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Clinical trials for cellular, acellular and matrix-like products (CAMPs): an evidence consensus

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CONSENSUS DOCUMENT

Clinical trials for cellular, acellular and matrix-like products (CAMPs): an evidence consensus

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Foreword

As Chair of the evidence consensus panel, I had the pleasure of convening the nation's top experts in the field of wound healing on August 1, 2025, in Washington D.C.. The goals for the expert panel were twofold: 1) to address the evidence gap around the efficacy of cellular, acellular, and matrix-like products (CAMPs) in the treatment of nonhealing wounds and 2) to develop guidelines for the conduct of CAMP clinical trials. In 2024, the Medicare Administrative Contractors (MACs) published nearly identical Local Coverage Determinations (LCDs) requiring clinical trial evidence for reimbursement of CAMP products for diabetic foot and venous leg ulcers. The LCDs analyzed the available evidence for CAMPs and, based on their review, approved several products. After several delays, the MACs require products not on the list to submit peer-reviewed evidence submissions by November 1, 2025.

I applaud CMS and the MACs for their reliance on clinical trial evidence; however, few of the patients enrolled in the approved RCTs published to date would meet the LCDs' requirements for medical necessity. Moreover, the LCDs do not provide any guidance on trial design or conduct to guide future research. The purpose of this evidence consensus is to define a practical, rigorous evidentiary bar spanning run-in requirements, consistent standard of care, pre-trial statistical analysis plans, validated clinical endpoints, complete datasets, and data transparency. In this way, investigators, sponsors, journals, and payers can align on what constitutes credible proof of benefit.

The implications of publishing this consensus are immediate and material: it creates a uniform template for trials intended to support Medicare coverage, improves comparability across products, reduces bias and opaque practices, and prioritizes outcomes that matter to patients and clinicians. By articulating standards that reflect current best practice and analytic methods, this consensus gives CMS and the MACs a defensible basis for reimbursement decisions while accelerating access to effective CAMPs for beneficiaries and steering industry investment toward studies that will withstand regulatory and peer scrutiny.

Dr. Thomas E. Serena. Chairman, Consensus Panel

Introduction

Over the last two decades, cellular, acellular, and matrix-like products (CAMPs) have become an integral and valuable intervention in stimulating repair and regeneration of injured tissues, especially on hard-to-heal wounds such as diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs).[1–7] In 2024, Centers for Medicare and Medicaid Services (CMS) issued a Local Coverage Determination (LCD) for these products, also termed skin substitutes and cellular and tissue based products (CTPs).[8] The LCD covers DFUs and VLUs only and is intended to ensure that Medicare covers products that have sufficient evidence of clinical efficacy. Randomized controlled trials (RCTs) for DFUs and VLUs were cited in the LCD; however, CMS is reviewing its coverage policies and has delayed the effective date until January 1, 2026. To assist in the review, CMS has requested peer-reviewed publications and high-quality findings about CAMPs be submitted to them by November 1, 2025.[9]

There is a lack of guidance on the essential elements that should be included in an RCT, which is the scientific gold standard for medical research. A consensus panel convened in Washington, D.C. on August 1, 2025, with the goal of providing guidance on the optimal design and conduct of clinical trials for CAMP reimbursement, in part because it was felt that the LCD criteria for a patient to be enrolled in a CAMP clinical trial designed for coverage and reimbursement was not met in the RCTs cited by CMS.

A meta-analysis of 35 of the RCTs cited by CMS was conducted; the criteria of previous RCTs and the criteria listed in the LCD were compared to determine if the criteria were met in the LCD trials. A panel discussion of each criterion resulted in recommendations which are presented in this paper; they will be presented to CMS as the evidentiary bar for future CAMPs studies seeking CMS reimbursement.

Overview of the evidence

The discussion began with a presentation of a hierarchical Bayesian meta-analysis of the 35 RCTs cited in Medicare's 2024 LCDs, which formed the evidentiary foundation for the coverage of 17 CAMPS products for DFUs in the Medicare population. The hierarchical beta-binomial framework allowed evidence to be integrated across trials, accounting for heterogeneity in design, comparators, sample sizes, and patient populations, while borrowing results of evidence across similar study arms to strengthen the estimates of treatment effect. Healing outcomes were standardized to 12 weeks with balanced sample sizes, and results consistently showed that CAMPS products outperformed standard of care.

Based on the meta-analysis, advances or criteria in trial design were considered, and comparisons were made across historical RCTs, as well as currently ongoing and future RCTs, including those which do, and possibly could,

incorporate adaptive and other novel design features (*Table 1*). From the discussion, a recommendation for each criterion was agreed upon by the panel and is presented here, together with pertinent discussion and considerations for each one.

Essential elements

1. The patient must have had 30 days of nonhealing documented prior to enrollment

The LCD states that a DFU or VLU that has failed to respond to standard of care (SOC) after 4 weeks (28 days) of treatment would be considered chronic and a CAMP application could be reasonable and necessary. The LCD further defines failed response as less than 50% reduction in size with the documented SOC, which must be recorded prior to the application of a CAMP. The trials cited in the LCD failed to meet this requirement. One approach suggested to meet this requirement is as follows: the patient could be seen, wound measurements documented, and 2 weeks of SOC provided. If, at the end of the 2 weeks the wound has decreased in size by less than 20%, the patient could be enrolled in the study. Enrollment is followed by a 2-week run-in period during which SOC is continued, and if at the end of that time (4 weeks from start of care), the wound has closed less than 40%, a CAMP can be applied and the patient can be enrolled in the treatment arm of the trial, assuming that occurs with randomization. Earlier studies indicated a percentage of area reduction (PAR) of 50% in 4 weeks was prognostic of healing; however, a more recent post-hoc analysis suggested that if a wound has closed less than 40% in 4 weeks, CAMP application is indicated.[10,11]

Another concern in protocols that specify a 4-week follow-up period prior to enrollment is whether the care during those 4 weeks has to take place at the same facility conducting the study. In practice, prospectively observing wounds for 4 weeks before study initiation while considering potential enrollment is often impractical. Therefore, the protocol should clarify whether photographs or electronic records from another facility may be used to document that the patient has indeed been receiving care for 4 weeks without the specified improvement prior to enrollment.

The panel experience has been that over two-thirds of all screen failures occur because the patient heals more than 40% during the screening and run-in periods, thus a run-in phase is recommended.

Recommendations:

- The trial should include a run-in phase during which the target ulcer fails to decrease in size by 40-50% in 4 weeks.[11,12]
- The run-in period must include SOC which is incorporated into the trial protocol.

2. The trial must mandate consistent standard of care

Most of the trials analyzed did not use consistent SOC across treatment arms. SOC can be highly variable among providers and patients. Challenges to managing these differences were discussed, and it was pointed out that they can be accounted for in statistical models to wash out the variable effects and better estimate the product effect. Providing supplies and training to all the sites and clinicians involved in a trial can improve homogeneity.

Heterogeneity in SOC creates a central challenge in trial design. Greater standardization strengthens internal validity; however, too much standardization risks reducing external validity and real-world relevance. Bayesian hierarchical models address this tension by explicitly modeling variability in healing outcomes across trials. In the beta-binomial framework, this variability is captured by the dispersion parameter κ, which reflects the degree of heterogeneity beyond what a simple binomial model would predict. Assessing κ provides a way to evaluate how much outcome variability arises from SOC itself, and comparing κ values between SOC and treatment arms establishes a benchmark for determining whether an intervention demonstrates effectiveness beyond the inherent variability of SOC.

The panel also discussed the need for debridement, defined as the removal of non-viable tissue and biofilm in a wound, and the feasibility of using newer tools to detect presence of biofilm and bioburden, and thus ensure more consistent debridement.[10,13–15] Some trials are now using fluorescence imaging pre- and post-debridement as a guide to targeted removal of bacteria prior to application of the CAMP. Additional future trials may use near-infrared spectroscopy (NIRS) to guide and evaluate the effectiveness of debridement.[16–19]

The inclusion of vascular studies for patients with DFUs was discussed at length with the acknowledgment that for some patients, especially those with renal failure, an ankle-brachial index (ABI) is not sufficient to predict healing potential. Toe/brachial indices, ankle pressures, and evaluation of waveforms are alternative assessments, as are newer technologies such as NIRS; however, the panel acknowledges these alternatives may not be available in some settings, such as rural home health. In addition, the International Working Group on the Diabetic Foot (IWGDF) Guidelines state that when toe pressures cannot be performed on a patient, transcutaneous oxygen pressure ($TcPO_2$) and skin perfusion pressures (SPP) may be prognostic of healing potential.[20]

TABLE 1 | A comparison of current randomized controlled clinical trials (RCTs), previously conducted CAMP RCTs listed in the final LCD, and the LCD requirements. A check mark signifies that the criteria are satisfied fully

Advances in trial design	Current RCTs	Previous RCTs	In the LCD
30 days of nonhealing documented prior to enrollment	✔	Absent. Patients enrolled would not have met the LCD criteria	✔
Run-in period with aggressive treatment prior to enrollment	✔	Most trials did not include a run-in period to ensure that the patients required advanced therapy	This is part of the nonhealing requirement in the LCD
Consistent standard of care (SOC)	✔	Most of the trials analyzed to not use consistent SOC across treatment arms. There is inconsistency in key interventions such as debridement and off-loading	✔
Complete outcome data.	✔	As noted in the LCD analysis, most of the CAMP trial results were biased due to missing data or high drop out and withdraw rates	The LCD Analyses listed most of the RCTs as high bias due to missing data
Statistical analysis plan (SAP) provides statistical justification for the trial's power	✔	All but a few of the CAMP RCTs are adequately powered. Some of the manuscripts pooled data without justification	The LCD notes the need for adequate power but does not provide guidance on the requirements for an appropriate SAP
Validation of outcome measures including independent assessment of the primary endpoint	✔	Few of the previous CAMP RCTs did not include validation of the outcome measures including the primary endpoint. This is essential in trials that cannot be blinded	The LCD does not provide guidance on clinical trial design; however, the analysis of current LCDs clearly identifies the need for validation of outcome measures
The use of recognized endpoints: closure at 12 weeks for DFU and VLU	✔	The CAMP trials conducted over the past 20 years have not always used accepted recognized endpoints	The LCD does not provide guidance on clinical trial design; however, investigators in the field of wound healing, including the Wound Care Collaborative Community, recognize the 12-week closure endpoint
Randomization plan	✔	Many of the CAMP trials did not publish their randomization plan	This importance of transparency in clinical trial conduct is emphasized in the final LCD
Data transparency	✔	The trials analyzed as part of the final LCD have not publicly posted all the clinical trial data. transparency in clinical trial conduct is emphasized in the final LCD	The LCD mentions that many of the trials analyzed had large numbers of withdrawals and dropouts without explanation. Transparency of the data is essential
Unrealistic healing rates reported in the results of the clinical trial	All data will be made available	Several trials report healing rates that are far outside the observed rates in other trials and real-world studies. The data reported in these studies are suspect	It is not in the public interest to approve products based on trials that are best described as outliers

TABLE 1 | A comparison of current randomized controlled clinical trials (RCTs), previously conducted CAMP RCTs listed in the final LCD, and the LCD requirements. A check mark signifies that the criteria are satisfied fully. (cont.)

Advances in trial design	Current RCTs	Previous RCTs	In the LCD
The authors of the trial manuscript report both intent-to-treat (ITT) and per protocol (PP) results.	✔	Many of the CAMP RCTs listed in the covered group did not report the ITT data. This information is necessary to evaluate potential bias in the trial	This is standard practice in reporting clinical trial results and necessary if the MACs are going to analyze evidence
The clinical trial must include racially diverse populations.	✔	Previous RCTs do not report plans to ensure the inclusion of a racially diverse population or report the use of a tool to gather this information	It is important that all Medicare beneficiaries have access to advanced care and that approved products demonstrate efficacy in all populations
Assess the nutritional status of all patients prior to enrollment using a validated tool	✔	Nutritional status is not assessed in any of the trials listed in the LCDs	✔
Trials should report patient-centered outcomes	✔	Previous CAMP trials infrequently and inconsistently reported patient-centered outcomes	Medicare requests that clinical trials report patient-centered outcomes
Independent conduct of the trial decreases bias	✔	Most of the trials analyzed in the LCD were conducted by industry	Medicare does not mandate the independent conduct of RCTs; however, there is desire for low-biased trials
Using master trial designs to garner evidence on multiple products simultaneously	✔	None of the RCTs listed in the LCDs used a master trial design	The final LCD stressed the importance of gathering evidence on individual products
Trials will generate data on comparative effectiveness using master trial designs	✔	There is no comparative effectiveness data for CAMP products	The final LCD suggests that investigators and companies gather comparative evidence data
Double blind trial designs reduce bias	Double blind studies have not been possible due to a lack of an inert placebo	None of the RCTs listed in the LCDs were blinded.	The final LCDs mention the importance of blinding in clinical trials
Multicentered trials conducted at geographically diverse locations and at a variety of patient care settings ensure generalizability of the data	✔	Many of the products listed on the approved list have trials that did not include geographically diverse sites or used a single type of trial setting (e.g. private office)	✔
Trials designed for Medicare coverage and reimbursement will analyze the efficacy of the investigational product in Medicare beneficiaries	✔	None of the trials listed in the final LCD report results in the Medicare population	Products must demonstrate efficacy in the Medicare population
Long-term follow up	✔	There is little data on both short term and long term follow up for CAMP trials. There is no long-term safety data. Some of the trials used a cross over design that does not permit long term follow up	The final LCD notes that most of the RCTs did not include follow up data

The panel discussed the necessity of including some method of monitoring diabetic control in SOC, either by assessing a patient's hemoglobin A1c or by using a continuous glucose monitor (CGM) for each patient. The challenge is the lack of standardized values for optimal healing[16,17] and availability of CGM equipment for all study participants. It was suggested that there be a standardized database or repository to record and maintain objective information about glucose control on every participant in a particular study, and if the values are not filled in for a study, an explanation would be provided.

Recommendations:

- SOC must be consistent and include adequate and appropriate debridement of the target wound with use of imaging technology to detect biofilm and bioburden (when available).
- In-depth training of providers in a trial can improve continuity and consistency of SOC.
- Information on the heterogeneity of SOC must be collected so that differences or variables can be considered statistically.
- SOC arms need to reflect up-to-date, current best practices.
- Vascular studies to assess perfusion in DFUs and a duplex study to confirm venous disease should be part of the protocol. Recommended studies include, but are not limited to, ABI, toe-brachial index (TBI), transcutaneous oxygen pressure ($TcPO_2$), and pulse volume recording.

3. The clinical trial report must include all outcome data

As noted in the LCD analysis, most of the CAMP trial results were biased due to missing data or high drop out and withdrawal rates. The panel discussed the potential for providing key source data to Medicare and MAC reviewers to support bias concerns (for example, data on dropout withdrawal rates and reasons for drop outs such as non-adherence with appointments, unexpected illness, or development of exclusionary criteria).

Concern was expressed about the failure of trials with a 12-week end-point to capture recurrence of wounds that may close but not be totally healed or remodeled sufficiently to prevent vulnerability to recurrence. This can be addressed by durability trials or long-term follow-up of patients who have been in trials. This would become the responsibility of the provider.

Generative statistical models address missing data by pooling information across patients and study levels, allowing robust inferences about missing observations.[21–23] Through partial pooling, these models borrow strength from the broader dataset to estimate what likely would have occurred for an individual patient—or, by extension, for an entire study arm—either across time or at a specific time point. This generative property provides a principled and transparent way to handle missing data.

Many of the CAMP RCTs listed in the LCD group did not report the intent-to-treat (ITT) data; information which is necessary to evaluate potential bias in a trial. It is essential that clinical trial publications include ITT as well as per protocol (PP) analysis.

Recommendations:

- Full data sets should be part of the trial report, including both ITT and PP results.
- Other methods of capturing data, such as adaptive pull trials, can be used to capture missing data on individual patients.

4. Confirmatory trials must have a statistical analysis plan (SAP) that justifies the trial's statistical power

Some of the LCD-cited trials did not have a robust SAP, for example the power justification is not reported or the calculations to determine sample size are not included. Even though the LCD notes the need for adequate power, it does not provide guidance about the requirements for adequate SAPs. Thus, few of the RCTs were adequately powered and some of the manuscripts pooled data without justification.

Discussion about FDA and CMS use of adaptive trials and Bayesian versus frequentist analysis indicated that FDA has been using adaptive trials for a long time and Bayesian analysis since 2007. The statistician felt that FDA standards are more stringent than CMS standards; however, in either case the rationale for a sample size needs to be part of the trial description. The panel suggests that tables, systems, or figures are helpful in showing that the required data is included in the trial description which will facilitate stronger meta-analyses. A future goal is for wound care trials to be confident enough to have data and analysis confirmed by an open-source process in which a code is given to a trial and other researchers can open source, test, and reproduce the findings of a trial.[24–26]

Recommendations:

- A complete SAP is an essential part of trial design because this is where landmarks are defined.

- The raw abridged data used in the analysis, summary tables, and statistical test/model should be open sourced for CMS through a repository and available upon request.

5. The trial must have validation of outcome measures including an independent assessment of the primary endpoint

Few of the CAMP RCTs indicated how the individual patient outcomes were validated, including the primary endpoint, an essential element in any trial that cannot be blinded. The LCD does not provide guidance on clinical trial design; however, the meta-analysis of LCD-cited trials clearly identifies the need for validation of outcome measures.

Panel discussion about how to validate outcomes focused on the value of photographs which can be independently validated; however, a photograph of a fully re-epithelialized wound does not indicate whether the tissue is fully healed beneath the new epithelium and does not verify drainage, which is another criteria for considering a wound closed. In addition, the tissue does not regain full function until the remodeling phase of healing is complete, a physiologic process that can take months to complete. Photographs also do not capture light reflection from the surface of new epithelium which the investigator can see with the naked eye. Exploratory endpoints using newly developed adjunct tools for assessing healing such as transepidermal water loss (TEWL)[27,28] and NIRS[29,30] could be considered.

A 2025 study by Sen showed that healed DFUs that have a higher TEWL as compared to a non-injured area on the contra-lateral foot are two times more likely to have recurrence, indicating that the water barrier function of the skin has not been restored.[31] There are several hand-held devices that detect changes in water vapor density and humidity over time and take into account environmental factors such as temperature, humidity, and airflow, making it a feasible and accessible evaluation tool. While wound healing has historically been defined as full re-epithelialization and no drainage for 2 weeks, 2 consecutive times after closure, measuring TEWL may be a more objective endpoint to define wound resolution; however, it has not yet been standardized, and the current standard remains assessment by an expert clinician.

NIRS provides visualization of subcutaneous oxygenation, and thus the revascularization that occurs during the healing process and inflammation that may not be otherwise detected.[32–34] A study by Clifford suggested that decreased intensity in the subcutaneous oxygenation reading correlated with better healing of the wound.[35] Objective information provided by this technology can help guide clinical decisions, such as when to transition a patient with a DFU from a total contact cast to a custom off-loading shoe.[32] When used in RCTs, NIRS can provide another objective endpoint of wound healing and prediction of recurrence.

Recommendations:

- RCTs must have validated outcome measures.
- Pictures are an integral part of following wound progress and indicating when a wound is fully epithelialized. Validated new technologies are advised for more objective endpoints to evaluate surrogate endpoints and vulnerability for recurrence.

6. The trials must use recognized chronological endpoints: closure of the wound at 12-14 weeks for DFU and VLU

The LCD does not provide guidance on clinical trial design; however, investigators in the field of wound healing, including the Wound Care Collaborative Community, recognize the 12-week closure endpoint for DFUs and 12-16 weeks for VLUs. In fact, CAMPs trials over the last 20 years have not always used accepted recognized endpoints. While the panel suggests a standardized time frame for all RCTs so that everyone is using the same length of time, it also acknowledges that wound size can affect the outcomes within a set time frame. Endpoints can also vary according to the diagnosis being treated in the RCT, for example, 12-16 weeks for VLUs or 20 weeks for pressure injuries. Adjustment for baseline wound area is recommended as a methodological best practice to improve precision and reduce bias in estimating treatment effect.[36]

The panel discussed the 2-week post-closure follow up that occurs with most clinical trials, in comparison with a MAC definition of 2 weeks 2 consecutive times, or 4 weeks total, follow up. One idea was that after two weeks, if there is going to be more follow-up, the patient goes into a durability trial.

Patient satisfaction as an endpoint was discussed and several tools for measuring the effect of a wound on quality of life (QoL) were reviewed in terms of feasibility in a clinical trial.

Recommendations:

- Time endpoints should be standardized for each wound etiology.
- Any QoL tool should be an ordinal model.
- QoL questionnaires work best if administered before and after an interval, not at every visit.

7. Trials should report patient-centered outcomes

Previous CAMP trials infrequently and inconsistently reported patient-centered outcomes. A 2023 scoping literature review by Lazar et al reported that RCTs on VLUs reported healing and pain but did not report on other outcomes that are important to patients, such as mobility, quality of life (QOL), reduced patient costs, and likelihood of infection or amputation. They also found that ultrasound duplex studies and patient risk factors for non-healing were not consistently reported.[37]

A 3-phase study conducted by Driver et al in conjunction with the FDA identified and validated criteria for qualifying endpoints relevant to clinical practice and patient-centered outcomes as primary outcomes in wound care RCTs.[38] Phase 1 was a survey to 628 expert wound clinicians and researchers to assess literature-based endpoints relative to both clinical practice and research and to improving QOL. Phase 2 was a systematic review of the literature to determine if FDA criteria for outcomes were being followed. Of the 485 references reviewed, more than 50 reported outcomes in the following areas: pain reduction, physical function and ambulation, infection reduction, time to heal, and PAR in 4-8 weeks.[39] Among these endpoints, only time to heal was recognized by the FDA as a primary outcome in RCTs.[39] Phase 3 of the study was an online survey in English and Spanish with 438 responders, in which the most valuable clinical outcomes were identified as reduced infection, recurrence, and amputation. The most valuable QoL outcomes were increased independence, reduced social isolation, and pain. The five most useful endpoints for measuring RCT success were time to heal, wound size, infection, recurrence, and pain.[40]

Recommendations:

- Patient-centered outcomes are an integral and necessary part of RCT endpoints.
- Validated scales and tools are advised to assess and report patient-centered outcomes.

8. The trial must have a randomization plan as part of the protocol

The randomization plan is an important and necessary aspect of transparency in any clinical trial; therefore, it should be included in the protocol and any publications about the trial. Randomization (or random allocation of subjects) eliminates accidental bias and minimizes confounding factors so that results can be attributed to the intervention.[41] Optimal technique can depend upon trial variables, e.g. sample size, and a discussion of the different techniques and their advantages/disadvantages is beyond the scope of this paper; however, a universally-accepted plan needs to be a part of any RCT.

Recommendations:

- A randomization plan appropriate for the details and design of any RCT needs to be part of the protocol and included in any publications about the trial to ensure transparency of the study.

9. Sponsors must adopt a policy of data transparency

Transparency of data is an essential part of any RCT and failure to do so affects its credibility. Many of the trials analyzed by CMS in developing the LCD had large numbers of withdrawals and dropouts without an explanation of the circumstances. In addition, some of the trials analyzed as part of the final LCD did not publicly post all their clinical data. Several of the trials report healing rates that are far outside the observed rates in other trials and in real-world studies, raising concerns about data validity and interpretation. It is not in the public interest to clear products for use based on trials that are best described as outliers.

A 2018 report by Fife et al compared real-world data from the US Wound Registry with RCTs to develop criteria for reporting wound outcomes.[42] A Wound Healing Index, a validated risk stratification model for predicting wound healing using patient- and wound-specific variables, has been developed for venous leg ulcers[43], diabetic foot ulcers[44], and pressure injuries.[45] These indices can be used to identify which patients will need adjunctive therapies or referral to other specialties, as well as creating more generalizable RCTs to determine the impact of clinical interventions.

Recommendations:

- Trials that report statistical outlier healing rates will make their raw data available upon request.

10. The clinical trial must include racially diverse populations

Previous RCTs do not always report plans to ensure inclusion of a racially diverse population, nor do they include the use of a tool to gather this information in the protocol. Having racial diversity in a trial has been mandated by the FDA and can be tracked by using a tool such at the Fitzpatrick skin score[46,47] or the Monk scale[48] and including the results in the patient demographics. The panel also discussed the potential inclusion of patients outside the United States to obtain greater diversity, both racially and economically, as socioeconomic and cultural barriers are likely to be more important than skin tone.

Based on a literature review, Clark et al identified the following 5 critical barriers to participation of racially and ethnically diverse patients in clinical trials: mistrust, lack of comfort with the clinical trial process, lack of information about clinical trials, time and resource constraints associated with participation, and lack of awareness about the existence and importance of clinical trials.[49] Then through a multi-step process with both participants and investigators, they developed the following themes that need to be communicated during enrollment in a clinical trial: reinforce the importance of personal health, ensure safety, confirm clear information is provided for decision-making, appreciate involvement, and emphasize available support.[49] The authors concluded that overcoming the barriers with enhanced communication would increase the willingness of diverse populations to participate in clinical trials.

Diversity of age also needs to be considered, especially in the DFU trials, as more younger individuals are developing type 2 diabetes with subsequent complications. Further information on FDA regulations and recommendations on including more diverse populations (including sex, age, and race) in clinical studies can be found in their publication, "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies: Guidance for Industry and Food and Drug Administration Staff."[50]

Recommendations:

- Racial and age diversity are encouraged in all RCTs as one way to ensure that all Medicare beneficiaries have access to advanced care.
- Reporting racial and age diversity in RCTs demonstrates efficacy of products in all populations.
- A certain percentage of patients should be allowed, but not required, from outside the US to help assess efficacy of a product in all populations, given that the protocols and SOC can be followed.
- Communication techniques during the enrollment process that encourage more diverse participation are advised for the protocol in clinical trials.

11. Clinical trials must assess the nutritional status

Nutritional status is not assessed in any of the trials listed in the LCD, although nutritional deficits are known to have a negative effect on wound healing potential.[51–53] Laboratory tests that can be used to assess a patient's nutritional status include serum albumin, prealbumin, transferrin, retinol-binding protein, and body mass index. Screening tools that can also assist in detecting malnutrition include the Mini Nutritional Assessment, Malnutrition Universal Screening Tool, LPZ questionnaire, and Subjective Global Assessment.[54] The Mini Nutritional Assessment has been validated for elderly patients in all clinical settings and is available in both its original and a short form.[55,56] The Global Leadership Initiative on Malnutrition (GLIM) developed the following two-step approach for diagnosing malnutrition: 1) using a validated screening tool to identify risk; and 2) assessing for diagnosis and severity using 5 criteria (non-volitional weight loss, low body mass index, reduced muscle mass, reduced food intake, and inflammation or disease burden).[57]

Recommendations:

- Patients' nutritional status as measured by a validated laboratory value or screening tool should be included in the protocol of all clinical trials.
- Workflow of the trial regarding standardized nutrition should be to screen the patient for malnutrition, optimize the nutrition, and then enroll in the trial.
- Malnourishment should be an exclusion criterion if it cannot be corrected.
- When using the Mini-Nutritional Assessment, the 18-item form is advised for research as it captures more information about the patient; however, the 6-item form is sufficient for clinical practice.

12. Sponsors and investigators should consider utilizing master trial designs to garner evidence on multiple products simultaneously

Most of the trials analyzed in the LCD were conducted by industry, and the panel acknowledges the necessary role of industry in advancing the research of wound healing. In fact, a 2024 systematic review by Milazzo et al found that the presence of industry support of RCTs in plastic surgery significantly increased enrollee adherence.[58]

The panel discussed strategies for structuring low-biased trials and agreed that using the master trial design is a potentially valuable option. There are three types of master design trials – platform, basket, and umbrella. The platform trial evaluates multiple interventions simultaneously within a single diagnostic group (e.g., DFU) using a shared SOC arm, improving efficiency and allowing products to be added or dropped adaptively. The basket trial tests one intervention across multiple wound types (e.g., DFU, VLU, PU), thereby enabling evidence generation for several diagnoses within a single framework. In basket designs, trial arms are dynamic, with interventions dropped, added, or reallocated as evidence accumulates, and subgroup analyses are readily incorporated to assess differential effects. The umbrella trial evaluates multiple interventions within a single wound type, such as pressure ulcers, by stratifying patients into subgroups like partial versus full-thickness or Staging classifications while maintaining a common SOC comparator.[59–62] Most of the studies about trial design were for either oncology or Covid-19 protocols; however, the

findings and suggestions for use may be applicable to wound care RCTs. Currently the FDA will only allow one wound type in a trial unless it is an early Phase 2 hypothesis generating trial, i.e. the trial is evaluating an intervention's efficacy in a larger group of patients than a Phase 1.

In planning protocols for trials using the basket model, matched controls from the database would be used to eliminate the necessity for a SOC arm; SOC could differ for all of the diagnoses included. For example, in a trial of lower extremity wounds that could include VLUs, as well as other diagnoses (such as sickle cell disease, pyoderma gangrenosum, congestive heart failure, lymphedema, or vasculitis), there would be no one SOC for all the subjects.

It was noted that the final LCD stressed the importance of gathering evidence on individual products, not CAMPs in its entirety. Currently there is no comparative evidence on any of the CAMPs products, something which the final LCD suggests investigators and industry could gather, and the trials being conducted are not large enough to gather comparative data. Although the focus of this document is RCTs, there are comparative real-world studies that have looked at both Medicare and commercial payor databases.[4,6,63–66]

The final LCD also mentioned the importance of incorporating blinding protocols in RCTs; however, the panel agreed that double blind studies are not practical, inert placebo products are not available, and blinding the provider is not feasible. In addition, it is difficult to blind the patient. Every time the blind is broken, it must be reported to the IRB that the blind was broken accidentally. An article by Kaptchuk provides an overview of the difficulties of double blinding an RCT.[63]

Recommendations:

- When possible, trials should generate data on comparative effectiveness of interventions using master trial designs.
- The basket design appears to offer the best approach to trialing one product on multiple wound types.
- Trials comparing multiple products would be beneficial.
- Confirmation of closure should be determined by an independent blinded evaluator.

13. Multicentered trials conducted at geographically diverse locations and at a variety of patient care settings improve generalizability of the data

Extending trials to include subjects from other countries outside the US has the potential to enroll more patients in diagnosis-specific trials. For example, there is a high sickle cell population in the Caribbean[64] and a relatively high epidermolysis bullosa population in Europe.[65,67,68] Many of the products listed in the LCD approved list did not include geographically diverse sites or used a single type of trial setting, e.g. a private office. The panel agreed that being able to include subjects from other countries could increase the number of subjects in a trial and increase the overall data set.

Recommendations:

- Trials can include populations from geographic locations outside the US if the SOC as described in the protocol can be provided.
- Trials can be conducted in a variety of patient care settings.

14. Trials designed for Medicare coverage and reimbursement will analyze the efficacy of the studied product in Medicare beneficiaries

None of the trials listed in the final LCD report results in the Medicare population, which is one of the criteria for LCD approval.

Recommendations:

- Products must demonstrate efficacy in the Medicare population to get CMS approval.
- Sponsors are advised to analyze data from Medicare beneficiaries.

15. Sponsors should consider long-term follow-up studies

Currently there are little data on both short-term and long-term follow-up for CAMP trials and none on long-term safety. Based on LCD terminology, a long-term study would be defined as 1 year on a wound at the same location. For patients with DFUs, long-term studies would include amputation-free survival. One of the limitations of long-term studies on DFUs is that the wound is only a symptom of the underlying disease, and comprehensive care must include treatment of the diabetes which would affect long-term outcomes. The same is true for wounds of any etiology that have an underlying disease process, such as congestive heart failure, venous reflux, or lymphedema. In addition, factors that may impede wound healing for any patient need to be identified and treated. To accomplish this type of comprehensive care, a multidisciplinary team is required.

Recommendations:
- Sponsors and investigators should consider conducting long-term or durability studies.
- Multi-disciplinary teams are required to ensure that underlying disease processes and inhibiting factors are identified and treated.

Indications beyond DFU/VLU
Pressure injuries
The panel stressed the importance of conducting CAMP trials on patients who have pressure injuries (PIs). There are case study reports of CAMPs being used on PIs,[69–73] and one of a CAMP plus NPWT on Stage 4 PIs compared with NPWT alone; however, the subject number was small.[74] There are several more trials on small patient populations currently being carried out, and a recent consensus panel addressing the use of CAMPs on PIs suggested that real-world evidence can provide useful information in this population.[75] Several problems exist in studying this population, including the fact that there are different classifications by depth of tissue and some of the stage 4 PIs have extensive size and depth. Also in stage 4 PIs, there may be exposed bone which increases the risk of osteomyelitis.[76] Other concerns recognized in this patient population are the high metabolic demand and the presence of tunneling and undermining.

Another issue to be considered when building trials for patients with PIs is the size discrepancy that occurs, which may need to be addressed by having size stratification in the studies, e.g. 0-50 cm^2 and 50-100 cm^2. A similar stratification could be made based on PI stage, e.g. stage 3 and stage 4, which considers differences in depth and type of tissue involved. Unlike DFUs and VLUs, PIs occur at multiple locations (e.g. sacrum, coccyx, ischium, heel, malleoli, scapula), a factor that could perhaps be managed in a basket trial. Challenges also exist in endpoints because of the differences discussed here. Most trials have a 12-week endpoint for a large stage 4 PI; however, 12 weeks may not be a feasible endpoint for closure, in which case the endpoint could be percentage decrease in size. The beginning of the endpoint is another consideration, for example, if the patient requires surgical debridement of a stage 4 PI, the date of surgery would be the beginning date of the trial, not the date of PI onset or other care provided.

Certain criteria for RCTs for PIs have been established, including 1) exclusion of stable eschar on a heel, 2) life expectancy of at least 6 months, 3) controlled incontinence, and 4) consideration of frailty or nutritional status. The panel also acknowledges that many patients with stage 4 PIs need a consultation with a plastic surgeon for flap reconstruction, and perhaps it is those who are not a good candidate for a flap who would benefit most from a CAMP application.

Standardization of care after CAMP application is required and involves the type of support surface the patient is on, turning frequency, and the secondary dressing used to reduce shear during bed mobility. Because of the number of variables in treating PIs, the trials currently in place use matched controls rather than a SOC arm and have a minimum number of 100 enrollees.

Thus far Medicare has made tunneling, undermining, and exposed bone disqualifications for reimbursement of CAMPs during trials on pressure ulcers, although they have approved 20 applications, which exceeds the number approved in the LCD for DFUs and VLUs. The necessity for the wound to be present and not responding to care for 4 weeks remains valid for PIs.

Recommendations:
- The panel stressed the importance of conducting trials for patients with PIs.
- A basket design which would allow inclusion of patients with PIs in different locations was suggested.
- Matched control studies are preferrable due to the lack of consistent SOC in this population.

Rescue therapy in RCTs
Providing rescue therapy in an RCT allows a participant in the SOC arm to have access to experimental intervention. This is usually done in trials that involve drug therapies that can have potential life-saving or dramatic effects, and is allowed before the end of the trial, meaning there can be statistical consequences.[75] However, enrolling patients from the SOC arm into a rescue trial that allows them to receive the product increases enrollment and patient satisfaction. The panel supports rescue therapy and notes it would provide important information to support the approval of CAMPs.

Patients who are in the SOC arm of a trial and fail to respond to care can also be included in a rescue trial (which is a completely new trial) as part of the experimental arm. The patient would complete the first trial and then be enrolled in the rescue trial. Knowing that there is potential for receiving the product if the wound does not close with SOC will also help increase the enrollment.

Orphan diagnoses

Trials with DFUs often have exclusion criteria that preclude patients with other diagnoses from being included in a trial, for example, end stage renal disease and being on hemodialysis. The panel agreed that inclusion of patients with orphan diagnoses is important and that Medicare should have a program similar to the FDA's orphan drug program in which a sponsor could garner reimbursement with a well-designed study in an orphan indication. It was felt that many patients on hemodialysis with DFUs would benefit from the application of CAMPs if all the other criteria for inclusion were met; however, the challenge may be to find enough patients on hemodialysis who would meet all of the trial criteria.

Future considerations

Several indicators for future research in the use of CAMPs were discussed and are summarized as the following:

- As more digital technologies are used to monitor and direct interventions of wounds, artificial intelligence (AI) has the potential to be of benefit to trials in analyzing data. One of the challenges is that thousands of images are needed for AI to become accurate in analyzing data.
- Technologies for assessing factors in a wound that may indicate the bacteria/bioburden level, the tissue perfusion, the transepidermal water loss, and the tissue types are being used at the clinical level and can be incorporated into more clinical trials, especially as they become available to more treatment settings.
- Durability trials are needed to assess long-term efficacy of CAMPs, not just in PAR, but also in recurrence rates, scarring, and functional gains.
- Using a basket master trial design would allow the study of a CAMP product on multiple diagnoses and perhaps reduce the number of trials and enrollees needed from less-frequent diagnoses and thus have a cost saving.
- There is a necessity to treat all contributing factors, underlying diseases, and factors that may impede wound healing for all individuals in a trial to get the best data needed to analyze the efficacy of a product. For example, a diabetologist or other professional is advised to be involved in a DFU trial to optimize patient management of the diabetes.

Summary

Based on a hierarchical Bayesian meta-analysis of the 35 RCTs cited in Medicare's 2024 LCDs and in-depth discussion of the essential elements of an RCT evaluating the efficacy of CAMPs on wound tissue repair/regeneration, an expert panel developed recommendations for building the optimal clinical study. The panel further recommends that these elements be incorporated into any trial that requests the CAMP application be approved for Medicare reimbursement. The recommendations cover multiple aspects of conducting and reporting an RCT for CAMPs, including building the protocol, conducting the study, reporting raw data on outcomes, and statistical analysis. The panel's hope is that these recommendations will be adopted by both clinical and industry researchers and used by CMS for RCT approval and reimbursement.

Conflicts of interest

Lou Roselli is an employee of BioWound Solutions; Matthew Davis works for Surgenex, which is a AATB tissue bank and produces placental based allografts; Dr. Charles Andersen has no conflicts of interest to declare. Thomas E Serena MD FACS is the CEO of a physician owned contract research organization that conducts research for multiple CAMP manufacturers; Arshdeep Kaur works for Tiger Wound Care; Chris Sabatino works for Convatec; Bert Slade works for BioStem. No other conflicts of interest to declare.

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