

Guiding Principles for Clinical Research in Chronic Wound Healing

A consensus document

The AdvaMed Wound Healing & Tissue Regeneration Sector

Introduction

Executive summary

This consensus document, developed and endorsed by the Wound Healing & Tissue Regeneration Sector of the Advanced Medical Technology Association (AdvaMed), presents recommendations for evidence-based guidelines for safety, efficacy and effectiveness in chronic wound research. The recommendations are presented as a series of consensus statements, each accompanied by discussion and relevant references.

Wound patients are complex; they often have multiple co-morbidities, such as obesity and diabetes, and are often elderly. In addition, these patients often receive care across health care settings – hospital, home and long-term care. These factors make evidence-based research in chronic wound healing and other chronic disease states challenging. In addition, wound healing devices and therapies are widely diverse, addressing multiple goals of wound management.

This document discusses the challenges specific to chronic wound research, including the practicalities of traditional randomized controlled trials (RCTs), as well as alternatives to RCTs where appropriate.

Skin substitutes, replacements, tissues, matrices and biologics have unique evidence requirements, FDA and payment processes, and are used primarily in conjunction with surgical

procedures. AdvaMed member companies manufacturing these types of products are developing a separate document to address these specific evidence-related issues, which will be available at a future date.

Audience

The AdvaMed Wound Healing & Tissue Regeneration Sector (hereinafter referred to as the AdvaMed Sector) has designed this document to be of use to clinicians, professional societies, payors – government & private, regulators and legislators.

AdvaMed and the AdvaMed Sector

AdvaMed advocates for a legal, regulatory and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology. AdvaMed member companies produce medical devices, diagnostic products and health information systems.¹

AdvaMed's members produce nearly 90 percent of the health care technology purchased annually in the United States and more than 50 percent purchased annually around the world; its members range from the largest to the smallest medical technology innovators and companies. The AdvaMed Sector comprises medical technology companies whose products and services focus on wound healing and tissue regeneration.²

AdvaMed and its members develop and market technologies that focus on improving patient outcomes. Members strive to ensure that products they bring to market have demonstrated safety, efficacy and effectiveness, working with regulatory oversight. Clinician and patient feedback are used to make continuous improvements.

¹ AdvaMed website, <http://www.advamed.org/MemberPortal/>, accessed June 21, 2010

² AdvaMed website, <http://www.advamed.org/MemberPortal/About/Industry/>, accessed June 21, 2010

AdvaMed members have a particular interest in enhancing both the feasibility and quality of chronic wound research, as major funders of research and development, with investments which have more than doubled over the past 20 years. Current estimates place investment at 12 percent of sales, more than four times the average for manufacturers overall.³ In 2003, Getz and Zisson, cited by Tunis, stated that, “Industry funding for clinical trials is several times greater than NIH spending (\$4.1 billion vs. \$850 million in 2000).”⁴

Origin of document

The AdvaMed Sector, whose companies represent much of the development of technology for the treatment of chronic wounds and who are major funders of research in the field, desire to share their experience and expertise to provide practical guidance to clinicians, professional societies, payors, regulators and legislators. Towards this end, in 2009, the AdvaMed Sector began a review of the state of the science in wound care. The process had three tracks: the science of wound healing and review of evidence; the translation of science into clinical practice; and the impact of public policy on access to and quality of wound care.

In conversations with The Centers for Medicare and Medicaid Services (CMS) and the Agency for Healthcare Research and Quality (AHRQ), the AdvaMed Sector learned that the Center for Medical Technology Policy (CMTP) was planning to host a July 2010 meeting to discuss the findings included in its (CMTP’s) August 2009 effectiveness guidance document, which covers comparative effectiveness research methods for treatment of chronic wounds. CMS and AHRQ encouraged the AdvaMed Sector to be part of that discussion. The group, therefore, postponed its state of the science work to plan its participation in the CMTP meeting.

³ AdvaMed website, <http://www.advamed.org/MemberPortal/About/Industry/>, accessed June 21, 2010

⁴ Getz, K., & Zisson, S. 2003, cited in Tunis, et al. 2003, p. 1628

To share the broad spectrum of expertise of the AdvaMed Sector, representatives from member companies met in April 2010, led by consensus expert moderator, Mikel Gray, Ph.D., to develop a series of consensus statements around chronic wound research. Consensus was considered reached when 80 percent of the companies present approved the final wording of a consensus statement. Most of the statements reached 100 percent consensus.

Subsequent work by the group expanded on the statements, reviewed the literature to add appropriate references and resulted in this consensus document. The final document has been reviewed and approved by the AdvaMed Sector.

Why chronic wound research is important

In the United States, chronic wounds affect 5.7 million patients and cost health care systems an estimated \$20 billion annually.⁵ The most common chronic wounds are pressure ulcers, venous leg ulcers and diabetic foot ulcers. These chronic wounds represent an enormous cost, in expense to the health care system, in reduced quality of life and in lost work days. The following statistics provide some examples of the prevalence and cost of the most common chronic wounds.

Diabetic foot ulcers

Diabetic foot ulcers are one of the most common complications of diabetes. Snyder and Hanft reported that they “have an annual incidence rate of 1 percent to 4 percent and a lifetime risk of 15 percent to 25 percent.”⁶ According to the same reference, “by 5 years, 45 percent to 55 percent of patients with neuropathic and ischemic DFUs, respectively, will die. These common complications of diabetes have higher mortality rates than cancers of the prostate, breast and

⁵ Branski, L.K., Gauglitz, G.G., Herndon, D.N., & Jeschke, M.G. 2009, *cited* in Fogg, E. 2009, p. 46

⁶ Snyder, R. J., & Hanft, J. R. 2009, p. 28

colon, as well as Hodgkin's disease."⁷ The authors went on to say that "Patients with unhealed DFUs experienced significantly greater physical limitations and pain that affected their daily activities and interfered with their social lives."⁸

Pressure ulcers

Pressure ulcers are common complications in both elderly and acute-care patients. In the *International Journal of Nursing Studies*, Sanada, et al., cited statistics on the prevalence of pressure ulcers. According to their research, it ranges from 14.3 percent to 15.6 percent in acute care settings and is 27.7 percent in long-term care facilities.⁹ According to Reddy, et al., the estimated cost of managing a single full-thickness pressure ulcer is as high as \$70,000.¹⁰ In 2006, the cost of hospitalizations including a diagnosis of pressure ulcers in the U.S. totaled \$11 billion.¹¹ Jones, et al., reported that "1.5 to 3 million adults in the United States (0.5 percent of the population) experience pressure ulcers (PrUs), with the elderly accounting for 70 percent."¹²

Venous leg ulcers

Leg ulceration associated with venous insufficiency affects approximately 1 percent of the Western population,¹³ and with an expected increase in the number of older people over the next decades, a corresponding increase in age-associated medical problems is to be expected.¹⁴

Thirteen to 29 percent of venous leg ulcers may take more than two years to reach complete healing.¹⁵

⁷ Snyder, R. J., & Hanft, J. R. 2009, p. 29

⁸ Snyder, R. J., & Hanft, J.R. 2009, p. 29

⁹ Horn, S. D., et al., 2002; Whittington & Briones 2004; cited in Sanada, H., et al. 2010, p. 280

¹⁰ Reddy, M., Gill, S.S., & Rochon, P.A. 2006

¹¹ Russo, C.A., Steiner, C., & Spector, W. 2006, <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb64.pdf>. Accessed July 8, 2009

¹² Jones, et al. 2007, p. 591

¹³ Callan, et al. 1985; Leach, M.J. 2004, cited in Scanlon, E., et al. 2005, p. 150

¹⁴ Burgess 1993, cited in Scanlon, E., et al. 2005, p. 150

¹⁵ Scanlon, E., et al. 2005, p. 151

Definitions

In discussing this vast area of medical treatment, it is helpful to define key terms. Therefore, in this document **safety** refers to the extent to which the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.¹⁶ **Efficacy** refers to explanatory trials that determine whether an intervention produces the expected result under ideal circumstances. **Effectiveness** refers to pragmatic trials that measure the degree of beneficial effect under “real world” clinical settings.¹⁷

Guidelines for safety in chronic wound research

CONSENSUS: Randomized controlled trials are historically recognized as the gold standard for demonstrating safety of drugs, biologics and devices. However, randomized controlled trials are not the **only** designs, nor always an appropriate design, for establishing safety of medical devices.

For all medical devices, safety comes first. To ensure products that come to market are safe, early studies of a product generally will begin at the concept phase, during the design stages of the product. As the concept is defined, studies are pursued in the laboratory to help understand what is to be expected in a clinical setting. Following those steps, it is often common, depending on the type of technology, to move to animal studies and refine the device and again gain understanding on how the product will perform clinically on humans. The last stage is engaging

¹⁶ 21 Code of Federal Regulations 860.7(d)

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=860.7>. Accessed June 28, 2010.

¹⁷ Godwin, M., et al. 2003

in human clinical studies, which requires the work of clinicians, research and development, statisticians and others to agree on study designs.

Other intermediate steps may include evaluations in small groups of healthy volunteers to help establish product tolerability and safety. Components of devices are also evaluated for potential toxicity risks, allergic reactions or sensitizations. Also, devices are studied to define bio-compatibility and safety and to ensure that they do not impede healing. Similarly, manufacturers understand that products must be used appropriately by the end-user or caregiver, or they may not be safe. AdvaMed agrees that patient safety, as defined by the Institute of Medicine, means avoiding injuries to patients from the care that is intended to help them, and must remain the first priority of all health care providers.¹⁸

Carter asked,

Which trial type provides the best safety data? In theory, data from an RCT should be the best because of the way the control and experimental groups are selected and treated. However, in practice, data may be limited either by the sample size or the length of the trial, both of which are issues in wound care.¹⁹

The inclusion criteria for RCTs often exclude those who would most benefit from clinical applications. Bolton, et al., stated:

Rigorous clinical studies produce much-needed evidence of comparative product or procedural safety and efficacy. However, the scientific rigor that makes such studies valuable as support for clinical decision making also isolates them from the realm of normal practice, because subjects are carefully selected based on rigid and specific inclusion criteria. This means that challenging 'real-world' wounds often are not included.²⁰

¹⁸ Institute of Medicine 2001

¹⁹ Carter and Warriner 2009, cited in Carter, M. 2010, p. 82

²⁰ Bolton, L., et al. 2004, p. 65

Comparison with standard of care is desirable. However, defining the standard of care is difficult, particularly when selecting among dressings or devices. Therefore we recommend a detailed description of elements of standard care offered to each group using the broad parameters identified by CMTP. According to the 2009 draft of the CMTP guidance document,

Currently, the following elements of standard care should be strongly considered for inclusion in the clinical management of both control and intervention patients (FDA, 2006; Sawaya et al., 2007; Bolton, 2004):

- Debridement of necrotic or infected tissue
- Infection control
- Nutritional support
- Maintenance of a moist wound environment (with protective dressings over pressure ulcers and moisture-permeable dressings over diabetic and venous ulcers).
- Weight off-loading (pressure and diabetic ulcers)
- Compression therapy (venous stasis ulcers)
- Blood glucose control (diabetic ulcers).²¹

As described by the U.S. Food and Drug Administration's (FDA) guidance document for the development of wound treatments, "Products intended for wound management may provide important patient benefit without improving the incidence or timing of wound closure relative to standard care. However, it is important to demonstrate that such products do not significantly impede healing."²²

There are other issues related to safety that go beyond RCTs. One is the incidence of adverse events, which should be monitored in every clinical study,²³ and continued once the product is commercially available. Close follow-up of adverse events helps authorities and

²¹ Center for Medical Technology Policy 2009, p. 8

²² U.S. FDA 2006,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071324.pdf>, accessed June 21, 2010, p. 13

²³ Gartlehner, G., et.al. 2006

manufacturers ensure the product is safe for very broad and large populations that were not included in clinical studies.

Results of product usage studies, including case series and ease-of-usage evaluations, also help establish device safety. In addition, careful attention to product labeling – both for clinicians and consumers/patient – is an important safety factor, and is becoming increasingly important as patients are treated in home care settings.

Guidelines for evaluating efficacy in chronic wound research

CONSENSUS: The AdvaMed Sector supports the guiding principles for wound care policy promulgated by the World Union of Wound Healing Societies. (See Appendix 1 for complete guidelines.)

According to the World Union of Wound Healing Societies,

Health care policy makers should consider that:

- Evidence of effectiveness for wound care products and services is not limited to randomized controlled trials and can be established through a combination of scientific evidence, expert knowledge and patient preference.
- Intermediate wound care outcomes (in addition to complete wound closure) are important benchmarks for evaluating effectiveness of wound care products and services.
- Early intervention (prevention and treatment) improves both clinical and economic outcomes by reducing healing times, treatment costs and recidivism rates.²⁴

²⁴ World Union of Wound Healing Societies, <http://woundpedia.com/index.php?page=theme&topic=16&docID=388&docLocation=woundpedia>, Accessed June 27, 2010

CONSENSUS: Randomized controlled trials are historically recognized as the gold standard for demonstrating efficacy of medical devices. While RCTs are appropriate for assessing treatment efficacy, they may not be the most relevant way to measure treatment outcomes.

The most appropriate study design is determined by the purpose of the study as well as ethical and practical considerations. The European Wound Management Association (EWMA) pointed out:

The design of studies is always debated as different audiences have different requirements. For example, regulatory authorities require the purest form of a RCT, which has a restricted population, in order to reduce the heterogeneity of the population and ensure that the study has sufficient internal validity to demonstrate efficacy. However, this restrictive approach to study design will not allow for the generalisation of the findings to patients who routinely present at clinics. For clinical practitioners, an effectiveness study, with its emphasis on whether or not the treatment works pragmatically in routine practice, may be more appropriate.²⁵

To demonstrate safety, efficacy and effectiveness, the point of care, type of intervention and patient population must be considered. According to Jones, et al.:

Randomized controlled trials are essential for establishing efficacy, although this does not ensure that typical patients in typical settings achieve the same results. Clinical outcomes studies are needed to evaluate the most effective approaches to wound care given practice setting constraints and risk variations among patients.²⁶

According to Carter, “Randomized controlled trials will continue to be the gold standard of trial design to evaluate treatment efficacy, but they often are poorly executed. The value of comparative observational trials is frequently underrated.”²⁷ She also cited deMaria, editor-in-chief of the Journal of the American College of Cardiology who said, “Data from RCTs

²⁵ Gottrup, F., Apelqvist, J., & Price, P. 2010, p. 263

²⁶ Jones, et al. 2007, p. 600

²⁷ Carter, M. 2010, p. 68

represent the beginning of the decision-making process, not the end.”²⁸ Added Carter, “Also, it may not be possible or ethical to test certain treatments with an RCT, in which case a well-conducted observational study can contribute to the evidence.”²⁹

CONSENSUS: Single or double blinding is intended to reduce bias, but may not be feasible or possible when studying individual dressings, support surfaces and/or select medical devices because of apparent differences in product appearance, application and construction as well as the type of care setting in which the trial is administered. Trials which cannot be made single or double blind should utilize the best available alternative methods for reduction of ascertainment, investigator and analytical biases.

According to APPAMED (Union of Medical Devices Industries, France),

Although in the case of randomized clinical trials (RCT) the evaluation of the results obtained by double blind is the Gold Standard, in the particular field of dressings (and medical devices in general) double blind, with rare exceptions, is impossible to do.³⁰

The AdvaMed Sector advocates use of a centralized reading center for the main outcome measure of individual studies, only where the validity of such an approach has been established, such as serial photography or planimetry to measure differences in wound surface area. This strategy will enable blinding to outcome measure.

CONSENSUS: We advocate use of a sham or placebo control when appropriate and feasible.

When not feasible, an alternative control is recommended to meet methodological requirements.

²⁸ DeMaria, A. N. 2008 cited in Carter, M. 2010, p. 79

²⁹ Carter, M. 2010, p. 79

³⁰ APPAMED 2009, p. 8

In considering the selection of an appropriate comparator, the population of study should be carefully considered. For example, the use of a sham or placebo should not engender greater risk to the subject than that of acceptable standard of care (e.g. the use of a placebo in the treatment of infection within a wound is not acceptable).

It is generally recognized that placebos should be used whenever possible. When the use of a sham or placebo is deemed to be inappropriate, the selection of an appropriate active comparator group is essential. Active comparators should be appropriate for the patient population of study and representative of optimal or standard care. The selection of comparator groups which are not consistent with current standards of wound care diminishes the ability to assess true incremental benefit associated with the therapy or intervention of study.

Wound care poses significant challenges to this selection, in that most wounds require a number of different therapies or therapeutic approaches to take a wound from early phase to complete closure. If, in good clinical practice, treatment modifications are made to ensure healing, the active control arm of a study should allow for such modifications to ensure acceptable standard of care. In addition to the selection of the primary wound therapy within the control arm, other factors such as offloading of pressure-related wounds, debridement and treatment of wound-related complications should be discussed clearly in the protocol, with an approach for handling of the subject and subject's data established *a priori*. While standardization of such potential confounders to healing may not be present within an observational study, data should be collected to understand their impact on overall outcome.

CONSENSUS: Enrollment of patients with co-morbidities likely to affect wound healing is desirable. However, patients with multiple co-morbidities render subgroup analysis particularly

difficult. The individual co-morbidities should be investigated in an adjusted analysis to understand their contribution to the overall modeling.

Examples of common co-morbidities with chronic wound patients include diabetes, cardiovascular disease, obesity, peripheral vascular disease. Fortin, et al., said:

RCTs targeting a chronic medical condition such as hypertension could find that, in a sample taken from family practice, most eligible patients have co-morbid conditions. Whether these patients are sampled or excluded should be reported. Research results intended to be applied in medical practice should take the complex reality of effective treatment of these patients into consideration.³¹

The European Wound Management Association also stated:

The main problem is comparability of patients as many wound patients are old, fragile and have several other diseases. Furthermore, it is debatable whether the pharmaceutical approach to measuring efficacy is directly applicable to dressings and medical devices.³²

The minimum target sample size for the primary endpoint should be based on the parameter estimates from previous clinical investigations and designed to detect a clinically meaningful difference. Following the E9 guidance from the ICH,³³ the chance of a type I and II error should not exceed 5 percent and 20 percent, respectively.

Prior to the initiation of any study, the power to detect a meaningful difference between the treatment groups for the secondary endpoints should be given serious consideration, and the hierarchical testing procedure to adjust for multiplicity should be pre-defined. Given that sample size estimates do not translate directly to exact probability values, simulations should be prepared to provide insight into the expected results, predicated on the exact statistical methodology. When possible, an adaptive design strategy should be considered, following the

³¹ Fortin, M., et al. 2006, p. 104

³² Gottrup, F., Apelqvist, J., & Price, P. 2010, p. 240

³³ Efficacy Guidelines, New Codification as of Nov. 2005, <http://www.ich.org/cache/compo/475-272-1.html>, accessed June 21, 2010

FDA guidance documents released in 2010 for implementation.³⁴ Fixed designs typically do not provide for the attenuation of the sample size without inflation of the type I error and may result in an under-powered result. Adaptive designs can overcome many of the unforeseen eccentricities that befall clinical studies without resulting in a biased and unsubstantiated finding.

The implementation and operation of an adaptive or flexible design is critical to maintaining the validity of the study. Simulations, based on the possible outcomes of the study, should be performed to demonstrate that there is no inflation to the type I error rate after an interim assessment or design modification. Adjustment to the final target sample size should follow a documented procedure, such as monitoring based on conditional power.³⁵

The process for transferring information from an unblinded interim assessment by a Data Monitoring Committee must be pre-specified and documented in a charter that is ratified by the independent committee. The process for monitoring the primary and secondary endpoints for an interim assessment must be carefully considered, given that the information from an unlocked database will be used to determine the final design elements of the study. Designs that implement a monitoring plan based on a prior distribution with either an informative or non-informative prior and based on predictive probability should be analyzed under a Bayesian framework. Adaptive designs conducted using a frequentist approach should be analyzed using an appropriate random-effects model under maximum likelihood, rather than method of moments.

Evidence standards will differ, based on the intended endpoint of a particular therapy, whether the study evaluates negative pressure wound therapy, topical antimicrobials, circulatory assist devices or something else. EWMA said that, “While the ultimate goal of treatment is

³⁴ Food and Drug Administration, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf>, accessed June 21, 2010

³⁵ Chen, Y. H., DeMets D. L., & Gordon Lan K. K. 2004

healing, many wound therapies focus on one specific issue or time phase within the healing process. In such cases, healing is not the appropriate primary endpoint.”³⁶

A consensus statement was not developed regarding cost effectiveness; however, AdvaMed has taken a position regarding how cost effectiveness should be considered in comparative effectiveness research:

Comparative effectiveness research should not be used by Medicare, insurance companies or other public or private payers to deny coverage. Comparative effectiveness research typically analyzes which medical intervention, on average, is usually more effective across a population. The intervention that is ‘generally best,’ however, may not be best for an individual patient. We believe that protecting patient access to optimal individual patient interventions is paramount. As a result, the entity should inform patients and physicians, but neither make recommendations about coverage or benefits, nor make coverage or benefit decisions.³⁷

Guidelines for evaluating effectiveness in chronic wound research

CONSENSUS: Clinical research trials that emphasize the “real world” environment of clinical practice are preferred to demonstrate effectiveness of drugs, biologics and devices. The goals of therapy, the point of care, type of intervention and patient population must be considered. A number of different study designs – such as observational studies, crossover designs and group sequential designs – may be appropriate, depending on the purpose of the study.

Carter, et al., pointed out that, “Randomized controlled trials (RCTs) are currently the strongest method for proving clinical efficacy... However, observational studies can be better at proving effectiveness.”³⁸ The European Wound Management Association said:

³⁶ Gottrup, F., Apelqvist, J., & Price, P. 2010, p. 251

³⁷ AdvaMed Position on Comparative Effectiveness Research. <http://www.advamed.org/NR/rdonlyres/66E43D28-1F5F-4028-99CC-256A7BE25D53/0/AdvaMedCEPrinciples22102407.pdf>, accessed June 25, 2010

³⁸ Carter, M. J., et al. 2009, p. 316

A further level of bias may be introduced if interventions are not used appropriately, in line with the manufacturer's instructions or as appropriate to the wound condition. Enforcing a purist approach can be particularly troublesome; the RCT design requires that the same intervention be used throughout the study period, which directly contradicts the clinical need to adapt treatment to the condition of the wound. There is a real tension between maintaining a purist approach and being pragmatic about the ways in which treatments are used in routine practice.³⁹

Historically, it has been difficult to comply with the rigorous requirements of a randomized controlled trial and still be able to conduct the research in a care setting that takes physician practice patterns into account and in a way that is relevant and representative of the care the patient would receive if not taking part in the trial. The usual care comparator is difficult to define; care standards often vary by region, by system, by facility and even within an individual facility. As noted earlier, chronic wound patients frequently have multiple comorbidities. Physicians often use multiple interventions to address the needs of a particular patient. Forcing a physician into a very rigid serial treatment plan for purposes of study is inconsistent with accepted clinical practice.

Hannan reminded us:

One reason why an RCT and an observational study [OS] on the same competing interventions may arrive at different conclusions is that they frequently apply to different patients. Randomized controlled trials have specific inclusion and exclusion criteria that are often quite restrictive, whereas OS usually apply to a much broader population and are frequently even population-based.⁴⁰

CONSENSUS: There are valid clinical study designs that use patients as their own control, such as crossover designs.

³⁹ Gottrup, F., Apelqvist, J., & Price, P. 2010, p. 263

⁴⁰ Hannan, E. L. 2008, p. 214

Patients with chronic wounds, in particular, often have multiple co-morbid conditions that create significant variability in their response to therapy and thus reduce the power of a study to detect differences without recruitment of a large study sample. Use of patients as their own control alleviates this problem, especially in situations where multiple wounds of similar etiologies often occur.

In the *New England Journal of Medicine*, Louis, et al., said:

Crossover studies (clinical trials in which each patient receives two or more treatments in sequence) and self-controlled studies (in which each patient serves as his or her own control) can produce results that are statistically and clinically valid with far fewer patients than would otherwise be required.⁴¹

In the *British Medical Journal*, Sibbald and Roberts reported:

The principal drawback of the crossover trial is that the effects of one treatment may 'carry over' and alter the response to subsequent treatments. The usual approach to preventing this is to introduce a washout (no treatment) period between consecutive treatments which is long enough to allow the effects of a treatment to wear off. A variation is to restrict outcome measurement to the latter part of each treatment period. Investigators then need to understand the likely duration of action of a given treatment and its potential for interaction with other treatments.⁴²

CONSENSUS: Some technologies for the treatment of chronic wounds are not always appropriately evaluated by measuring wound closure, since wound closure may not be their intended immediate goal. Examples of alternate endpoints include control of exudate, reduction of odor, stimulation of tissue growth to decrease wound volume and/or surface area, alleviation of pain with dressing change or between dressing changes, reduction of bacterial bioburden, and protection of the periwound skin.

⁴¹ Louis, T. A., et al. 1984, p. 24

⁴² Sibbald, B., & Roberts, C. 1998, p. 1719

CONSENSUS: When combination or sequential interventions are necessary to achieve wound closure, relevant intermediate endpoints short of healing can be appropriate measures for product efficacy and effectiveness.

Healing within the wound is a multi-phase process, thus endpoints other than wound closure are valid in research design. Healing is not always the goal of a particular therapy; however, that therapy can ultimately lead to healing. To optimally understand if a given therapy delivers the intended effect or benefit, the best and most direct measure of that effect is also the most accurate measure of effectiveness. Applying a measure not directly related to the purpose of the therapy would be suboptimal. The European Wound Management Association pointed out:

Alternative endpoints are therefore needed, especially when a wound intervention is performed for reasons other than healing (for example, control of exudation, wound debridement, reduction of pain, rate of granulation, dressing performance). The primary outcome measure selected for any wound study should, therefore, be appropriate to the intended purpose of the intervention.⁴³

In 2006, Armstrong, et al., convened an inter-disciplinary task force to define success in diabetic foot wound studies.⁴⁴ The need for defining success originates from the fact that “wound healing is an orchestrated process requiring the interactions of many cell types and homeostatic mechanisms. While healing a wound is the ultimate goal of treating an individual with a diabetic foot ulcer, achieving this goal is physiologically complex, requiring the initiation and interaction of many events and therefore unlikely to be achieved by one compound.” Because this fact has largely been ignored by regulators, “seemingly disparate wound treatment modalities have been assessed in nearly identical fashions.” The task force went on to recommend intermediate

⁴³ Gottrup, F., Apelqvist, J., & Price, P. 2010, p. 251

⁴⁴ Armstrong, D.G., et al. 2009

endpoints that can be assessed along the continuum of wound care, depending on the intended effect of the treatment under study.

The European Wound Management Association considered this issue and stated that, “While the ultimate goal of treatment is healing, many wound therapies focus on one specific issue or time phase within the healing process. In such cases, healing is not the appropriate primary endpoint.”⁴⁵ The ability to assess a therapy’s ability to achieve its intended goal, such as granulation or exudate control, may be clouded by response to other therapies administered before or after the therapy of interest, when complete wound healing is the only observation of efficacy or effectiveness.

CONSENSUS: We support continued research into the validity of intermediate endpoints such as wound measurement at four weeks and wound healing trajectories with respect to long-term clinically relevant outcomes and impact of point of care on results.

Using the incidence of complete wound healing or the time to complete wound healing as the main outcome measure of a study is not always a feasible or desirable goal. EWMA stated that, “Ideally, all patients should be followed until healing is achieved. However, this is often not feasible due to patient characteristics, comorbidity and the type of ulcer.”⁴⁶

Complete epithelialization of a full thickness chronic wound such as a Stage III or IV pressure ulcer requires up to 24 weeks. Given the frailty that characterizes the typical patient with a pressure ulcer and the likelihood of dropouts or patient deaths during such a lengthy trial, the difficulty of maintaining an adequate sample size to prove superiority or non-inferiority must be recognized. In a study of venous leg ulcers, Gelfand, et al., stated that “These surrogate

⁴⁵ Gottrup, F., Apelqvist, J., & Price, P. 2010, p. 251

⁴⁶ Gottrup, F., Apelqvist, J., & Price, P. 2010, p. 254

markers for venous leg ulcer healing may allow for early clinical trials to be more efficient, and can allow clinicians to identify patients unlikely to heal early in the course of treatment in order to expedite referral to specialty centers or for the selection of stepped treatment algorithms.”⁴⁷

EWMA pointed out that that, “If the only gold standard was total wound closure, no therapy would ever be considered efficacious.”⁴⁸

CONSENSUS: Measurement of quality of life is an especially important endpoint for evaluating the effectiveness of wound healing technologies for treatment of chronic wounds. We further advocate development, refinement and use of condition-specific instruments to measure quality of life.

In *Ostomy Wound Management*, Snyder and Hanft reported that, “Results of the Cardiff Wound Impact Scale showed patients with unhealed ulcers experience frustration and anxiety associated with their wounds, had difficulties with activities of daily living and footwear and complained of having a limited social life.”⁴⁹

As is the case with the majority of medical treatments, modalities used to treat chronic wounds can profoundly influence the quality of life. In addition to a modality’s effect on reversing the negative impact of a health condition, wound patients require additional consideration with respect to how administration of the modality will impact quality of life. For example, the following parameters are involved in treatment administration: frequency of dressing or device application time/effort requirements for such applications, patient comfort and effect on chronic pain while bed bound or during dressing change, device operation or provision of routine care, odor control, cosmetic effect and its influence on psychological status, including

⁴⁷ Gelfand, J., et al., 2002, p. 1420

⁴⁸ Gottrup, F., Apelqvist, J., & Price, P. 2010, p. 251

⁴⁹ Snyder, R. J., & Hanft, J. R. 2009, p. 29

depression and anxiety. According to Soon and Chen, “Outcome studies assess the effect of interventions on endpoints that are important to patients; health-related quality of life, functional status, patient satisfaction, cost, quality of care, practice standards/patterns and patient perspectives on new technology.”⁵⁰

Evaluation of pain is an especially important variable, and can be an important outcome when evaluating the safety, efficacy, effectiveness of dressings, support surfaces or devices for the treatment of chronic wounds. Snyder and Hanft shared an example relating to diabetic foot ulcers: “DFUs can be painful and limit daily and social activities, leading to reduced quality of life (QoL)”⁵¹ And Takahashi stated that, “Venous ulcers can be painful and consume a great deal of patient, family and caregiver effort.”⁵² We advocate further development, refinement and use of condition specific instruments for measuring the cyclical pain (associated with dressing changes) and chronic pain experienced by patients with chronic wounds in addition to the generic tools for measuring pain such as the Visual Analog Scale or the McGill Pain Questionnaire.

An appropriate quality of life measure should minimize the influence of co-morbidities on interpretation of the treatment’s quality of life impact (i.e., condition-specific measures). Chronic wound patients are highly compromised in several health aspects such that general quality of life questionnaires such as Short Form 36 (SF-36) may not detect changes due to the treatment effect under study.

⁵⁰ Soon, S. L. & Chen, S. C. 2004, pp. 150-151

⁵¹ Snyder, R. J., & Hanft, J. R. 2009, pp. 28-29

⁵² Takahashi, P. Y., et al. 2010, p. 61

Conclusions

A multiplicity of technologies exist in the field of wound treatment. The experience of the AdvaMed Sector, which is supported by published literature, is that there is no one single appropriate gold standard trial design; trial design is dependent on the objective of the research. Further, endpoint selection should assess as directly as possible the success of the intervention of interest in bringing about its desired effect, given the multiplicity of resources. Given this, endpoints other than wound healing may be the most appropriate to evaluate an intervention.

The ultimate goal of any research is its implementation in clinical practice, and the results of RCTs can be deemed impractical and therefore discarded by practitioners. As Horn, et al. stated:

Restrictive selection criteria limit the generalizability of a study's findings (external validity) to the types of people represented in the study...Clinicians may be prone to dismiss RCT findings, because they deem their patients to be quite different from those seen in a clinical trial.⁵³

The position of this consensus document is that valid and appropriate design of clinical trials involving chronic wounds includes non-randomized designs. Although considered the gold-standard for minimizing bias, RCTs have inherent limitations that prevent broad-use understanding of treatment effect. Rather than being justified *a priori*, study designs are justified within each trial protocol, depending on the type and intended goals of the treatment under study.

This work is an important first step, but does not address the complete state of the science in wound care. Research is important because it is the basis for making clinical practice decisions and the basis for making public policy decisions. Addressing approaches to chronic wound

⁵³ Horn, S. D., et al. 2005, p. S9

research indicates a need for continuing discussion for what this means for clinical practice and public policy.

The conditions that are frequent causes of chronic wounds continue to increase, and our population is continuing to age. From this we know that the issue of chronic wounds will continue to be of major importance, indicating a need for continued research and innovation in wound care.

Appendices

Appendix 1: Complete World Union of Wound Healing Society Guiding Principles for Wound Care Reimbursement and Health Policy

Appendix 2: Definitions and abbreviations

Appendix 3: Relevant websites

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Appendix 1: Guiding Principles for Wound Care Policy

World Union of Wound Healing Societies

Recommendations

Persons with wounds and their families should expect that:		
1	Timely, holistic assessments are performed in order to appropriately manage both wounds and associated conditions.	Level of Evidence 5
2	Continuity of care is maintained in all settings for optimal outcomes.	Level of Evidence 5
3	They will be educated on their roles and responsibilities in developing and adhering to comprehensive treatment plans.	Level of Evidence 5

Health care professionals should strive to incorporate:		
4	All available categories of evidence should be evaluated to provide evidence-informed wound care knowledge is used for timely assessment and re-evaluation of wounds and associated conditions.	Level of Evidence 5
5	Appropriate products and therapies (used separately or in tandem) are incorporated into the wound care treatment plan based on the type and severity of wounds and associated conditions.	Level of Evidence 5
6	Care is coordinated among all caregivers (professional and non-professional) involved in the patient's overall health management plan.	Level of Evidence 5

Health care policy makers should consider that:		
7	Evidence of effectiveness for wound care products and services is not limited to randomized controlled trials and can be established through a combination of scientific evidence, expert knowledge and patient preference.	Level of Evidence 5
8	Intermediate wound care outcomes (in addition to complete wound closure) are important benchmarks for evaluating effectiveness of wound care products and services.	Level of Evidence 5

9	Early intervention (prevention and treatment) improves both clinical and economic outcomes by reducing healing times, treatment costs and recidivism rates.	Level of Evidence 5
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Background

Draft statements that are the Guiding Principles for Wound Care Reimbursement and Health Policy were developed for the WUWHS in conjunction with the Coalition of Wound Care Manufacturers and the Alliance of Wound Care Stakeholders. They are based on the value that all patients with wounds have the right to timely access to wound care expertise, devices and supplies to optimize healing. The WUWHS wants to inform wound care policy makers about the interprofessional team approach to all aspects of wound care practice and research and to encourage their recognition of its complexity in the reimbursement for wound care devices and supplies. Therefore, it is necessary to educate all stakeholders: patients, healthcare professionals and payers concerning guiding principles for Wound Care Policy.

With different healthcare systems and reimbursement plans, patients have varying access to care. On the basis of a quantitative study, Eaton (2005) reported on the effect of the change from a traditional reimbursement system to Prospective Payment System (PPS). Comparison of data from 2000 before PPS and 2001 post PPS indicated the deleterious effect on home health care nursing, i.e., ulcer healing, discharge distribution and length of stay were affected negatively. In a recent publication, Fette (2006) discussed such important topics as cost effectiveness studies, the absence of evidence for evidence-based healthcare, guidelines based on case studies and expert opinion, the effect of purchaser negotiations with industrial representatives, and their relationships with reimbursement and quality of wound care.

In decisions about reimbursement, the goal is to provide the best wound prevention and care for the least money. However, one must recognize the importance of interpreting the data appropriately. A good example is the comparison of dressings by Capasso and Munro (2003). A similar rate of wound healing for wet-to-dry normal saline gauze dressings was found compared to amorphous hydrogel dressings in patients with infrainguinal arterial disease and diabetes. However, the cost of wound care was on average \$1140.00 higher in normal saline gauze group due to a higher number of home nursing visits. The difference in mean cost of wound supplies was not significantly different even though the mean cost was \$47.00 more in the hydrogel dressing group. Despite this, treatment with hydrogel dressings was more cost effective.

One assumes that unbiased economic evaluations and analyses have been completed. Clinical evaluations and cost analyses are done frequently by groups that have a vested interest in the wound products. It is sometimes difficult for clinicians, policy makers and payers to detect conflicts of interest when cost information is provided without appropriate context.

Published reports of the costs involved in preventing and treating chronic wounds are few. The specific costs have been determined and assessed in a variety of ways.

1. Direct costs that include nursing and dressing costs have been determined to calculate the cost of care.
2. Indirect costs, e.g., time lost from work, effect on quality of life, have been determined less often.
3. Cost effectiveness, that describes the cost of care in relation to the clinical outcome, has also been determined.
4. Cost utility or cost benefit are methods that have been used to determine the cost of a particular intervention in relation to another intervention.

Recently in discussing the difficulties of persons with diabetic foot disease, Boulton et al (2005) proposed that costing should include more than the cost of treating an ulcer episode; it should include social services, home care, subsequent ulcer episodes, quality of life and final outcome.

The data for making cost determinations are reported to have come from a variety of sources, including the following.

1. Prospective collection of clinical data and/or cost data. For example, Friedberg et al (2002) collected prospective data using a descriptive survey to determine the cost of treating venous leg ulcers in Home Care in a region in Canada. They made the precise determination that the mean treatment time 26 minutes, the mean travel time 17 minutes, for a cost of \$80.62. Supply costs were \$21.06. They were then able to estimate the regional annual Home Care expenditures to be \$1.3 million.

2. Retrospective analysis of national databases or clinical databases. For example, Bennett et al (2004) used a bottom-up approach to estimate the cost of treating pressure ulcers in the UK. Good clinical practice protocols were developed and costs assigned using representative UK NHS unit costs at 2000 prices for the various stages of severity and potential healing trajectories, i.e., normal healing, critical colonization, cellulitis, and osteomyelitis. The cost per patient per day ranged from £38 for normal healing of a Grade 1 ulcer to £196 for a Grade 4 ulcer with osteomyelitis.

Kantor and Margolis (2001) performed a cost effectiveness analysis of data from published clinical trials, meta-analyses, and a database that includes data on 26,599 patients with diabetic neuropathic foot ulcers wounds. Cost:effectiveness ratios for platelet releasate (PR) versus standard care (SC) and becaplermin versus SC were 414.40 and 36.59, respectively. The incremental cost of increasing the odds of healing by 1% over standard therapy was \$414.40 for PR and \$36.59 for becaplermin.

3. Statistical modelling with assumptions based on clinical or published data that drive statistical determinations of cost predictions. For example, Ghatnekar et al. (2001) used clinical data obtained about the efficacy of becaplermin based on the 20-week healing rate from meta-analysis of clinical trials involving 449 patients. They performed a Markov analysis and predicted that patients who received becaplermin plus good wound

care (GWC) would spend 0.81 more months (24% longer) free of ulcers, and have 9% lower risk of a lower extremity amputation than individuals who received GWC alone. With these benefits there were estimated net cost saving in Sweden, Switzerland and the UK, but not in France. Predictions were affected by intercountry differences in wound care and reimbursement practices.

Markov analysis has been used in several other studies of diabetic foot ulcers in the Netherlands to predict the cost-effectiveness of prevention and treatment of the diabetic foot. (Ortegon et al, 2004) and in Austria to determine the costs and benefit of intensified diabetic foot care (Habacher 2007).

Another example is the decision analysis model developed recently by Fleurence (2005) for cost effectiveness of alternating pressure mattress replacements and overlays for prevention and treatment of pressure ulcers. He used epidemiological and effectiveness data from clinical literature; device costs from manufacturers; and treatment costs from literature. Based on data collected and assumptions made to build the model, alternating pressure overlays may be cost effective for prevention, and alternating pressure mattress replacements for treatment of pressure ulcers. Uncertainty exists due to paucity of research to inform model building.

There is a dearth of information about the economics of prevention and treatment of the various wound types, especially pressure ulcers and venous leg ulcers. In addition, the interpretation of economic studies that are needed to inform reimbursement strategies is not well understood. Nevertheless, the impact is felt by patients who need to receive the most efficacious interventions, by professionals whose responsibility it is to provide the most effective and efficient interventions, and by policy makers whose responsibility it is to make cost effective devices and supplies available to professionals and patients.

References

Essential Publications

1	Economic evaluation - pressure ulcers	Quality Indicator not assessed	Type:
Bennett G, Dealey C, Posnett J. The cost of pressure ulcers in the UK. Age and Aging 2004;33:230-235.			
Estimated costs of treating Stage I to IV pressure ulcers in the UK based on 2000 pricing			
2	Review of economics of diabetic foot care	Quality Indicator not assessed	Type: Narrative Review

Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. *Lancet* 2005;366:1719-1724.

Review of the cost of treating diabetic foot ulcers and lower extremity amputations.

3	Economic evaluation - dressings	Quality Indicator not assessed	Type: Retrospective Analysis
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Capasso VA, Munro BH. The cost and efficacy of two wound treatments. *AORN Journal* 2003;77(5):984-1004.

Cost effectiveness of wet-to-dry normal saline gauze dressings compared with amorphous hydrogel dressings in patients with infrainguinal arterial disease and diabetes. Data were collected by retrospective chart review.

4	Economic evaluation - reimbursement systems	Quality Indicator not assessed	Type: Retrospective Analysis
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Eaton, M.K. The influence of a change in Medicare reimbursement on the effectiveness of stage III or greater decubitus ulcer home health nursing care. *Policy. Polit. Nurs. Pract.*, 2005, 6, 1, 39-50.

Study in the US that compared Pre Prospective Payment System (PPS) in 2000 with post PPS 2001 - outcomes ulcer healing, length of stay, discharge disposition.

5	Review of economics in relation to quality of care	Quality Indicator not assessed	Type: Narrative Review
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Fette A. Discussing the relationship between quality care and cost-effective care in Swiss pediatric wound care. *Plastic Surgical Nursing* 2006;26(4):184-188.

Review of cost effectiveness studies, highlighting the author's opinions about topics including: the absence of evidence for evidence-based healthcare, guidelines based on case studies and expert opinion, the effect of purchaser negotiations with industrial representatives, and their relationships with reimbursement and quality of wound care.

6	Economic evaluation - bed surfaces	Quality Indicator not assessed	Type: Narrative Review
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Fleurence RL. Cost-effectiveness of pressure-relieving devices for the prevention and treatment of pressure ulcers. *International Journal of Technology Assessment in Health Care*, 21:3 (2005), 334-341.

Cost-effectiveness study in which a decision analysis model was created to compare alternating pressure overlays with alternating pressure mattress replacements for patients with pressure ulcers.

7	Economic evaluation - leg ulcers	Quality Indicator not assessed	Type: Narrative Review
Friedberg EH, Harrison MB, Graham ID. Current home care expenditures for persons with leg ulcers. J.Wound Ostomy Continence Nurs., 2002, 29, 4, 186-192.			
Determination of the cost of treating leg ulcers in a home care setting in Canada using precise prospective data collection methods.			
8	Economic evaluation - diabetic foot	Quality Indicator not assessed	Type: Narrative Review
Ghatnekar O, Persson U, Willis M, Å-degaard K. Cost Effectiveness of Becaplermin in the Treatment of Diabetic Foot Ulcers in Four European Countries. Pharmacoeconomics 2001; 19 (7): 767-778.			
Cost effectiveness determined through modelling based to compare becaplermin with standard care in patients with diabetic foot ulcers in Sweden, Switzerland, the UK and France.			
9	Economic evaluation - diabetic foot	Quality Indicator not assessed	Type: Narrative Review
Habacher 2007 A model to analyse costs and benefit of intensified diabetic foot care in Austria. Journal of Evaluation in Clinical Practice 2007;13:906-912.			
Cost comparison determined through statistical modelling for intensified versus standard treatment of diabetic foot ulcers of Grades A to D until healing.			
10	Economic evaluation - diabetic neuropathic foot	Quality Indicator not assessed	Type: Narrative Review
Kantor J, Margolis DJ. Treatment Options for Diabetic Neuropathic Foot Ulcers: A Cost-Effectiveness Analysis Dermatol Surg 2001;27:347-351			
Cost effectiveness analysis in the US, comparing standard care, standard care in specialized wound care center, platelet releasate (PR), and becaplermin. Effectiveness was assessed as a percentage of ulcers healed at 20 and 32 weeks.			
11	Economic evaluation - diabetic foot	Quality Indicator not assessed	Type: Narrative Review
Ortegon MM, Rederof WK, Niessen LW. Cost-effectiveness of prevention and treatment of the diabetic foot. A Markov analysis, Diabetes Care 2004; 27:901-907.			

Cost-effectiveness was determined by statistical modelling to determine the cost of current care versus guideline-based care in the Netherlands.

12	Economic evaluation - diabetic foot	Quality Indicator not assessed	Type: Retrospective Analysis
Stockl K, Vanderplas A, Tafesse E, Chang E. Costs of lower-extremity ulcers among patients with diabetes. Diabetes Care 2004;27:2129-2134.			
This costing study involved the retrospective analysis of US medical and pharmacy claims data Jan 2000-Dec 2001 to determine direct health costs of an ulcer episode.			

Source: WoundPedia™: World Union of Wound Healing Societies

<http://woundpedia.com/index.php?page=theme&topic=16&docID=388&docLocation=woundpedia>

Accessed July 9, 2010

Appendix 2: Definitions and Abbreviations

Definitions

a priori: Reasoning from causes to effects; deductive; logically independent of experience; not derived from experience; assumed without investigation (Source: www.historyhome.co.uk/peel/dict.htm)

Double blind: Term used to describe a study in which both the investigator and/or the participant are blind to (unaware of) the nature of the treatment the participant is receiving. Double-blind trials are thought to produce objective results, since the expectations of the researcher and the participant about the experimental treatment such as a drug do not affect the outcome. (Source: www.medicines.net)

Cardiff Wound Impact Schedule (CWIS): A condition-specific questionnaire to assess health-related quality of life (HRQoL) in patients with chronic wounds of the lower limbs, developed by the Wound Healing Research Unit, University of Wales, College of Medicine, in 2004. (Source: Price, P. & Harding, K. 2004.)

Chronic wounds: Wounds which have failed to proceed through an orderly and timely reparative process to produce anatomic and functional integrity over a period of 3 months. (Source: Mustoe, et al. 2006.)

Co-morbidities: The coexistence of two or more disease processes (Source: www.medterms.com)

Crossover study: A type of clinical trial in which the study subjects receive each treatment in a random order. With this type of study, every patient serves as his or her own control. (Source: www.medterms.com)

Effectiveness: The quality of being able to bring about an effect, specifically in real-world practice or the extent to which an intervention is beneficial when implemented under the usual conditions of clinical care for a group of patients (Sources: Carter, M. 2010 and *AMA Manual of Style* 2007.)

Efficacy: The capacity or power to produce a desired effect or the degree to which an intervention produces a beneficial result under the ideal conditions of an investigation. (Sources: Carter, M. 2010, and *AMA Manual of Style* 2007.)

Epithelialization: The regrowth of skin over a wound. (Source: www.lhsc.on.ca/Health_Professionals/Wound_Care/glossary.htm)

Evidence-based medicine: The practice of evidence-based medicine means integrating individuals' clinical expertise with the best available external evidence from systematic research. (Source: Sackett, D.L., et al.1993).

Granulation tissue: New connective tissue and tiny blood vessels that form on the surfaces of a wound during the healing process. (Source: <http://wordnet.princeton.edu/>)

Group sequential analysis: A group sequential design involves dividing patient entry into a number of equal-sized groups so that the decision to stop the trial or continue is based on repeated significance tests of the accumulated data after each group is evaluated. A group sequential design can sometimes be statistically superior to standard sequential designs where the results are tabulated after each patient completes the study. (Source: <http://www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/UCM209179.pdf>)

McGill Pain Questionnaire: An assessment tool that combines a list of questions about the nature and frequency of pain with a body-map diagram to pinpoint its location. (*A Dictionary of Nursing*. 2008. Retrieved June 27, 2010 from Encyclopedia.com: <http://www.encyclopedia.com/doc/1O62-McGillPainQuestionnaire.html>)

Medical device: Any article or health care product intended for use in the diagnosis of disease or other condition or for use in the care, treatment, or prevention of disease that does not achieve any of its primary intended purposes by chemical action or by being metabolized Examples Diagnostic test kits, crutches, electrodes, pacemakers, catheters, intraocular lens. (Source: *McGraw-Hill Concise Dictionary of Modern Medicine*. © 2002 by The McGraw-Hill Companies, Inc.)

Medical Outcomes Survey – SF 36: The SF-36 Health Survey is an instrument that can be used to assess medical outcomes. It was developed by John Ware. Many researchers and organizations have tested and/or used the SF-36. (Source: QualityMetrics, see http://www.sf-36.org/news/JCE_Release_013008.pdf, accessed July 1, 2010).

Randomized controlled trial: The study includes a treatment and one or more comparison groups, and participants are randomly assigned to each group. The intervention is given and the groups are observed. Outcomes such as improvement or harms are noted. RCT are considered the most reliable type of study. (Source: www.bidmc.org/YourHealth/HealthResearchJournals.aspx)

Visual Analog Scale: A Visual Analogue Scale (VAS) is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. For example, the amount of pain that a patient feels ranges across a continuum from none to an extreme amount of pain. (Source: Gould, D., et al., Blackwell Publishing, http://www.blackwellpublishing.com/specialarticles/jcn_10_706.pdf)

Abbreviations

AHRQ – Agency for Healthcare Research and Quality

CMS – Centers for Medicare and Medicaid Services

CMTP – Center for Medical Technology Policy

DBRT – Double blinded randomized trial

DFU – Diabetic foot ulcer

EBM – Evidence-based medicine

HRQoL – Health-related quality of life

NIH – National Institutes of Health

ICH - The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

PrUs – Pressure ulcers

RCT – Randomized controlled trial

QoL – Quality of life

Appendix 3: Related Websites

Associations/Societies	
Association/Society	Website
American Professional Wound Care Association	http://www.apwca.org/
Association for the Advancement of Wound Care	http://www.aawconline.org/
European Wound Management Association	http://ewma.org/
National Alliance of Wound Care	http://www.aawconline.org/
National Pressure Ulcer Advisory Panel	http://www.npuap.org/
Symposium on Advanced Wound Care	http://www.sawc.net/
World Union of Wound Healing Societies	http://www.wuwhs.org/
World Wide Wounds	http://www.worldwidewounds.com/
Wound Care Education Institute	http://www.wcei.net/
Wound Care Information Network	http://medicaledu.com/
Wound Healing Society	http://www.woundheal.org/mc/page.do?sitePageId=100295&orgId=whs
Wound, Ostomy and Continence Nurses Society	http://www.wocn.org/

Journals	
Journal Name	Website
Advances in Skin and Wound Care	http://journals.lww.com/aswcjournal/pages/default.aspx
International Wound Journal	http://www.wiley.com/bw/journal.asp?ref=1742-4801
Journal of Wound Care	http://www.journalofwoundcare.com/
Journal of Wound, Ostomy and Continence Nursing	http://journals.lww.com/jwocnonline/pages/default.aspx
Ostomy Wound Management	http://www.o-wm.com

Other helpful sites	
Organization	Website
AdvaMed	http://www.advamed.org
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov
Center for Medical Technology Policy (CMTP)	http://www.cmtynet.org/
Centers for Disease Control and Prevention (CDC)	http://www.cdc.gov
Centers for Medicare and Medicaid Services (CMS)	http://www.cms.gov
The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)	http://www.ich.org
National Institutes of Health (NIH)	http://www.nih.gov
U.S. Department of Health and Human Services (HHS)	http://www.hhs.gov
U.S. Food & Drug Administration (FDA)	http://www.fda.gov
WoundPedia	http://woundpedia.com/