ALLIANCE OF
WOUND CARE
STAKEHOLDERS
POWER THROUGH COLLECTIVE ADVOCACY

November 21, 2016

Janice M. Soreth, M.D.
Associate Commissioner for Special Medical Programs
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane Room 1061
Rockville, Maryland 20852

Submitted electronically to Evella.Washington@fda.hhs.gov

Re: Docket Number FDA-2016-N-2147 General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting: Establishment of a Public Docket; Request for Comments

Dear Dr. Soreth;

On behalf of the Alliance of Wound Care Stakeholders ("Alliance"), we are pleased to submit follow-up comments in response to the September 20-21, 2016 Food and Drug Administration's meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee. Our first set of comments were submitted on September 1, 2016 to educate the Panel before its meeting.

The Alliance is a nonprofit multidisciplinary trade association of physician medical specialty societies, clinical and non-clinical associations, and business entities whose mission is to promote quality care and access to products and services for people with wounds through effective advocacy and educational outreach in the regulatory, legislative, and public arenas. These comments were written with the advice of our members who not only possess expert knowledge in the care of complex chronic wounds, but also in wound care research. Since our healthcare provider members prescribe and use antimicrobial wound care products in their practices and our company members manufacture these products, we are critically interested in this issue. A list of our members can be found at: www.woundcarestakeholders.org.

GENERAL COMMENTS

The Alliance members are in agreement with the recommendations of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee to the FDA that antimicrobial wound care products (i.e., Solid Wound Dressings combined with Drugs and Wound Dressings combined with Drugs formulated as a Cream, Gel, or Ointment) should be classified in Class II with special controls. The Alliance also agrees with the FDA's use of multiple product classification categories for antimicrobial products currently regulated in the FRO category (i.e., solids, cream/gel/ointment and liquid washes).

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While we recognize that there are more FRO products on the market today then in 2005, the Alliance also agrees with the Agency's rationale in 2005 when it proposed to classify pre-amendment antimicrobial wound care products into Class II for the following reasons:

- *We have years of experience regulating these devices (since 1976)*
- *We understand the device specifications and performance characteristics (bench testing, animal testing and clinical data) needed to evaluate and control their safe and effective use.*
- *Classification to Class II meets the FDA mandate to apply the "least burdensome" approach to regulating medical devices.*

The Agency's rationale for identifying a Class II designation as appropriate is based on the long history of safe and effective use of these devices over the past 100 years and the scarcity of adverse event reports in the medical literature and the FDA's Medical Device Reporting System. The Agency proposes that all of the potential risks to health can be ameliorated via a special controls guidance document that includes recommendations and advice on device materials, device performance, animal testing, clinical testing, device sterilization, biocompatibility and device labeling.

Our specific comments focus on:

- Issues discussed at the meeting that need to be emphasized due to their importance
- Issues that need to be clarified based upon the discussion of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee

We recommend that the FDA keep in mind the following as the Agency makes a decision on classification of these products:

ISSUES THAT NEED TO BE EMPHASIZED DUE TO THEIR IMPORTANCE

1. In their presentations at the Panel meeting, both Dr. Eric Lullove and Dot Weir addressed the complexities of treating the wound care patient and the valuable role of antimicrobial wound care dressings in their practices by emphasizing the following:

   - Wound healing is a complicated process. The chronic wound changes as it progresses, with the need for multiple modalities, procedures and products to be used for treatment, some at that same time and different ones over the course of healing. This has complicated studies of wound dressings where only full wound healing was considered the primary outcome of wound management.
   - Antimicrobial wound care dressings are only one of many tools that the wound care clinician uses to manage the chronic wound. These products are often used with debridement, special washes and physical medicine approaches in the care of chronic wounds.

2. There is tremendous clinical value to the patient, medical staff and hospital in the use of antimicrobial dressings to control the bacterial load of wounds. For example, clinically significant numbers of bacteria (hundreds of colony forming units) are aerosolized during the changing of a non-medicated wound dressing that contains a heavy growth of bacteria. This spreads bacteria onto the patient, the nurses, and the physicians who are doing the dressing change as well as

contaminating the air and surfaces (bed rails, linens, walls, floors, etc.) surrounding the patient. Thus, there is tremendous clinical value to the patient, medical staff and hospital to use dressings that contain antimicrobials and therefore do NOT allow growth of bacteria in the wound dressing itself.

3. **Antibiotic Resistance**—FDA noted that a major reason for the panel discussion was the concern around increasing antibiotic resistance in the U.S.

   The wound care products in the FRO category containing such items as silver, PHMB, Cadexomer iodine and honey under discussion at the Panel meeting should be categorized as antiseptics and do not appear to contribute to antibiotic resistance. They should not be confused with dressings or ointments containing mupirocin, bacitracin etc., which are antibiotic in nature, since they are used to treat infection and are not products generally used for managing the majority of chronic wounds; nor should they be confused with antibiotics used orally or intravenously to treat infections such as Tobramycin, Ciprofloxacin.

   Also at the Panel meeting, Dr. Randall Wolcott addressed the concern about contributions of these wound dressings to the antibiotic resistance issue by stating:

   "……if we just indiscriminately start using the antimicrobial products to protect every dressing, then aren't we going to drive resistance? Well, the short answer is probably not. We use silver as an example, and that can be generalized out across other antimicrobial agents. But what we see is that silver has four independent mechanisms by which it can kill bacteria. So that bacteria, in a planktonic state, can become somewhat tolerant, but antibiotics have a single target, and they can have true resistance. "

   He went on to note that FDA in its presentation described bacterial resistance to antibiotics and how it is spread among bacteria. This is unlikely to happen when there are multiple mechanisms of action with the types of antiseptics used on wound dressings. He also noted that multiple papers have stated that resistance to these antimicrobials is overstated and quite rare.

   The authors that Dr. Wolcott referred to and were noted in his slides:

   - **Bowler: "**Despite the **sporadic evidence** of bacterial resistance to silver, there have been very few studies undertaken and documented to ascertain its prevalence. The risks of antibacterial resistance developing from the use of biocides may well have been **overstated**."[i]

   - **Percival: "**Results suggest that presence of silver resistance genes is **rare** and that genetic resistance **does not necessarily translate** to phenotypic resistance to silver."[ii]

As the Alliance stated in its first set of written comments: Many products in the FRO category do however contain silver. After decades of use of silver wound care products, we are unaware of any journal report where there was development of silver resistant organisms due to the use of silver containing wound care products. We believe that any current data is insufficient to consider this a significant public health problem at this time. In the article, "The increasing use of silver-based products as antimicrobial agents: a useful development or a cause for concern?" Dr. Chopra states

that even though silver resistance has been documented, current evidence suggests the clinical threat is low." [iii]Silver has been used in wound care for many decades without serious problems.

ISSUES THAT NEED TO BE CLARIFIED FROM THE DISCUSSIONS AT THE GENERAL AND PLASTIC SURGERY DEVICES PANEL OF THE MEDICAL DEVICES ADVISORY COMMITTEE

Indications for Use/Intended Use

There was much discussion and confusion at the Panel meeting regarding what are the indications for use/intended uses for antimicrobial wound care dressings. To clarify, antimicrobial wound care dressings are not intended to **treat** or **heal** the wound; instead the specific claims made in the labeling for these products include: maintain a moist wound environment, covers and protects the wounds, provides a barrier to penetration of microbes to the wound, which may reduce the risk of infection, to enhance the microbial barrier function and minimize growth of microbes in the wound dressing, minimize contamination/colonization of the dressing.

Confusion on Terminology- Antibiotic versus Antimicrobial versus Antiseptic

The terms "antibiotic", "antimicrobial" and "antiseptic" were all used during the Panel meeting and the Panel members interchanged the terminology during discussion. For the products that the Panel was dealing with, wound dressings with drugs would be considered antimicrobials since these products in the FRO category contain, silver, PHMG, Cadexomer iodine and honey. There needs to be a clear distinction made that dressings containing antibiotics such as mupirocin and bacitracin are not used to manage chronic wounds and were not the subject of the meeting which was stated many times during the Panel meeting. (i.e. pg. 101 of the Day 1 transcript).

In the Alliance's previous comments, the definitions used were those that are on the FDA website to define these terms:

- Antimicrobial agents are substances that kill or inhibit the growth of microorganisms. In many instances in which the antimicrobial acts outside the body, such as antimicrobial sterile drapes and gloves used in patient procedures, FDA does not treat the antimicrobial as a drug. FDA has regulated such products as devices rather than combination products. Today these products meet many of the general requirements for combination products.
  http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm071396.pdf
- Antibiotics- FDA's definition of antibiotics is a subset of antimicrobials- often known as antimicrobial drugs, are drugs that fight infections caused by bacteria- http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/antibioticsandantibioticresistance/default.htm
- Antiseptics- Health care antiseptics are antimicrobial agents that are intended to reduce the number of micro-organisms on the skin. http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/economicanalyses/ucm447035.pdf)

Issues Regarding Clinical Practice Guidelines

In the September 21st, FDA presentation, the FDA staff stated that for diabetic foot ulcers, antimicrobial dressings are not recommended and that for venous leg ulcers, three guidelines do not recommend the use of antimicrobial dressings. These guidelines serve as examples in which there was confusion on how one used the term "antibiotic" versus "antimicrobial" as they pertain to antimicrobial wound care dressings. Many of the guidelines specify that use of antibiotics is not recommended for non-infected wounds or specify that routine use of antibiotic and in some cases antimicrobials for non-infected wounds is not recommended. The FDA then interpreted this to mean that antimicrobial wound dressings were not recommended, which is not the case in many instances.

Here are some examples of:

- Guidelines that are supportive of the use of antimicrobial dressings that were not cited by the FDA
- Those in the Guidelines/ Documents cited in the Executive Summary which were reviewed by FDA but are not identified as supportive data for antimicrobial dressings' use, but in closer review actually do recommend their use
- Address the misinterpretation of the use of the routine use of antibiotics to mean the use of antimicrobial dressings.

Pressure Ulcers/Venous Stasis Ulcers/Diabetic Foot Ulcers

- **Canadian Association of Wound Care (CAWC): Pressure ulcers, diabetic foot ulcers, venous ulcers. (2006)**
  Sibbald, RG, Orsted H. Best Practice Recommendations for Preparing the Wound Bed: Update. Canadian Association of Wound Care. 2006 *Wound Care Canada.* 4(1): 25.
    - Clean wounds with antimicrobials (list provided)
    - Two-week trial of antimicrobial dressings, if wound isn't healing with optimal care (increased bacterial burden, covert infection, critical colonization suspected).

- **WHS: Chronic Wound Care Guide (2006)**
    - **Chronic Wounds (VU, AU, DFU, PU)**
        - "topical antimicrobial dressings may be beneficial in management of chronically/ heavily colonized wounds, decreasing their bacterial load and helping wound healing"

Venous Leg Ulcers

- **Expert Working Group: Simplifying Venous Leg Ulcer Management: Consensus Recommendations (2015)** Harding K, Dowsett C, et. al. *Wounds Intern J* 2015
    - Antimicrobial dressings may be used short-term for the treatment of wound infection.
    - Use antimicrobial dressings for local infection or for prevention of infection in wounds at high risk.

- **WHS: Chronic Wound Care Guide (2006)**
  - **Arterial insufficiency ulcers** - topical antimicrobial dressings may be beneficial in management of chronically / heavily colonized wounds, decreasing the bacterial burden and helping with healing.

- **AAWC Venous Ulcer Guidelines (2012) - NOT included in FDA Review, new evidence**
  - Use topical antimicrobial solutions, dressing, gels, ointments effective against Gram -/+ and anaerobes with sustained-released silver, iodine, other agents.
  - Initiate antimicrobials on clean ulcers with delayed healing despite 2-4 weeks optimal care
  - Re-evaluate every 2 weeks, D/C when wound progresses

Pressure Ulcers

- **National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel, and Pan Pacific Pressure Injury Alliance (2014): Treatment of pressure ulcers. In: Prevention and treatment of pressure ulcers: clinical practice guideline.**
  - Consider using cleansing solutions with surfactants and/or antimicrobials to clean pressure ulcers with debris, confirmed infection, suspected infection, or suspected high levels of bacterial colonization.
  - Consider the use of tissue appropriate strength, non-toxic topical antiseptics for a limited time period to control bacterial bioburden.
  - Consider the use of topical antiseptics in conjunction with maintenance debridement to control and eradicate suspected biofilm in wounds with delayed healing.
  - Consider the use of topical antiseptics for pressure ulcers that are not expected to heal and are critically colonized/topically infected.
  - Consider using silver-impregnated dressings for pressure ulcers that are clinically infected or heavily colonized or at high risk of infection.
  - Avoid prolonged use of silver-impregnated dressings. Discontinue silver dressings when wound infection is controlled.
  - Consider the use of medical-grade honey in heavily contaminated or infected pressure ulcers until definitive debridement is accomplished.
  - Consider using Cadexomer iodine dressings in moderately to highly exuding pressure ulcers.
  - Limit the use of **topical antibiotics** on infected pressure ulcers, except in special situations where the benefit to the patient outweighs the risk of antibiotic side effects and resistance.

- **AAWC (2010) Pressure Ulcer NOT included in FDA Review, new evidence**
  - Use topical antimicrobial solutions, dressing, gels, ointments effective against Gram -/+ and anaerobes with sustained-released silver, iodine, other agents.
  - Initiate antimicrobials on clean ulcers with delayed healing despite 2-4 weeks optimal care
  - Re-evaluate every 2 weeks, D/C when wound progresses

- **UK NICE Guideline (2014)**
  - Consider using topical antimicrobial dressings to treat a **pressure ulcer** where clinically indicated in neonates, infants, children and young people, for example, where there is spreading cellulitis.
  - Do not routinely use topical antiseptics or antimicrobials to treat a **pressure ulcer** in adults.

- Antimicrobial dressings may be considered to help reduce bacterial numbers in **wounds**, but should be avoided unless the wound is infected or there is a clinical risk of the wound becoming infected.

- **UK Nice Guideline (2015)**
  - Antimicrobial dressings may be considered to help reduce bacterial numbers in **wounds**, but should be avoided unless the wound is infected or there is a clinical risk of the wound becoming infected.
  - "topical antimicrobial dressings may be beneficial in management of chronically/ heavily colonized wounds, decreasing their bacterial load and helping wound healing"

Non-healing Wounds

- **EWMA Document: Antimicrobials and Non-healing wounds, evidence, controversies, suggestions.**
  Gottrup E, Apelqvist J, et.al. *J Wound Care* 2013;22(5):S1-S89.
  - One approach to manage biofilms in non-healing wounds has been suggested, whereby physical removal of the biofilm with sharp debridement is immediately followed by antimicrobial strategies targeted at planktonic bacteria to prevent the re-establishment if the biofilm.[54, 108.]
  - "The bacterial resistance described in the literature is primarily in relation to use of **antibiotics.**"
  - Systemic review of the literature including RCT and nonrandomized studies, identified 14 studies w/ 1,285 patients [228] that shows evidence that silver dressings had positive effects on infected wounds.
  - A study also showed a PHMB dressing reduced bacterial burden in infected wounds at 4 weeks compared to a foam comparative dressing. [226]
  - The use of honey and silver-coated bandages improved the outcomes in malignant wounds [216]
  - An RCT study comparing Manuka honey hydrogel to a hydrogel, the Manuka honey eradicated MRSA from 70% of VLU vs. 14% for the hydrogel alone. [217] The potential to prevent infection was thought to be increased by removal of the MSRA.

- **AAWC (2010) Pressure Ulcer [NOT included in FDA Review]**
  - Use topical antimicrobial solutions, dressing, gels, ointments effective against Gram -/+ and anaerobes with sustained-released silver, iodine, other agents.
  - Initiate antimicrobials on clean ulcers with delayed healing despite 2-4 weeks optimal care
  - Re-evaluate every 2 weeks, D/C when wound progresses

ISSUES REGARDING RCT LITERATURE REVIEW, ENDPOINTS AND THE USE OF REGISTRIES

In its presentation, the FDA concluded in its RCT literature review that:

- there is a lack of appropriate trials supporting the use of antimicrobial dressings versus non-antimicrobial dressings
- for diabetic ulcers, venous ulcers, surgical wounds and burns, there is no evidence to support that antimicrobial dressings versus non-antimicrobial dressings provide a meaningful difference in preventing wound infections.

The Alliance has concerns regarding these statements in that:

- Many of the RCT's in the literature have complete wound healing as their endpoint, and as noted above, complete wound healing is not the endpoint most appropriate for the way these dressings are used in wound care
- There are appropriate trials using other endpoints conducted by Alliance members that address this issue as noted below.
- The second conclusion is faulty since these antimicrobial wound care dressings do not have indications for use for wound healing. In fact, the wound healing endpoints are inappropriate. Efficacy for antimicrobial dressings in controlled trials or effectiveness in "real world" studies is NOT about wound healing. The main goals and claims for antimicrobial dressings are not directed primarily at complete wound healing. In addition, given the chronicity of these wounds, most trials cited were not large enough or long enough to properly analyze complete wound healing. This is why the majority of systematic reviews did not find evidence for wound healing. Furthermore, as discussed in the Panel meeting, RCTs do not reflect the real world because the criteria for enrollment, given the endpoints exclude the majority of real world wound care patients.

The Panel members were asked to discuss what endpoints should be used for future clinical studies. In her presentation to the Panel, Dr. Marissa Carter presented a table (Attachment1) regarding silver-impregnated dressings that addressed what in these trials were the secondary endpoints of odor, exudate management and pain reduction. She stated that classic infection endpoints such as quantitative bacterial counts have been used but only make sense when systemic antibiotics are not used (confounding issues). Most controlled trials carried out to date have included safety endpoints based on alternative endpoints but these are not helpful. The targets not only for controlled trials but very useful in the real world, include those noted above, odor, exudate management, and pain reduction.

Long before the FDA looked to classify antimicrobial wound care dressings, Dr. Marissa Carter and Dr. Robert Warriner articulated these concepts in further detail in their 2009 article "Evidence-Based Medicine in Wound Care: Time for a New Paradigm," (Attachment 2) which included the following:

> *Most topical wound care products, dressings and treatments are not used over the entire duration of care but in a manner to achieve specific interval benefits in the support of wound*

stabilization and closure. Another way of stating this conceptually is that most wound care treatments are not intended to reverse all healing deficiencies present in any given patient. For example, silver-impregnated dressings are designed to manage wound infection and exudates, remove or reduce increasing bioburden in burns and open wounds and act as a barrier, which permits further healing, such dressings are never utilized for the entire duration of the wound, but for a few weeks at most."

During the Panel meeting, Panel members and Commissioner Califf articulated the importance of real world data that registries can provide, as well as the need for them in the wound care space. The good news is that registries devoted to wound care do exist. In her oral testimony at the Panel meeting, Dr. Caroline Fife stated that the U.S Wound Registry could help in providing real world data which is an excellent source of information to expand the understanding of the use of these products. She also noted that the US Wound Registry worked with the Alliance to create over 20 wound care quality measures that physicians can use to report their work.

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In conclusion, the products containing antimicrobial agents, but not antibiotics, that have been regulated in the FRO category have a long history of use in contributing to the care of chronic wounds. They are often used with other modalities to care for these wounds and none of them used alone claim to be sufficient to lead to complete wound healing. For these products to be classified into class II, and to be reviewed by FDA under the 510(k) program, they must be found to be of low or moderate risk, the risks should be well understood and appropriate controls for those risks be identified. These products have a long, well understood history of use, their risks are known and characterized, and can be well controlled with appropriate testing, similar to what the manufacturers perform today in support of these products. The Alliance believes the panel's recommendation to classify these products into Class II is appropriate and the FDA should move to propose this classification with special controls including the development of a guidance document and class labeling.

On behalf of the Alliance of Wound Care Stakeholders, we appreciate the opportunity to submit these comments. If you have any questions or would like further information, please do not hesitate to contact me.

Sincerely,

Marcia Nusgart R.Ph.

Marcia Nusgart R.Ph.
Executive Director

[i] Percival, S. L., Bowler, P. G., & Russell, D. (2005). Bacterial resistance to silver in wound care. *J Hosp Infect, 60*(1), 1-7. doi:10.1016/j.jhin.2004.11.014

[ii] Percival, S. L., et.al. (2008). Prevalence of silver resistance in bacteria isolated from diabetic foot ulcers and efficacy of silver-containing wound dressings. *Ostomy Wound Manage, 54*(3), 30-40

[iii] Chopra, Ian, "The increasing use of silver-based products as antimicrobial agents: a useful development or a cause for concern?" Journal of Antimicrobial Chemotherapy 2007

Presented at Meeting of the FDA's General and Plastic Surgery Devices Advisory Panel
September 20-21, 2016

Trial Design, Endpoints, and Resistance

Marissa J. Carter, PhD, MA, MAPWCA
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Silver-Impregnated Dressings: RCTs, Secondary Endpoints

SS: statistically significant

Study	Use (days)	# Dressing Changes	Epithelial-Izationincrease	Odor	Exudate Management	Pain reduction
Dimakakos**	63	18				SS
Jorgensen	28	6		SS	SS	
Jude	56	>=8				
Jurczak	14	Ave 11			SS	SS
Lazareth	28	Unknown				
Meaume	14	10				
Munter	28	10-15 exudate	SS	SS	SS	SS
Wunderlich & Orfanos	42	Unknown	SS			

Evidence-Based Medicine in Wound Care: Time for a New Paradigm

Marissa J. Carter, PhD, MA, and Robert A. Warriner III, MD, FACA, FCCP, FCCWS

Clinicians today face many challenges as diabetes health-related problems continue to increase exponentially and patients live longer. Part of that challenge is how to define wound healing efficacy when conventional study approaches that use complete wound-healing outcomes in randomized controlled trials (RCTs) may no longer be appropriate, as patients present with a variety of wound etiologies and multiple comorbidities and often have a poor nutrition history. In addition, the recruitment and retention of heterogeneous wound care populations in clinical trials and the comparison of results from many types of ever-changing technologies are issues that need to be better addressed.

Presently, US total costs to treat diabetic foot ulcers, venous ulcers, and pressure ulcers are estimated at $20 to $25 billion.[1–3] In fact, this cost estimate may be conservative because it does not include a societal perspective. In Europe, simply treating venous ulcers absorbs 1% of the annual health care budget, indicating that the problem is not confined to the United States.[4] These figures might suggest that wound care is a large market from a financial point of view, but the reality is that it comprises a myriad of specialized technologies and treatments.

CALL FOR CHANGE

Clinicians, researchers, manufacturers, and payers all want to see improved cost-effective treatments in wound care and ensure that the most robust forms of clinical trials are performed. However, most wound care RCTs, which tend to be small and sometimes underpowered, use composite or partial wound-healing outcomes instead of complete wound healing—the only currently accepted end point of effectiveness. Moreover, many do not address real-world clinical practice questions, such as population heterogeneity, or the fact that the average wound care patient often has other chronic conditions that interfere with wound healing. Thus, critical questions need to be addressed in a thoughtful and productive dialogue that can encourage the development of more cost-effective solutions between all interested parties. To that end, the authors propose 3 open-ended questions for consideration and comment:

1. How relevant are traditional RCTs using complete wound healing as the only acceptable end point in relation to ''real-world'' chronic wound care?
2. Are intermediate or surrogate end points, including resolution of infection or inflammation or partial wound-healing outcomes, clinically meaningful outcomes that should be acceptable in clinical trial design?
3. What trial designs would be clinically relevant as alternatives or, perhaps in some circumstances, improvements upon traditional RCT design?

When addressing wound care research issues, the perspectives of 4 separate groups must be considered. Researchers want the best quality science to create foundations for new products and treatments. Clinicians want clinically relevant guidance from meaningful clinical trials that address real-world patient challenges and goals. Manufacturers want an economically fair environment in which product life cycle, cost of product development, and return on investment allow for new products and technologies with demonstrated benefit to reach the marketplace. Finally, payers from the private and public sectors are charged with evaluating the evidence generated by the clinical trials of wound care products and treatments to determine if they merit widespread use before paying for them.

The staggering cost of chronic wound care is driven by a number of factors, the largest of which is that chronic wound patients are treated over a long period. In clinical practice, wound durations of years are not uncommon. This poses the additional complexity of coordinating several different assessments and treatments over a period of over 6 to 12 months, which increases the risk of wound infection and its sequiturs. For example, despite aggressive treatment of diabetic ulcers, some 16% to 21% of individuals undergo amputation of the foot or leg.[5] Most topical wound care products, dressings, and treatments are not used over the entire duration of care but in a

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manner to achieve specific interval benefits in the support of wound stabilization and closure. Another way of stating this conceptually is that most wound care treatments are not intended to reverse all healing deficiencies present in any given patient. For example, silver-impregnated dressings are designed to manage wound infection and exudates, remove or reduce increasing bioburden in burns and open wounds, and act as a barrier, which permits further healing[6]; such dressings are *never* utilized for the entire duration of the wound, but for a few weeks at most.

Many chronic wound patients have a large number of comorbidities and are older than 60 years. Thus, healing abilities are often compromised in such individuals, as evidenced by the presence of multiple wounds, high incidence rates of recurrence, and infection episodes (as high as 50%) over the course of a wound. Often, underlying conditions must be treated before effective wound healing can begin. Therefore, in older patients with venous ulcers complicated by peripheral arterial disease, revascularization of the lower extremities via surgery may be a prerequisite to effective ulcer treatment.

EXAMINING THE EVIDENCE

Given these challenges to improve the efficacy of treatment in wound care, evidence-based medicine (EBM) is increasingly making inroads into day-to-day practice in the form of clinical practice guidelines,[7] backed up by systematic reviews and meta-analyses (where appropriate) of clinical trials. Although the gold standard continues to be the appropriately powered RCT, chronic wound care patients present some unique challenges to this clinical trial methodology.

Large, complex RCTs are enormously expensive and require considerable resources at all levels to design, conduct, and analyze. In the United Kingdom, Snowdon et al[8] found that lack of funding, cost overruns, and the compromises between the wishes of the trial applicants versus those of the funding organizations, especially industry sponsorship, were pervasive and caused issues that proved difficult to resolve. Moreover, although problems with large drug trials in recent years have caused many medical journals to insist on better reporting procedures in an attempt to improve the quality of RCTs, doubt continues to be cast on many pharmaceutical or manufacturer-sponsored trials because of bias or inaccurate representation of results. Because of this situation, the Medicare Coverage Advisory Committee in its March 2005 meeting on ''Usual Care of Chronic Wounds'' recommended that the National Institutes of Health be given funding for wound care trials instead of the burden always falling on the manufacturers.

Financial constraints and difficulties in recruiting suitable populations have caused smaller RCTs to become the norm in

wound care compared to large drug trials, which poses a unique set of problems. A small trial population means less ability (statistical power) to evaluate an observable clinical treatment effect (technically the effect size of the treatment) between 2 groups and difficulty in properly executing non-inferiority trials, which can lead to type I errors (ie, assuming that the treatments are equivalent when they in fact are not).[9] However, multiple measures of the same individual can improve statistical power, provided data are analyzed correctly.[10] In addition, when wound care trials are designed, investigators want to maximize their chances that a statistically and clinically significant outcome will occur by using narrow inclusion criteria that limit the number and/or severity of comorbidities, thus excluding complex patients.

Although the rationales for some exclusion criteria are often perfectly legitimate, when they are carried to an extreme, such trials may be criticized on the grounds that the outcomes do not apply to complex chronic wound care patients. The authors' work suggests that this is a common situation in wound care.[11]

Comprehensive chronic wound care frequently involves the use of concurrent multiple interventions for effective treatment of the patient at different stages of wound healing. If an RCT is testing only 1 intervention, then its results may not be applicable to a real-world population because its outcomes may not account for other concurrent interventions.

Another issue in question is the definition of end points of successful outcomes in wound care RCTs. Current Food and Drug Administration requirements of efficacy and safety for wound care technology approval consider complete wound healing as the only acceptable outcome.[12,13] Most wound care trials last 4 to 8 weeks and show little difference between complete wound healing of the treatment versus control arms because few patients in total have achieved complete wound healing. This has led to trial protocols that use a variety of primary outcomes, such as changes in wound size area or volume, time required for wound bed preparation, wound granulation fill, or infection parameters if relevant to the product. Composite outcomes that combine several outcome parameters are also used to judge the overall efficacy of the trial; however, clinical opinions differ regarding the definition and utility of surrogate outcome markers or composite outcomes in clinical trials that can be used as evidence appropriate to guide care and reimbursement policy for technology. The validation and acceptance of alternative end points by all stakeholders in wound care are probably the most critical point in developing more cost-effective wound care technologies.

Heterogeneous wound care populations are common in wound care. In their study of patients with diabetic neuropathic foot ulcers, Robson et al[14] demonstrated 2 distinct populations: a population whose ulcers healed relatively quickly and a second population in which wound healing was delayed. The time estimated for wound closure in this study was estimated to be at least 9 months. Not only would an RCT that lasted 9 months be prohibitively expensive, but ensuring that a reasonable proportion of the patients stayed in the trial would be challenging because a substantial number of patients would be on a slower healing trajectory and possibly discouraged.[14] In this context, a dropout rate that exceeds 20% is often a threshold criterion in many EBM scoring schemes for deciding whether an RCT is of high quality.

HOW CAN THE SITUATION BE IMPROVED?

Investigators charged with the design, conductance, and analysis of RCTs could do much to improve transparent reporting and adherence to Consolidated Standards of Reporting Trials guidelines.[15] When this fails to happen, systematic reviewers often downgrade the rating of such trials. Likewise, trials should be adequately powered to detect the treatment effects they purport to measure. Too often, EBM reviewers faced with analyzing several underpowered trials and 1 or 2 adequately powered trials will judge the evidence equivocal. Composite or quasi end points may be popular, but do not always imbue confidence in reviewers that wound care treatments actually demonstrate efficacy; they also make comparison between RCTs difficult.

What are the possibilities for paradigm shifts in study design for wound care? Despite challenges with conducting RCTs, the RCT will likely remain the standard by which products and treatments are evaluated by both government agencies and physicians alike until other alternatives are deemed acceptable. Large observational trials (case-control and cohort designs) can provide similar information to RCTs,[16] but currently, these kinds of designs are considered lower in the EBM hierarchy and are sometimes scored as "B" evidence, although the Agency for Health Care Policy and Research regards well-conducted cohort studies as "A"-level evidence.[17] Tunis[18] also encapsulated this argument by stating, "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." In other words, there is a clear need for different trial designs to complement RCT data and other types of assessment (such as cost-effectiveness studies).

Partial wound-healing outcomes that can be extrapolated in terms of projecting time to heal may be a valuable alternative to conducting RCTs if the methods can be sufficiently validated and accepted in the wound care community. For example,

percentage area of wound reduction has been shown predictive of healing in diabetic foot wounds.[19,20]

SUMMARY

In the context of these issues, stakeholders must reconcile these challenges for continued improvement in cost-effective wound care treatments. Wound care technologies vary by product life cycles and manufacturing costs, with surgical dressings having shorter product life cycles than devices or biologically based products. In some cases, the projected income of a given product may not justify the expense of an RCT, which ultimately means that the evidence base for use of such a product in wound care is poor. On the other hand, users, regulatory agencies, and payers are concerned that any ''changes in the rules of EBM'' in wound care will adversely impact the quality of its evidence. In the current situation, manufacturers should make every attempt to include RCTs in their wound care research, whereas payers may need to modify their expectations of the evidence base for wound care. The alternative is to develop a new paradigm, which incorporates new validated EBM-based rules that encourage flexibility but still achieves the level of evidence required to demonstrate efficacy.

We believe that by raising all the issues of constructing better-designed RCTs, partial wound healing end points, and alternative clinical trial designs that would complement RCT data, a thoughtful and productive dialogue can be stimulated to encourage the development of more cost-effective solutions between all interested parties. ●

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