion/chorion membrane; ICER—incremental cost-effectiveness ratio; NAT—no advanced therapy; NMB—net monetary benefit; QALY—quality adjusted life year; WTP—willingness to pay. Model assumes 0.251% incidence of venous leg ulcers of which 30% become chronic and a 28.6% market share of DHACM; all calculations have been rounded to the nearest second or third place

initiated at four weeks for all enrolees with a VLU which failed to close by 40%, and applied routinely thereafter until ulcer closure. Additionally, patients prone to infections or other complexities will likely achieve ulcer closure 14.3 days sooner when receiving DHACM FPFU.[20] When ulcers close in faster timelines,[34–36] patients avoid many VLU complications, opportunities for infection are reduced, and costly hospital use avoided[11] (Fig 2). When physicians effect the transition of Medicare enrolees with either a chronic VLU or those identified as having a complex VLU to DHACM FPFU, the NMB in the first year is positive at a WTP of $100,000 USD (Table 6). This current work provides patients, practitioners and payors with real-world insight into strategies to close VLUs, including a robust monetary incentive to invest upfront in patient health.

Another study[4] of Medicare patients with hard-to-heal wounds found that VLUs were the third most costly hard-to-heal wound per beneficiary, behind surgical wounds and pressure ulcers. Furthermore, while their research shows an overall decrease in hard-to-heal wound-related costs, expenditures for VLUs significantly increased from 2014–2019,[4] emphasising the importance of reducing costs while improving outcomes for patients with VLUs. While the specific reasons for the rise in VLU costs are unknown, contributing factors driving overall wound care costs down are hypothesised to include CMS prior authorisation programmes for non-emergent indications;[58] proposed changes in the payment of CAMPs which reduce access for patients with larger wounds;[59] and limitations to Medicare Advantage contracts for hospital facility fees. In general, CMS is driving the transition of healthcare from fee-for-service, which incentivises quantity of care, towards incentivising quality and cost-effective care.[60]

Value-based reimbursement strategies have been previously proposed,[61,62] and implemented by Medicare for chronic conditions, such as cardiovascular disease[63] and cancer.[64,65] Medicare should work with health systems to appropriately increase reimbursement rates or incentives for early intervention in chronic wounds, such as VLUs. Again, the Medicare data evaluated in this study indicate that DHACM FPFU provides a cost-effective solution for improving patient lives while reducing costs to Medicare.

Another take-home message highlighted by this analysis is that the number of applications per episode can vary considerably (Fig 3, Table 5), likely influenced by patient comorbidities, wound features and socioeconomic factors. Even the 23% of VLUs that were complex and treated with DHACM FPFU in this study provided cost-effective results. Fig 3 highlights an inflection point in the application distribution (dotted red line) where evaluating whether a patient is responsive to additional treatment may be prudent. While complex VLUs may require a greater number of applications to reach closure, this population would otherwise have very high hospital use (Fig 2) and subsequent costs. It is anticipated that early closure of a VLU reduces infections and subsequent hospital use, and powers the cost-effectiveness of DHACM FPFU.

As the ratio of working contributors to Medicare beneficiaries decreases to about 2.5:1 in 2030,[2] there will be an increasing need to enact policies that promote cost efficiency. Health systems that implement early and regular intervention will need to be appropriately incentivised by Medicare payments for performance measures to be sustainable. Anticipated savings of over $81,000 USD per million enrolees when DHACM is applied FPFU exemplifies an opportunity for Medicare to reduce costs and improve outcomes (Table 6). Standards are still developing within the wound care field, and evidence-driven quality metrics have been published.[66] It should be expected that there will be upfront costs for treatments such as DHACM. Nevertheless, payors and providers should support programmes that incentivise early intervention when it averts the more considerable downstream chronic wound care costs and improves patient health.

Limitations

This study has several limitations. First, the work is based on retrospective analysis of claims data, and caution in assigning causality from retrospective data is warranted. The authors anticipate the lowest fidelity on qualitative data (e.g., subjective claim notations, such as pain or inflammation), and higher certitude on quantitative data (number of patients, VLUs, DHACM applications, etc.). The uncertainty of model assumptions was captured in sensitivity analyses (Figs 3, 4).

The economic model developed for this work did not control for variability in the population of patients with VLUs, of which there are many sociodemographic causes. The demographics of Medicare patients with VLUs in this study were quantified.[11] However, the model does not provide a mechanism to address patients predisposed to health disparities, who have access issues due to a rural geography, or have other challenges in accessing specialty care for VLUs, all of whom may have less predictable outcomes.[67] The intended effort of future research is to elucidate the socioeconomic variables of Medicare recipients.

Conclusion

DHACM FPFU, in this economic evaluation, is a cost-effective alternative to NAT for Medicare patients with a complex VLU. Medicare should update its reimbursement strategies to incentivise the deployment of AT in timely and routine applications, thus allowing providers to follow evidence-based best practices related to CAMP use more readily. Most patients will see benefits, but patients with a VLU at risk for complications should be eligible early in the treatment process. Establishing such policies would lower the elevated costs of healthcare use for those with chronic wounds while favourably impacting clinical outcomes for patients who currently face the arduous cycle of VLU formation, closure and recurrence. JWC

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Reflective questions

- What factors contribute to the cost of a venous leg ulcer (VLU)?
- Why are infections a challenging complication for patients with a VLU?
- Why might early intervention in the case of a VLU be warranted?
- How might dehydrated human amnion/chorion membrane (DHACM) applied following parameters for use be cost-effective in the first year?
- At what willingness-to-pay threshold do DHACM savings become cost-effective? Why?

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Notes