

Alliance Comments Regarding AHRQ Draft Technology Assessment

Report on “Skin Substitutes for Treating Chronic Wounds.”

The Alliance is a nonprofit multidisciplinary trade association of physician specialty societies, clinical and patient associations whose mission is to promote evidence-based quality care and access to products and services for people with chronic wounds (diabetic foot ulcers, venous stasis ulcers, pressure ulcers and arterial ulcers) through effective advocacy and educational outreach in the regulatory, legislative, and public arenas. We appreciate the opportunity to comment on the AHRQ Draft Technology Assessment (TA) Report on “Skin Substitutes for Treating Chronic Wounds”. These comments were written with the advice of Alliance clinical specialty societies and organizations who not only possess expert knowledge in treating complex chronic wounds, but also in wound care research. A list of our members can be found on our website.

As stated both in our general and specific comments, we have severe concerns regarding this AHRQ TA. Many of these concerns were expressed in our 2012 comments; however, many of these same issues are again in the 2019 version. Therefore, we would appreciate the opportunity to again meet with AHRQ staff and ECRI authors to address our concerns and recommendations.

GENERAL

We would like to commend AHRQ for this very detailed analysis since it is very difficult to perform. However, the Alliance has some significant concerns with portions of the Technology Assessment (TA) which impact its findings and have provided specific comments on the areas in which we disagree with the assessment as well as areas in which we have identified inconsistencies.

Short Turnaround to Respond to the AHRQ TA

As a general matter, while we appreciate the opportunity to offer our comments, we are very disappointed in the short amount of time that the AHRQ allowed for a deadline to respond to this very dense and complex document that is so critical to wound care stakeholders. While the TA Program provides 3 weeks for public review of its draft reports, we request in the future to allow stakeholders more time to evaluate and offer valuable and meaningful comments to these assessments.

Assumption that Reader is Familiar with 2012 AHRQ TA

In addition, while the Alliance commented on the draft AHRQ 2012 TA on “Skin Substitutes for Treating Chronic Wounds (Dec 2012) and met with staff to explain our comments, we have concerns that the authors assume that the reader is familiar with the concepts and issues addressed in the Dec 2012 document since they referenced it in the 2019 TA. When we attempted to access it from the link on the AHRQ website, we discovered that the link was broken. Thus, we recommend that AHRQ fix this in the future.

Use the Clinically Accurate Term “Cellular and/or Tissue Based Products for Skin Wounds (CTPs)” Instead of “Skin Substitutes”

Moreover, the Alliance would like to request that AHRQ change the title and terminology utilized throughout this TA. The AHRQ refers to the products being assessed as “skin substitutes”. The term “skin substitutes” is clinically inaccurate and does not describe the technology. The Alliance recommends that “skin substitutes” be replaced with a more inclusive descriptor “Cellular and/or Tissue Based Products for Skin Wounds (CTPs)”. CTPs accurately describes all technologies in this sector, is broad and is inclusive of both current and future technology. This term was created and adopted by an Alliance workgroup of scientists, clinical associations and business entities in 2012 and used the following criteria to determine the new term of CTPs:

- be based on science
- be inclusive of all products in marketplace today with eye towards what is in the “pipeline”
- be neutral in regards to FDA--- nothing that would be offensive and not allow manufacturers to get their products approved in the future if needed
- ensure that all products are eligible for Medicare coverage as drugs and biologicals consistent with their USP monographs
- easily understood by clinicians
- easily linked to the existing CPT codes for the application of the products

The Alliance believes that the term “skin substitute” is misleading and inaccurate to describe the products that are the subject of this assessment for the following reasons:

1. The FDA does not allow these products to be called “skin substitutes” because they do not actually substitute for skin.
2. Both CMS and AHRQ have concerns with the terms and did the following:
 - AHRQ in its 2012 final technology assessment on skin substitutes inferred that these products were not “skin substitutes” since *“A true “skin substitute” would act like an autologous skin graft in adhering to the wound bed while providing the physiological and mechanical functions of normal skin.*
 - CMS abandoned the term in the code descriptors for these products in 2010 when the Agency agreed that these products are not skin substitutes and instead issued Q codes for each individual product by its brand name.
3. ASTM, the international standard setting organizations thought so highly of this new terminology that in February 2016 it published a definitive standard (F3163-16) devoted to the nomenclature for these products titled “Standard Guide for Classification of Cellular and/or Tissue-Based Products for Skin Wounds.” The workgroup that created this standard included FDA (who agreed with the term), scientists, engineers and clinicians who worked collaboratively to ensure that the standard is inclusive of all the products in this space. It is now not only used by them but by those who do wound care research. We are using parts of this standard throughout our comments as noted below.
4. Payers in their LCDs are using this term. Of the four Medicare Administrative Contractors who have a LCD for these products, three of them either use the term CTPs in the body and/or title of the

coverage policy. For instance, CGS titles its LCD- “Wound Application of Cellular and/or Tissue Based Products (CTPs), Lower Extremities.”

5. This term has been adopted by the wound care community and is currently used by physicians when speaking at national wound care conferences and in clinical articles in scientific journals.

As such, the Alliance recommends that AHRQ not utilize the term “skin substitute” in its TA and instead use the more clinically accurate term “cellular and/or tissue based products for skin wounds (CTPs)”.

As a result of this request, the Alliance recommends making the following changes:

1.Delete the paragraph below in the draft TA describing skin substitutes:

***Skin Substitutes** Skin substitutes are used as an adjunct to established chronic wound care methods to increase the likelihood of complete healing.²⁰ According to Ferreira et al.,²¹ “skin substitutes are a heterogeneous group of biological and/or synthetic elements that enable the temporary or permanent occlusion of wounds. Although dermal substitutes can vary from skin xenografts or allografts to a combination of autologous keratinocytes over the dermal matrix, their common objective is to achieve the greatest possible similarity with the patient’s skin.” Skin substitutes should have functional and structural characteristics that closely match autologous skin. The ideal skin substitute would be durable, completely autologous, and endothelialized and contain adnexal structures and adult stem cells, but such a construct does not yet exist.²⁰ Commercially manufactured skin substitutes should protect the integument from water loss and infection; provide a stable, biodegradable scaffold to promote the synthesis of new dermal tissue; allow host or other cells to proliferate within the scaffold that will act as functional dermal cells rather than scar tissue; and resist tearing forces while being easy to handle.²²⁻²⁴ Growth factors and other components of the skin substitute may promote cell proliferation, reduce wound degradation caused by matrix metalloproteinases within the wound, and promote wound vascularization. These properties may enhance the wound healing potential of skin substitutes beyond that of wound dressings.*

2. Replace it by using the title “Cellular and/or Tissue Based Products for Skin Wounds and use the definition from the ASTM Standard.

The updated definition of CTP should be taken from the ASTM International Standard Guide: F3163-16 Classification of Cellular and/or Tissue-Based Products (CTPs) for Skin Wounds. ASTM International, one of the largest voluntary standards developing organizations in the world, provides a forum for the development and publication of international voluntary consensus standards for materials, products, systems and services. They develop technical documents that are the guidelines for manufacturing, management, procurement, codes and regulations for dozens of industry sectors.

The ASTM CTP standard, published by ASTM in January 2016 (from which the CTP definition is taken) is the product of four years of negotiations among a multidisciplinary group of stakeholders, including representatives from the United States Food and Drug Administration (FDA), clinical medicine, scientific research and industry. This standard was voted on and approved by the ASTM Committee F04 on Medical and Surgical Materials and Devices. This process, which reflects the ASTM values of participation, transparency and agreement among members worldwide, ultimately resulted in an

international standard that has been designed to accommodate the rapid evolution of innovative wound care technologies.

We recommend that it be replaced by this definition from the ASTM standard:

CTPs are defined primarily by their composition and comprise of cells and/or the extracellular components of tissue. CTPs may contain cells (viable or nonviable), tissues, proteins, and other materials for which there is a rationale for benefit beyond that achievable with conventional wound coverings. CTPs may additionally include synthetic components.¹

Additionally, another way to define a CTP is as a material used to cover wounds and burns where areas of skin are missing. It is a heterogeneous group of products that can be composed of synthetic, xenogeneic, autologous, allogeneic or composite matrices. Such matrices can be cellular, devitalized or acellular. All current CTPs except one serve as temporary grafts, which cover a wound and support the natural wound healing process of the host by providing structural matrix and growth factors to the cells in the wound area required for their cellular activities to facilitate healing. The fate of these grafts is to be resorbed/remodeled overtime. The exception is the autologous skin grafts, which permanently replace lost skin.

Concerns with Specific Problematic Meta-Analysis, Terminology in TA and Transparency

With respect to The Paggiaro et al. meta-analysis utilized in this TA, the Alliance respectfully requests that this analysis be withdrawn from the TA as it is heavily flawed with significant errors. Numerous system reviewers have pointed out the egregious mistakes in this paper and currently Dr. Marissa Carter is working with the authors and journal to ensure it is corrected.

There are a few areas in which the nature of the topic being discussed in the TA is a bit sensitive and the Alliance would like to request that AHRQ be more respectful to those that have donated tissue. Specifically, – there are a few areas in this document in which AHRQ refers to tissue being “harvested”. “Harvested” is an insensitive term that should be removed from all literature which describes any HCT/P as these tissues are graciously consented donated human gifts. In the same vein, in deference to donor and donor families, we ask that any reference to “human cadaver” dermis or just the term “cadaver” be replaced with the term “donated human dermis” (or a variation thereof). Using the term “cadaver” dehumanizes and disrespects the deceased and their family who have donated this gift of life. As such the Alliance requests that these terms be modified in this final version of the TA.

Finally, AHRQ states that they consulted with 6 KIs as well as some peer reviewers who provided input into this TA but did not mention the identity of these informants and reviewers. AHRQ merely stated that the names of those individuals would be published only in the final document. The Alliance is disappointed that AHRQ did not identify the names of the people who influenced this report. As the Alliance has often publicly stated, there needs to be more transparency when reports such as these are issued. In fact under the 21st Century Cures Act, it is required. Based on the language in the 21st Century Cures Act the names and affiliations of all key informants and reviewers utilized by AHRQ should have been included not only in

¹ Standard Guide for Classification of Cellular and/or Tissue Based Products (CTPs) for Skin Wounds. ASTM International. February 2016 DOI:10.1520/F3163-16

AHRQ’s final 2019 Technology Assessment document but also in this Draft given that it is important for stakeholders to better understand which key informers helped shape all aspects of the draft and final reports.

SPECIFIC COMMENTS- METHODS

Risk of Bias (pg 7)

One of the areas the Alliance has significant concerns with this technology assessment lies in some of the questions posed in the Risk of Bias section and ultimately in the conclusions reached based on the analysis of those questions. Listed below are some of our concerns:

- It appears that the reviewers chose a non-validated approach to assess bias, 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.
- What criteria did the reviewers use to judge that a study used appropriate randomization methods or concealment of treatment group allocation?
- The authors seem to have singled out wound size/duration and number of comorbidities as the only important baseline parameters, suggesting 15% as the split point. We question 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- rater reliability) statistics.

Our comments below are specific to questions 3, 4,5, 6, 7 and 10 under “Risk of Bias” (page 7) and address each of these questions separately.

Question 3 - Were the numbers of comorbidities similar (no more than a 15% difference) at the start of treatment between groups?

First, this criteria does not seem to be based on any known standard and in itself will limit the population for clinical trials. Second, this approach implies that all comorbidities have an equal weight in terms of the potential to affect wound healing, and that all are in the same direction (for example, BMI for reasons we don’t full understand can be “protective.”) Third, in the majority of wound care RCTs, it is standard practice to adjust the primary endpoint for *all* imbalances between groups in some type of regression. The authors of the study have ignored this approach altogether.

Question 4 - 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” situations 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. This factor can be adjusted for in analysis as stated in the comment to Question 3.

Question 5 -Were the mean wound duration 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. Chronic wounds of longer duration have 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 (see comment to Question 3).

Question 6 - Was the method of measure wound condition at enrollment reported?

This question is ambiguous and needs far more definition to make sense. What do the authors mean by “wound condition?”—area, severity of wound, how much slough, necrotic tissue, etc.? In the vast majority of RCTs, there is a screening period during which many of these factors are measured (and inclusion/exclusion criteria are applied) and the wound is debrided if appropriate. We don’t understand the purpose nor the origin of this question.

Question 7- Was the wound assessor blinded to the patients treatment group?

It is important to have the patient be blinded, but AHRQ did not address this in the technology assessment. It would have been a more appropriate risk of bias question to have been posed rather than a question which automatically will incite bias as it is impossible to blind the wound assessor.

The Alliance recommends a standard in which 2 blinded assessors agree to wound closure. This would eliminate investigator bias.

Question 10 - Was there a 15 percent or less difference in completion rates in the study arms?

This criteria does not seem to be based on any known standard and is irrelevant. Drop out rates of > 20% are important and large differentials between groups are important, too, but we don’t know the critical number. Most systematic review methods accept 20% as a break point. More importantly, the difference in censoring rates and loss of endpoint and variable data *between groups* is the more worrisome.

COMMENTS ON GUIDING QUESTIONS

Guiding Question 1: What skin substitutes currently used to treat chronic wounds are being regulated by the U.S. Food and Drug Administration (FDA) under the following pathways: PMA, 510(k), PHS 361/21 CFR 1270 and 12711?

There is particular confusion about device classification, patient risk, and device effectiveness concerning wound care products. The FDA device classification system is based on patient risk, not on effectiveness. The much higher complexity of the regulatory process associated with the higher risk Class III devices has no relationship to their effectiveness. Lower risk devices (Class I and II) often have the same or higher effectiveness than Class III products. This fact is borne out by examining published clinical studies.

Only a well-run clinical study can demonstrate effectiveness. Many people make the false assumption that clinical studies are only required and performed for Class III devices. High quality clinical studies can be, and are, conducted on Class II devices. In fact, the FDA requires clinical studies for 10-15% of Class II devices as a condition of approval. Risk-based classification does not provide a reliable gauge of whether effectiveness has been shown in a clinical study. Furthermore, the quality of the study does not correlate with the device classification. For example, a study published in the Journal of Vascular Surgery in late 2006 reviewed and ranked sixty-eight potentially relevant randomized clinical trials (RCTs) previously published in the treatment of venous leg ulcers. Included were clinical studies of Class II and Class III products. In the final analysis, only 2 RCTs contained all 7 elements of a quality study, and both showed statistically significant benefit for healing chronic venous ulcers. Those two RCTs were for OASIS Wound Matrix (a Class II device) and Apligraf (a Class III device).

There is also an assumption that within Class II, all devices with the same 3-letter FDA product code (or PRO code) are equally effective. This is not true. Some devices within a particular PRO code undergo extensive clinical testing to demonstrate effectiveness, while others do not. The PRO code is simply an internal "bucket" into which FDA sorts devices by intended use, composition, etc. It is not intended to indicate relative effectiveness or safety. In direct communication with high ranking officials in CDRH, we have been told categorically that the PRO code classification is for "FDA administrative purposes only" and is not intended to be used for reimbursement decisions. There are good reasons for the FDA to make such a statement. Different devices within the same code have different technologies and vastly different levels of clinical data to support their claims of effectiveness. This leads to the conclusion that the most effective device with the greatest proven clinical utility may also be the one with the lowest cost and lowest risk. In the FDA device classification system, Class III (highest risk) does not necessarily equate with increased effectiveness; in fact, it may be quite the opposite.

As such, the Alliance recommends that AHRQ should include all studies on CTPs that FDA permits to be marketed in the U.S. and guiding question should be changed to reflect this.

Guiding Question 2: What classification systems have been developed to categorize skin substitutes? What are important skin substitute parameters and active components currently being used when classifying skin substitutes?

AHRQ has used in its document the 2018 Davison-Kolter method of classifying CTPs. The Alliance questions why this classification system was chosen? First of all, we have concerns that since it is so new, it has not been widely accepted or validated. Secondly, we question the reason for the classification or its usefulness. There are many classifications that exist already. For instance, if the intent was for the FDA to adopt this classification, this probably would not happen since the FDA has its own classification system which is how the products are classified when they enter the marketplace.

AHRQ provides a lengthy discussion on the Davison-Kolter system and grouped products accordingly but the real question is why go through this type of exercise to group/classify the products and then do nothing with the classification? The Alliance would like to know what AHRQ and other entities will ultimately do with the groupings of products based on this classification system.

We were surprised that AHRQ had not included the classification system from the ASTM standard guide on CTPs. The Alliance recommends that AHRQ use instead the classification that is included in the ASTM International Standard Guide: F3163-16 Classification of Cellular and/or Tissue-Based Products (CTPs) for Skin Wounds.

The ASTM classification² of CTPs includes the following groupings based also on their composition:

6.1.1 *Biosynthetic*

6.1.2 *Biosynthetic and Animal Based*

6.1.3 *Non-Living Tissue Based*

6.1.3.1 *Non-Living Tissue Based – Human Based*

6.1.3.2 *Non-Living Tissue Based – Animal Based*

6.1.4 *Living Cells Biological*

6.1.4.1 *Living Cells Biological – Minimally Processed*

6.1.4.2 *Living Cells Biological – Cultured*

6.1.4.3 *Living Cells Biological – Cultured and Animal*

Products Listed as CTPs which are Surgical Dressings

In both Questions 1 and 2 there are charts that list the CTPs. Unfortunately, there are products listed which even though they have collagen in them and have gone through the 510(k) process, they are not classified as CTPs by the Centers for Medicare and Medicaid Services. Instead they are coded, covered and paid as surgical dressings and therefore, do not belong in these tables. The following are examples but are not all inclusive: CollaSorb® collagen dressing, Endoform™ dermal template and Puracol® and Puracol Plus® Collagen Wound Dressings. A simple check of the PDAC website would have allowed AHRQ to confirm that these products were surgical dressings not CTPs.

² Standard Guide for Classification of Cellular and/or Tissue Based Products (CTPs) for Skin Wounds. ASTM International. February 2016 DOI:10.1520/F3163-16

Inconsistencies

Within the AHRQ technology assessment, there are inconsistencies and inaccurate information contained in the assessment which need to be rectified prior to being published in final. With respect to inconsistent or inaccurate information related to a particular product, since the AHRQ TA may be used by CMS and other payers to define products, possibly for coverage or reimbursement purposes, it is critical that the AHRQ TA be corrected to accurately describe all products. The Alliance has highlighted several of those areas for AHRQ so the document can be revised prior to being finalized. Examples include:

- Graftex is correctly listed as a “cellular” product in some parts of the document, and incorrectly listed as an “acellular” product in other parts of the document. (Page 20, Table 11 – Graftex is listed as a cellular product (correct), Pages 26, 27, 31, 32, 33, 34, 38 Graftex is listed as acellular (incorrect), In the Appendix, Graftex is listed as acellular in the evidence tables on pages C-9 and C-18, C-23 (this incorrectly describes the product in the context of the evidence as it is presented. For example, the Graftex vs. Dermagraft RCT compares to cellular products to each other.)
- “Theraskin (Table 13) is a cryopreserved human, living, split-thickness allograft that contains fibroblasts and keratinocytes. The tissue is procured within 24-hours postmortem from an organ donor. When procured, the allograft is washed with antibiotics and cryopreserved. According to the manufacturer, living cells survive through harvesting, cryopreservation, and thawing. FDA regulates Theraskin as human tissue for transplantation.” This information should be corrected to read, “TheraSkin (Table 13) is a cryopreserved human, living, split-thickness allograft that contains living cells, growth factors, and an architecturally-preserved human ECM scaffold that vascularizes. Around 7-14 days after application, the epidermal cells and any antigenic components are removed but the dermal scaffold and the matrix is retained. The tissue is safely procured according to industry standards developed by the FDA and AATB within 24-hours postmortem from an organ donor. According to the manufacturer, living cells survive through procuring, cryopreservation, and thawing. FDA regulates Theraskin as human tissue for transplantation.”
- AHRQ made the following statement in the findings section (p. 15): “Natural human dermis must be sterilized to prevent potential disease transmission.” This statement is inaccurate. Tissues obtained from human donors may have the risk of infectious disease transmission; however, industry standards developed by the FDA and AATB may be utilized to minimize and eliminate this risk without requiring sterilization.³ If this statement is edited to “Animal tissues must be sterilized to prevent potential disease transmission.” then the statement would be accurate.
- In the Findings section (p. 15) AHRQ states, “Cells within the transplanted dermis would typically lead to rejection within 10 to 15 days; therefore, the donated skin tissue must be processed to remove the cells.” The statement that cells must be removed is not accurate since in the context of chronic wounds, these tissues are intended to be used externally rather than for implantation. In the context of

³ (See reference: *Kagan RJ, Robb EC, Plessinger RT. Human skin banking. Clin Lab Med. 2005 Sep;25(3):587-605.*)

chronic wounds, the antigenic components are removed by the host but the remaining dermal components become incorporated.”⁴

Guiding Question 3: What are the study design characteristics (such as those listed below) in each included investigation for each chronic wound type?

Evidence

In this AHRQ analysis, RCT studies limit the population that can be included in the studies to limit the variability between the study populations. This allows for valid comparison of the results between the groups. Therefore, studies have exclusion criteria (i.e. uncontrolled diabetes, poor vascularization, immunosuppressive drugs, end stage renal disease, infection, or required restrictions by FDA labeling). These factors are excluded because they can unpredictably impact the clinical outcomes and make appropriate patient matching nearly impossible. RCTs are conducted to remove the variables that can artificially impact the outcome and mask the “effect” of the study product. At the same time, they have inclusion criteria that includes wounds that have not responded to standard usual treatment to be evaluated. As AHRQ noted, this can result in a more healthy population in the RCT studies than in real world situations.

It is important to note the following information from the The US Wound Registry (USWR) which illustrates the shortcomings of RCTs especially for the wound care patients who have multiple comorbidities.

An analysis of 2014 Medicare cost data demonstrated that chronic wounds affect nearly 15% of Medicare beneficiaries and that Medicare’s annual spend to treat them could reach \$96.8 billion.⁵ This national Medicare dataset revealed that patients generally have more than one ulceration and they remain unhealed for at least a year. In fact, chronic wounds are not a disease but a symptom of disease. The average Hierarchical Condition Category (HCC) score of physicians participating in the USWR is 2.9, and the prevalence of only some major comorbid diseases (based on Medicare data from physician NPI) is as follows:

1.	Hypertension	73.5%
2.	Chronic kidney disease	52.5%
4.	Diabetes	47.8%
5.	Heart Failure	38.6%
6.	Ischemic Heart disease	49.7%
7.	RA and osteoarthritis	49.7%
8.	Afib	19.9%

⁴ (See references: (a) Kagan RJ, Robb EC, Plessinger RT. Human skin banking. *Clin Lab Med.* 2005 Sep;25(3):587-605. (b) Vig K, Chaudhari A, Tripathi S, Dixit S, Sahu R, et.al. Advances in skin regeneration using tissue engineering. *Int J Mol Sci.* 2017 Apr 7;18(4).)

⁵ Nussbaum SR, Carter MJ, Fife CE, DaVanzo J, Haught R, Nussgart M. An Economic Evaluation of the Impact, Cost, and Medicare Policy Implications of Chronic Nonhealing Wounds., *Value in Health*, 2018, Vol.21, Issue 1, P27-32.
[http://www.valueinhealthjournal.com/article/S10983015\(17\)30329-7/pdf](http://www.valueinhealthjournal.com/article/S10983015(17)30329-7/pdf) <http://dx.doi.org/10.1016/j.jval.2017.07.007>

9.	Alzheimer's	22%
10.	Asthma	30.6%
11.	COPD	27%
12.	Depression	34%
13.	Cancer	13.8%

The US Wound Registry (USWR) which hosts the Cellular and/or Tissue based Therapy Registry (CTPR: ClinicalTrials.gov Identifier: NCT02322554) was able to conduct an evaluation of the difference between patients with chronic wounds and the subjects enrolled in clinical trials. All prospective trials involving diabetic foot ulcers (DFUs) and venous leg ulcers (VLU) used virtually identical exclusion criteria which were: ⁶

- For DFU studies, no DFUs > Wagner Grade II (most enrolled only Wagner 1)
- Diabetes as a co-morbid condition for any study other than DFU
- Venous stasis except in VSU trials
- Alcohol/drug abuse
- Anticoagulant treatment
- Cellulitis or local wound infection
- Cancer or recent cancer treatment
- Collagen vascular disease/connective tissue disease
- Rheumatoid arthritis/autoimmune disease, any type
- Scleroderma/lupus, any autoimmune disease
- Charcot foot changes in DFU
- Corticosteroid treatment any reason
- Deep venous thrombosis/pulmonary embolus
- Gastrointestinal disease of any kind /any Liver disease/Hepatitis
- Renal impairment/ESRD/Renal dialysis/Renal transplant
- Any organ transplant
- In diabetics, HbA1c > 8-10
- Nutritional impairment/Albumin < 3.0 mg/dl
- Osteomyelitis
- Peripheral arterial disease

Using the above exclusion criteria, among 8,611 wound center outpatients, approximately 88% would have been excluded from all pivotal wound care RCTs. Even more troubling, based on propensity scoring, 3 of 4 major trials that brought new products to market enrolled patients healthier than the “man on the street.”

The value of real-world data was again clearly demonstrated in 2007 when the FDA required the company KCI (now Acelity) to evaluate the safety of Negative Pressure Wound Therapy (NPWT) in comparison to moist wound care in the outpatient setting. The USWR was able to assess the risk of infection and bleeding in nearly 1,000 NPWT patients, 200 of whom were on Coumadin, compared to nearly 9,000 moist wound

⁶ Carter M, Fife CE, Walker D, Thomson B. Estimating the Applicability of Wound-care Randomized Controlled Trials to General Wound Care Populations by Estimating the Percentage of Individuals Excluded from a Typical Wound Care Population in Such Trials: 2009, 22: 316-24.

care patients. NPWT RCTs had excluded all patients on anticoagulants so the only way to evaluate the safety of NPWT among patients on blood thinners was via real-world data.

The most common wounds are NOT diabetic foot ulcers but dehisced surgical wounds. Surgical wound dehiscence, also the most expensive wound, only occurs because patients have some underlying medical problem which prevented normal healing. Nearly 20% of wounds are simply classified as “chronic ulcers” because they don’t fit into any specific wound category. Thus, RCTs in wound care do not address the most common chronic wound types. Besides excluding all the patients with serious co-morbid diseases which are not only common among chronic wound patients but are in fact, the cause of the chronic wound, RCTs also select only very small and superficial wounds.

RCTs have failed to enroll representative patients because in the past, there was no way to risk stratify patients and/or serious wounds based on their likelihood of healing given the numerous factors that affect this complex process. The USWR in collaboration with the Institute for Clinical Outcomes Research (ICOR) created a risk stratification for wounds now called the Wound Healing Index (WHI).⁷⁸⁹ The WHI can be used to create matched cohorts for retrospective comparative effectiveness (CER). Using USWR data, it is possible to control nearly every aspect of patient care mathematically.¹⁰ The WHI also makes it possible to quantify the difference between real world patients and the subjects enrolled in RCTs.

In terms of this AHRQ TA, wound care experts have therefore conducted evidence-based studies to allow for more diverse groups of patients with longer duration wounds and more complex or larger wounds to understand effectiveness in a ‘real world’ application. Unfortunately, AHRQ has not identified these studies in their review or included them in their analysis. We would like to urge AHRQ to include studies other than RCT information in this report, and in fact, it should apply the same tools (risk of bias, consistency, directness and precision) to give a more realistic picture of clinical evidence available for CTPs. Additionally, AHRQ should consider obtaining real world evidence from some of the wound registries (e.g. U.S. Wound Registry, Net Health) that are available.

Real World Evidence

AHRQ has recognized that studies that are more representative of clinical practice and the typical patient population utilizing CTPs should be included. In the findings section AHRQ states, “KIs suggested that patient inclusion criteria could be expanded to include patients more representative of clinical practice and of poorer health than typical patients included in RCTs.” We strongly support this statement which is why real-world evidence (RWE) is so important and necessary in chronic wound care.

⁷ Horn SD, Fife CE, Smout RJ, Barrett RS, Thomson B. Development of a Wound Healing Index for Patients with Chronic Wounds. *Wound Rep Reg.* 21; 823-832, 2013.

⁸ Fife CE, Horn Susan D, Smout RJ, Barrett RS, Thomson B. A Predictive Model for Diabetic Foot Ulcer Outcome: The Wound Healing Index. *Adv Wound Care.* 5(7): 279-287, 2016. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4900227/>

⁹ Horn S, Fife CE, Barret R, Thomson B. A Predictive Model for Pressure Ulcer Outcome: The Wound Healing Index. *Adv Skin Wound Care.* 28(12): 560-572, 2015.

¹⁰ Carter MJ, Fife CE. Clinic Visit Frequency in Wound Care Matters: Data from the US Wound Registry. *J Wound Care.* 26(Sup1): S4-S10, 2017.

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.¹¹ The percentage of “real world” patients excluded in such studies in wound care can be high.¹² 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.¹³ A good example of why some promising wound care products do not work well in all 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”¹⁴ or as a combination of the following three factors: (1) best research evidence; (2) best clinical experience; and (3) consistent with patient values.¹⁵ In other words, the approach does not only consider 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.”¹⁶ As it is difficult to conduct prospective, real-world clinical studies due to the high number of variables which would make data analysis extremely complicated, using data from a number of wound registries and EHR systems would be advantageous.

Because the authors of this systematic review chose only to examine RCTs published in the peer-reviewed literature, much of the evidence on CTPs is missing, and thus, the conclusions in terms of coverage of these products are skewed. Additionally, as the search excludes RCTs published prior to 2012, many CTPs with valid RCT results are excluded from the conclusions drawn in this TA. This, as well as the inaccessibility of the previous AHRQ TA from 2012, implies that those CTPs are no longer effective, which is not true.

Since RCTs may not treat the same patients treated in clinical practice, as has been recognized by AHRQ in this TA, evidence from RCTs may have limited value in predicting clinical outcomes in the real-world. However, there are a few real-world trials for CTPs published prior to September 2018 and they could have been included in this TA if for nothing else to provide context. These real-world trials have in some cases shown outcomes similar to that seen in RCTs, and in some case shown significant differences.

¹¹ Serena T, Bates-Jensen B, Carter MJ, et al. Consensus principles for wound care research Obtained using a Delphi process. *Wound Repair Regen* 2012; 20:284-93.

¹² Carter MJ, Fife CE, Thomson B, Walker D. Estimating the applicability of wound care randomized controlled trials to general wound-care populations by estimating the percentage of individuals excluded from a typical wound-care population in such trials. *Adv Skin Wound Care* 2009;22:316-24.

¹³ van Rijswijk L, Gray M. Evidence, research, and clinical practice: a patient-centered framework for progress in wound care. *Ostomy Wound Manage* 2011;57:26-38.

¹⁴ Gray JA. *Evidence-based Health Care: How to Make Health Policy and Management Decisions*. London: Churchill Livingstone, 1997.

¹⁵ Institute of Medicine (2001). *Crossing the Quality Chasm: A New Health System for the 21st Century*, Washington, DC: National Academy Press.

¹⁶ Tunis SR. A clinical research strategy to support shared decision making. *Health Aff (Millwood)* 2005;24:180-4.

In addition to the RWE studies, there are several studies that we believe that AHRQ should have reviewed as part of this TA. They include (but are not limited to) the following:

- *Budny AM, Ley A. Cryopreserved allograft as an alternative option for closure of diabetic foot ulcers. Podiatry Management. 2013 Aug;131-136.*
- *Desman E, Bartow W, Anderson LH. Human skin allograft for patients with diabetic foot ulcers, venous leg ulcers, or surgical/traumatic wounds: a retrospective, descriptive study. Ostomy Wound Manage. 2015 Jul;61(7):16-22.*
- *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*
- *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.*
- *Landsman AS, Cook J, Cook E, Landsman AR, Garrett P, Yoon J, Kirkwood A, Desman E. A retrospective clinical study of 188 consecutive patients to examine the effectiveness of a biologically active cryopreserved human skin allograft (TheraSkin®) on the treatment of diabetic foot ulcers and venous leg ulcers. Foot Ankle Spec. 2011 Feb;4(1):29-41.*
- *Landsman A, Rosines E, Houch A, Murchison A, Jones A, Qin X, Chen S, Landsman AR. Characterization of a cryopreserved split-thickness human skin allograft: TheraSkin. Adv Skin Wound Care. 2016 Sep;29(9).*
- *O'Donnell TF Jr, Lau J. A systematic review of randomized controlled trials of wound dressings for chronic venous ulcer. J Vasc Surg 2006;44:1118-25.) This study 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.*
- *Raspovic KM, Wukich DK, Naiman DQ, et al. Effectiveness of viable cryopreserved placental membranes for management of diabetic foot ulcers in a real world setting. Wound Repair Regen. doi: 10.1111/wrr.12635. Accessed 27 July 2018.*
- *Wilson TC, Wilson JA, Crim B, Lowery NJ. The use of cryopreserved human skin allograft for the treatment of wounds with exposed muscle, tendon, and bone. Wounds. 2016 Apr;28(4):119-125.*

Grading

The Alliance has concerns with the grading system identified in this TA. It is too inflexible and does not have specific risk of bias.

Guiding Question 6: What best practices in study design could be used to produce high quality evidence on skin substitutes?

Study Design- Run In Period

As part of the Key Messages, in the section on Study Design under Question 6 and on pg 46 regarding “What should future study designs have in common?”, AHRQ states, “future studies may be improved by using a 4-week run-in period before study enrollment and at least a 12-week study period. They should also report whether wounds recur during 6-month follow up.” The Alliance is concerned regarding the recommendation

of a 4 week run in period as that time frame is too long for a patient with a chronic wound. If AHRQ is going to make this recommendation, the run in period should only be 2 weeks.

In trials, patients have already failed at least 4 weeks of standard wound care (SOC). The 2-week run in period means that patients will receive a minimum of 6 weeks of SOC prior to enrollment in the trial and showed little to no improvement. All published clinical guidelines recommend using adjunctive advanced therapy after 4-weeks of failed SOC based on data reported by Sheehan et al. *Diabetes Care* 26:1879–1882, 2003 that shows percent area reduction (PAR) of a wound at 4 weeks is a good predictor of the 12-week healing rate. Margolis et al. *Diabetes Care* 22:692–695, 1999 showed SOC continued for 12 weeks has a healing rate of 24%, and at 20 weeks is 30%. There is no need to extend the run-in period for trials. However, reporting PAR during failed SOC and standardizing the inclusion/exclusion criteria for SOC and PAR would allow for a better comparison of data between RCTs. In the 17 published RCTs for CTPs there are trials where the 12-week healing rate in the SOC group is much higher than the 24% reported by Margolis. The Alliance recommends using “relative improvement” (the percentage difference between the healing rates of the treatment and control group) as a standardized method to compare trials. Relative improvement provides a more accurate picture of the product effectiveness vs SOC, and accounts for the differences in study populations treated in different trials.

As different chronic wounds are significantly variable, it is incredibly difficult to have a standardized study designs that include standardized run-in periods. Should AHRQ determine a need to move forward with the standardized run-in period, currently we have found that when appropriately structured, 2 weeks is sufficient to bring all wounds to the same level with 2 weeks of good wound care, which is the real point of having a screening phase in the first place. In addition, it is sufficient time to eliminate fast healers, which dilutes the clinical responders of each group, as well as being enough time to properly apply inclusion and exclusion criteria. Finally, 4 weeks would mean higher screening failure rates for trials, which makes the trial longer, put more patients at risk, and make the trial more expensive and at higher risk for not being completed, all of which are undesirable.

Evidence Gaps

The TA states: Industry funds the large majority of published studies, which raises concern about publication bias or selective outcome reporting in that poor results may not be published. Independent funding of skin substitute research would reduce potential for bias and make comparisons of products more likely. The evidence gaps will be only partially addressed by currently registered ongoing trials, which are largely funded by industry. Only four of the ongoing RCTs are comparing two skin substitutes.

Alliance response: Unrelated to the questions posed with respect to bias, there is an undertone to the assessment in which AHRQ implies a critical slant that all CTP evidence was funded by manufacturers. This is misleading because nearly all research conducted across the entire health care industry is funded by manufacturers. Reputable manufacturers invest in evidence for their products to ensure coverage for their products and for commercialization purposes. The fact reported in the AHRQ that only 13 products out of 74 included in the analysis (18% of brands) have published evidence is proof that no outside source of funding is conducting studies for products. AHRQ should qualify the comments to provide the context that across the entire health care industry there is very little funding of clinical trials, and manufacturers are relied upon to fund research on their products.

Furthermore, the source of investment for a clinical study is not an automatic cause of bias or concern for the integrity of data generated. The Alliance 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. Across the healthcare spectrum, 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 or perhaps in the future funded by NIH, PCORI or AHRQ.

Similarly, as the federal and state governments are limited in the funds that they can provide to conduct randomized controlled trials 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 or drug manufacturers that have to fund these studies in order to obtain the clinical evidence that is needed to obtain approval/clearance to market the products. 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.

As stated, the source of investment for a clinical study is not an automatic cause of bias or concern for the integrity of data generated.

CONCLUSION

In this AHRQ TA, even with the key questions and guiding questions posed as answered, the Alliance has questions regarding the actual findings. There should have been a detailed summary based on the statistics which included what is known, what is missing and what are gaps that need to be filled with respect to CTPs. The Alliance does not have a clear understanding regarding any of that which we believe the assessment should have provided.

Moreover, we are in agreement with the statements recognizing that the data reviewed (RCTs) is not the best evidence to review when assessing the evidence for chronic wound care patients, as the exclusion criteria eliminates most of the patients that would benefit from the treatment of CTPs. There was recognition by the AHRQ that real world evidence would be beneficial. Yet, AHRQ either eliminated or did not review any studies which would provide real world data and help to answer some of the questions posed in this TA. Until AHRQ reviews real world evidence for CTPs, the Alliance believes that this TA is incomplete.

The Alliance appreciates the opportunity to provide you with our comments and feedback on this TA. We would appreciate the opportunity to meet with your staff responsible for this TA and the ECRI authors of the study.

Sincerely,



Marcia Nusgart R.Ph.
Executive Director