



EFFECTIVENESS GUIDANCE DOCUMENT

Methodological Recommendations for Comparative Effectiveness Research on the Treatment of Chronic Wounds

VERSION 2: DRAFT

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TABLE OF CONTENTS

TABLE OF CONTENTS	ii
EXECUTIVE SUMMARY	iii
PREFACE	v
INTRODUCTION	1
RECOMMENDATIONS	3
• Study Design	3
• Populations	7
• Comparators	11
• Outcomes	16
References	22
Appendix A: MEMBERS OF THE TECHNICAL WORKING GROUP	35
Appendix B: GENERAL OVERVIEW OF EGDs	36
• Background and Purpose	36
• Target Audiences and Intended Uses	36
• Evidentiary Framework for EGDs	37
• Potential benefits of EGDs	37
• Relationship of EGDs to Other Documents Providing Methods Recommendations	38
• Scope and Topic Selection	39
• Development Process	39
• Conflicts of interest	40

EXECUTIVE SUMMARY

The Center for Medical Technology Policy (CMTP) supports the development of Effectiveness Guidance Documents (EGDs) to provide specific recommendations on the design and reporting of prospective clinical studies intended to inform decisions by patients, clinicians and payers. The recommendations are targeted to clinical researchers conducting studies of specific clinical interventions or health conditions. EGDs are intended to be analogous and complementary to Food and Drug Administration (FDA) guidance documents, but are focused on design elements that are particularly relevant to clinical and health policy decision making. The recommended methods aim to balance internal validity with relevance and feasibility, in order to provide these decision makers with a reasonable level of confidence that the intervention improves net health outcomes. These documents are developed through an extensive consultative process involving a broad range of experts and stakeholders. A summary of the EGD development process is included in the preface, and a more detailed version is available in an appendix to this document. A detailed overview of the purpose of EGDs, target audiences, intended uses, topic selection, and related information can be found in the [EGD overview](#), which is also included in the appendix to this EGD. The [EGD development process](#) is also available by clicking on the preceding link.

Purpose and Scope of This EGD

The purpose of this EGD is to provide specific recommendations to product developers and clinical researchers on the design of comparative effectiveness studies for the treatment of chronic wounds, specifically those pertaining to arterial and venous disease-related ulcers, diabetic foot ulcers, pressure ulcers, and burn wounds.

It is estimated that 2.8 million people in the United States suffer from chronic wounds and that this number will grow coincident with an aging population and increasing rates of diabetes. Recent systematic reviews of treatments for chronic wounds have identified a number of methodological limitations in many clinical studies in the field, offering insights into potential approaches to improve the quality and relevance of evidence. The ten recommendations contained in this EGD are intended to reflect the types of evidence that would be useful to patients, clinicians, guideline developers, payers and other “post-regulatory” decision makers in making health care decisions at the individual and population level.

The specific recommendations are provided in the text box on the following page. While incorporating all ten recommendations in future study design is highly desirable, it is recognized that may not always be feasible. Incorporating at least some of these recommendations in future studies would substantively advance the quality of wound care studies available for decision makers.

Key EGD Recommendations

1. Use Randomized Clinical Trials (including Pragmatic Clinical Trials) except under circumstances where there are barriers to the conduct of such a trial that can be identified and explained;
2. Conduct multi-center trials across a range of settings;
3. Blind the evaluation of wound closure and conduct expectation assessment prior to collecting Patient Reported Outcomes (PROs);
4. Stratify or conduct separate trials by both etiology and by risk factors for not healing;
5. Draw a substantial fraction of patients representative of clinical settings reflective of those in which wound care is actually delivered;
6. Include a standard of care arm that follows widely accepted, evidence-based clinical guidelines;
7. Follow the same protocol for concomitant treatment (primarily pain and comorbid conditions) in all study arms;
8. Clearly describe all interventions and use the same models / versions of devices for all patients;
9. Primary outcomes should include both the measure and the timing of an endpoint appropriate to the etiology and severity of wounds included in the study; and
10. Include secondary outcomes important to patients and other decision makers.

Providing Comments on the EGD

Obtaining feedback is critical to ensuring EGDs reflect the best thinking on the design of chronic wound treatment studies. To make the process of providing comments as easy as possible, CMTP offers an online questionnaire available at: <http://www.surveymonkey.com/s/SLCJNZ5>. By using this form, we will be able to more rapidly include your recommendations into the final document.

PREFACE

Purpose

The Center for Medical Technology Policy (CMTTP) supports the development of Effectiveness Guidance Documents (EGDs) to provide specific recommendations on the design of prospective studies intended to inform decisions by patients, clinicians and payers. EGDs do not provide general methodological advice, but rather offer specific study design recommendations that are relevant to a defined clinical condition and/or category of clinical interventions. The purpose of EGDs is to better align the design of clinical research with the information needs of patients, clinicians, and payers. EGD recommendations will generally address one or more of the following elements of study design: patient inclusion/exclusion criteria, choice of comparators, research settings, selection of outcomes, duration of follow-up and other key elements of trial design that are most relevant to the topic of each guidance. A detailed overview of the purpose of EGDs, target audiences, intended uses, topic selection, and related information can be found in the [EGD overview](#), which is also included in the appendix to this EGD.

The primary audience for EGDs is clinical researchers who are developing research protocols for studies that are intended to be helpful to patients, clinicians and/or payers in making clinical or health policy decisions. This would include researchers from life sciences companies with clinical development responsibilities, or other clinical researchers receiving funding from public sources, foundations, etc. EGDs are intended to be analogous to FDA guidance documents, which are also targeted to product developers and clinical researchers, and provide guidance on the design of clinical studies that are intended to support regulatory decision making. EGD recommendations are not intended to establish minimum standards for research to be considered adequate with respect to coverage, payment or pricing decisions. They are likely, however, to be aligned with the expressed evidence preference of public and private payers, as they are developed with payer input.

The methods recommendations in EGDs are guided by the objective of achieving an acceptable balance across a number of desirable dimensions, including internal validity, relevance, feasibility and timeliness. Overall, the objective of EGDs is to offer study design recommendations that would give decision makers a reasonable level of confidence that the intervention studies would improve net health outcomes.

There are a number of potential benefits of the creation and use of EGDs. First and foremost, they could help increase the consistency with which the body of clinical research that is reflective of the information needs articulated by patients, clinicians and payers. In addition, EGDs could contribute to greater consistency of trial design across studies of related treatments within specific clinical conditions, allowing for higher quality meta-analysis and systematic reviews due to reduced heterogeneity across multiple studies. By considering existing regulatory guidance in the EGD process, it is hoped that EGDs will help to achieve optimal alignment between study design elements intended for regulatory approval and study design elements targeted to clinical and health policy decision making.

There are three primary features that distinguish EGDs from the majority of other methods guidance documents. First, EGDs focus on a specific clinical area or category of interventions, while most other available methods guidance are more general and apply across a broad range of clinical conditions or technologies. Second, a number of the other documents provide guidance on reviewing the quality of existing studies, while EGDs provide recommendations for the design of future studies. Finally, we are not aware of any other documents that actively engage patients, clinicians and payers in the process of

Methodological Recommendations for Comparative Effectiveness Research on the Treatment of Chronic Wounds

developing recommendations, with the goal of ensuring that the information needs of these decision makers is given significant attention in generating methods recommendations.

A detailed [EGD overview](#) is available by clicking on the preceding link and in the appendix to this document.

Process

EGD recommendations are developed through an extensive consultative process involving a broad range of experts and stakeholders, including mechanisms for broad public review and comment. CMTP develops EGD recommendations with the support of a Technical Working Group consisting of experts in clinical care and research methods specific to the clinical domain that is the focus of the EGD, and also includes patient, clinician and payer representatives. Draft EGDs are made available for public comment through targeted distribution to all key stakeholders, posting draft documents on the CMTP web site, and public meetings including one or more invitation methods symposia to address the most complex or controversial issues. All feedback on the draft EGD is reviewed by CMTP staff and the Technical Working Group in developing a “final” version of the EGD, which is posted on the CMTP web site and widely distributed. Interested parties may comment on this specific EGD by visiting the CMTP website at: <http://www.surveymonkey.com/s/SLCJNZ5>. Full details about the EGD development process are available in an appendix to this document and at <http://www.cmtpNet.org/cmtpNet-research/guidance-documents/egd-development-process-and-overview/EGDProcess.pdf>.

INTRODUCTION

Chronic wounds commonly are defined as wounds that do not heal within an expected time frame, or have proceeded through healing without the accompanying expected improved functional outcomes. Arterial and venous diseases, diabetes and unrelieved pressure are the source of most chronic wounds, all impacting quality of life and incurring high health care costs. These factors all contributed to the focus of this guidance document on recommendations for designing comparative effectiveness research concerning the treatment of venous and arterial ulcers, diabetic ulcers and pressure ulcers. It is estimated that 2.8 million people in the United States suffer from chronic wounds and that this number will grow coincident with an aging population and increasing rates of diabetes (American Diabetes Association, 2007). Several recent systematic reviews of treatments for chronic wounds have identified a number of methodological limitations in many clinical studies in this field (Lo et al., 2008; Kranke et al., 2004; Hinchcliffe et al., 2008), offering some insights into potential approaches to improve the quality and relevance of evidence. This situation is compounded by the proliferation of treatment options for chronic wounds, with specific products including cell therapies, gene therapies, tissue and tissue-based products, xenotransplantation products, blood and blood products, combination products and devices.

In recognition of the need to improve the quality of clinical studies in this field, a number of organizations have recently produced recommendations for the conduct of clinical research for chronic wounds. These include AdvaMed's Guiding Principles for Clinical Research in Chronic Wound Healing (AdvaMed, 2010); the World Union of Wound Healing (WUWH) Societies' recommendations (WUWH, 2010); the European Wound Management Association's Outcomes in controlled and comparative studies on non-healing wounds (EMWA, 2010); the Alliance of Wound Care Stakeholder's Power Principles (Alliance of Wound Care Stakeholders, 2010) and others. The FDA has also issued guidance for industry for clinical trials design to develop products for the treatment of chronic cutaneous ulcer and burn wounds (FDA, 2006). Drawing upon these and other relevant documents, CMTF developed this Effectiveness Guidance Document (EGD) for the design of comparative effectiveness research studies for the treatments of chronic wounds. As noted in the preface, this EGD provides specific recommendations on the design of prospective studies intended to inform decisions by patients, clinicians and payers.

The remainder of this document provides detailed descriptions, rationale and implementation instructions for the following ten recommendations:

1. Use Randomized Clinical Trials (including Pragmatic Clinical Trials) except under circumstances where there are barriers to the conduct of such a trial that can be identified and explained;
2. Conduct multi-center trials across a range of settings;
3. Blind the evaluation of wound closure and conduct expectation assessment prior to collecting Patient Reported Outcomes (PROs);
4. Stratify or conduct separate trials by both etiology and by risk factors for not healing;
5. Draw a substantial fraction of patients representative of clinical settings reflective of those in which wound care is actually delivered;

**Methodological Recommendations for Comparative Effectiveness Research
on the Treatment of Chronic Wounds**

6. Include a standard of care arm that follows widely accepted, evidence-based clinical guidelines;
7. Follow the same protocol for concomitant treatment (primarily pain and comorbid conditions) in all study arms;
8. Clearly describe all interventions and use the same models / versions of devices for all patients;
9. Primary outcomes should include both the measure and the timing of an endpoint appropriate to the etiology and severity of wounds included in the study; and
10. Include secondary outcomes important to patients and other decision makers.

DRAFT

RECOMMENDATIONS

STUDY DESIGN

RECOMMENDATION 1: Use Randomized Clinical Trials (including Pragmatic Clinical Trials) except under circumstances where there are barriers to the conduct of such a trial that can be identified and explained

Rationale. While CER calls for studies that inform decisions being made by physicians, patients, and payers, studies must be well designed to provide information of sufficient quality to serve as a basis for decision making. Randomized Controlled Trials (RCTs) are strongly recommended unless there is evidence suggesting that the investigational technology may be superior to standard care and patients are at risk of serious and irreversible health outcomes (e.g., amputation in the case of diabetic ulcers) if they do not receive the interventional treatment. When designing RCTs for wound care therapies, standard computerized randomization should be employed, and stratified randomization should be used when studies include multiple, prospectively defined subgroups, as is often the case for chronic wounds. This is achievable in the majority of studies of wound treatment and would have a large impact on improving the quality of research on chronic wound therapies.

Implementation. Because many wound care products enter the market through mechanisms not requiring randomized trial data, clinical trials of wound care therapies are likely to be conducted once products are already in clinical use. This could be helpful in fulfilling the desire of payers to see effectiveness in real world settings. We use effectiveness throughout this document to mean performance in actual settings of care with intended patients including clinical trials if they are pragmatic. It is likely that pragmatic trials will play an important role in generating information about the comparative effectiveness of chronic wound therapies. Pragmatic clinical trials differ from traditional RCTs in that they are designed with the intention of providing information needed for decision making by patients, physicians, payers and regulators rather than with the primary goal of revealing biological effects of therapies. While these are still experimental trials, they address questions about the risks, benefits and costs of treatments as they are intended to be used in clinical care. Pragmatic clinical trials are characterized by three key features often missing from traditional RCTs; generalizability of results due to broad inclusion criteria for the study population, active comparators and consistently measured outcomes relevant to decision makers (Tunis et al., 2003; Thorpe et al, 2009). Pragmatic clinical trials yield more “real-world” information about the comparative effectiveness of therapeutic interventions than do traditional RCTs, and are gaining acceptance in the post-regulatory evaluation of therapies. When considering pragmatic trial designs for evaluating chronic wound treatments, guidelines for best practices should be followed, recognizing that different elements of trials may need to be more or less pragmatic in any given trial (Zwarenstein, 2008; CMTP, 2010). The use of data from clinical trials for decision making also may be compromised by unclear reporting of exclusion criteria for RCTs (Van Spall, 2007). RCTs should follow the CONSORT guidelines (Schulz, 2010) and the extensions for pragmatic RCTs (Zwarenstein, 2008; CMTP, 2010). In cases where patients switch treatment arms after enrollment, analyses should follow intention to treat rules. This allows an assessment of the level of effectiveness likely to occur in clinical care settings for a population represented by the study group (Price, 2008).

There has been tension between those who advocate the use of traditional, rigorous RCTs and those who believe that such designs are not consistent with understanding outcomes of chronic wound treatment in clinical settings. Poorly conducted RCTs will not provide high-quality data for decision makers and RCTs can be expensive and lengthy and recruitment may be difficult. However, it is important that those intending to use observational studies to create evidence recognize that high quality observational studies may be as lengthy and expensive as RCTs (Port, 2000).

Some of the barriers to conducting RCTs for chronic wound healing include the common use of multiple therapies over the course of treatment of a chronic wound that might be difficult to replicate in a trial based setting and the difficulty of blinding in some settings (see recommendation 3). It also may be difficult to enroll patients into a randomized study when both study treatments are available outside of the trial as many patients and physicians have strong preferences for one type of therapy over another. It also is not uncommon for physicians to have concerns about referring their patients to a trial where they may be assigned to a standard care arm. This can result in only selected groups of patients being referred to trials (e.g., patients with the fewest comorbid illnesses, those perceived to have the lowest risks for adverse events, or those who have not responded to standard treatments (Kass, 1978; Halpern, 2002)). In such situations the generalizability of results from the clinical trial may be severely limited. However, barriers to randomization are not insurmountable and where appropriate, randomization will provide a clearer picture of the true differences in outcomes due to therapy, not patient characteristics. Cluster randomization may overcome the concerns of physicians as they would know which treatment a patient under their care would be receiving. Another option may be the conduct of “patient-preference” trials alongside RCTs. These trials follow a cohort of patients receiving the intervention they select and study them in parallel with a randomized trial. These designs may broaden the generalizability of study results (King et al., 2005).

In areas where clinical trials have been performed, but the primary remaining questions concern applicability in usual clinical practice, if pragmatic clinical trials are not an option, well-designed observational studies may provide insight into the applicability of evidence derived from randomized trials by including patients and conditions often not found in randomized trials. These studies may also be useful if the goal is to more fully understand current treatment practices where decision makers desire information that requires long term follow up or very large patient numbers (Dreyer, 2010). The GRACE Principles provide excellent guidance on when observational studies can provide data to fill the evidence gaps left by clinical trials, including providing information on subgroups of special interest, broader populations, certain conditions, treatment combinations and sequences, and understanding the effectiveness of actual use (The GRACE Initiative, 2010). In the area of wound care, observational studies may play an important role in studies of wound recidivism or recurrence studies investigating durability of healing, both of which could require long-term follow up. However, in situations where non-interventional studies are used, the quality of data collected should be comparable to clinical trials data. Observational studies should be based on an a priori hypothesis and methods to adjust for possible baseline differences in populations, such as instrumental variable analysis and propensity scoring, should be included in the design. Instrumental variable analysis has been shown to produce less biased estimates of treatment effects compared to standard modeling in cardiac management studies (Stukel

et al., 2007) and propensity scoring has been broadly used in arthritis, cancer and cardiovascular studies to control for baseline differences in population (Maradit-Kremers et al., 2005; Doyle et al., 2005; L'Allier, 2004; Tewari et al., 2004; Moss et al., 2003). At this time, these methods have not appeared in published studies of chronic wound treatments. Observational studies should only be used when the use of the treatment is generally accepted (i.e. loss of equipoise); the condition has an established and predictable history; the therapy is not expected to have substantial side effects that would compromise the potential benefit to the patient; there is a justifiable expectation that the potential benefit to the patient will be sufficiently large to make interpretation of the results of a non-randomized trial unambiguous (a 'signal-to-noise' ratio of 10 or more has been recommended); and/or the scientific rationale for the treatment is sufficiently strong that a positive result would be widely accepted (Rawlins, 2008). Most chronic wound therapies are unlikely to meet all of these conditions, so the best use of observational studies is likely to be as adjuncts to trials. Methods do exist for statistically combining data from RCTs with observational data, but are not in widespread use. Begg and Pilote (Begg & Pilote, 1991) proposed a meta-analytic approach to combining different sources of data and testing for bias using a random effects model.

In addition to observational studies, the addition of registries alongside RCTs may prove helpful in increasing the amount of data gathered on patients who may choose not to be randomized. It has been suggested that increased use of databases and registries, when coupled with better reporting of the characteristics of trial participants, would enable decision makers to more easily evaluate outcomes in routine use (Juni et al., 2001; Padkin et al., 2001). Registries containing patient level information about interventions and outcomes may provide data supporting evidence-based therapeutics by both accessing information about the generalizability of the results of RCTs and providing further safety information (Rafferty et al., 2005).

RECOMMENDATION 2: Conduct multi-center trials across a range of settings

Rationale. Wound care is characterized by fragmented treatment practice, both in terms of setting (the treatment may involve inpatient, outpatient and home care) and caregivers (medical professionals with specialized or generalized expertise, or patients themselves in conjunction with their families). Multicenter trials are strongly preferred because they provide a better ability to generalize trial findings to other investigational and clinical care settings (ICH, 1998). Trials should include patients from more than one center and from settings of care representative of those in which the therapies being studied are intended to be used, across the range of levels or settings of care throughout the treatment and healing process. This may include one or more of inpatient or outpatient care in hospitals or wound care centers, home care with or without provider visits and nursing homes (Levin et al., 2007; Bowen et al., 2009). Based on the likelihood of patients moving across settings of care, a pragmatic trial of wound care in Canada including five levels of care- outpatient wound care clinics, inpatient care, home care, primary practice, nursing homes- was undertaken from 2008 to 2010 (clinicaltrials.gov, 2008). At least half of enrolled patients should be receiving care in settings other than tertiary wound care referral centers except in the case where the technology being studied would be used only in that setting. Efforts should be made to enroll sufficient numbers in each setting and at each site to evaluate potential differences in outcomes across sites, particularly when there are significant differences in expertise

across sites, when a high degree of protocol standardization is not feasible, or when the same mix of patient characteristics at all centers is not feasible. The FDA recommends that where variability in standard of care across sites cannot be avoided, that stratification by study site be included in the analysis (FDA, 2006). Statistical methods that allow testing for differences across study sites should be considered, but sufficient sample size across strata is critical. For complex devices, investigators should be well trained and reasonably proficient in using the investigational technology, and have obtained relevant credentialing when available. Selecting institutions with previous institutional experience with the technology of interest should be considered. The level of experience, extent of training, and certification (if any) of the clinicians providing the treatment should be described in the study protocol, and a baseline of education and training in the methods and therapies being investigated in the trial should be given to all clinicians treating patients. This allows the use of practitioners who the patients would see in the real world, assess effectiveness of clinicians with real-world skill sets using the treatment technology, but would standardize this effect across all settings (Mulder, 2004).

Implementation. To increase the usefulness of trial outcomes to decision makers, CER should be conducted in usual clinical practice settings where the technologies being evaluated are intended to be used. A pragmatic clinical trial approach to this is to allow some leeway in treatment protocols (care delivery and monitoring) so that they follow more closely actual clinical practice, while analyzing from an intent-to-treat basis and documenting existing practice variation.

Research networks are increasingly used in clinical research to provide more options to trial designers for conducting multi-center trials in different settings. Research networks are cooperatives between multidisciplinary teams at different sites in different settings. Primarily they strive to reduce the time to recruit the target population by broadening the patient base in different settings, but the infrastructure put in place to establish these networks often results in researchers having improved access to facilities and research support personnel, particularly in real world settings. Research networks could also allow for investigators across settings to be sufficiently proficient in using the new technology so that learning effects do not confound study outcomes.

Development of research networks for wound care that expand beyond academic centers and tertiary wound care referral centers would increase the ability of researchers to follow this recommendation. The NCI Oncology cooperative groups are one model of research networks. For example, The Eastern Cooperative Oncology Group (ECOG) members include universities, medical centers, Community Clinical Oncology Programs (CCOPs), and Cooperative Group Outreach Programs (CGOPs) and accrues 6,000 patients annually with 20,000 patients currently in follow up. Another model is the recently founded Johns Hopkins Clinical Research Network that links an academic center with community practices (MDNews.com, 2010). Special attention should be given to the model used by the Medicare Chronic Care Practice Research Network (MCCPPN), which was founded in 2009 to “serve as the leading national resource available to advance the science and operational standards of care management for the chronically ill Medicare population with attention to widespread adoption and relevance to new and improved payment policies.” (MCCPPN, 2011) Their network is designed to provide information on treatments which yield the greatest benefit at the lowest cost for particularly complex chronic illnesses.

Another useful model is the UK Clinical research network, which provides a model for multi-center, multi-specialty research in a number of fields (Clinical Discovery, 2007).

RECOMMENDATION 3: Blind the evaluation of wound closure and measure expectation for assessment of Patient Reported Outcomes (PROs)

Rationale. Blinding minimizes bias by eliminating the possibility that analysts, evaluators, and/or patients can be affected by expectations they may have that the intervention in question will or will not work (Atkins et al., 2004; Sawaya et al., 2007; CMS, 2008; ICH, 2009). While it may not be possible to blind patients and clinicians to their treatment assignment with some interventions, for example the use of the Unna boot versus standard dressing and debridement, it should be possible in nearly all cases to ensure that those individuals gathering data on wound size and other study outcomes are blinded to the treatment assignment of the patients that they are evaluating.

Implementation. Where routine blinding is infeasible, blinding to treatment assignment can be achieved through methods such as photographic assessment which has been shown to have a high degree of validity in blinded assessment (Baumgarten, 2009). Patient blinding is recommended where feasible for assessment of primary outcomes. For valid assessment of patient reported outcomes, such as quality of life (QOL) and symptom assessment, measures of outcome expectation should be performed prior to collection of outcome measures. Measures of outcome expectations have been used in cancer studies (Graves & Carter, 2005), in assessing patient self-reporting in asthma studies (Finkelstein et al., 2001) and epilepsy studies (Kobau & Dilorio, 2003). The methodology for this approach has been explored most deeply in the context of trials for complementary and alternative therapies (Mehling, 2005). To date, it has not been applied in the setting of chronic wounds. In circumstances when blinding may be particularly challenging, such as for hyperbaric oxygen therapy and for studies involving limb salvage, it is important that researchers explain these considerations in the study protocol and report, and discuss how the lack of blinding might impact the study results. This is particularly important in light of work which has shown that studies without blinding tend to overestimate treatment effects when compared with similar trials with adequately blinded design (Moher, 1998; Kjaergard, 2001) as well as in light of the FDA guidance which states that “clinical trials, where patients and investigators are aware of assigned therapy, are rarely adequate ...”. (FDA, 2009)

POPULATIONS

RECOMMENDATION 4: Stratify or conduct separate trials by both etiology and by risk factors for not healing

Rationale. Heterogeneity in patient populations exists based on wound etiology, wound severity, patient comorbidity and wound duration prior to study enrollment. Different approaches to stratification are appropriate for each of these and appear in Table 1.

Table 1. Recommendation for Stratification or Separation of Different Patient Populations

Patient Population	Include population in same study, without stratification	Include population in same study with stratification	Conduct separate studies for this population
Wound etiology	---	Recommended	Acceptable Alternative
Wound severity	Acceptable Alternative	Recommended	---
Patient comorbidity or underlying disease severity	Recommended	---	---
Duration of wound prior to enrollment	---	Strongly Recommended	---

Both wound healing and response to intervention vary by etiology (Stillman, 2010; Mustoe, 2006; Seamen, 2002), and different interventions may be more appropriate depending on the severity and chronicity of the wound (Jones, 2007; Blume, 2007; Haan, 2009; Armstrong, 2007). The inclusion of heterogeneous populations in prior studies is cited as a major barrier to interpreting data concerning the efficacy or effectiveness of interventions for wound healing (Mouës et al., 2004; Joseph et al., 2005; Braakenburg et al., 2006), making stratification particularly important for comparative effectiveness research. Because wound size, location, etiology, and co-morbidities all impact the clinical management of chronic wounds, all must be controlled for or used as factors for stratification in clinical trials in order to facilitate generalizability. However, we recommend that no more than two levels of stratification be included in each treatment arm to ensure sufficient sample size and appropriate assignment by randomization.

Implementation. Assessment of etiology is usually possible by obtaining patient history and examining the physical characteristics of the wound. The following additional diagnostic methodologies to confirm etiology are presented in the FDA guidance document on chronic cutaneous ulcer and burn wounds, but are not appropriate in all cases.

- Doppler sonography to qualify and quantify vascular insufficiency: arterial or venous (deep, superficial, or mixed);
- Transcutaneous oxygen tension (tcpO₂) measurements;
- Ankle/brachial index;
- Filament testing to quantify sensory neuropathy;
- Measurement of laboratory markers for diabetes mellitus; and

- Histopathology of ulcer biopsies to exclude neoplastic, immune-mediated, or primary infectious disease (FDA, 2009).

There is greater difficulty stratifying patients participating in studies of chronic wound therapies by severity because wound severity definitions are not standardized. There exist several proposed wound severity scores (Lazarus, 1994; Lavery, 1996; Jeffcoate, 1993; Armstrong, 1998; Shea, 1975; Knighton, 1986), but none are universally accepted or used in clinical research. Surface area or wound volume are good indicators of severity, but alone they are insufficient indicators of severity (Margolis, 2007). The Wound Healing Society has promoted the use of the TIME acronym (Tissue debridement, Infection management, Moisture balance, and Edge effect) to comprehensively define, communicate, and address the key aspects of impaired wound healing, however this method is not well validated, nor in widespread use (Ayello, 2004).

Need for Development of an Evidentiary Standard. The EMWA recently expressed an “urgent need for a validated scoring system with regard to wound condition”. (EMWA, 2010) More research is required to develop widely accepted standards for wound severity, particularly given the strong recommendations for stratification on wound severity. In clinical trials to date stratification by wound severity has been based on a variety of characteristics including wound type (Meaume et al., 2005), wound severity using the Gustilo-Anderson wound classification (Govender et al., 2002; Scimma, 2002), risk level for chronicity (Driver & DeLeon, 2008; Lyder, 2002), wound size (Cullum et al., 2007; Lavery, 2007) and for both wound severity and duration together (Houghton, 2010). Until such time as a standard is developed, consistency in measurement will improve the ability of comparison across studies and meta-analytic combination of study results. For linear measurements, many recommendations suggest that the ellipse formula will improve reliability (Bowling et al., 2009; Goldman & Salcido, 2002) and is easy to implement in clinical practice. Wound volume measurements appear more problematic (Brown, 2000) as the contact methods for measurement carry additional risk to the patient including:

- Potential for disrupting the tissue when contact is made;
- Risk of contamination of the wound site;
- Fluids may be spilled on the bed or clothing may become a vector for the spread of pathogens from the wound site to other patients or clinical staff; and
- Failure to account for other information such as surface area, color, or presence of granulation tissue. (Krouskop et al., 2002).

Among scoring systems, for pressure ulcers, there exist several tools that provide reproducible results, but are criticized for their lack of sensitivity and ability to predict healing. For diabetic foot ulcers, there are several measures, none of which have been widely accepted and for lower extremity ulcers, a validated measure (Leg Ulcer Measurement Tool) exists, but is most often used to measure healing progress rather than wound severity (Woodbury et al., 2004).

RECOMMENDATION 5: Draw a substantial fraction of patients from clinical settings reflective of those in which wound care is actually delivered

Rationale. Incorporating patients from a broader and more representative array of clinical settings allows increased sample sizes and the participation of more diverse patients in clinical studies. In prior clinical trials and other studies of wound care, patients at the greatest risk of chronic wounds are often excluded or enrolled in lower proportions than those occurring in the population of patients with chronic wounds. This tendency may be exacerbated when planning RCTs for wound care as in other diseases (Van Spall, 2007). The Alliance Power Principles specifically state that vulnerable populations are under-represented in wound care research and state that, “practice-based data suggest that many if not the majority of patients with chronic wounds are members of vulnerable groups.” (Alliance of Wound Care Stakeholders, 2010) These patients include the elderly, patients with co-morbidities, patients with chronic renal failure, and obese patients. Pragmatic clinical trials recommend broadening the inclusion criteria for trials, using stratification even beyond that described in recommendation 4, and including statistical analyses methods that allow exploration of the impact of patient factors on therapeutic effectiveness.

Implementation. When expanding patient populations every effort should be made to include those patients who make up a large proportion of the population with chronic wounds, but who are historically underrepresented in clinical trials, specifically patients with end stage renal disease (ESRD), the elderly and patients with multiple comorbidities. In addition, broadening inclusion of patients from nursing homes may lead to closer reflection of populations afflicted with chronic wounds. Patients in nursing homes are more likely to suffer from chronic diseases, such as cancer and arthritis, which may limit mobility and increase the risk of pressure ulcers (Keelaghan et al., 2008).

Further considerations in wound care treatment and effectiveness of these treatments is provided in a recent review by Pieper (Pieper, 2009). This paper discusses the impact of race, culture and insurance status on outcomes of chronic wound treatment and points to some of the difficulties that would be expected in conducting research in these settings, but also emphasizes the importance of doing so to provide effective care for these populations. Difficulties identified include the effects of racial/ethnic care disparities, immigration, low income, uninsured or underinsured status, and literacy/health literacy on health and wound care. The literature reviewed by Pieper also shows that care is not always perceived to be equitably provided across different ethnic and economically diverse populations. Pieper recommends that in order to provide effective care for these populations clinicians should strive to listen to and interact non-judgmentally with vulnerable patients. Each patient's physical and psychosocial concerns must be considered and clinicians must work together with community, state, and federal agencies to enhance access to necessary services. Pieper also recommends the development of wound care patient teaching materials suitable for the literacy and language skills of the community served. Pieper stresses that once clinical care has been determined, wound care practitioners must consider patient teaching, vulnerability, cultural, and economic constraints of care, along with strategies for prevention of complications and hospitalizations in order to provide effective care for all patients.

Regardless of settings of care, patient inclusion criteria must be clearly reported, which has not always been the case in prior reports of wound treatment trials (Cochrane Review, 2006). Ideally a study should focus on one type of chronic wound (e.g. pressure ulcers) across a broadly defined patient population. If the study enrolls patients with several wound types, patients should be stratified based on etiology as discussed above.

COMPARATORS

RECOMMENDATION 6: Include a standard of care arm that follows widely accepted, evidence-based clinical guidelines

Rationale. In practice, the FDA guidance recommends a comparator arm for *many* wound treatment trials (FDA, 2006). However, the 2006 Cochrane review of trials in wound care found that while almost all trials do use some form of standard care, the therapies provided in the control arm were not well described (Cochrane Review, 2006). It is important to compare treatments with standard care in order to assess whether the intervention modality provides additional, clinically meaningful benefits over care that complies with accepted standards of current medical practice. Therefore, the standard of care (as opposed to a placebo) should be included as a control arm to ensure that the trial is ethical. In addition, to interpret the data, the treatment and control arms must be comparable. The standard care arm of the trial should include standard care alone that follows evidence based clinical guidelines for the management of chronic wounds (Al-Benna, 2010). The protocol should include a detailed description of standard care that will be provided and any deviations in either the control or new therapies group should be documented. Currently, there are recommendations that the following elements of standard care should be included for both control and treatment arm patients (FDA, 2006; Sawaya et al., 2007; Bolton, 2004):

- Debridement of necrotic or infected tissue;
- Infection control;
- Nutritional support;
- Maintenance of adequate circulation or perfusion;
- 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);
- Bowel and bladder care where necessary to prevent infection (pressure ulcers);
- Compression therapy (venous ulcers); and
- Blood glucose control (diabetic ulcers).

However, these elements are dependent on the wound and on the patient and it should be noted that it would be very difficult to standardize debridement methods or comparator dressings as they are utilized based on wound and patient characteristics and not standards across the continuum of wound healing within a single wound, much less across etiologies or severity. Categories of treatment by etiology appear in Table 2.

Table 2. Categories of Treatment and Supportive Interventions

Etiology of Wound	Categories of Treatment / Supportive Intervention
Pressure Ulcers	<ul style="list-style-type: none"> - Positioning and support surfaces, - Nutrition, - Infection, - Wound bed preparation, - Dressings, and - Surgery and adjuvant therapies (Whitney et al., 2006).
Venous Ulcers of the Lower Extremities	<ul style="list-style-type: none"> - Diagnosis, - Compression, - Infection Control, - Wound Bed Preparation, - Dressings, - Surgery, - Adjuvant Agents (Topical, Device, Systemic), and - Long-Term Maintenance (Robson et al., 2006).
Diabetic Ulcers of the Lower Extremities	<ul style="list-style-type: none"> - Diagnosis, - Offloading, - Infection control, - Wound bed preparation, - Dressings, - Surgery, - Adjuvant agents (topical, device, systemic), and - Prevention of recurrence(Steed et al., 2006).
Arterial Insufficiency Ulcers	<ul style="list-style-type: none"> - Diagnosis, - Surgery, - Infection control, - Wound bed preparation, - Dressings, - Adjuvant therapy (device, systemic, local/topical), and - Long-term maintenance(Hopf et al., 2006).

Implementation. There exist a number of clinical guidelines for standards of care across chronic wound etiologies (Frykberg et al., 2000; Albrant, 2000; McGuckin, 1997; Bergstom, 1994), although the American Diabetes Association provides guidelines for the treatment of the diabetic foot ulcer but intentionally does not clearly delineate standard of care, ostensibly allowing for advances in this area

(American Diabetes Association, 2000). The Alliance of Wound Care Stakeholders held a conference on for chronic wounds in 2008, which included information on usual care and needed improvements (Nusgart, 2008). The 2010 EMWA guidance recommends three different standard of care, one for each of leg ulcers, pressure ulcers and diabetic foot ulcers (EMWA, 2010). Variability in standard of care practices used in different arms, settings, or centers can affect the quality of data about the effect of the treatment being studied. Both well-defined inclusion criteria and a run-in period of optimally delivered standard care may minimize this variability (FDA, 2006; Samson, 2004). Additionally research protocols should include protocols for the standard care arm. The protocol need not be exact, but must be detailed enough to effectively minimize variability. For example, in guidance describing dressings to be used in one treatment arm, instructions to use an “advanced dressing” would be appropriate; however the brand need not be defined. “Clinically-indicated care” is care that would require investigators to adhere to protocol-prescribed care (Meade, 2002) where the protocol is based on a formal guideline appropriate to the clinical setting in which care is delivered. Using clinically indicated care in trial design would allow incorporation of practice variability without moving away from accepted care practices into “inappropriate care”.

Need for Development of an Evidentiary Standard. As revealed by the Cochrane Review (2006), most clinical trial reports fail to describe fully the standard of care being administered in conjunction with treatment in the treatment arm or as a comparator in the control arm. The quality of evidence in CER studies will be improved by the development of guidelines for standard of care for chronic wounds by etiology and severity and protocols for this care should be incorporated into CER study design and specification. The Wound Healing Society has published clinical guidelines based on published evidence for the treatment of wounds according to etiology, including venous ulcers (Robson et al., 2007), pressure ulcers (Whitney et al., 2006), diabetic ulcers (Steed et al., 2006) and arterial insufficiency ulcers (Hopf et al., 2006). Different guidelines also have been published by the Association for the Advancement of Wound Care for venous ulcers (Boulton et al., 2006), the American College of Radiology (American College of Radiology (ACR), 2009) and device manufacturers including ConvaTec (ConvaTec, 2008). Despite over 30 unique guidelines for clinical care of ulcers listed with the National Guideline Clearinghouse written by national government agencies, medical specialty societies, professional associations, private non-profit organizations and private for-profit organizations, no guideline has been broadly accepted and implemented in clinical practice.

RECOMMENDATION 7: Follow the same protocol for concomitant treatment (primarily pain and comorbid conditions) in all study arms

When expanding the patient population and associated comorbid conditions, it may be necessary to provide concomitant treatment, both for wound related issues such as pain or infection and for other aspects of the underlying disease (e.g. glycemic control in diabetes, pharmacologic therapy for arterial ulcers) or comorbidity that may contribute to wound healing. Study protocols should include plans for their treatment as well as for the direct treatment of the chronic wound.

Rationale. It is widely recognized in other clinical specialties that the management of comorbidities presents its own set of challenges (Chang et al., 2006). This must be recognized in the treatment of

chronic wounds and trial protocols should specify standardized concomitant treatments for any comorbidities or concomitant conditions that are not explicitly excluded from the trial.

Implementation. The FDA provides guidance for reporting of concomitant medications in drug trials, suggesting that stratification by potentially confounding factors that are clinically significant should be considered to minimize imbalances among treatment groups, thus reducing the difficulty of detecting treatment effect. The FDA also recommends that similar principles should be applied for management of co-morbid conditions or symptoms associated with chronic wounds (FDA, 2006). Particular attention should be taken to standardize concomitant care for pain control, pressure unloading, infection control, pharmacological intervention for arterial ulcers and glycemic control for diabetic ulcers. In the case of diabetic foot ulcers, in addition to glycemic control, successful treatment requires concomitant careful attention to the wound by both the physician and the patient. Careful and repeated cleansing and debridement, using proper wound dressings, and ensuring that the ulcerated limb is non-weight-bearing are critical to a successful outcome. To be treated at home, patients must be willing and able to take care of their wound and to stay off the affected foot until healing is assured. Concomitant treatment for serious wound infections includes initial complete sharp surgical debridement, revascularization of the foot, and parenteral granulocyte colony-stimulating factor (Reiber et al., 1998). Glycemic control is crucial as patients with poor glucose control are at significantly higher risk of ulceration (Lavery et al., 1998). In the case of arterial ulcers prostaglandin therapy is commonly administered orally (Linhart, 1998) in an attempt to address the underlying arterial and venous insufficiencies. This pharmacological therapy should be continued to prevent future recurrence.

RECOMMENDATION 8: Clearly describe all interventions and use the same models/versions of devices for all patients enrolled in a trial

Rationale. In all cases, but particularly when there are different models of a technology, the specific model being investigated should be clearly described in the research protocol. If the investigational technology is being compared to an existing model, the improvement it offers should be discussed to allow a clear understanding of the expected differences and improvements, and how those will be evaluated in the study.

When multiple versions of a particular device are available, the same version should be used for all treated patients in all sites participating in the research study. The technical parameters of the technology should be consistent across all sites and any exceptions should be described and explained in the study report. This will reduce the chances that any possible inconsistencies in the study results would be attributable to differences in the technology used to treat study patients. The FDA guidance for industry also recommends stratification by study center to minimize any imbalances among study arms where variation in treatment is unavoidable among clinical study sites (FDA, 2006).

Special training, experience or credentialing requirements that were applied in selecting clinicians providing care with the new technology during the study should be described in the study protocol.

Implementation. In contrast to drugs, surgical procedures, clinical management of patients and actual devices may be modified and refined during the conduct of clinical trials. These modifications can be

accommodated in the design of clinical trials, most specifically by recruitment of sufficient patients to allow subgroup analysis. These issues are currently in flux and in February of 2010, the FDA convened a workshop that included a discussion of how to deal with incremental changes to devices cleared for marketing through the 510(k) process. From a scientific standpoint, allowing excess difference in the context of a trial makes statistical inference from trial data more challenging and conclusions less reliable.

Garber discusses the tension in deciding when it is necessary to conduct a new study of a device, stating, “Without new clinical studies, it is not easy to determine whether an incremental change in a device increases risk or impairs effectiveness. But treating every modification as the equivalent of a new drug would make incremental improvements prohibitively time-consuming” (Garber, 2010). This sentiment is echoed in PwC’s recent report “Medical Technology Innovation Scorecard: The Race for Global Leadership” stating that the challenges associated with obtaining trial approval and clearance in the United States is causing the movement of technology innovation abroad (PwC, 2011). To eliminate need for a new study for every device change, Bayesian analysis and/or an adaptive study design may be used. The FDA is becoming increasingly interested in evaluating trials based on Bayesian analyses, particularly for medical devices (FDA, 2006). Manufacturers are increasingly using Bayesian designs in phase II and III trials (Berry, 2006; Berry, 2005; Grieve, 2007; Chang & Boral, 2008) and there are several examples of the successful use of Bayesian design in wound care studies (Lavery et al., 2008; Marston et al., 2003). Additionally, it has been argued that Bayesian meta-analyses based on literature surveys can effectively inform coverage decisions (Berry et al., 2010). When an adaptive design is used, the following provisions should be implemented in the research design (Chow & Chang, 2008; Coffey & Kairalla, 2008; FDA, 2006):

- Describe measures designed to assure that the validity and integrity of trial results will not be compromised;
- State rules for prospective adaptation (e.g., adaptive randomization, premature stopping, sample size re-estimation, or dropping/picking up individuals with inferior/superior treatment response);
- Plan to report the rationale for any concurrent (ad hoc) adaptations (e.g., changes in protocol);
- Consider an enrichment design when a single wound is the study focus. For example, patients who fail to respond to treatment within a pre-specified period of time may then be randomized to an alternative treatment or control; and
- Obtain consensus from an outside party for any retrospective adaptation, which should be conducted before unblinding. Switching from a superiority to a non-inferiority hypothesis for outcomes identified as "primary" or "secondary (key)" in the following section is not recommended unless there is previous evidence that outcomes identified as "secondary (optional)" may be superior or the trial has been designed to explore optional secondary outcomes.

The FDA is continuing to adapt its review processes to address this issue as well as issues involving equivalence with older technologies and the degree of incremental change that should trigger new review

(<http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM201345.pdf>). Currently, the FDA does provide guidance for addressing changes in device design when a device is subject to Pre-Market Approval (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm>).

OUTCOMES

RECOMMENDATION 9: Primary outcomes should include both the measure and the timing of an endpoint appropriate to the etiology and severity of wounds included in the study

Rationale. Incidence of complete wound closure is the primary endpoint for studies of chronic wound treatment. Time to this endpoint is also important. The most commonly used endpoint is incidence of complete wound closure between 12 and 24 weeks. Discussion has centered on more flexibility of these standards, but a more appropriate approach is selecting the outcome based on etiology as seen in Table 3.

Table 3. Recommendations for Endpoints for Wound Healing by Etiology

	Venous and Arterial Ulcers	Pressure Ulcers	Diabetic Foot Ulcer
Time to achieve complete wound closure	Recommend (secondary importance)	Recommend	Recommend
Proportion achieving complete wound closure at 12-16 weeks	Recommend (primary importance)	Recommend	Recommend
Rate of wound recurrence after one year	Recommend (tertiary importance)	Recommend	---
Rate of secondary amputation at 4-6 months	N/A	N/A	Recommend

For some studies, it may be more appropriate to examine the average time to complete wound closure, although this might require longer follow-up times for trials. In addition, healing may not be the stated goal of all therapies, especially those intended for early stage treatment. Such targets may include reduction of exudation, increase of granulation or reduced pain. For example, in trials of technologies used for debridement, the goal is not healing, but the establishment of a wound bed with good quality

granulation, allowing use of the next step toward wound closure. In such trials, the appropriate outcome might be a graft ready wound, as opposed to time to complete wound closure. Similarly, negative pressure wound therapy is not intended to be a closure methodology, so an appropriate primary endpoint must be defined that is in-line with the product's intended use. However, even in these cases, the time to expected improvement or achievement of the outcome should be included in the description of the primary outcome. Other important endpoints include graft success rates and reduction of amputation (in cases of lower extremity traumas or diabetic foot ulcers). In such cases it is important to note that complicated chronic wounds, such as those with exposed bone and tendon, are especially challenging as there are only few approved therapies to treat them. However, statistics show that salvage of the limb is often the most cost-effective endpoint (Amputee Coalition of America, 2008). Lower extremity trauma is common, and in severe cases treatment options are salvage or amputation. Chung et al. performed a cost-utility analysis of limb salvage versus amputation in lower extremity injury and found that the lifetime cost to a patient is in excess of \$509,000 as compared to \$163,000 for patients where the limb was salvaged (Chung et al., 1965).

Implementation. The EMWA guidance summarizes outcomes used in chronic wound studies from 2003 - 2009 (outcomes from studies prior to 2003 were summarized by Matousek et al., 2007). Their work separates outcomes into 11 categories and reports on the use of each as well as the common occurrence of outcomes without definition or with incomplete or unclear definitions. The most common outcomes are wound healing outcomes including wound closure, reduction in wound area and healing time. It is important to note that complete wound closure at 12 weeks might not be practical for CER studies because few real-world patients would achieve complete closure in that short time. However, the 12 week marker becomes significant if a wound has completely healed; in wound healing, collagen equilibrium occurs at three weeks and at three months 80% of strength is restored. Therefore, complete wound healing should not be assigned to a wound that completely heals and then recurs within 3 months. Recurrence can only happen after three months and any failure to heal within three months should not be classified as wound closure (Atkinson et al., 2005; Burke, 1998; Townsend, 2001; Broughton et al., 2006). Follow up is also crucial to monitor durability of healing and instances of recurrence. For diabetic foot ulcers the study duration should be 12 weeks with 3-month follow up and for uncomplicated venous leg ulcers it should be a minimum 20 week duration with 3-month follow up.

Some researchers have advocated the relevance of reducing wound exudate, controlling odor, preventing infection, and relieving pain as legitimate primary endpoints (Enoch, 2004). However this document considers these as valid secondary endpoints (see recommendation 10).

Further research is needed on the validity of intermediate outcomes and their predictive value for definitive clinical outcomes. There is some research supporting the use of 4-week outcomes (Gelfand, 2002; Kurd et al., 2009), but this is not universally accepted. There are also increasing data on using biomarkers or molecular changes to measure healing, but these technologies are not yet accepted in clinical research (Mosely, 2004). Acceleration of healing also has been shown in RCTs to be predictive of eventual healing. The rationale for having a surrogate outcome is to save time and money, but there is controversy in the medical literature about the validity of surrogate outcomes to evaluate the efficacy in

wound healing (Gelfand et al., 2002; Margolis et al., 2003; Hill et al., 2004; Margolis & Mani, 2007; Quan et al., 2007; Cardinal et al., 2008, Coeper et al, 2008). The most important of these concerns is the use of wound healing rates as a surrogate outcome for the incidence of, and time to, complete wound closure.

Comparative effectiveness research is theoretically conducted to focus solely on outcome, however when considering the use of therapy in actual clinical care settings, the relative resource intensity of alternative therapies cannot be ignored. Within the clinical research setting, outcome measures should include detailed reporting of resources required in each study arm when targeting a given endpoint. For example, if a great deal of increased nursing care is prevented by having a wound close two weeks earlier, this may be important despite the ultimately identical outcome if time to healing is not considered.

Based on current literature trial designers could consider the following indicators as outcomes for technologies designed to proceed to complete healing:

- For pressure ulcers and venous leg ulcers percent healing and ulcer area between weeks 3 (Phillips et al., 2003) and 4 (Kurd et al., 2009) are reasonable predictors of complete ulcer healing for venous ulcers; and
- For diabetic foot ulcers more than 82% healing at 4 weeks is an acceptable predictor of complete healing at 12 weeks (Sheehan et al., 2003). Other prognostic factors that are useful predictors at 4 weeks include wounds $\leq 2 \text{ cm}^2$, wounds ≤ 2 months old, and wound of grade ≤ 2 (Kurd et al., 2009). Other studies have used regression models to examine the relationship between early healing at healing at 16 weeks (Lavery et al., 2008).

Need for Development of an Evidentiary Standard. The most accepted intermediate measure of wound healing is healing at 4 weeks, however there is little consensus in the literature about either primary or intermediate outcomes. In June 2010, EMWA conducted a literature review of 176 wound care studies and identified 313 endpoints (EMWA, 2010) and in 19% of these studies which used wound healing as an outcome, no clear definition was given for complete healing (EMWA, 2010). Primary endpoints used in recent RCTs include time to healing of the largest eligible ulcer (Watson et al., 2011; Dumville et al., 2009), reduction in ulcer size (Shigematsu, 2010), proportion of patients with complete healing of all ulcers (Inglesias et al., 2004), proportion of completely healed ulcers after three months (Parsch & Horakova, 1994), proportion of patients with complete healing within six months (Sipponen et al., 2008), proportion of completely healed ulcers at 500 days (Milic et al., 2007), amputation rate at 100 days for a study of patients with diabetes mellitus and critical limb ischemia (Kusumanto et al., 2006), and absolute (mm^2) and relative (%) wound size reduction at 6 weeks compared to baseline (Lucas et al., 2003). The most recent statistical analysis investigating intermediate endpoints in chronic wounds was conducted in 1992 (Freedman et al., 1992). Intermediate endpoints used in recent RCTs include the proportion of patients healed at 12 and 24 weeks (Inglesias et al., 2004), partial healing of the ulcer, and successful eradication of bacterial strains cultured from the ulcers at study entry (Sipponen et al., 2006), a 15% increase in pressure indices (ankle-to-brachial index and toe-to-brachial

index) for a study of patients with diabetes mellitus and critical limb ischemia (Kusumanto et al., 2006) and median change in Norton scores at 6 weeks (Lucas et al., 2003).

Until further research establishes primary and intermediate outcomes we recommend use of the recommended outcomes in Table 3 for consistency.

RECOMMENDATION 10: Include secondary outcomes important to patients and other decision makers

Secondary outcomes of importance to patients include infection, pain, therapy specific complications, wound recurrence, odor, avoidance of amputation and whole patient outcomes such as quality of life and functional status. Specific selections of patient reported outcomes will be dependent on the subpopulations included in the trial.

Rationale. These adjunctive outcomes are important as wounds can be socially isolating because of their odor and appearance. Wounds can also impair ambulation and give rise to psychosocial effects and psychopathological responses (Van Loeve et al., 2003). Several studies have shown that patients with chronic wounds have decreased health related QoL (Phillips, 1994; Franks, 2001). Also, because changes in behavior and treatment decisions may be important in the successful treatment of chronic wounds, design studies should include outcomes that are important to patients and physicians. Inclusion of such outcomes is not common in trials in general. For example, in studies of diabetes less than half of trials included outcomes important to patients and such outcomes were less common in parallel design RCTs (Gandhi, 2008). In chronic wound treatment, this problem is further amplified by the lack of rigorous assessment of which outcomes patients do consider most important.

Implementation. Infection is a commonly occurring complication of chronic wounds. Recently two classifications have been accepted for assessing the severity of diabetic foot ulcer infection (IWGDF and IDSA citations), however similar classifications do not exist for other wound etiologies. In addition, there is little clarity on how infection should be included in studies of wound care and whether the goal should be prevention of infection, incidence of or time to resolution of infection.

Pain is a common symptom associated with chronic wounds and has profound impacts on the patient's overall health-related quality of life. Health related quality of life, including ulcer-related pain, has been successfully included as a secondary outcome in RCTs (Dumville, 2009). A review of instruments for measuring pain in chronic leg ulcers indicates differences in the appropriateness of alternate instruments (Nemeth et al., 2003). The FDA guidance states that, "Wound pain amelioration endpoints should be accompanied by assessment instruments that are prospectively defined and appropriate to measure the type of pain for which an indication will be sought" (FDA, 2006). Appropriate pain scales include:

Strongly recommended scales:

- Visual analog scale (VAS); validated for chronic pain (Price et al., 1983); previously used in wound healing studies (de Laat et al., 2005; Shukla et al., 2005; Guarnera et al., 2007);

Methodological Recommendations for Comparative Effectiveness Research on the Treatment of Chronic Wounds

- Short-Form or complete McGill Pain Questionnaire. Validated for general use (Melzack, 1975); previously used in wound healing studies (Roth et al., 2004; de Laat et al., 2005; Vuerstaek et al., 2006).

Other validated pain scales:

- Numerical Rating Scale (Roth et al., 2004; Waldrop and Serfass, 2008);
- Faces Rating Scale (de Laat et al., 2005) ; and
- Verbal Pain Rating Scale (Shukla et al., 2005; Vuerstaek et al., 2006).

Additional morbidities associated with chronic wounds include humiliation and depression (Joseph et al., 2000) and because chronic wounds can have a major impact on many aspects of patients' well-being, health-related quality of life or functional status may be appropriate secondary endpoints in CER. The FDA guidance recognizes the validity of quality of life as an endpoint and states that it is possible to establish labeling claims related to quality of life where clinically significant improvement in daily living are assessed with a clinically relevant validated instrument. Quality of life measures that have provided useful outcomes in wound care studies include:

- Medical Outcomes Study SF-36 (general health status) (McHorney et al., 1994);
- Medical Outcomes Study SF-12 (Guarnera et al., 2007);
- World Health Organization-5 Well-Being Index (Jorgensen et al., 2006; WHO, 1998a); and
- EuroQol (utility weights) (Vuerstaek et al., 2006; EuroQol, 2008).

Health related quality of life has been successfully used as a secondary outcome in recent RCTs for venous leg ulcers (Watson et al., 2011; Shigematsu et al., 2010; Dumville et al., 2009).

Functional status, scarring and odor should also be included in wound healing studies, in addition to pain and infection.

Recurrence must be considered as the most important secondary outcome in cases of pressure ulcers, with patients suffering from spinal cord injuries being most at risk from a lifetime of recurrence due to limited mobility, lack of sensation and other physiologic changes. Recurrence is most likely to occur within 4 months at the same anatomical site and when healing of the initial pressure ulcer was incomplete (Bates-Jensen et al., 2008). The National Pressure Ulcer Advisory Panel has recommended specific pressure ulcer staging definitions (NPUAP, 2007) which have been successfully used as secondary outcomes measure in recent RCTs (Gupta et al., 2009) however there is no consensus on measures with which to assess severity of wound healing.

Need for Development of an Evidentiary Standard. More research is needed to yield universally accepted evidentiary standards for secondary outcomes in wound care in order to incorporate outcomes that are meaningful to patients as well as clinical meaningful outcomes that will inform decision makers. Recurrence has been used as a secondary outcome measure during compression therapy RCTs, but it is not uniformly assessed; in one recent instance it was only monitored during continued treatment (Milic., 2007) and in other studies recurrence parameters are not clearly defined (Lavery et al., 2007). In the same document the EMWA both states that it is important that researchers are able to differentiate between ulcer recurrence and the development of a new ulcer on the same site, but acknowledges that, during the planning of wound care studies, a sufficient follow-up time for when a wound can be considered to have healed, compared with reopening/recurrence not related to the intervention, has still not yet been clearly defined (EMWA, 2010), although 3 months has been accepted as having a biological basis (Atkinson et al., 2005; Burke, 1998; Townsend, 2001; Broughton et al., 2006).

Health related quality of life is most closely related to pain, but can extend to generic measures, condition-specific measures and utility measures. Health related quality of life measures that are universally accepted for a given wound etiology must be established in order to facilitate comparisons between different studies and across different therapies.

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APPENDIX B: GENERAL OVERVIEW

Background and Purpose

The Center for Medical Technology Policy (CMTTP) supports the development of Effectiveness Guidance Documents (EGDs) to provide specific recommendations on the design of prospective studies intended to inform decisions by patients, clinicians and payers. EGDs do not provide general methodological advice, but rather offer study design recommendations that are specific to a defined clinical condition and/or category of clinical interventions. The purpose of EGDs is to better align the design of clinical research with the information needs of patients, clinicians, and payers. This is achieved by engaging these decision makers in formulating the recommendations.

EGD recommendations will generally address one or more of the following elements of study design: patient inclusion/exclusion criteria, choice of comparators, research settings, selection of outcomes, and duration of follow-up. Other key elements of trial design that are most relevant to the topic of each guidance document also may be addressed. Each EGD will focus on those aspects of study design that are most likely to improve the quality and relevance of clinical evidence for the selected EGD topic.

Target Audiences and Intended Uses

The primary audience for EGDs is clinical researchers who are developing research protocols for studies intended to provide useful information to patients, clinicians and/or payers making clinical or health policy decisions. This would include researchers from life sciences companies with clinical development responsibilities and other clinical researchers receiving funding from public sources or foundations.

Secondary audiences for EGDs include groups or individuals that judge the quality and relevance of clinical research from the perspective of its utility for clinical and health policy decision making. These groups may find it useful to evaluate the extent to which EGD recommendations were considered in the design of studies under review. Such organizations include research funders, scientific review committees, developers of clinical guidelines and quality measures, producers of patient education materials, health technology assessment organizations, and groups developing coverage and payment policies.

EGDs are intended to be analogous to FDA guidance documents, which are also targeted to product developers and clinical researchers and provide guidance on the design of clinical studies that are intended to support regulatory decision making. EGDs will serve as a comparable resource for product developers and other clinical researchers, but are primarily focused on the design of clinical studies to support decisions by patients, clinicians and payers.

The study design recommendations in EGDs may be relevant to the design of either pre-market studies or post-market research. In some cases, specific recommendations will include guidance on the desirable phase of product development for consideration of that recommendation. EGDs are carefully aligned with existing regulatory guidance documents when those have been developed and are not intended to replace or conflict with regulatory guidance.

EGDs recommendations are not intended to establish study design requirements for research to be considered adequate with respect to coverage, payment or pricing decisions. However, because EGDs are developed with input from public and private payers about their perspectives on evidence relevant to their decision making,

the recommendations may be a useful guide to trial designers in developing study protocols that are more closely aligned with the expressed evidence preferences of payers. In some cases, coverage with evidence development or other forms of conditional approval will be useful policy tools to facilitate additional studies of technologies for which evidence has been produced that is consistent with the EGD recommendations.

Evidentiary Framework for EGDs

The methods recommendations in EGDs are guided by the objective of achieving an acceptable balance across a number of desirable dimensions, including internal validity, relevance, feasibility and timeliness. Recommendations are not intended to describe an approach to designing 'gold standard' studies. It is understood that there are often trade-offs required in designing studies that retain an adequate degree of methodological rigor, while adopting features that make the results more generalizable to routine clinical practice. Furthermore, compromises also may be desirable to increase the likelihood that studies can be implemented successfully and in an acceptable time frame. Overall, the objective of EGDs is to provide study design recommendations that would give decision makers a reasonable level of confidence that the intervention studied would improve net health outcomes.

A core premise behind the EGD development process is that the participation of a broad range of stakeholders improves the likelihood of achieving a reasonable balance of validity, relevance, feasibility, and timeliness. Each phase of the process involves active efforts to solicit and incorporate the full range of views of all relevant perspectives. It is recognized that it will not always be possible to arrive at consensus across stakeholders and ultimately, it will be necessary to render judgments about what constitutes a reasonable recommendation. As a general principle, while the perspectives of patients are central to our process, all stakeholder views are considered in determining the final recommendations. Where significant differences of opinion exist, all views will be documented in the text accompanying the specific recommendation.

Adoption of EGD recommendations is not intended to be obligatory, nor do they represent the only possible approach to study design. As noted above, the intent is to accurately reflect the evidence preferences of patients, clinicians and payers as a resource to trial designers who may benefit from a better understanding of these perspectives. It is anticipated that clinical researchers will have legitimate reasons to select study design approaches other than those described in the EGD recommendations. When this occurs, it would be valuable for the researchers to explain their rationale for their chosen design approach in the study protocol and/or when reporting the results of their study. The justification for these alternative study design approaches will also assist decision makers when considering the implications of the research results. In addition, these explanations would provide valuable feedback to EGD developers as these documents are updated and refined over time.

Potential benefits of EGDs

There are a number of potential benefits of the creation and use of EGDs. First and foremost, they could help increase the consistency within the body of clinical research that is reflective of the information needs articulated by patients, clinicians and payers. More relevant and applicable evidence would improve the decision making process and should also lead to better health outcomes.

In addition, EGDs could contribute to greater consistency of trial designs across studies of related treatments within specific clinical conditions, allowing for higher quality meta-analysis and systematic reviews due to reduced heterogeneity across multiple studies. This could also improve the reliability of indirect comparisons between related interventions in separate studies, when head to head comparative studies are not feasible or are unavailable.

Life sciences companies may benefit from EGDs by virtue of having greater clarity and consistency with respect to the type of evidence desired by the range of key decision makers that will be making judgments about their products. This should support greater certainty in decision making throughout the clinical development process, including very early decisions with respect to the commitment of resources to pursue for further development and key decisions at each phase of the clinical development process.

By considering existing regulatory guidance in the EGD process, and including the relevant FDA regulatory experts throughout the course of developing EGD recommendations, it is hoped that EGDs will help to achieve optimal alignment between study design elements intended for regulatory approval and study design elements targeted to clinical and health policy decision making. This may reduce the need for multiple separate studies to address both regulatory and post-regulatory evidentiary expectations and also reduce the frequency with which products obtain regulatory approval but fail to achieve market access due to lack of evidence targeted to other clinical and health policy decision makers. The process of FDA/CMS parallel review could be enhanced as a result of clarifying the informational needs of both decision makers in developing EGD recommendations, and including those elements in studies intended for simultaneous review by both FDA and CMS.

Relationship of EGDs to other documents providing methods recommendations

There are a number of other documents that provide recommendations on the design and reporting of clinical research that are generally complementary with, and not duplicative of, EGDs. These include a number of methods manuals produced by the Agency for Healthcare Research and Quality, the Cochrane Collaboration, the International Society for Pharmacoeconomics and Outcomes Research, the CONSORT guidelines, etc. There are three primary features that distinguish EGDs from the majority of these other documents. First, EGDs are focused on specific clinical topics or categories of interventions, while most other available methods guidance describes methods that would generally apply across a broad range of clinical conditions or technologies. Second, a number of the other documents provide guidance on the review of existing studies, rather than providing recommendations for the design of future studies. Finally, we are not aware of any other documents that actively engage patients, clinicians and payers in the process of developing recommendations, with the goal of ensuring that the information needs of these decision makers is given significant attention in generating methods recommendations.

As part of the initial background research done early in the EGD development process, we identify all existing methods documents and other guidance that would be relevant to the topic of the EGD in order to ensure that the insights from these products can be considered as the EGD recommendations are developed.

Clinical practice guidelines, systematic reviews and health technology assessment on the same or similar topics to are particularly useful in the development of EGDs. Of greatest value are insights that are provided by the authors of these documents regarding the methodological limitations of the existing body of research, as well as some best practices. These insights offer a useful starting point for identifying potential recommendations that would assist designers of future studies in adopting the best practices of previous studies and to avoid repetition of past study design approaches that reduce the validity, relevance, or feasibility of the research.

The methodology committee of the Patient-Centered Outcomes Research Institute (PCORI) is directed by statute to develop methodological standards for comparative effectiveness research. Their purview will have to address the entire scope of CER methods, including systematic reviews, modeling, retrospective data analysis, prospective observational studies and clinical trials. Given this broad range, it is unlikely that they will pursue the development of guidance for specific clinical domains or categories of health interventions.

However, this experience in crafting a process for the development of methods guidance for CER should provide useful insights to the PCORI methodology committee as they determine how best to respond to their legislative mandate.

Scope and Topic Selection

Each EGD focuses on a specific category of health care technologies and/or a specific clinical condition. Examples of EGDs being developed by CMTTP include treatments for chronic wounds, treatments for atrial fibrillation, patient-reported outcomes in oncology drug trials, cardiac imaging for diagnosis of coronary disease, and molecular diagnostics for choice of therapy in oncology, among others. Methodological considerations for the design of clinical studies will often be specific to defined categories of technologies or clinical conditions and the scope of EGDs must therefore be sufficiently narrow to provide study design recommendations that are specific and actionable. Although retrospective studies may be informative for decisionmaking, CMTTP's work on EGDs focuses only on prospective observational studies and clinical trials (with emphasis on pragmatic designs).

EGD topics are identified and prioritized by CMTTP through a structured process involving internal staff and external advisory groups. The criteria used to select high priority topics include disease prevalence, public health impact, unmet medical need, number of products or procedures under development, observed deficiencies in the quality and relevance of existing research, and economic impact. Potential topics are identified through review of horizon-scanning and health technology assessment reports and by consultation with clinical and research experts. A working group of patients, clinicians, payers, and clinical researchers assists CMTTP in developing a prioritized list of topics from a set of candidate topics that are identified using the sources and criteria described above.

More detailed information about topic selection and instructions on nominating a potential EGD topic for consideration is available at <http://www.cmtppnet.org/get-involved-1/topic-selection-process>.

Development Process

EGD recommendations are developed through an extensive consultative process involving a broad range of stakeholders and including mechanisms for broad public review and comment. A brief summary of this process is provided below, while full details about the EGD development process are <http://www.cmtppnet.org/cmtpp-research/guidance-documents/egd-development-process-and-overview/EGDProcess.pdf>.

After selecting a high priority EGD topic as described above, the initial work focuses on refining and focusing the topic, developing a clinical framework and completing a summary of the state of the evidence around this particular topic. This involves CMTTP conducting background research to identify leading clinical and research experts in the field as well as key documents (FDA guidance, clinical guidelines, methods papers, etc). The background research includes a substantial number of semi-structured interviews with content experts, contributing to the appointment of the Technical Working Group that is actively engaged throughout the remainder of the process. The Technical Working Group consists of 8-12 experts in clinical care and research methods specific to the clinical domain that is the focus of the EGD and also includes patient, clinician and payer representatives. CMTTP staff work closely with the Technical Working Group to develop a set of initial study design recommendations, the rationale for these recommendations, and references that support them. Recommendations, typically 10 to 12, are clear and actionable statements providing guidance on the specific questions (such as type of patient, outcome measures) and specific design issues that should

be considered in the design of maximally informative clinical studies. These recommendations serve as the foundation for the initial draft of the EGD.

Draft EGDs are made available for public comment through three primary mechanisms: 1) the document is circulated to a large group of individual and organizations that are likely to have an interest in the EGD topic, with a request that the draft EGD be further distributed by those that receive it; 2) the document is posted on the CMTP website along with a link to a survey to collect comments, and 3) CMTP convenes a methods symposium of 30-60 experts, stakeholders and decisions makers to address the most complex and controversial issues identified in the course of developing the EGD. All feedback on the draft EGD is reviewed by CMTP staff and the Technical Working Group in developing a “final” version of the EGD, which is posted on the CMTP web site and widely distributed. In face of rapidly changing evidentiary base and the importance of incorporating a wide range of views, EGDs are considered to be living documents. Once a final version is posted, CMTP continues to accept comments and suggestions on these recommendations, and EGDs will be updated as new scientific evidence, methodological advances and technologic improvements emerge.

Conflicts of interest

Members of the Technical Working Group are selected to represent a broad range of relevant expertise and perspectives, and are expected to have both strong intellectual biases and financial interests related to the topic under consideration. Such “conflicts of interest” are inherent in any multi-disciplinary, multi-stakeholder process, and it is understood that these conflicts are in some cases an important factor in the methodological views of the Technical Working Group members. There are multiple opportunities in the EGD development process for experts and stakeholders with a range of views to provide feedback on draft recommendations, and CMTP assumes final responsibility for capturing and distilling this range of viewpoints in the EGD recommendations.

CMTP has written conflict of interest guidelines for individual staff and the organization, which can be found at <http://www.cmtmpnet.org/cmtmp-research/Conflict%20of%20Interest%20Policy.pdf>. Funding for EGDs comes from unrestricted funds contributed to CMTP or from foundation grants and no funds from the life sciences industry or health plans are used for this work. CMTP is supported by unrestricted contributions from health plans and life sciences companies, government and foundation grants and contracts and meeting sponsorships. The sources and distribution of financial support for CMTP can be found at <http://www.cmtmpnet.org/about-cmtmp>.