COALITION OF

Wound Care Manufacturers

January 17, 2012

Coalition of Wound Care Manufacturers Comments on AHRQ Technology Assessment on Skin Substitutes For Treating Chronic Wounds

General:

On behalf of the Coalition of Wound Care Manufacturers ("CWCM"), I am submitting the following comments in response to the AHRQ Technology Assessment on Skin Substitutes For Treating Chronic Wounds. I serve as the Executive Director of the CWCM. The CWCM represents leading manufacturers of skin substitutes, of negative pressure wound therapy and other medical devices and supplies used by Medicare beneficiaries for the treatment of wounds.

While we appreciate the opportunity to offer our comments, we are very disappointed in the short amount of time (a little over two weeks) that the AHRQ allowed for a deadline to respond to this very dense document that is so critical to wound care stakeholders. It is our understanding that the Technology Assessment Program provides 2 weeks for public review of its draft reports. However, releasing the report on December 28 and then extending the due date to January 17 includes two holidays (New Years and Martin Luther King's birthday) along with many taking vacations during this time does not constitute a meaningful public comment period.

The Coalition has treated writing our comments to this draft very seriously, and has convened many conference calls, conversations and emails to ensure that all stakeholders' input will be included. Since we still do not believe there is enough time to give this important document the careful consideration that it needs, we are submitting these comments, but intend to supplement our filing as we receive more information from our members.

This section will be a summary of the issues that we will be addressing later in our comments

1. The Coalition has many serious concerns with this draft – from the products included in the draft to the terminology used to the methodology utilized which led to faulty conclusions. We believe that there was good intent in writing this, but wound care is very complex and different from burns and other diseases. The

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Coalition would be pleased to meet with ECRI, AHRQ as well as CMS staffs to discuss these issues in detail.

2. The Coalition has concerns with the nomenclature "skin substitutes" used throughout this document and in the title of this technology assessment in reference to the products/materials being considered. The term "skin substitutes" is not appropriate for these items and the term "dressing" does not work either since they have different connotations for both FDA and CMS. Therefore, if the terms "skin substitutes" do not really describe these items, and "biologic dressings" have negative connotations for coverage in the eyes of the CMS contractors, then we would propose the term for this document "cellular and engineered tissue alternatives." Alternative meant that these tissues are not substitutes but are different in function and structure. We submit that this terminology would include all the items correctly described in the document.
3. The Coalition has many issues with regards to the discussion of bias in this technology assessment. One of our concerns is that ECRI believes that if a manufacturer funds a study then there is automatically bias. First of all – as manufacturers – we question where the studies will come from if they are not funded by manufacturers. The types of studies that CMS and the FDA require either now or in the future in order for our products to come into the market place are not the subject of those studies currently funded by NIH, PCORI or AHRQ. Secondly – the source of investment for a clinical study is not an automatic cause of bias or concern for the integrity of data generated. The Coalition believes that there is no bias to a study funded by the manufacturer as long as the investigators have no financial conflict of interest with the manufacturer. Yet ECRI does not mention this in its assessment.
4. As stated in the Methods part of our remarks, we would have appreciated ECRI including more non-RCT studies which would more likely demonstrate the "effectiveness" of the cellular and engineered tissue alternatives than the "efficacy of the RCTs. By using these studies, there would have been more real-world patients.

Executive Summary:

The Coalition has concerns with the following issues:

1.Semantics and definitions used in this document to define "dressing" and "skin substitutes" by the FDA may have different meanings and uses by CMS and its contractors. This leads to confusion for all stakeholders. There needs to be consistent terminology for these items in all of the regulatory agencies.

The Coalition has concerns with the nomenclature "skin substitutes" used throughout this document and in the title of this technology assessment in reference to the products/materials being considered. The term "skin substitutes" is not appropriate for these items and the term "dressing" does not work either since they have different connotations for both FDA and CMS. For example:

- In Tables 2-4, one notes that under FDA's product code—the products for chronic wounds are ALL referred to as "dressing" no matter what the materials are or the process regulated under the FDA. Thus, one might therefore conclude that all the regulatory agencies could adopt this term.
- In fact, in the ECRI draft, page ES-1 in the fourth paragraph under "Background" states that "However, for chronic wounds a skin substitute should be able to provide a temporary biologic dressing that stimulates the host to regenerate lost tissue and replace the wound with functional skin." One could conclude that these materials could then be called "biologic dressings".
- However, if one looks at the CMS contractors, the A/B MACs', local coverage determinations for these products, one will not find coverage in many circumstances for those products which are "biological dressings."
- Moreover, there is additional confusion with the term "dressing" used in the Medicare Part B area by the DMEMAC coverage policies which include such products as hydrogels and hydrocolloids and name them as "surgical dressings" designated as "A codes".
- The term "skin substitute" may not be a correct term to use anymore. It is not used by the FDA in its classification as demonstrated by the tables 2-4. CMS' division that addresses HCPCS coding for these products also abandoned this term effective in 2010 when a manufacturer requested that CMS delete this term since it was an incorrect descriptor. The manufacturer stated at the 2010 CMS HCPCS Public Meeting that that this language was wrong since allografts are mislabeled as "skin substitutes." Allografts differ in structure, tissue origin, and in some cases differ from cellular and engineered tissue in terms of how they are approved by the FDA (human skin for transplantation not devices). CMS thus changed the descriptors and eliminated the term "skin substitutes" from all of its Q codes for these items.
- If one uses a medical dictionary to also look at the definitions for skin substitutes—one would see that it states it as a wound covering—which does not fare well to obtain coding and coverage under CMS; likewise, the biologic dressing has it being used for burns rather than chronic wounds.
    - Farlex's online medical dictionary confirms the differences of using products to treat a wound versus to protect a wound (as a wound cover dressings).
        - Skin Substitute: "a material used to cover wounds and burns where extensive areas of skin are missing, *to promote healing.*
        - Biologic Dressing: "one used in treatment of a burn or other large denuded area of skin to *prevent infection and fluid loss.*

      See http://medical-dictionary.thefreedictionary.com/skin+substitute (Accessed November 17, 2011) uses Miller-Keane Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health, Seventh Edition. © 2003 by Saunders, an imprint of Elsevier, Inc.)

Therefore, if the terms "skin substitutes" do not really describe these items, and "biologic dressings" have negative connotations for coverage in the eyes of the CMS contractors, then we would propose the term for this document "cellular and engineered tissue alternatives." Alternative meant that these tissues are not substitutes but are different in function and structure. We submit that this terminology would include all the items correctly described in the document.

2. Grouping of "cellular and engineered tissue alternatives"

This draft attempts to create a common grouping for these wound care products. Unfortunately, as is true for many devices, using FDA classifications do not always help. The groupings are not "like" based on mode of action of the products, material components, or how they are clinically used. If ECRI's goal is to create a generalizable assessment of the products then the authors must understand wound care better by knowing how these products are used and not how the FDA chooses to categorize them. Many of the products in the listing would not be used for all wounds and several are very rarely used. Finally, based on FDA practices many of these products did not need to provide evidence of comparative efficacy to gain approval. Thus, they do not have this level of evidence.

3. Evidence for Skin Substitutes

Question #1 of this paper is devoted to how the FDA regulates cellular and tissue engineer alternatives. The Alliance has the following concerns about this section:

- Why was this question chosen?
- One of the statements in the "Background" is not correct:
    - "Skin substitute products are regulated by the U.S. Food and Drug Administration (FDA) under one of four categories depending on the origin and composition of the product: Human derived products regulated as HCT/Ps, human and human/animal derived products regulated through premarket approval (PMA) or humanitarian device exemption (HDE), animal derived products and synthetic products regulated under the 510(k) process." The regulatory process is risk-based, not product origin-based. For example, PMA devices are products that the FDA deemed as a Class III device (devices that "support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury.")Therefore, these devices are deemed Class III because they "present a potential, unreasonable risk of illness or injury."

- In the Methods of the Review section, ECRI states that as part of the review, it developed Key Questions to answer, which included "What are the U.S. Food and Drug Administration (FDA) regulated skin substitutes that fall under each of the following pathways: PMA, 510(k), PHS 361[21CFR 1270 & 1271]?" However, it is unclear why this question is important for the evaluation of device *efficacy*, as

FDA classifications also don't indicate whether a device is an *effective* treatment modality. The executive summary only comments on the 3-letter classifications that are used to designate the different categories of products and specific terminology that is used in the FDA indication statement.

- Moreover, we have concerns about the emphasis that ECRI places on this specific terminology that is used in the FDA indication statements ("treatment" or "management") since the way that they are used by the FDA to delineate the products may be totally different than how they would be used in its sister agency, CMS. Both agencies have their separate and distinct regulatory processes and their own definitions and terminology.

  To further illustrate this point, when determining whether a product is a biological the FDA follows its own guidance – as ECRI has described earlier. CMS follows the Social Security Act (SSA) definition of drugs and biologicals which is:

  > *t)(1) The term "drugs" and the term "biologicals", except for purposes of subsection (m)(5) and paragraph (2), include only such drugs (including contrast agents) and biologicals, respectively, as are included (or approved for inclusion) in the United States Pharmacopoeia, the National Formulary, or the United States Homeopathic Pharmacopoeia, or in New Drugs or Accepted Dental Remedies (except for any drugs and biologicals unfavorably evaluated therein), or as are approved by the pharmacy and drug therapeutics committee (or equivalent committee) of the medical staff of the hospital furnishing such drugs and biologicals for use in such hospital.*

  Since CMS commissioned this study there may be a linkage of the two agencies on this issue, which would be inappropriate. For instance, CMS' goals as stated in this report are:

  - To determine the extent of available clinical evidence in support of the efficacy of the various cellular and engineered tissue alternatives products regulated by the FDA and to determine the strength of this evidence base. (page 50)
  - To facilitate CMS's evaluation of HCPCS coding for skin substitutes and information obtained by CMS will be used for consideration of coding changes. (page 12)

  We would not want CMS to misinterpret the intent of FDA's classification and terminology of "management" and "treatment" when these same cellular and tissue engineered products obtain Medicare coverage, coding and payment.

4. <u>ECRI should only list of "cellular and engineered tissue alternatives" in this draft document</u>

The list of products included in the report are not all marketed or indicated for use in chronic wounds, as noted by the researchers, and would not have clinical data in the literature for chronic wounds. In addition, some are used for burns and, as stated in this report, are not supposed to be included. Some are also "surgical dressings" and should be removed. Therefore, the Coalition recommends the following products should be removed from this assessment. We would also recommend that in ECRI's final report that only those which are cellular and engineered tissue alternatives be included.

- AlloDerm Regenerative Tissue Matrix, Allopatch HD, Flex HD, Matrix HD, Puros Dermis [dental implant tissue], Repliform
- Epicel, Transcyte
- E-Z Derm, InteXen, Permacol, Strattice , Tissuemend
- BioBrane -biosynthetic dressing constructed of a silicone film with a nylon fabric w/ trifilament thread to which collagen is chemically bound used for burns
- Hyalomatrix - non-woven pad dressing made a benzyl ester of hyaluronic acid, and a semi permeable silicone membrane
- Laserskin & Jaloskin -transparent film dressing composed of a benzyl ester of hyaluronic acid]: benzyl esters of hyaluronic acid
- LyoFoam Extra "C"- polyurethane foam dressing
- Suprathel- absorbable, synthetic wound dressing of polyalactic acid for donor sites and burns

5. Specific comments on Background

1- "This report specifically examined the use of skin substitutes for the treatment of the following chronic wound types: diabetic foot ulcers, pressure ulcers, and vascular ulcers (includes venous ulcers and arterial ulcers). Treatment of burn wounds with skin substitutes is outside the scope of this report."

This statement is incorrect since Epicel and Transcyte have been cited. We believe it should be restricted to chronic wounds as stated above.

2- "Skin substitutes were developed as an alternative to skin grafts especially for burn patients."

Good statement, we now know these skin substitutes are "just" biological dressing. Therefore they should not be called skin substitutes

3- "The ideal skin substitute should adhere to the wound bed and provide the physiological and mechanical function of normal skin while not being rejected by the host. This ideal situation is not likely to be provided by any current skin substitute."

This is not completely true, Steven Boyce has worked on a skin replacement for burns with autologous cells and biomateriaux. See for example: Boyce ST, Hansbrough JF. Biologic attachment, growth, and differentiation of cultured human epidermal keratinocytes on a graftable collagen and chondroitin-6-sulfate substrate. Surgery 1988;103:421-31. Boyce ST, Kagan RJ, Greenhalgh DG, et al. Cultured skin substitutes reduce requirements for harvesting of skin autograft for closure of excised, full-thickness burns. J Trauma 2006;60:821-9.

6. Definition of usual wound care

In its second question, ECRI asks "For patients with chronic wounds (pressure ulcers, diabetic foot ulcers or arterial ulcers) are skin substitutes more effective than usual care (synthetic dressings, growth factors, skin grafts or other treatments used as a control) in promoting wound healing for the following outcome measures…."

The Coalition disagrees with the definition of usual wound care utilized by the researchers to compare to cellular and engineered tissue alternatives treatment for chronic wounds. The usual care group that was stated is not a standard care arm but an advanced care arm and should be properly identified as such. Usual care for chronic wounds was addressed in the 2005 MedCAC meeting – and the Coalition agreed with its conclusion. CMS had stated that usual care was defined as: debridement, cleansing, dressing, compression, antibiotics and off-loading. In FDA's Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds- Developing Products for Treatment, usual care for chronic cutaneous ulcers include the following:

- Removal of necrotic or infected tissue
- Off-loading
- Compression therapy for venous stasis ulcers
- Establishment of adequate blood circulation
- Maintenance of a moist wound environment
- Management of wound infection
- Wound cleansing
- Nutritional support, including blood glucose control for subjects with diabetic ulcers
- Bowel and bladder care for subjects with pressure ulcers at risk for contamination

Others have stated that usual standard wound care is the removal of necrotic or nonviable tissue from the wound [debridement], management of the local wound environment [exudate control, maintenance of moist healing environment, cleaning of debris], protection from bacterial invasion, treatment of infection or gross contamination, protection of viable tissues from pressure, friction and shear through offloading or pressure reduction and reduction of edema and improved venous return with sustained, graduated compression for leg ulcers.

These approaches will vary throughout the course of a particular wound's cycle of healing and are not consistent from wound to wound. Hence, in the study of chronic

wounds, reference to 'usual wound care' would include the use of various types of wound dressing over the course of a study as the local wound environment changes, different intervals and numbers of debridement procedures as required for a particular wound, inclusion of antibiotic therapy as needed, varying intervals for the application of compression therapy, offloading techniques, pressure reduction all the 'usual wound care approached. As indicated in your review, if a wound fails to respond within 30 days to usual 'standard' care, the clinician will then evaluate the most appropriate 'advanced approach' to facilitate wound healing.

As stated above, ECRI has included advanced methods of wound treatment in their definition of usual care including growth factor therapy, surgical autologous skin grafts, skin substitutes, and other treatments. These are considered advanced treatments and *not* part of standard usual care. They, like cellular and engineered tissue, are utilized after standard care fails to progress the healing of a chronic wound.

Some of these advanced modalities are not utilized throughout the entire healing process, but have specific functions during the course of healing, and therefore would not be a suitable and appropriate as a comparator for a cellular and engineered tissue trial to evaluate clinical effectiveness.

7. Inclusion of Studies

In ***Table 3***, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original approval date was 2000.

In ***Table 5***, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers was omitted.

8. Concerns about Methodology

The executive summary addresses in its evidence and conclusion issues which we have concerns with such as the methodology—please see the Methods part of our comments to obtain this information.

Introduction/Background:

- In the ***Complementary or Competing Products*** portion of this section, the focus does not seem to be on products; instead the focus seems to be more upon factors that need to be controlled in any treatment algorithm for all wounds.

- In the ***Usual Care for Chronic Wounds*** portion of this section, the authors state:

  > " 'Standard of care' (SOC) was commonly used in the studies included in this report when referring to the control group wound care or base wound care to which a skin substitute was added…Standard of care is also frequently used in

presentations on manufacturer Web sites. However, as described above, usual care or standard of care is not a consistent term that describes an agreed upon set of procedures to be used when treating chronic wounds."

Standard of care (SOC) is an industry vernacular that is used to describe the prescribed treatment that is most *currently* accepted to be effective, which means that this is the treatment that is most currently used.

- In the ***U.S. Food and Drug Administration Regulations Governing Skin Substitute Products*** portion of this section, the authors provide an expanded explanation of the regulatory categories; however, as above, there is no explanation as to how this relates to this review. In this discussion, statements such as, "Therefore, wound care products regulated under the PMA process will require evidence that they promote wound healing before they are approved for marketing." and "Therefore, wound care products regulated under the 510(k) process will typically require less evidence that they promote wound healing compared to products regulated under the PMA process." These statements are untrue as these FDA categories are ***risk-based*** categories, which mean that higher risk classifications (Class III devices approved through PMA) may mean that less is known about whether the product is safe. As such, there are devices that may have been cleared by the FDA without clinical data (e.g. Specturm 5000Q Electroconvulsive Therapy Device by Mecta Corporation)

- Additionally, the discussion of these categories is inconsistent with the Executive Summary statement:

  "Skin substitute products are regulated by the U.S. Food and Drug Administration (FDA) under one of four categories depending on the origin and composition of the product: Human derived products regulated as HCT/Ps, human and human/animal derived products regulated through premarket approval (PMA) or humanitarian device exemption (HDE), animal derived products and synthetic products regulated under the 510(k) process."

  This issue has also been addressed in our comments in the Executive Summary.

Methods:

General Comments

This section states that the review will facilitate CMS' evaluation of HCPCS coding for skin substitutes by providing CMS with relevant studies and information for consideration of coding changes. We have concerns about this and would request a meeting with CMS staff to discuss this.

Methodology of the Systematic Review

The methodological approach of this review has several major flaws: (1) selection of studies; (2) outcomes; (3) bias assessment; and (4) reporting.

Selection of studies

While randomized controlled trials (RCTs) represent the highest level of evidence regarding individual studies, such studies only provide evidence for efficacy of a treatment in relatively healthy patients and typically exclude vulnerable populations and wounds that are more severe in terms of their characteristics.[1,2] The percentage of "real world" patients excluded in such studies in wound care can be high.[2] RCTs are appropriate for establishing an effect under controlled conditions but are problematic when solely used to translate outcomes to "real-world" patients with chronic wounds because many patients do not fit the populations used in RCTs.[3] A good example of why some promising wound care products do not work well in all wound care populations despite having reasonable successful outcomes in RCTs is that wound care RCTs are of limited duration to keep trial costs down, which limits the size/depth, and type of wound that can be treated and expected to heal within the trial time frame. This is one reason why evidence-based practice (EBP) came into being. It can be defined as "an approach to decision making in which the clinician uses the best evidence available, in consultation with the patient, to decide upon the option which suits the patient best"[4] or as a combination of the following three factors: (1) best research evidence; (2) best clinical experience; and (3) consistent with patient values.[5] In other words, the approach does not only look at RCTs. In this regard, Tunis observed that "There is an urgent need to increase the capacity to conduct simple, real-world, prospective clinical studies to efficiently provide reliable data on the risk, benefits, and costs of new and emerging technologies."[6]

Because the authors of this systematic review chose only to examine RCTs published in the per-reviewed literature, much of the evidence on cellular and engineered tissue is missing, and thus the conclusions in terms of coverage of these products are therefore skewed. Furthermore, it is a puzzling why the authors apparently searched the gray literature but did not report on it. Why do this in the first place? Typically, Cochrane reviews look for abstracts, unpublished material, ongoing clinical trials, and so forth, so as to minimize publication bias, particularly when conducting meta-analysis, which was not done in this review. Granted, it can be very difficult to analyze such studies published as abstracts or research letters, but their inclusion is important, even if detailed analysis is not possible. Furthermore, there is no excuse not to search for evidence published in the peer-reviewed literature if that evidence is not published in English. Given the extensive effort that was put into searching, the authors could have found studies that would have had English abstracts, and then decided upon their relevance and had them translated. Not doing so is another form of selection bias.

We also believe that many studies should have been included in this section. For example - The O'Donnell systematic review of randomized controlled trials of wound dressings for chronic venous ulcers (. J Vasc Surg 2006;44:1118-25.) should have been included as should any other systematic review that the authors have dismissed merely

for the fact that it is a review. As systematic reviews provide the highest level of evidence for products if the review shows that a study is a quality study, these should not be omitted from this analysis. Two other studies should also be included since they are "head to head" studies of two "skin substitute" products:

- Landsman A, Roukis TS, DeFronzo DJ et al. Living cells or collagen matrix: which is more beneficial in the treatment of diabetic foot ulcers? Wounds 2008 20:111-6
- DiDomenico L et al, "A Prospective Comparison of Diabetic Foot Ulcers Treated with Either a Cryopreserved Skin Allograft or a Bioengineered Skin Substitute." WOUNDS 2011;23(7);184-189

Outcomes

The authors of this report chose to ignore many valuable outcomes that are linked to partial wound healing, in part because they chose to ignore observational trials, although sometimes this information is reported in RCTs. This is important because healing chronic wounds often requires many repeated, sequential, or overlapping treatments to completely heal a wound,[1,7] and this approach cannot be easily accomplished in an RCT.[8] For example, a venous leg ulcer would have to receive adequate compression, and might be treated with silver-impregnated dressings to reduce infection before receiving Apligraf to ensure that the wound is not clinically infected . There is an increasing body of evidence that partial wound-healing outcomes, such as time to reach 50% reduction wound area, are valid and clinical useful endpoints that can be used in real world wound care patients to determine whether the wound is clinically responding to a given treatment regimen.[9-16] In ignoring these types of outcomes and focusing only on RCTs, the reviewers seem to have entirely dismissed evidence-based practice altogether.

Bias assessment

The Coalition is concerned of ECRI's condemnation of the comparative efficacy studies with respect to bias. The authors should note that many of these studies were designed with respect to the FDA requirements and thus can be very difficult to conduct these studies in a blinded fashion.

We note that the reviewers chose a non-validated approach to assessing bias assessment, which does not seem to have been reported in the literature. While some of the elements listed are certainly crucial, definitions of yes, no, or not reported are missing. For example, by what criteria did the reviewers judge that a study used appropriate randomization methods or concealment of treatment group allocation? Second, the authors seem to have singled out wound size/duration as and number of comorbidities the only important baseline parameters, suggesting 15% as the split point. How did they arrive at these specific criteria? In wound care studies it is important to list all relevant parameters to wound healing at baseline and adjust for them in such fashion through stratification or regression, or both. Numbers of comorbidities are not helpful because

only specific comorbidities and lifestyle factors (e.g., BMI or smoking) have a direct impact on healing. There is also no reporting of how the reviewers judged these criteria, how they arrived at a consensus, or even kappa (inter-relater reliability) statistics.

Finally, there was no GRADING reported. GRADE is becoming one of the most important techniques by which the synthesis of the evidence is evaluated in terms of the quality of evidence across studies for each important outcome; which outcomes are critical to a decision; the overall evidence across these critical outcomes; the balance between benefits and harms; and the strength of recommendations.[17] Instead, the reviewers used the EPC approach, which is conceptually similar to the GRADE system of evidence rating; it requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains to be used when appropriate include dose-response association, presence of confounders that would diminish an observed effect, strength of association, and publication bias. Strength of evidence receives a single grade: high, moderate, low, or insufficient.[18] This would have been a reasonable approach had it been followed in a thorough fashion. Instead there are only one or two sentences in the entire 121-page report devoted to directness and consistency, and precision was entirely ignored at the expense of pages on risk of bias. We would submit that according to ECRI's own procedures and criteria that this systematic review was poorly done. Consequently, its conclusions must be regarded as uncertain.

Reporting

The gold standard for reporting systematic reviews are the PRISMA guidelines. In this review, several items were missing (e.g., method of data extraction, and summary measures presented as differences in means and risk ratios). Moreover, no rationale was given for not conducting meta-analysis, as this is usually a key part of any systematic review.

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Specific Comments--List of Quality Assessment Questions and Concerns:

#3. Was the wound assessor blinded to the patient's treatment group?

We disagree with ECRI that there is high risk for bias when the investigating clinician (unblinded) evaluates the wound parameters. These measurements (wound size/ depth measurements, percent of granulation or epitherial tissue, wound margins, percent necrotic tissue, etc.) are confirmed with scaled graft measurement tools and/ or digital photography which are used by the clinicians and difficult to blind. These parameters are 'hard' endpoints, not open to

interpretation, recorded at standard intervals during the study for both arms of the study. Therefore, we are in agreement with the authors that these do not require a blinded evaluator to ensure an introduction of bias. We believe allocation concealment is most important.

#5 Were the mean wound sizes at the start of treatment similar (no more than a 15% difference) between groups?

This criteria does not seem to be based on any known standard and in itself will limit the population for clinical trials. It reduces the pool of results information that can be generalized to 'real world' situation of chronic wounds. Most clinical trials in wound care select a size range of wounds for inclusion which is often broader than 15% difference to ensure randomization reflects as best as possible the wound sizes seen in clinical practice. This arbitrary selection introduces less 'valuable' information for clinicians.

As stated earlier in our comments, this factor can be adjusted for in analysis.

#6 Were the mean wound durations at the start of treatment similar (no more than a 15% difference) between groups?

This is also another artificial restriction for conducting clinical trials and is not validated in any known standard for clinical trials. Longer duration of a chronic wound has been already shown in the literature to respond differently to treatment, and should not be restricted to a 15% difference. Again, this factor can be adjusted for in analysis.

 # 10. Was the study funded by an organization other than the skin substitute manufacturer?

The source of investment for a clinical study is not an automatic cause of bias or concern for the integrity of data generated. The Coalition believes that there is no bias to a study funded by the manufacturer as long as the investigators have no financial conflict of interest with the manufacturer. One must also question – where will the studies come from if they are not financed by the manufacturer? The types of studies that CMS and FDA either require now or in the future for commercialization in the marketplace are not the subject of those studies currently funded by NIH or PCORI or AHRQ.

Similarly, as the federal and state governments are limited in the funds that they can provide to conduct randomized controlled trial and academic institutions are limited in the funds that they receive from government entities and non-for-profit organizations for conducting randomized controlled trials, it is often device manufacturers that have to fund these studies in order to obtain the clinical evidence that is needed to obtain approval/clearance to market the devices. All of these studies have to be reviewed by

institutional review boards at each clinical study site and are subject to scrutiny by the FDA.

Results

The Coalition recognizes that by submitting our answers to AHRQ by section rather than in a full paper online, different reviewers may be reading different areas—however, since we believe we have not been given enough time to thoroughly respond in full to all of the questions, we would ask that the reviewers of this section to please read our comments in the Executive Summary since they pertain to this section also. We do have some specific comments as noted below.

Specific Comments

- In answering Key Question 1, the authors list several products, such as AlloDerm Regenerative Tissue Matrix, Flex HD, Puros Dermis, Repliform, InteXen, and Permacol, which are not used/ cleared for the treatment of chronic wounds.
- In answering Key question 1 the authors erroneously describe Theraskin
  1. Lines 1-4 should read. ”TheraSkin is a biologically active, cryopreserved real human skin allograft, composed of living cells, fibroblasts and keratinocytes and a fully developed extra cellular matrix. TheraSkin does not contain any synthetic or animal materials.”
  2. P. 24. Please change the last sentence to “SWAI (Virginia Beach, VA) is registered with the FDA as an establishment providing HCT/P’s.”
  3. P 24, line 6, word 3 should be “provided” not “distributed”

- In ***Table 8***, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original approval date was 2000.

- In answering Key Question 2, the authors state that their searches identified 14 RCTs that met the inclusion criteria. However, one notable study that was missed was Landsman et al., 2008 that compared OASIS Wound Matrix to Dermagraft in the treatment of diabetic foot ulcers.

- In ***Table 10***, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers was omitted.

Quality of the Evidence Base

- In the ***Quality of the Evidence Base*** portion of this section, the authors state:

"All four studies of Oasis were considered at high risk of bias because wound assessor blinding was not reported. Reporting of comorbidities was absent in three of the studies."

It is not always possible to blind the wound assessor to wound care treatments, as the treatments often result in differences in wound appearance during the course of treatment. As such, there are objective wound evaluation techniques, such as wound dimensions and depth that are incorporated into the assessment of wounds. Additionally, there are publication limits (i.e. space constraints of the manuscript), which means that many of the unreported data fields are eliminated because they are insignificant in relation to outcome.

Page 44- Study Design, Patient Enrollment Criteria, Description of Treatment, Patient Characteristics.

"Several important areas of study design and patient information of interest to this report were poorly reported. Prior wound treatments were not reported in any of the studies and reporting of comorbidities was sparse."

- Chronic wounds may have been present for months up to over a year before entrance into a clinical study. Patients may have been seen by several clinicians over that time. It is virtually impossible to list all prior treatments for each subject in a wound healing study. This will vary widely across the patient population and has minimal value in determining the effect of the current treatment. Therefore it is not tracked and evaluated in chronic wound studies.

- A majority of clinical studies define exclusion criteria that ensure the use of another advanced treatment, prior to enrollment in the current study, must not have occurred within a certain timeframe before entering the study. This helps eliminates the cross-over effect of other treatment(s).

- Patients with chronic wounds typically have multiple medical conditions which contribute to the development of their wound. Co-morbidities are not specifically identified in chronic wound studies as a data point for analysis since only a few are directly linked to non-healing. However, medical conditions that may impede the healing process to such an extent that the patient would highly likely not respond to the study treatment are usually identified in the exclusion criteria (i.e. end stage renal disease, autoimmune compromised patient, uncontrolled diabetes, severe vascular insufficiency, etc.). The studies include these exclusion criteria to ensure patients' major health conditions are in relative control, to eliminate patient with reduced ability to respond to either the study treatment or the control.

Page 44- "*Wound duration and wound severity prior to enrolling in a study were also poorly reported. Patients were generally excluded from studies if their health was*

suboptimal, they were taking medication that would interfere with wound healing or their wounds were infected."

- Removing the patients on medication which interferes with wound healing is appropriate in wound healing trials, since those patients would adversely affect the outcomes for any arm of the study. Unless all patients are taking the medication, it is not appropriate to include them in the study as this will impact the data results negatively.

- Removing patients with infected wounds from skin substitute clinical trials is medically appropriate since healing does not occur in the presence of infection. Many of the listed biological materials are required by the FDA labeling, to be applied only to a non-infected wound. It would be medically negligent to apply an active biological material to an infected wound knowing the tissue graft would fail.

Page 44- "Several studies also indicated they excluded patients who responded to usual care during screening periods (see studies of Apligraf, Dermagraft, and Oasis described below for details)."

Most studies in chronic wounds include a 2-3 week screening period with standard care to identify wounds that will progress to healing adequately with standard care. This is to ensure the wounds evaluated in skin substitute or other advanced treatment trials are truly non-responding 'chronic wounds'. This is essential to eliminate these patient's from the study that will heal without the need for an advanced treatment and that would not be a candidate in the 'real world' for advanced treatment.

Discussion/Conclusion:

The Coalition recognizes that in submitting our comments to AHRQ online in the various sections rather than in one total paper, different reviewers may be reading different areas—however, since we believe we have not been given enough time to thoroughly respond in full to all of the questions, we would ask that the reviewers of this section to please read our comments in the Executive Summary since they pertain to this section also. However, we are copying below some of our responses in the Methods section since they are so relevant to the discussion and conclusions. We will first give you some our specific comments and then the information from the Methods section.

Only five of 31 products listed in the report were examined in RCTs:

- 19 products listed in the report are not indicated or labeled for clinical treatment of chronic wounds and would therefore not have been identified in chronic wound studies. 6 of the 19 are wound dressings used to cover and protect the wound and

are not biological cellular and engineered tissue alternatives. These products should not be included in the analysis.

Only one of the 14 studies compared two skin substitute products (OASIS vs. Hyaloskin):

- This assumption is incorrect. OASIS is a bovine collagen matrix (biological skin substitute) which is surgically applied for tissue re-growth. Hyaloskin is a manufactured dressing with fibers of collage blended in the dressing center and is a cover dressing that is meant to be removed at selected time during wound management. This reference needs to be corrected.
- One notable study that was missed was Landsman et al., 2008 that compared OASIS Wound Matrix to Dermagraft in the treatment of diabetic foot ulcers.
-

Only generally healthy patients were enrolled in studies. *The researchers noted patients with infected wounds, who used medications that could impede wound healing, had clinically significant medical conditions, significant peripheral vascular disease, malnutrition, or uncontrolled diabetes were excluded.*

- The exclusion criteria for wound studies for diabetic patients and those for vascular/ arterial ulcers must be consistent with the (FDA) labeling and be compliant with medical appropriateness and coverage policy criteria. All of the cellular and engineered tissue alternatives are not indicated for use on an infected wound or a wound with inadequate vascular supply to support tissue growth. Malnutrition and uncontrolled diabetes will affect healing and therefore must be corrected before a skin substitute would be medically appropriate.

  In almost all Medicare and private coverage policies, they include criteria for coverage which are medically appropriate. Some examples are:
  - Applied to wounds reasonably expected to heal and not applied to wounds demonstrating such hostile host environment that destruction of the substitute is highly likely.
  - Applied to wounds that are clean and free of infection.
  - Applied only to wound with adequate circulation/oxygenation to support tissue growth/wound healing as evidenced by physical examination with presence of acceptable peripheral pulses and/or Doppler toe signals and/or ankle–brachial index (ABI) of no less than 0.65.

FROM THE METHODS SECTION: Methodology of the Systematic Review

The methodological approach of this review has several major flaws: (1) selection of studies; (2) outcomes; (3) bias assessment; and (4) reporting.

Selection of studies

While randomized controlled trials (RCTs) represent the highest level of evidence regarding individual studies, such studies only provide evidence for efficacy of a treatment in relatively healthy patients and typically exclude vulnerable populations and wounds that are more severe in terms of their characteristics.[1,2] The percentage of "real world" patients excluded in such studies in wound care can be high.[2] RCTs are appropriate for establishing an effect under controlled conditions but are problematic when solely used to translate outcomes to "real-world" patients with chronic wounds because many patients do not fit the populations used in RCTs.[3] A good example of why some promising wound care products do not work well in all wound care populations despite having reasonable successful outcomes in RCTs is that wound care RCTs are of limited duration to keep trial costs down, which limits the size/depth, and type of wound that can be treated and expected to heal within the trial time frame. This is one reason why evidence-based practice (EBP) came into being. It can be defined as "an approach to decision making in which the clinician uses the best evidence available, in consultation with the patient, to decide upon the option which suits the patient best"[4] or as a combination of the following three factors: (1) best research evidence; (2) best clinical experience; and (3) consistent with patient values.[5] In other words, the approach does not only look at RCTs. In this regard, Tunis observed that "There is an urgent need to increase the capacity to conduct simple, real-world, prospective clinical studies to efficiently provide reliable data on the risk, benefits, and costs of new and emerging technologies."[6]

Because the authors of this systematic review chose only to examine RCTs published in the per-reviewed literature, much of the evidence on cellular and engineered tissue is missing, and thus the conclusions in terms of coverage of these products are therefore skewed. Furthermore, it is a puzzling why the authors apparently searched the gray literature but did not report on it. Why do this in the first place? Typically, Cochrane reviews look for abstracts, unpublished material, ongoing clinical trials, and so forth, so as to minimize publication bias, particularly when conducting meta-analysis, which was not done in this review. Granted, it can be very difficult to analyze such studies published as abstracts or research letters, but their inclusion is important, even if detailed analysis is not possible. Furthermore, there is no excuse not to search for evidence published in the peer-reviewed literature if that evidence is not published in English. Given the extensive effort that was put into searching, the authors could have found studies that would have had English abstracts, and then decided upon their relevance and had them translated. Not doing so is another form of selection bias.

We also believe that many studies should have been included in this section. For example - The O'Donnell systematic review of randomized controlled trials of wound dressings for chronic venous ulcers (. J Vasc Surg 2006;44:1118-25.) should have been included as should any other systematic review that the authors have dismissed merely

for the fact that it is a review. As systematic reviews provide the highest level of evidence for products if the review shows that a study is a quality study, these should not be omitted from this analysis. Two other studies should also be included since they are "head to head" studies of two "skin substitute" products:

- Landsman A, Roukis TS, DeFronzo DJ et al. Living cells or collagen matrix: which is more beneficial in the treatment of diabetic foot ulcers? Wounds 2008 20:111-6
- DiDomenico L et al, "A Prospective Comparison of Diabetic Foot Ulcers Treated with Either a Cryopreserved Skin Allograft or a Bioengineered Skin Substitute." WOUNDS 2011;23(7);184-189

Outcomes

The authors of this report chose to ignore many valuable outcomes that are linked to partial wound healing, in part because they chose to ignore observational trials, although sometimes this information is reported in RCTs. This is important because healing chronic wounds often requires many repeated, sequential, or overlapping treatments to completely heal a wound,[1,7] and this approach cannot be easily accomplished in an RCT.[8] For example, a venous leg ulcer would have to receive adequate compression, and might be treated with silver-impregnated dressings to reduce infection before receiving Apligraf to ensure that the wound is not clinically infected . There is an increasing body of evidence that partial wound-healing outcomes, such as time to reach 50% reduction wound area, are valid and clinical useful endpoints that can be used in real world wound care patients to determine whether the wound is clinically responding to a given treatment regimen.[9-16] In ignoring these types of outcomes and focusing only on RCTs, the reviewers seem to have entirely dismissed evidence-based practice altogether.

Bias assessment

The Coalition is concerned of ECRI's condemnation of the comparative efficacy studies with respect to bias. The authors should note that many of these studies were designed with respect to the FDA requirements and thus can be very difficult to conduct these studies in a blinded fashion.

We note that the reviewers chose a non-validated approach to assessing bias assessment, which does not seem to have been reported in the literature. While some of the elements listed are certainly crucial, definitions of yes, no, or not reported are missing. For example, by what criteria did the reviewers judge that a study used appropriate randomization methods or concealment of treatment group allocation? Second, the authors seem to have singled out wound size/duration as and number of comorbidities the only important baseline parameters, suggesting 15% as the split point. How did they arrive at these specific criteria? In wound care studies it is important to list all relevant parameters to wound healing at baseline and adjust for them in such fashion through stratification or regression, or both. Numbers of comorbidities are not helpful because

only specific comorbidities and lifestyle factors (e.g., BMI or smoking) have a direct impact on healing. There is also no reporting of how the reviewers judged these criteria, how they arrived at a consensus, or even kappa (inter-relater reliability) statistics.

Finally, there was no GRADING reported. GRADE is becoming one of the most important techniques by which the synthesis of the evidence is evaluated in terms of the quality of evidence across studies for each important outcome; which outcomes are critical to a decision; the overall evidence across these critical outcomes; the balance between benefits and harms; and the strength of recommendations.[17] Instead, the reviewers used the EPC approach, which is conceptually similar to the GRADE system of evidence rating; it requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains to be used when appropriate include dose-response association, presence of confounders that would diminish an observed effect, strength of association, and publication bias. Strength of evidence receives a single grade: high, moderate, low, or insufficient.[18] This would have been a reasonable approach had it been followed in a thorough fashion. Instead there are only one or two sentences in the entire 121-page report devoted to directness and consistency, and precision was entirely ignored at the expense of pages on risk of bias. We would submit that according to ECRI's own procedures and criteria that this systematic review was poorly done. Consequently, its conclusions must be regarded as uncertain.

Reporting

The gold standard for reporting systematic reviews are the PRISMA guidelines. In this review, several items were missing (e.g., method of data extraction, and summary measures presented as differences in means and risk ratios). Moreover, no rationale was given for not conducting meta-analysis, as this is usually a key part of any systematic review.

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Tables:

- In ***Table 3***, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original approval date was 2000.

- In ***Table 5***, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers was omitted.

- In ***Table 8***, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original approval date was 2000.

- In ***Table 10***, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers was omitted.