Devices for Local Treatment of Chronic Wounds

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Goals and Objectives

- Describe clinical studies that provide decision makers with reasonable confidence a medical technology improves health outcomes
- Provide a technology-specific methodological roadmap for the design of prospective comparative effectiveness research.
- Facilitate a dialog among patients, clinicians, payers, policy makers, methodologists, and industry about evidentiary standards within a specific medical technology area

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Preface

Purpose

Effectiveness Guidance Documents (EGDs) provide specific recommendations to product developers and clinical researchers about the design of clinical studies that will produce evidence to inform decision making by patients, clinicians and payers. The goal is to describe clinical studies that would provide these “post-regulatory” decision makers with a reasonable level of confidence that the technology improves health outcomes. In this respect, they are intended to provide technology-specific methodological roadmaps for the design of prospective comparative effectiveness research.

The primary target audiences for EGDs are product developers and clinical researchers who are interested in designing clinical studies that will be informative to patients/consumers, clinicians and payers. They should also be useful to these decision makers themselves as they assess and appraise research that has already been conducted. They will be able to compare the design of available clinical studies to the recommendations contained in the EGD.

Each EGD is focused on a specific category of health care technologies-, for example, radiation therapy for cancer, cardiac imaging for diagnosis of coronary disease, gene expression profiling for breast cancer, mechanical interventions for chronic wounds. Methodological considerations for the design of clinical studies will be specific to defined categories of technologies, and recommendations for study designs can be more concrete and specific when targeted to a well-defined group of related technologies. For therapeutic interventions, the primary focus will be on evidence of comparative clinical effectiveness and for diagnostic intervention the primary focus will be on comparative clinical utility.

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 a comparable function for product developers and clinical researchers, but are focused on the design of clinical studies to support post-regulatory decision making. These post-regulatory decision include individual clinical decisions made by patients/consumers, clinical recommendations made by clinicians, clinical policies generated by medical professional societies, and reimbursement decisions made by payers. Because the FDA has regulatory oversight over all health care technologies, that organization is naturally positioned to develop guidance documents providing recommendations on studies intended for regulatory approval. Because there has not been a single organization that represents the universe of post-regulatory decision makers, CMTP is providing a forum in which study design recommendations can be generated reflecting the perspective of key decision makers (patients, clinicians, payers, and policy makers) in the design of comparative effectiveness research.

By including the relevant FDA regulatory experts in the EGD development process, it is hoped that EGDs will reflect optimal alignment between study design elements intended for regulatory approval and study design elements targeted to clinical and health policy decision making. This may help to reduce the need for multiple separate studies to address these different evidentiary purposes.
The EGD recommendations are not intended to describe the design characteristics of “gold standard” clinical studies. The recommendations aim to achieve a balance across a number of important considerations associated with these studies, including scientific validity, feasibility, time requirements cost. In other words, EGDs seek to achieve a balance between scientific consideration and practical considerations, recognizing the there is an inevitable trade-off between the level of certainty that can be achieved through clinical research with the cost/time/burden required to achieve that level of certainty. EGDs aim to strike a balance of a reasonable level of certainty at a reasonable level of burden. In order to determine what constitutes a reasonable balance, the process used by CMTP to produce EGDs (described in more detail below) integrates the perspectives of all knowledgeable and affected experts and stakeholders.

Because they do not describe “gold standard” studies, EGD recommendations are not intended to imply that further and more rigorous studies should not be done on any specific technology. Many important questions are likely to remain even after studies are completed that are consistent with the study design recommendations of the EGD, and further research will be valuable to pursue for most technologies. In some cases, coverage with evidence development will be a useful policy tool to facilitate additional studies of technologies for which there is evidence that meets the EGD recommendations.

**Funding**

The Center for Medical Technology Policy (CMTP) is a private, non-profit organization that provides a neutral forum in which patients, clinicians, payers, product developers and researchers can work together to improve the process for generating reliable and credible information about the real world risks, benefits and costs of promising new medical technologies. CMTP has been structured to be a transparent organization that engages with all key stakeholders while retaining complete independence in the formulation of its conclusions and recommendations. CMTP is funded through a diverse combination of sources; funding is not accepted from product developers or private insurers to develop EGDs on specific technologies. Since its inception, CMTP has received funding from the following sources:

- Aetna
- Agency for Healthcare Research and Quality (AHRQ)
- Amgen
- Blue Shield of California Foundation
- California Health Care Foundation
- Commonwealth Fund
- Institute of Medicine (IOM)
- Johnson and Johnson
- Kaiser Permanente
- National Pharmaceutical Council
- Pfizer
- United Healthcare

More information on CMTP’s mission and products can be found at: [http://www.cmtpnet.org](http://www.cmtpnet.org)
Purpose, Scope and Definitions

The purpose of this EGD is to provide recommendations to product developers and clinical researchers on the design of comparative effectiveness studies for devices intended for local treatment of chronic wounds. This EGD is relevant to chronic wounds including venous stasis ulcers, diabetic foot ulcers, pressure ulcers, and burn wounds.

Devices addressed by the recommendations in this EGD include, but are not necessarily limited to, negative pressure wound therapy (NPWT), electrotherapy and electromagnetic therapy, pulsed monochromatic light therapy, low level light laser therapy, low energy ultrasound therapy, and topical oxygen therapy (Cullum et al., 2001; Enoch et al., 2006; Leach et al., 2006; Bishop, 2008; Jull et al., 2008; Reddy et al., 2008; Ubbink et al., 2008). Topical therapies, biological agents, and systemic therapies are outside the scope of this EGD, and the study design recommendations discussed below were not developed with the intent of informing trial design for these types of interventions.

Throughout this report we use the definition for a chronic wound as one “that has failed to proceed through an orderly and timely series of events to produce a durable, structural and cosmetic closure” (Bradley et al., 1999). Chronic wounds may also be defined in terms of chronicity - that is, a wound that fails to respond to standard therapy within 30 days or has not resulted in the expected improved functional outcome (NPWT: Technology Assessment, 2009).

As noted in the preface to this document, the EGD recommendations are intended to reflect the type 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 objective is to describe features of study design, implementation and reporting that would provide these decision makers with a reasonable level of confidence that the technology improves health outcomes. The relative importance and weight assigned to each recommendation is characterized as “important”, “strongly preferred” or “preferred”. Different decision makers may weigh these individual characteristics of studies differently, and the EGD attempts to integrate input from the full range of potential decision makers. The recommendations are not intended to comprehensively address every potential aspect of trial design, and should not be used as a all-inclusive “recipe” for protocol development. Because each recommendation in the EGD reflects the views of at least one important category of decision makers, it will be useful for clinical researchers and product developers to have a clear rationale for designing studies that deviate from these recommendations. Finally, because the EGD recommendations reflect what would produce a “reasonable level of confidence” for decision makers, it will generally be the case that additional clinical research will almost always be useful.
Guidance Recommendations

1. TECHNOLOGY

Describe the device clearly and use the same device model for all study subjects (IMPORTANT)

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.

Special training, experience or credentialing requirements that were applied in selecting providers using the technology during the study should be described in the study protocol.

2. PATIENT POPULATION

Clearly describe the patient population enrolled in the study and the intended target population for the technology (IMPORTANT)

A. Characteristics of the Target Study Group

The goal of comparative effectiveness research is to provide evidence that reflects the health outcomes that can be expected when applied to typical patients in typical clinical settings (IOM, 2009). It is therefore desirable to enroll a broad range of patients in these studies with the minimum possible exclusion criteria, which will enhance generalizability of the results. Correct interpretation of these studies requires that the study population is clearly described, along with a discussion of the degree to which it represents the patient population of interest.

In selecting the study patients, the following considerations may be applied:

- **Definition of chronic wound**: Subjects must have had the wound open for at least 4-6 weeks from the first day that they are seen for a trial screening visit. Ulcers which decrease in area by >30% during the 2 week run-in period should not be enrolled in the trial.

- **Wound Type**: Studies that include a single type of chronic wound are most straightforward to interpret and should be strongly considered (i.e. all enrolled patients would have the same wound type - venous ulcers, diabetic ulcers, pressure ulcers, burns). As an alternative, studies could enroll patients with multiple wounds when all
wounds are known to share a common etiology of wound healing failure, and the technology being studied is specifically targeted to address the shared etiology of failure to heal. It would be important to have identified the presumed shared etiology of the multiple wound types in advance. For such studies, it is important for the researchers to show both aggregate results across all wounds, and also show results separately for each type of wound.

- **Patient Clinical Characteristics:** The clinical characteristics of the patients enrolled in the trial should be representative of the patients with the type of wound under study. Inclusion of patients with common major co-morbidities and relevant risk factors that could affect healing should be strongly considered, and should be accompanied by *a priori* plans for subgroup analysis based on these factors. Risk factors that could slow healing include, but are not limited to: cardiovascular disease, diabetes, obesity, PVD, systemic steroid or immunosuppressant use (as in diabetic transplant recipients) and smoking. Furthermore, it is important to describe in detail the chronicity and severity of their wounds (e.g., requirement of surgery and prior therapy).

- **Patient Demographics:** The demographic mix (e.g., white versus nonwhite, age stratification, gender) of the study patient population should be clearly documented and described. When appropriate, due to epidemiological considerations of prevalence or incidence of wound types or underlying conditions, pre-specified patient populations may be oversampled. Given the potential importance of genetic and molecular predictors of response to treatment, collection of biological samples that would allow molecular characterization should be strongly considered.

- **Setting of Care:** The setting of care for the study (hospital, long-term care, home, clinic) should be described. If there are significant differences in settings of care at different research sites, plans for subgroup analysis should be considered. In addition, the rationale for including a variety of settings in the study (e.g., patients with the study wound type may receive wound care across settings of care by different care providers) should be provided.

- **Exclusion criteria:** In general, it is important for exclusion criteria to be minimized to the greatest extent possible, and a specific explanation should be provided for each exclusion criterion for which the rationale is not self-evident. Patients with chronic wounds often have several chronic co-morbidities, and automatic exclusion of such patients would limit the generalizability of study results. A number of exclusion criteria would be commonly expected for most studies of chronic wound treatments, including:
  
  - Allergy or other specific contraindication to one or more components of the study intervention
  - Psychiatric patients whose clinical status would significantly impair compliance with the therapy or the ability to collect follow up data
  - Other patient characteristics or circumstances that would impair reasonable compliance with any aspect of wound care
  - Malignancy in the wound.
  - Systemic sepsis
  - Connective tissue disease unless one of the goals of the study is to assess the impact of this risk factor.
  - Simultaneous treatment with other experimental wound care procedures, biologics, or devices, unless an appropriate control group is included.
B. Characteristics of a Control Group

i. **Comparison with standard care** (defined below): 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.

- Investigators should strongly consider providing control group patients and intervention group patients with standard care that follows widely accepted, evidence-based clinical guidelines developed for clinicians who manage chronic wounds. The study protocol should provide a detailed description of the elements of usual care provided to patients in the trial, and an explanation of any significant deviations from standard care for either control group or intervention patients enrolled in the study. Currently, the following elements of standard care should be strongly considered for inclusion in the clinical management of both control and intervention patients (FDA, 2006; Sawaya et al., 2007; Bolton, 2004):
  - Debridement of necrotic or infected tissue.
  - Infection control
  - Nutritional support
  - Maintenance of a moist wound environment (with protective dressings over pressure ulcers and moisture-permeable dressings over diabetic and venous ulcers).
  - Weight off-loading (pressure and diabetic ulcers)
  - Compression therapy (venous stasis ulcers)
  - Blood glucose control (diabetic ulcers).

In developing a control group for comparison in these studies the following points should be considered:

- Patients in the control group should be similar to the treatment group with regard to characteristics such as wound size, wound chronicity and etiology, co-morbidities, age, and sex. Therefore, the control group and intervention group should be selected from the same pool of patients.

- Both intervention and control groups should follow the same protocol with respect to additional concomitant treatment; e.g., if pain is an outcome to be measured, pain medication regimens should be similar for both groups.

ii. Placebo control or sham treatment control may both be considered, if the technology under study lends itself to placebo or sham. It is also acceptable when the technology is intended to be an add-on to, rather than a replacement for, standard care. In this situation, both groups would also receive identical standard care.

iii. Using patients as their own controls is not recommended. Studies that use this approach should provide a strong rationale for selecting this design, as well as a discussion of the barriers to conducting alternative designs that provide more reliable comparators.
iv. An active comparison group is important for studies that are intended to demonstrate significant clinical differences between two or more active interventions (those that include novel treatment modalities that are not considered part of standard wound care). Such studies should also include a standard care comparison arm if there have not yet been definitive studies demonstrating that at least one of the active interventions is superior to usual care alone.

3. STUDY SITE

Multi-center trials are more desirable than single center trials. (STRONGLY PREFERRED)

For studies conducted at single centers, it would be important for the investigators to provide a rationale for limiting the trial to a single institution, and to provide some discussion about why the trial results might be generalizable to other investigational and clinical care settings. Multicenter trials are strongly preferred because they provide better ability to generalize trial findings to other investigational and clinical care settings (ICH, 1998). The following recommendations apply to the conduct of multicenter trials in general (ICH, 1998) and to multicenter trials planned to assess effectiveness of novel devices for the local treatment of chronic wounds in typical community practice:

• Reasonable efforts should be made to enroll sufficient numbers at each site to evaluate potential differences in outcomes across sites, particularly when there are significant differences in expertise across sites, if a high degree of protocol standardization is not feasible, or if the same mix of patient characteristics at all centers is not feasible.

• The majority of sites should offer other interventions in addition to the one being studied.

• 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.

• All participating sites should follow a common protocol and reasonable effort should be applied to ensure that procedures are performed in a standard fashion.

• Patient demographic and clinical characteristics should be compared across sites to ensure that there are no major differences in the distribution of patient characteristics across centers.

• Statistical methods that allow testing for differences across study sites should be considered. Data from different centers may be combined if there is no significant heterogeneity among centers.

4. STUDY DESIGN CONSIDERATIONS

A randomized controlled trial (RCT) design is always the desired design unless specific barriers to the conduct of such a trial are identified and explained. Blinding is an
additional mechanism to control for bias for the evaluation of complete and partial wound closure, but not for wound recurrence. (STRONGLY PREFERRED)

High quality prospective comparative studies without randomization may be considered in situations when randomization is not feasible, and where sufficient baseline information is available to allow for sophisticated statistical methods to adjust for potential differences in patient characteristics.

A. Randomization and use of controls

A randomized controlled trial (RCT) design is strongly recommended unless there is strong evidence 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.

If using a RCT design, standard computerized randomization should be employed, and stratified randomization should be used for subgroup analyses as needed. If appropriate and feasible (as a method of allocation concealment), blinding should be considered, as discussed below in greater detail.

Non-randomized, comparative prospective studies may be considered, as long as they are designed based on an a priori hypothesis. For these trials, advanced methods to adjust for possible baseline differences, including instrumental variable analysis and propensity scoring should be used. The quality of data collected for these studies should be comparable to other clinical trials data.

Studies that retrospectively analyze routinely collected data such as claims and EMR data are not recommended as a reliable method to assess the comparative effectiveness of novel treatments for chronic wounds, though such methods may be useful to identify potentially beneficial treatments and strategies.

B. Blinding

Blinding is recommended for the evaluation of complete and partial wound closure, but not for wound recurrence. 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 completely blind patients and clinicians to their treatment assignment with some interventions, 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. Patient blinding is strongly recommended for assessment of primary outcomes, and is particularly important for valid assessment of patient reported outcomes, such as quality of life (QOL) and symptom assessment.

In circumstances when blinding may be particularly challenging, such as for hyperbaric oxygen therapy and for studies involving limb salvage, it is important for the researchers to explain these considerations in the study protocol and report, and to discuss how the lack of blinding might impact the study results.
C. Bayesian study design and analysis may be considered where the historical control is the basis of the prior distribution. Testing against an optimistic and pessimistic prior with a contemporaneous control is an accepted model.

When as adaptive design is used, the following provisions should be strongly considered (Chow and Chang, 2008; Coffey and Kairalla, 2008; FDA: Guidance for Industry, 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.
- Obtain consensus from an outside party for any retrospective adaptation, which should be conducted before unblinding. Switching from a superiority to a noninferiority 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.

5. SAMPLE SIZE CONSIDERATIONS

The sample size should be derived from calculations on the expected magnitude of the differences in outcomes between treatment groups, the type of predictor and outcome variable and appropriate statistical test, and the hypothesis (null versus superiority).

(IMPORTANT)

A. Superiority versus Equivalence / Noninferiority:

The use of superiority versus noninferiority/equivalence studies has been an issue of debate (Gøtzsche, 2006; Kaul and Diamond, 2006; Farjah and Flum, 2007).

The following points should be considered:

- If a study uses 1-sided hypothesis testing, a lack of evidence to support superiority does not establish noninferiority or equivalence because the possibility of inferiority cannot be excluded (Farjah and Flum, 2007).
- With the use of a 2-sided 95% confidence interval, superiority can be assessed within a noninferiority trial. The same trial can assess noninferiority or equivalence for some outcomes and can assess superiority for other outcomes (e.g., complication rates). While this seems to be a more cost-effective and efficient approach to gather research data, the flexibility of this design permits manipulation of the data (Gøtzsche, 2006).
- Noninferiority studies should therefore follow established standards and report all steps of the analysis in detail, and must include the following components (Gøtzsche, 2006):
Defined noninferiority/equivalence margins (IMPORTANT: These margins should be small. If the margins are too large, an inferior treatment may falsely appear to be noninferior or equivalent.)

- Sample size calculations based on these margins.
- Both an intent-to-treat and per-protocol analysis.
- Confidence intervals for the results.

B. Power Recommendation:

Power of \( \geq 80\% \) is recommended to establish superiority with respect to the primary outcome or study endpoint. Superiority is defined as producing a clinically meaningful treatment effect. Convention dictates 80\% to 90\% power to detect expected differences in outcome.

If incidence of complete wound closure at 12 weeks is the primary outcome, the study should be powered to detect 20\% superiority (absolute percentage-point difference). (See section 6 for more on recommended outcome measures.) Previous multicenter RCTs have defined a 20\% absolute difference in rate of healing at 16 weeks as clinically significant (Armstrong and Lavery, 2005; Blume et al., 2008). (A sample size of 206 had 80\% power to detect this difference in the 2008 study by Blume and colleagues.)

Sample size based on power calculation for the primary endpoint should be adjusted to account for the expected patient dropout rate so that adequate power is retained.

6. OUTCOME MEASURES AND ENDPOINTS

Clearly define how outcomes will be measured and the time points for measurement so that endpoints are assessed in a standardized manner across all sites. Calculate power to detect clinical and/or statistical significance on the primary (key) endpoint(s).

(IMPORTANT)

The outcome measures discussed below have been identified as the most valid and meaningful patient-centered outcomes, after a review of the clinical research literature on wound healing (Argenta and Morykwas, 1997; Müllner et al., 1997; Philbeck et al., 1999; Mouës et al., 2005; Armstrong and Lavery, 2005; Braakenburg et al., 2006; Stannard et al., 2006; Vuerstaek et al., 2006; Armstrong et al., 2007; Frykberg and Williams, 2007; Kim and Hong, 2007; Blume et al., 2008; Körber et al., 2008).

In some circumstances, the purpose of a wound intervention may be for reasons other than healing (for example, management of exudate, wound debridement, reduction of pain at dressing changes), and the primary outcome measure selected for any wound study should be appropriate to the intended purpose of the intervention. It is important that the study protocol state clearly what the primary intent of the wound care treatment and provide the rationale for the selection of the outcome measures selected to reflect the primary intent of the treatment. Selection of one of the primary outcomes discussed below should be strongly considered.

Wound size is measured in different ways: length, width, and perimeter (Kantor and Margolis, 1998) or area, the most commonly reported measurement in clinical trials (Sheehan P, et al., 2003; van Rijsijk and Polansky, 1994; van Rijsijk, 1993).

A. Primary (key) Endpoints:
Use one or more of the following primary endpoints is strongly recommended:

- Incidence of complete wound closure at 12 weeks. Complete wound closure is defined as complete reepithelialization, lack of exudate, and no continued need for wound dressing. These parameters were derived from multicenter RCTs that have used a composite outcome measure (Armstrong and Lavery, 2005; Blume et al., 2008).
- Average time to complete wound closure.
- Success of secondary wound closure. The definition of this outcome depends on the procedure; an example is graft take rate.
- Reduction of amputations (foot for diabetic ulcers only)

Wound healing trajectories may be considered as a surrogate outcome, however a clear explanation for the use of this surrogate should be provided by the investigators.

There is excellent data on the 4-week change in wound area change as a potential surrogate endpoint (Margolis et al., 2003). Use of this endpoint may be considered, but should be accompanied by a rationale for its use as a primary outcome, rather than a more direct measure of complete wound healing.

Area measurements are recommended for shallow wounds, whereas volume measurements are recommended for deep wounds (Gelfand et al., 2002; Goldman and Salcido, 2002; Margolis et al., 2003; Hill et al., 2004; Kolesnik and Fexa, 2005; Steed et al., 2006; Margolis and Mani, 2007; Quan et al., 2007; Ahn and Salcido, 2008; Cardinal et al., 2008; Lavery et al., 2008; Coerper et al., 2009).

Evaluation of wound size is best assessed by two blinded raters. Investigators should strongly consider measuring and reporting the rate of inter- and intra-rater agreement. Any statistically significant difference for either inter- or intra-rater disagreement should be discussed in the study report. The method for resolving discrepancies should also be clearly described.

B. Secondary Endpoints

Each of the following secondary outcomes may be considered in wound healing trials, depending on the primary and secondary intent of the intervention:

i. Complication rates that may be useful to report in wound healing trials:
   - Death.
   - Infection (aerobic and anaerobic).
   - Pain during dressing changes.
   - Fistula formation.
   - Any type of therapy-specific complication (e.g., aural barotraumas in hyperbaric oxygen therapy).
   - Wound recurrence rate at 12 months (Vuerstaek et al., 2006)

A number of disease-specific scales have been developed for symptoms, quality of life and functional status for patients with chronic wounds. The scales recommended below are widely recognized and validated instruments and/or have been used in previous wound care research (as indicated by citations). Using scales that have been used in
previous wound therapy research helps with the interpretation of research findings and allows decision makers to compare different therapies along the same dimensions.

The following domains of quality of life may be thought of as patient reported outcomes (PROs). An a priori definition of what constitutes a completed instrument is strongly recommended.

- **Pain, 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).
  - 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).

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

- **Quality of Life (QOL):**
  - 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).
  - EuroQol (utility weights) (Vuerstaek et al., 2006; EuroQol, 2008).

- **Depression scales:**
  - Beck’s Depression and Anxiety Inventories (BDI) (Richter et al., 1998; Leyfer et al., 2006).
  - Major Depression Inventory (MDI) (WHO, 1998b).
  - Hospital Anxiety and Depression Scale (HADS) (Jones et al., 2006).
  - Center for Epidemiologic Studies Depression Scale (Roth et al., 2004).
7. LENGTH OF FOLLOW-UP OR STUDY DURATION

The length of follow-up should be sufficient to ascertain that differences between the novel mechanical intervention and standard therapy do not reflect a short-term advantage while ultimate healing rates are unchanged. (IMPORTANT)

The following length of follow up is recommended for assessing primary endpoints:

- Minimum 12 weeks to assess incidence of wound closure, with exceptions as noted in the discussion of surrogate endpoints above.
- 12 months of follow up of patients is recommended to assess recurrence of the same wound (Vuerstaek et al., 2006).
- Loss to follow-up: High quality trials should be able to provide data on the primary outcomes for ≥ 90% of patients enrolled. If drop-out rates are greater than 10 percent, an explanation for this should be provided, as well as a discussion of the potential impact of the missing patients on the study results.
- Stopping rules: An interim analysis should be planned and definitive criteria defined a priori. If interim results show the novel technology to be superior to standard treatment and its use would prevent otherwise irreversible severe health outcomes (e.g., amputation), then it may be necessary to stop the trial. Premature termination is also advised when the novel technology is associated with significantly higher rates of severe, irreversible complications (e.g., death, drastic increase in wound size and/or wound severity). Every trial should therefore develop a priori stopping rules describing circumstances in which a patient would be harmed. Blinding of the investigators has to be maintained (ICH, 1998).

8. REPORTING ISSUES

For RCTs, follow the CONSORT guidelines (Altman et al., 2001) and the extensions for pragmatic RCTs (Zwarenstein et al., 2008). (STRONGLY PREFERRED)

The following steps are important and should be considered:

- **Register RCTs with ClinicalTrials.gov Database.** Posting trials on this website during recruitment is an important way of maintaining transparency and allowing stakeholders to monitor publication of results.
- **Provide complete data for all outcome measures.** Failure to report results from some outcome measurements can lead to biased conclusions. Furthermore, the appearance of investigator bias can be reduced if the publication includes complete data sets for all outcome measures and follow-up dates. Otherwise, the reader may suspect that these data did not support the clinical effectiveness and safety of the technology in question and that only positive data were included in the publication.
- **Account for missing data.** Reporting the nature of, quantity, and reasons for missing data helps clarify how reliable the study results are. Missing data may result when study participants choose to drop out of a study or are unavailable for one or more follow-up dates. In this situation, use the last observation carried forward (LOCF) method. Also, present separate analysis to show whether conclusions would change if dropouts who showed wound healing at last observation were counted as wound recurrence.
• **Use intention-to-treat (ITT) analysis.** ITT analysis counts patients in the treatment group to which they were originally assigned. This is especially important for the type of research addressed by this EGD—clinical effectiveness research. In actual practice, some patients or clinicians will switch to another treatment or discontinue treatment for various reasons. ITT allows an assessment of the level of effectiveness to be expected in a population represented by the study group.

9. **CONFLICTS OF INTEREST / MINIMIZING INVESTIGATOR BIAS**

*Address conflicts of interest in the conduct and publication of studies. (IMPORTANT)*

If a manufacturer funds the study, an impartial clinical trial management company should be engaged.

Other points to consider include:

• At the completion of the study, all investigators should have full access to the study data.
• Findings should be published in the peer-reviewed medical literature.
• The principal investigator (PI) should not have financial interest in products being studied, other than compensation for conducting studies.
• Participating investigators and institutions should not have a financial stake in the success of the product, e.g., stock or patents.
• All financial ties of investigators to product(s) being investigated should be disclosed.
• Report negative as well as positive results.
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