LEGACY MEDICAL
CONSULTANTS

June 5, 2024

To: CMS Medicare Administrative Contractors (MACs)
Sent via email

Re: Legacy Medical Consultants Response to Skin Substitute Grafts/Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

Legacy Medical Consultants (LMC) writes to urge you to issue corrections, revisions, and additions to its proposed Local Coverage Determination (LCD) (DL39756, DL36377, DL39828, DL39760, DL39764, DL35041, DL39806, DL39865) entitled "**Skin Substitute Grafts/Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers"** recently released on 4/25/24. LMC is a supplier of proprietary regenerative biomaterial products processed from human amniotic membrane and other birth tissues. We are concerned that if implemented, the proposed LCD will increase risk of amputations and death, disproportionately impact patients from marginalized communities, put providers out of business, and set a precarious precedent by not collaborating with the FDA regulatory framework. We are committed to ensuring that patients with diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) have access to the treatments they need while ensuring that these products are not inappropriately utilized. For these reasons we are urging your to address the serious errors and inconsistencies, detailed below, before the LCD is finalized.

1. **The proposed LCD does not account for consequential supply chain deficits due to non-coverage of the majority of skin substitute products, significantly decreasing patient access to reasonable and necessary care for their non-healing wounds.**
   We are writing to express serious concerns that the proposed LCD threatens the lives and health of millions of Medicare beneficiaries suffering from venous insufficiency and diabetes who would lose access to skin substitutes as a result of this proposed LCD. Placental membranes, acellular matrices, and bioengineered skin substitutes are recommended by the American Diabetes Association as adjunctive treatment for chronic diabetic foot ulcers.[1,2,3] Inadequate wound care can lead to persistent and/or life-threatening infections, including cellulitis, abscesses, and osteomyelitis, an increased risk of amputation,

[1] Boulton AJM, Armstrong DG, Löndahl M, Frykberg RG, Game FL, Edmonds ME, Orgill DP, Kramer K, Gurtner GC, Januszyk M, Vileikyte L. New Evidence-Based Therapies for Complex Diabetic Foot Wounds. ADA Clinical Compendia 1 February 2022; 2022 (2): 1–23.
[2] El Sayed NA, Aleppo G, Aroda VR, et al., American Diabetes Association. 12. Retinopathy, neuropathy, and foot care: Standards of Care in Diabetes—2023. Diabetes Care 2023;46(Suppl. 1):S203–S215
[3] Boulton AJM, Armstrong DG, Kirsner RS, et al. Diagnosis and Management of Diabetic Foot Complications. Arlington (VA): American Diabetes Association; 2018 Oct. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538977/

and even death.[4,5,6,7] Chronic wounds and related complications can also lead to pain, reduced mobility, psychological effects such as depression and anxiety, and a significant impact on the quality of life.[8,9,10,11,12]

The implications of this proposed LCD for the American population are significant: 38.4 million Americans, or 11.6% of the population, have diabetes, but it is far more prevalent in the Medicare population, where 16% of Medicare beneficiaries have the disease.[13] There are significant health inequities in the incidence of amputation for patients with diabetic foot ulcers and foot infections: African-American and female patients have shown increased risk of receiving transfemoral amputation as a result of poor wound care, and those undergoing a major lower extremity amputation risk an increase in their five-year mortality rate of up to 56.6%.[14,15] These studies suggest that marginalized communities would be most at risk of suffering as a result of a lack of coverage for proper wound coverings.[14,16]

We are particularly concerned that the very few products that would be covered under the proposed LCD cannot, according to industry research, be scaled up in both manufacturing efficiency as well as quality to meet patient needs, further perpetuating patient suffering and adverse outcomes. We understand that four of the remaining fifteen covered products in the proposal are no longer manufactured, and the other eleven products do not exist in sufficient quantity to meet patient need. We urge the MACs to cover additional skin substitute products given the supply chain limitations and impacts to patient access to ensure patient care is not compromised.

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[4] Armstrong DG, Swerdlow MA, Armstrong AA et al. Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer. J Foot Ankle Res 2020; 13(1):16.
[5] Wu S, Armstrong DG. Risk assessment of the diabetic foot and wound. Int Wound J 2005; 2(1):17–24.
[6] Rankin TM, Miller JD, Gruessner AC, Nickerson DS. Illustration of cost saving implications of lower extremity nerve decompression to prevent recurrence of diabetic foot ulceration. J Diabetes Sci Technol 2015; 9(4): 873–880.
[7] Lavery LA, Armstrong DG, Wunderlich RP et al. Risk factors for foot infections in individuals with diabetes. Diabetes Care 2006; 29(6):1288–1293.
[8] Herber OR, Schnepp W, Rieger MA. A systematic review on the impact of leg ulceration on patients' quality of life. Health Qual Life Outcomes. 2007 Jul 25;5:44.
[9] Lim JZ, Ng NS, Thomas C. Prevention and treatment of diabetic foot ulcers. J R Soc Med 2017; 110(3):104–109.
[10] Pedras S, Carvalho R, Pereira MG. Quality of life in Portuguese patients with diabetic foot ulcer before and after an amputation surgery. Int J Behav Med 2016; 23(6):714–721.
[11] 4. Prinz N, Ebner S, Grunerbel A, Henkeludecke U, Hermanns N, Hummel M, Schafer C. et al. Female sex, young age, northern German residence, hypoglycemia and disabling diabetes complications are associated with depressed mood in the WHO-5 questionnaire - A multicenter DPV study among 17,563 adult patients with type 2 diabetes. J Affect Disord. 2017;208:384–391.
[12] Chapman Z, Shuttleworth CM, Huber JW. High levels of anxiety and depression in diabetic patients with Charcot foot. J Foot Ankle Res. 2014;7:22. doi: 10.1186/1757-1146-7-22.
[13] https://www.cms.gov/About-CMS/Agency-Information/OMH/Downloads/Data-Snapshots-Diabetes.pdf
[14] Centers for Medicare & Medicaid Services. *CMS National Coverage Analysis Evidence Review - Proposed Guidance Document*. Accessed May 28, 2024. https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx
[15] Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ*. 2015;350:h2147.
[16] Arad N, Khan BB, Staton E, Graunke H, Lopez MH. Medicare Coverage of Monoclonal Antibody Treatments for Alzheimer's Disease: Key Issues from the CMS Proposed Coverage Decision. Accessed May 23, 2024. https://healthpolicy.duke.edu/sites/default/files/2022-01/AD%20mAbs%20Key%20Issues%20CMS%20Draft%20Decision%20Memo%20Analysis.pdf

2. **The proposed LCD is overly restrictive of qualifying clinical evidence to support coverage decisions.**
While we agree with the proposed LCD that "…to be considered reasonable and necessary for coverage, each skin substitute/CTP must demonstrate net positive health outcome(s) in a well-defined patient population", requiring demonstration of "wound closure attributable to the individual product(s) proven in clinical trials with meaningful degree of certainty…" is overly restrictive of qualifying clinical evidence.

   As defined in CMS guidance ("Medicare Program Integrity Manual Chapter 13 – Local Coverage Determinations"), when conducting a review, the "MACs shall use the available evidence of general acceptance by the medical community, such as published original research in peer-reviewed medical journals, systematic reviews and meta-analyses, evidence-based consensus statements and clinical guidelines."[17] CMS and the MACs often rely on data from randomized controlled trials (RCTs) to inform coverage decisions, though **as defined in CMS guidance, the MACs are responsible for reviewing and considering multiple other forms of evidence**.[17]

   Unlike the data generated from RCTs, real world data (RWD) is data that relates to patient outcomes and the delivery of health care collected routinely from a variety of sources, including administrative data and electronic health records (EHRs). Real world evidence (RWE) constitutes evidence about the clinical utility and potential benefits or risks of therapies and devices derived from studies conducted using RWD.[18] RWE studies, published in peer-reviewed medical journals and generally accepted by the medical community, offer valuable insights, providing a more comprehensive basis for coverage decisions. Incorporating RWE into the standards for coverage decisions offers a more comprehensive and realistic assessment of new therapies and medical devices. RWE can provide broader population insights on long-term outcomes, real-world effectiveness, and faster access to information. In its National Coverage Analysis Evidence Review Guidance document, **CMS noted that "observational studies can be more representative of actual clinical practice and may answer questions that RCTs cannot answer**" and can achieve the high credibility CMS expects, particularly when discussed with CMS and the Agency for Healthcare Research and Quality (AHRQ) before study execution.[14] By integrating both types of evidence, CMS and the MACs can achieve a balance between internal validity (from RCTs) and external validity (from RWE), ensuring that coverage decisions are both scientifically robust and applicable to real-world practice.

[17] Centers for Medicare & Medicaid Services. Medicare Program Integrity Manual Chapter 13 – Local Coverage Determinations.; 2019. Accessed May 23, 2024. https://www.cms.gov/regulations-and-guidance/guidance/manuals/downloads/pim83c13.pdf
[18] Corrigan-Curay J, Sacks L, Woodcock J. Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness. JAMA. 2018;320(9):867-868.

Full consideration of RWE offers CMS and the MACs the ability to make more informed, equitable, and effective coverage decisions that better serve the diverse and dynamic needs of the Medicare population. We urge the MACs to include all forms of evidence in any review.

3. **The Proposed LCD fails to include all the published evidence on human amniotic membranes in DFU and VLU that validates the class of product's clinical utility.**
LMC commissioned its own analysis of the benefits of amniotic membranes on DFU, which included 3 additional RCTs and 2 additional systematic reviews and meta-analyses as compared to the citations in the proposed LCD. One of the systematic reviews and meta-analyses not cited in the proposed LCD was Mohammed et al. (2022),[19] in which the authors examined the pooled effect estimate from 11 randomized controlled trials that compared dehydrated human amnion and chorion allograft (DHACA) to standard of care (SOC)—defined as the quartet of pressure relief/offloading, debridement, infection management, and revascularization when indicated. The analysis showed that DHACA was superior to SOC with regards to complete wound healing at both 6 weeks (RR = 3.78; 95% CI: [2.51, 5.70]; p<0.00001) and at 12 weeks (RR = 2.00; 95% CI: [1.67, 2.39], p<0.00001) after intervention. Further, the authors found that the meta-analysis favored the DHACA treatment with regards to the average time to heal in the 12th week (mean difference = -12.07, 95%CI: [-19.23, -4.91], p=0.001) as well as wound size reduction (mean difference = 1.18, 95%CI: [-0,10, 2.26], p=0.03). This systematic review and meta-analysis demonstrated that using DHACA with SOC is safer and more effective than using SOC alone for patients with non-healing diabetic foot ulcers.

When examining the patient populations within each of these trials, many of the patients are either currently eligible for Medicare (age $\geq$65) or will be eligible within a few years: the average ages for each study ranged from 55.1 years old to 63.3 years old with the standard deviations for each study ranging from 7 years to 18.3 years. Consistent with the literature showing diabetic foot ulcers occur at a rate 1.5 times higher in men than women, approximately 70% of all patients enrolled were male and 30% were female.[20,21,22]

As in the proposed LCD, the authors of Mohammed et al. (2022) assessed the risk of bias using the tools described in the Cochrane Handbook for Systematic

[19] Mohammed YA, Farouk HK, Gbreel MI, Ali AM, Salah AA, Nourelden AZ, Gawad MMA. Human amniotic membrane products for patients with diabetic foot ulcers. do they help? a systematic review and meta-analysis. J Foot Ankle Res. 2022 Sep 14;15(1):71.
[20] Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. Ann Med 2017;49:106–116
[21] Rossboth S, Lechleitner M, Oberaigner W. Risk factors for diabetic foot complications in type 2 diabetes-A systematic review. Endocrinol Diabetes Metab 2020;4:e00175
[22] Lin C, Liu J, Sun H. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a meta-analysis. PLoS One 2020;15:e0239236

Reviews of Interventions 5.1.0. The authors flagged that most studies had low risk in the domains of random sequence generation, incomplete outcome data, selective reporting, and other bias; high risk in the domain of blinding of participants and personnel; and unclear (or mixed) risk in the domain of allocation concealment and blinding of outcome assessment. Although the lack of blinding can introduce bias into the experimental design of these randomized controlled trials, blinding can be difficult in wound care treatment studies, as they often involve physical products such as bandages, dressings, or topical agents that are visually distinctive or unique in appearance, smell, or mode of application, making it difficult to mask their identity from both the patients and the caregivers. Altogether, this **meta-analysis and the 11 individual RCTs have demonstrated clinical benefit of the skin substitute products as a class, and we urge the MACs to recognize these products as a class for coverage purposes.**

4. **The proposed LCD makes additional unsubstantiated representations about risk and disparate safety and effectiveness profiles among skin substitutes.**
   Given the reviewers' desire to focus only on peer-reviewed double-blind clinical trials, it is concerning that the MACs assert that there is a risk of contamination and/or infection with no reference to citable peer-reviewed publications. Amniotic membrane products, if processed appropriately, have been described as having both antimicrobial properties and a very favorable safety profile,[23] thereby implicating minimal risk.

   The MACs also make the assertion—without a reference—that these are heterogeneous products needing independent evidence generation, despite the **general consensus in the field (including descriptions in medical literature) that amniotic grafts are homogenous as far as technology and composition.** For example, meta-analyses combine multiple products to determine a positive class effect on both wound closure and time to wound healing outcomes, and virtually all of the individual trials demonstrate similar positive effects.[19,24,25,26] Additionally, the systematic review and meta-analysis by Mohammed et al. (2022) demonstrated a statistically significant lower number of adverse events after including 11 RCTs in their study.[19] Disbanding this homogenous class and requiring RCTs for each and every product is not only counter-intuitive to the homologous nature of these products, but it is in direct conflict to the prevailing practice that treats these products as interchangeable in

[23] Munoz-Torres JR, Martínez-González SB, Lozano-Luján AD, Martínez-Vázquez MC, Velasco-Elizondo P, Garza-Veloz I, Martinez-Fierro ML. Biological properties and surgical applications of the human amniotic membrane. Front Bioeng Biotechnol. 2023 Jan 9;10:1067480.
[24] Haugh AM, Witt JG, Hauch A, Darden M, Parker G, Ellsworth WA, Buell JF. Amnion Membrane in Diabetic Foot Wounds: A Meta-analysis. Plast Reconstr Surg Glob Open. 2017 Apr 25;5(4):e1302.
[25] Laurent I, Astère M, Wang KR, Cheng QF, Li QF. Efficacy and Time Sensitivity of Amniotic Membrane treatment in Patients with Diabetic Foot Ulcers: A Systematic Review and Meta-analysis. Diabetes Ther. 2017 Oct;8(5):967-979.
[26] Paggiaro AO, Menezes AG, Ferrassi AD, De Carvalho VF, Gemperli R. Biological effects of amniotic membrane on diabetic foot wounds: a systematic review. J Wound Care. 2018 Feb 1;27(Sup2):S19-S25.

all characteristics relevant to product safety and effectiveness. We urge the MACs to ensure that all requirements for coverage in the final LCD align with peer reviewed published research and standards generally accepted by the medical community, as required by CMS guidance,[27]

5. **The proposed LCD sets an unbased limitation on number of treatments with amniotic grafts.**
   For the covered products, the LCDs **limits treatment to 4 applications, which wound care clinicians advise is contrary to the standard of care, is based on a misreading of the clinical literature, and is inconsistent with patient care needs**. As described in the proposed LCD using data from Armstrong et al. (2021), "In the largest reported cohort of 12,313 ulcers treated with skin substitute grafts, the mean number of applications was 3.7 with a standard deviation of 3.6."[28] Notably, only lack of wound size data was considered an exclusion criteria rather than relative size of the wounds being studied in a retrospective study. However, given the variation in the number of applications required in a large, nationally representative dataset, the restriction to four applications does not accommodate the variability in clinical need. As seen in several trials referenced in the LCD, there are many patients that require more than 4 applications as seen by both large variability (high standard deviation) and left-skewed data (relatively few patients requiring only 1 application). Many patients require more than 4 applications to achieve optimal healing, and thus, the imposed limitation fails to reflect the true clinical scenario and may hinder patient outcomes by not allowing sufficient treatments based on individual needs. Therefore, we urge the MACS to increase the covered applications to 8 to allow providers to use their clinical expertise to determine the number of applications needed a patient, thereby allowing the provider to be the determiner of the practice of medicine rather than the MACs.

6. **The proposed LCD lacks prior notice of requirement and transparency of the coverage decision process going forward, including for products soon to initiate RCTs.**
   LMC initiated development of an RCT and RWE (including Medicare claims studies) processes for several of our products prior to the publication of the proposed LCD. The LCD has not defined an ongoing process of reviewing new evidence and as described above there is **no consistency in evidence being accepted and no transparency as to what metrics were or will be utilized to review the evidence**. The first of several LMC RCTs is registered on ClinicalTrials.gov, and the protocol utilizing the Orion product is currently being submitted to the Institutional Review Board and sites are being recruited.

[27] https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27
[28] Armstrong DG, Tettelbach WH, Chang TJ, De Jong JL, Glat PM, Hsu JH, Kelso MR, Niezgoda JA, Tucker TL, Labovitz JM. Observed impact of skin substitutes in lower extremity diabetic ulcers: lessons from the Medicare Database (2015-2018). J Wound Care. 2021 Jul 1;30(Sup7):S5-S16.

Orion is an amnion membrane allograft that is processed through a multi-step process including cleaning and rinsing followed by folding to create a "double layer," drying, cutting, packaging, and irradiation.

On October 14, 2022, the FDA Tissue Reference Group (TRG) issued a letter addressing Orion, which states that Orion "meets the criteria for regulation solely under section 361 of the PHS Act and the regulations in 21 CFR part 1271."[29] CMS has acknowledged the FDA TRG feedback: Based on the TRG's letter related to Orion, CMS created HCPCS code Q4276, effective July 1, 2023, in recognition that Orion is appropriately classified as an HCT/P.[30] Given the above noted concerns, we urge the MACs to give provisional approval to the Orion product until the trial is completed.

Most skin substitute products are regulated under section 361 of the PHS Act and the regulations in 21 CFR part 1271 as products for wound management—not wound healing or treatment. Under the proposed LCD, the skin substitutes must "have quality supporting evidence to demonstrate the product's safety, effectiveness, and positive clinical outcomes in the function as a graft for DFUs and/or VLUs.[4,10] Predicate products are not sufficient evidence for an individual product." In light of the FDA regulatory process—which groups these products in a class of HCT/Ps regulated solely under section 361 of the PHS Act—it is unclear if any new formulations of wound covering grafts would necessitate new evidence not required by the FDA to meet the standard of evidence advocated by the LCD. It is also unclear what the threshold of manipulation to composition of a covered product can be as this LCD does not define how a product with a Q-code may have variability post initial marketing and development of clinical evidence (i.e. RCT).

7. The proposed LCD inappropriately divides a class of products, creating confusion for manufacturers, and undermining trust with providers and patients.

The proposed LCD seeks to limit coverage to products that have demonstrated efficacy through RCT, which is a level of evidence not required by the FDA or the TRG, nor have they historically been required by CMS for skin substitutes. FDA has determined this class of products to be in a class of HCT/Ps regulated solely under section 361 of the PHS Act and has determined them to be safe and sufficiently low risk. If the MACs choose to cover skin substitutes, they should do so as a class, in line with the regulatory oversight determination from FDA, especially in the absence of data indicating a therapeutic disadvantage in the currently available products between those with RCT data and those without.

[29] FDA, TRG Letter for Zenith 1 (Feb. 22, 2021).
[30] CMS, HCPCS Application Summaries for First Quarter 2023 Coding Cycle for Drug and Biological Products 27, *available at* https://www.cms.gov/files/document/2023-hcpcs-application-summary-quarter-1-2023-drugs-and-biologicals-updated-07/05/2023.pdf.

> As mentioned above, the confusion for manufacturers and potential for abuse of the proposed new standards is clear. But picking and choosing between products the FDA has previously regulated as a class of HCT/Ps regulated solely under section 361 of the PHS Act will introduce considerable uncertainty among providers, patients, and their families. Patients count on FDA to ensure that the products and tools used to provide care are properly regulated, and the integrity of the health care system counts on the regulator's role to do so. Recognizing that the FDA has determined these products are regulated as a low-risk class, we urge the MACs to either cover or not cover skin substitutes as a class.

With supply chain shortages limiting patients' access across the United States, severely restricting an entire class of currently covered and effective skin substitutes has the potential to negatively impact tens of thousands of patients without further discussion and consideration by the MAC regarding the evidence of these products and their manipulation post launch. LMC therefore strongly urges the MACs to reconsider their coverage policies according to the points outlined above in order to ensure that patient outcomes are prioritized in any coverage decisions.

Further, LMC writes to urge the MACs to issue a 24-month extension before the proposed LCD goes into effect. This extension will allow for comprehensive review and necessary revisions to ensure that the proposed LCD does not inadvertently harm patients, particularly those from marginalized communities, by limiting access to essential treatments. It will also provide sufficient time to address supply chain deficits, incorporate diverse clinical evidence, and ensure alignment with the FDA regulatory framework, ultimately ensuring that patient care is not compromised.

Sincerely,

Jonathan Knutz
CEO, Legacy Medical Consultants