Electrical Stimulation or Electromagnetic Therapy as Adjunctive Treatments for Chronic Skin Wounds

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Executive Summary

The objective of this Assessment is to determine whether electrical stimulation and/or electromagnetic therapy are effective adjunctive treatments for chronic skin wounds. Chronic skin wounds are defined as wounds of at least 8 weeks in duration that fail to heal with standard therapy. They are common and associated with a high burden of illness. Electrical stimulation and electromagnetic therapy are proposed as adjunctive treatment modalities for skin wounds that do not heal after an adequate trial of standard therapy. Electrical stimulation involves the direct application of an electric current to the area of a skin wound; electromagnetic therapy is a related treatment that uses an electromagnet to generate an electrical current. Both of these treatments have been shown to induce a variety of physiologic responses in both in vitro and animal models that may promote wound healing.

This Assessment will focus on randomized, controlled trials (RCTs) comparing standard wound care plus either electrostimulation or electromagnetic therapy to standard wound care alone. RCTs are essential in determining the efficacy of therapies for wound healing because of the variability in the natural history of wounds and the potential confounding factors in healing. The most important clinical outcome is complete wound healing as measured by the percent of wounds that heal completely and/or the time to complete healing. Secondary outcomes such as decrease in the size of the wound (healing rate), pain, quality of life, and facilitation of surgical closure are less useful, but will also be considered in the review of evidence.

Based on the available evidence, the Blue Cross and Blue Shield Medical Advisory Panel made the following judgments about whether electrical stimulation or electromagnetic therapy as an adjunctive treatment for chronic skin wounds meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria:

1. The technology must have final approval from the appropriate governmental regulatory bodies.

No electrical stimulation device or electromagnetic therapy device is currently cleared or approved by the U.S. Food and Drug Administration (FDA) for the specific indication of wound healing. A number of devices have been cleared for marketing for other indications. Use of these devices for wound healing is an off-label indication.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The evidence is not sufficient to permit conclusions on the efficacy of electrical stimulation or electromagnetic therapy as adjunctive treatments for wound healing. The body of evidence for electrical stimulation and electromagnetic therapy consists of numerous small RCTs (n=10 for electrical stimulation; n=5 for electromagnetic therapy). To conclude that either of these technologies is an effective

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adjunctive treatment for wound healing, the body of evidence must have certain properties. Well-designed and well-conducted sham placebo-controlled RCTs are needed that consistently show better outcomes for active treatment over placebo, reflected in statistically and clinically significant results. The available evidence does not convincingly demonstrate that electrical stimulation or electromagnetic therapy results in clinically significant improvement in the most important outcome, i.e., the percent of patients that heal completely.

Wound healing treatment trials must show that an intervention has efficacy independent of the many confounding factors and the variable natural history of the disorder. Such trials will ideally have the following features: 1) enroll patients with one type of wound; 2) assess patients on a wide range of baseline characteristics, and demonstrate that potential confounders are equally distributed among groups; 3) use a double-blind design, with a sham placebo control; 4) ensure that optimal standard care is delivered to both treatment and control groups; 4) report on the percent of patients with complete healing, and/or time to complete healing; 5) assess outcomes in an independent, blinded fashion; and 6) follow up patients for at least 3 months to assess complete healing and recurrences.

Electrical Stimulation. Only 5 of 10 electrical stimulation studies report on the key health outcome, complete healing. The other 5 studies found statistically significant advantages for electrical stimulation in percent reduction in ulcer size, with follow-up periods ranging between 3 weeks and 8 weeks across studies. While greater change in wound size suggests better healing with electrical stimulation, follow-up is generally short, and this outcome is not a substitute for measuring the incidence and timing of complete healing. Only 2 of the 5 studies that reported complete healing found results that significantly favored electrical stimulation. The strongest study included 71 patients, and there was confounding of baseline characteristics favoring the control group. Adjustment for confounders was not employed but the proportion of complete healing at 8 weeks was 58% in the electrical stimulation group and 3% in the placebo group ($p<0.0001$). The other study (n=64) achieving statistical significance had more significant flaws: confounding of unclear direction, no statistical adjustment, and high overall loss to follow-up (20%). At 12 weeks, 42% in the electrical stimulation group achieved complete healing, compared with 15% in the placebo group ($p<0.05$).

A study of 80 patients with 192 wounds showed a pattern of higher complete healing with electrical stimulation, but confounding of unclear direction was present and no statistical test results were given. The 2 remaining studies do not provide support for the efficacy of electrical stimulation. In both, confounding appeared to favor electrical stimulation, but neither found a statistically significant result. While some of the results from electrical stimulation trials are favorable, methodologic flaws were common, and statistical significance was achieved in only 2 studies reporting on the primary outcome of complete healing.

Electromagnetic Therapy. For electromagnetic therapy, the evidence follows a similar pattern, with a lesser quantity of evidence. Of the 5 available studies, 3 report on the outcome of complete healing, and only 1 study reports statistically significant differences in favor of the electromagnetic therapy group. One of the 5 studies reports a shorter mean time to healing for the electromagnetic therapy group. Three of the 5 studies report a larger decrease in wound size for the electromagnetic therapy group, and 2 studies report better pain scores for the electromagnetic therapy group.

The results suggest that electrical stimulation and electromagnetic therapy may promote wound healing or some aspect(s) of wound healing, but considerable uncertainty remains as to whether these modalities lead to clinically significant health outcome benefits, given various flaws in how studies were conducted. To demonstrate efficacy for these treatments, larger, well-conducted, randomized, controlled trials are needed. These trials should focus on one type of wound, demonstrate baseline comparability on important confounders, and account fully for dropouts. Statistical analysis should include both multivariate approaches to controlling for confounders and methods to account for loss to follow-up. The outcome of complete healing should be the primary outcome in these studies, and follow-up should be long enough to assess recurrences.

3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives.

The evidence does not permit conclusions as to whether electrical stimulation or electromagnetic therapy as an adjunctive treatment for chronic skin wounds improves health outcomes or is as beneficial as established alternatives.

5. The improvement must be attainable outside the investigational settings.

Whether electrical stimulation or electromagnetic therapy as an adjunctive treatment for chronic skin wounds improves the net health outcome has not been established in the investigational settings.

Based on the above, electrical stimulation or electromagnetic therapy as an adjunctive treatment for chronic skin wounds does not meet the TEC criteria.

Contents

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Assessment Objective

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Background

Wounds and Wound Healing

A 2004 Technology Evaluation Center (TEC) Evidence-based Practice Center (EPC) evidence report for the Agency for Healthcare Research and Quality (AHRQ) on newer wound-healing technologies (Samson et al. 2004) reviews in detail the etiology, pathophysiology, standard treatments, and methodologic issues in wound-healing research. This Assessment will briefly review these background concepts of wound healing; readers are referred to the 2004 TEC EPC AHRQ evidence report (Samson et al. 2004) for further detail.

Definition and Classification of Skin Wounds/Ulcers. Skin ulcers are a heterogeneous and complex group of disorders with a variety of apparent causes (Pierce 2001). Approximately 70% are due to pressure ulcers, diabetic ulcers, and vascular ulcers (Valencia et al. 2001; Stadelman et al. 1998a). Other less-frequent causes include inflammatory conditions, malignancies, burns, and radiation injuries (Valencia et al. 2001). Often the causes of ulcers are multifactorial, such as in the diabetic patient who has both arterial insufficiency and peripheral neuropathy (Valencia et al. 2001). Chronic wounds are defined as wounds of at least 8 weeks in duration that have failed to proceed through an orderly and timely process that produces anatomic and functional integrity (Lazarus et al. 1994). Chronic wounds either require a prolonged time to heal, do not heal completely, or recur frequently.

Mechanisms/Phases of Wound Healing. There are 3 phases of wound healing: inflammation, proliferation, and remodeling (Steed 2003b, Harding et al. 2002). These phases are distinct but overlap in time during the healing process. Nonhealing wounds are often "stuck" in one of these stages, usually continued inflammation or proliferation (Douglas 2003; Henry and Garner 2003). There are a large number of factors that can impede wound healing and may predispose a patient to the development of chronic wound(s) (Steed 2003b; Williams and Barbul 2003). These include both systemic factors (poor nutrition, metabolic derangements, and drugs) and local factors (tissue hypoxia, infection, dry wound bed) (Stadelman et al. 1998b). Identification of the specific factors that impair healing may help direct therapy in cases in which the identified culprits are treatable (Pierce 2001).

Standard Treatment of Chronic Skin Wounds. Optimal management of wounds starts with prompt recognition and accurate diagnosis to properly treat wounds at the earliest stage possible. Standard treatment for established wounds incorporates common principles that apply to the management of all wounds, combined with treatment modalities targeted to each type of wound and the patient's clinical characteristics (U .S. Food and Drug Administration 2000; Lionelli and Lawrence 2003; Steed 2003a) (Table 1). Surgical intervention, such as skin grafting, is often considered for wounds that do not heal with standard treatment (de Araujo et al. 2003; Valencia et al. 2001).

Table 1. Overview of Components of Standard Care for Skin Wounds

	Wound-specific Treatments			
Common Treatments	Pressure Ulcers	Diabetic Ulcers	Vascular Ulcers	Burns
– Debridement of necrotic or infected tissue – Maintenance of a moist wound environment – Control of infection, and – Nutritional support	– Weight off-loading – Regular repositioning – Protective dressing(s) – Unna boot – Bowel/bladder care for patients at risk for contamination	– Weight off-loading – Moisture-permeable dressing – Blood glucose control – Unna boot	– Moisture-permeable dressing For venous ulcers: – Compression therapy – Elevation of legs For arterial ulcers: – Establishment of adequate circulation	– Hemodynamic resuscitation – Management of comorbidities – Infection control – Pain control – Nutritional support – Rehabilitation

In clinical practice, there is a high degree of variability in wound treatment, and evidence that standard wound care deviates substantially from optimal guidelines (ECRI 1996). The setting in which wounds are treated varies widely, from home treatment to specialized wound treatment centers, and this may have a large influence on the specific type and intensity of treatment provided. Thus, patients who present with nonhealing ulcers may not have received similar prior care. It is possible that many of these "nonhealing" ulcers may actually heal with an adequate trial of optimal care. The variability in prior care is also a concern for clinical trials, since this variability contributes to the heterogeneity of the study sample.

Methodologic Issues in Wound Healing Research

Natural History of the Disorder. There is a large amount of variability in the natural history of chronic skin wounds. Most wounds heal spontaneously; however, some do not heal in spite of intensive treatment. Refractory wounds are defined as those that do not heal after an adequate trial of standard care. However, since standard care varies widely in actual practice, it is difficult to determine whether a patient has actually received an adequate course of standard treatment, and whether a nonhealing wound should truly be called "refractory."

In controlled trials, a relatively large proportion of "refractory" wounds heal with standard treatment (control arm). In 2 recent RCTs of bioengineered skin substitute versus standard care (Falanga et al. 1998; Veves 2001), 38% and 49% of "refractory" ulcers, respectively, healed completely in the standard-care arm. Even in wounds present for at least 1 year (Falanga and Sabolinski 1999), a substantial minority (19%) healed with standard treatment.

Therefore, it is difficult to interpret outcomes from single-arm trials that lack a control group, since improvement may be related to the natural history of the disorder rather than the treatment provided. Single-arm trials also cannot determine the effect of other nonspecific factors. These nonspecific effects can be numerous, incorporating such factors as the increased intensity of treatment associated with enrollment in a clinical trial, and the placebo effect. Also, the multiple local (e.g., size/depth of wound, presence of infection) and systemic (e.g., age, functional/nutritional status, comorbid illness) factors having an impact on wound healing (Harding et al. 2002), are all potential confounders in clinical trials.

Randomized, controlled trials are the best way to minimize the impact of these methodologic issues, and thus to determine the incremental improvement in healing attributable to a specific treatment. Randomized treatment assignment is the best way to minimize the possibility that confounding factors will be unequally distributed among groups. A concurrent control group is the best way to determine the incremental improvement of a specific treatment above any nonspecific effects of a trial.

The U.S. Food and Drug Administration (FDA) issued a draft guidance document on methodologic issues in wound healing that affirmed the necessity of high-quality RCTs in determining the effectiveness of proposed therapies (U.S. Food and Drug Administration 2000). This document included a number of specific recommendations for the performance of RCTs in this area, as outlined in the following paragraphs.

The study population should ideally consist of patients with one particular type of skin wound, because of the different pathophysiology of each type of wound and potential differences in response to therapy. A standardized definition of an adequate course of optimal care should be used to enroll a population that is truly "refractory." Thorough assessment prior to treatment is important in accurately characterizing the features of the wound and in measuring potential confounders of outcome. Accurate recording of wound size, depth, and duration are especially important since these are major predictors of healing (de Araujo et al. 2003). Other potential confounders include patients' clinical and demographic characteristics, comorbid medical conditions, and prior treatment received.

Double-blinding of treatment is the optimal study design to minimize bias in treatment delivery and outcome assessment. A sham placebo should be considered in the control arm to allow for double-blinding. It is also important to ensure that standard treatment modalities are identical between groups to avoid performance bias. The experimental treatment arm should not include additional elements of standard care that are not delivered to the control group, nor incorporate a greater intensity of standard care.

The importance of equal intensity of care was demonstrated in a prior multicenter trial of platelet-derived growth factor for chronic wounds. In this study, the rate of healing was significantly higher in centers that incorporated more frequent debridement (Cross and Mustoe 2003).

Outcome measurement should focus on outcomes that are quantitative and clinically meaningful (Steed 2003b; Jeffcoate and Harding 2003). The most important outcomes to be considered are the percent of patients with complete healing and time to complete healing. Other outcomes that may also be clinically meaningful are 1) facilitation of surgical wound closure, 2) change in wound size, 3) improved cosmesis, 4) improved activities of daily living (ADL), 5) improved quality of life, 6) pain, 7) transcutaneous oxygen tension, 8) infections, and 9) need for debridement. Ascertainment of outcomes should be ideally performed by an independent, blinded individual. This is especially important in situations in which patients and/or treating physicians are not blinded to treatment.

Electrical Stimulation and Electromagnetic Therapy

Electrical stimulation involves the placement of electrodes in direct contact, or in close proximity, to a skin wound, thereby creating an electrical current that passes through the wound. The use of electrical stimulation as an adjunctive treatment for wound healing has been proposed for many years, since the recognition that the skin possesses an electrical field and that the presence of a wound disrupts this electrical field.

The application of electrical current results in a variety of physiologic responses. In vitro experiments have established that many human cell types involved in wound healing, including granulocytes, macrophages, and keratinocytes, migrate toward an electrical field, a phenomenon termed “galvinotaxis” (Braddock et al. 1999; Ojingwa and Isseroff 2002). In vitro studies have also shown an increase in protein synthesis and incorporation of DNA precursors into cells when fibroblasts are exposed to an electrical current (Ojingwa and Isseroff 2002). More recently, it has been demonstrated that an electrical current induces the production of vascular endothelial growth factor (VEGF), thus stimulating angiogenesis (Zhao et al. 2004). Animal studies have demonstrated that treatment with electrical stimulation results in an increase in the number of fibroblasts, increased collagen production, and greater tensile strength of wounds. These physiologic changes have been accompanied by an increased rate of wound closure in animal models (Ojingwa and Isseroff 2002).

In clinical practice, there is substantial variability in regimens for delivering electrical stimulation treatment. The current may be one of several types (Ojingwa and Isseroff 2002): 1) direct current, defined as continuous and unidirectional in flow from the cathode to anode; 2) pulsed current, defined as short bursts of direct current followed by interval periods of no current; 3) alternating current, defined as a current that changes direction frequently from positive to negative. Because the skin has high resistance to electrical current, there is a greater risk of thermal skin injury with direct current than with the other modalities. For this reason, pulsed current is more commonly used than direct current. Alternating current is used in some currently available devices such as transcutaneous electrical nerve stimulation (TENS) units, and these have been adapted for use in wound healing.

There may also be variability in the dose, frequency, and duration of electrical stimulation treatment. The electrical stimulation dose that is applied varies, and the precise amount of current that reaches the wound may also differ according to the exact placement of the electrodes. Some treatment regimens specify multiple treatments per day, while others treat only several times per week. The duration of treatment also varies, with no standardized treatment length. In clinical trials, it is common to continue the treatment throughout the course of the study or until complete healing.

Electromagnetic therapy is a related therapy, with some distinct differences. This approach utilizes nonthermal pulsed electromagnetic energy to create an electrical current. The application of electromagnetic energy has been shown to cause many of the same tissue and cellular effects seen with the direct application of an electrical current. These include increased blood flow, collagen formation, granulocyte infiltration, and phagocytosis (Salzberg et al. 1995b).

There are a variety of other emerging, alternative and/or adjunctive treatments for skin

ulcers that are in various stages of development (Lionelli and Lawrence 2003; Petrie et al. 2003; Cross and Mustoe 2003; Eming et al. 2002). These include 1) topical growth factors, 2) bioengineered skin products, 3) vacuum-assisted wound closure, 4) therapeutic ultrasound, 4) novel dressings (hydrocolloids, alginates), 5) hyperbaric oxygen, and 6) gene therapy. However, none of these treatments is currently considered a component of standard care for skin ulcers.

Prior Systematic Reviews. A number of prior systematic reviews have attempted to define the efficacy of electrical stimulation as an adjunctive treatment for chronic skin wounds. Cullom et al. (2001) reviewed electrostimulation and electromagnetic therapy as part of a larger technology assessment on wound care management completed for the U.K. National Health Service. This systematic review was restricted to RCTs that reported objective outcomes, such as the percent of patients with complete healing, time to complete healing, or the rate of ulcer healing. Sixteen studies were included, 11 for electrostimulation and 5 for electromagnetic therapy. This set of studies has a large degree of overlap with those in the current TEC Assessment, which includes 7 of the 11 studies on electrostimulation and 4 of 5 on electromagnetic therapy.

The authors determined that methodologic weaknesses across this body of literature precluded definitive conclusions on the efficacy of electrostimulation and electromagnetic therapy. For electrostimulation, they stated that the evidence suggests a benefit for treating pressure ulcers, but that the evidence was insufficient to draw conclusions for other categories of ulcers. For electromagnetic therapy, they concluded that the trials did not offer sufficient evidence of benefit for any ulcer type.

Gardner et al. (1999) performed a systematic review and meta-analysis for studies of electrostimulation, including both RCTs and nonrandomized clinical studies. A total of 15 studies were included in their analysis, 9 RCTs and 6 nonrandomized studies. Of the 9 RCTs included, 7 are also included in the current TEC Assessment. The authors performed a pooled analysis of controlled studies on the rate of healing, which was the most common outcome measure reported. The combined value for percent healing per week was 22.5% for electrical stimulation (95% CI: 15.4–29.6) and 9.0% for control (95% CI: 1.1–16.9). Subgroup analysis of healing rates by type of stimulation or by type of wound did not uncover definitive patterns. Conclusions from this review were that electrical stimulation improves the healing rate for chronic wounds, but that more research was needed to determine which types of stimulation are most effective and whether there is differential efficacy for different types of chronic wounds. Electromagnetic therapy was not included as part of this review.

A technology assessment report was produced by ECRI in 1996 (ECRI 1996) that included studies of both electrical stimulation and electromagnetic therapy. This review identified 14 controlled studies of electrical stimulation and 5 controlled studies of electromagnetic therapy that met their inclusion criteria. As with the other reviews, there was a large degree of overlap in this set of studies and the current TEC Assessment (10 of 14 for electrical stimulation; 4 of 5 for electromagnetic therapy). The authors performed a detailed quality assessment on the included studies and concluded that although all the studies had at least one methodologic weakness, some conclusions could be drawn from the body of literature. They concluded that electrical stimulation facilitates complete healing and improves the healing rate for chronic skin wounds. They determined that decubitus ulcers were more likely to heal completely when treated with electrical stimulation than were venous ulcers. For electromagnetic therapy, they concluded that the healing rate for stage II decubitus ulcers was improved, but that conclusions for other types of ulcers could not be made. The overall conclusions of this report also stated that electrical stimulation and electromagnetic therapy are “not markedly inferior or superior to other conventional or alternative treatments for chronic wounds.”

The ECRI report was used as a key component for decision-making in coverage decisions by the Centers for Medicare and Medicaid Services (CMS). The most recent CMS decision memo for electrical stimulation was produced in 2002. At that time, they issued a positive coverage decision for the use of electrical stimulation in stage III and stage IV pressure ulcers, arterial ulcers, diabetic ulcers, and venous ulcers that had not responded to conventional therapy after at least 30 days of treatment. In 2003, an additional decision memo was issued for

electromagnetic therapy, stating that the results of studies on electromagnetic therapy were similar to those for electrical stimulation, and that therefore were expanding their coverage determination to include electromagnetic therapy for the same classes of ulcers. The decision was effective July 1, 2004.

FDA Status

Electrical Stimulators. Per a CMS decision memorandum (2002), the U.S Food and Drug Administration (FDA) has granted premarket application (PMA) approvals for electrical stimulators as Class III devices for the indications of bone stimulation and deep brain stimulation. FDA has also cleared electrical stimulators as Class II devices when indicated for muscle stimulation. However, the FDA has not cleared or approved the use of electrical stimulation for the treatment of wounds. The FDA has concluded that the use of these devices for the treatment of wounds is significantly different than the use of these devices for the indications currently covered under a 510(k) clearance. They are considered Class III devices, and, as such, require approval via the PMA process. Manufacturers cannot market electrical stimulators for wound healing. However, lack of approval does not preclude physicians and other healthcare providers from providing this therapy as an off-label use.

Electromagnetic Devices. Per another CMS decision memorandum (2003), the FDA has also cleared electromagnetic energy devices under the 510(k) marketing clearance process. The FDA considered Diapulse® (one such electromagnetic device) a Preamendment Class III device that was formally "grandfathered" on March 27, 1987. Diapulse Corporation did provide the FDA animal and human studies with their application. The classification device for products in this category is a "diathermy device," for use other than applying deep heat.

In a letter dated March 1991 from the FDA to the Diapulse Corporation, the FDA stated that the Diapulse® device could only be marketed as adjunctive therapy in the palliative treatment of postoperative edema and pain in superficial soft tissue. The FDA has not cleared or approved the use of any electromagnetic device for the indication of wound healing. Similar to the case for electrical stimulators, the use of electromagnetic devices for wound healing is considered to be significantly different than the use of these devices for the indications currently covered under a 510(k) clearance and any application would have to be approved via the PMA process. However, lack of approval for this indication does not preclude physicians and other healthcare providers from providing this therapy as an off-label use.

Methods

Search Methods

A MEDLINE search was performed via PubMed for the period of 1980 through March 2005 using the following search terms: "electrostimulation" OR "electrotherapy" OR "electromagnetic." These terms were cross-referenced with the terms "skin wound" OR "skin ulcer" OR "pressure ulcer" OR "neuropathic ulcer" OR "venous ulcer" OR "arterial ulcer." The search was limited to English-language articles involving human subjects. The electronic search was supplemented with the "related articles" function in PubMed, hand searching of relevant bibliographies of recent publications and systematic reviews, and search of the Cochrane Library.

Study Selection

Studies were selected for inclusion in this Assessment that met the following criteria:

- Full-length publication in a peer-reviewed, English-language journal
- Published between the dates of 1980-present
- Study design was a randomized, controlled trial in which one group is treated with electrostimulation (or electromagnetic therapy) in combination with standard care, and compared with standard care alone
- Reports at least one of the relevant outcomes of percent of patients with complete healing, time to healing, decrease in ulcer size, pain, quality of life, or facilitation of surgical closure
- Includes at least 10 patients per treatment arm for electrostimulation and 5 patients per treatment arm for electromagnetic therapy

Study Quality Assessment

The study selection criteria acted as the initial quality screen. Only studies that were randomized, controlled trials were selected for analysis. Second, general quality indicators applicable to controlled trials were used, based on the quality assessment approach outlined by the U.S. Preventive Services Task Force (USPSTF) (Harris et al. 2001) and modified

slightly based on TEC's prior experience in applying these indicators (Flamm et al. 2002). The quality indicators were assessed as met or not met by consensus of 2 TEC senior staff. The 5 indicators used are:

- initial assembly of comparable groups (adequacy of randomization, allocation concealment, and equal distribution of confounders among groups);
- maintenance of comparable groups (attrition, crossovers, contamination, non-adherence);
- measurements equal, reliable, and valid in all arms (includes masking of outcome assessment);
- clear definition of interventions;
- appropriate analysis of results.

An overall level of quality of "good," "fair," or "poor" is assigned based on these 5 parameters. Studies rated as good meet all 5 of the quality indicators and are considered to be of high quality. Studies rated as fair do not meet all quality criteria, but the limitations do not represent "fatal flaws." Studies that receive a poor rating have one or more "fatal flaws" that severely limit the validity of the reported results.

For the purpose of this quality review, definitions for whether quality criteria were met is based on a previous framework used in the TEC EPC AHRQ evidence report on newer interventions for wound healing (Samson et al. 2004). "Comparability of groups at baseline" was defined by 2 measures: the adequacy of randomization and the distributions of 3 major confounding variables (age, wound size, wound duration). For the criterion of "appropriate analysis of outcomes," 2 measures were used: whether all important outcomes were considered and whether appropriate analysis was performed to account for dropouts. To meet "all important outcomes considered," a study was required to include the outcome of percent of patients with complete healing. The threshold used for high overall loss to follow-up was an overall dropout rate greater than 20%, and differential dropout was defined as more than a 20% absolute difference in the percent of dropouts between groups.

Several general criteria were used to define the presence of a "fatal flaw" that would result in a poor quality rating. First, if neither an adequate randomization scheme nor equal distribution of confounders were demonstrated, this was considered a "fatal flaw." Also, if the overall dropout rate was >20%, (and/or there was demonstrated differential dropout) and the statistical analysis did not use methods to account for dropouts, e.g., intent-to-treat analysis, this was also considered a "fatal flaw" and the study was assigned a poor rating.

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on February 8, 2005. To maintain the timeliness of the scientific information in this Assessment, literature searches were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the table(s) and text where appropriate. There were no studies that would change the conclusions of this Assessment.

Formulation of the Assessment

Patient Indications

Potential candidates for electrostimulation and electromagnetic therapy are patients with chronic skin wounds that have not healed with standard therapy. A chronic skin wound is generally defined as one that has been present for 8 weeks or more. The vast majority of chronic skin wounds are classified as pressure ulcers, vascular insufficiency ulcers, or diabetic neuropathic ulcers, although there are many other less common etiologies for chronic wounds.

Technologies to be Compared

Electrical stimulation and electromagnetic therapy plus standard wound care will be compared to standard wound care alone. The optimal regimen for standard wound care is difficult to define with precision, but involves some general principles of wound care common to all skin wounds in combination with specific modalities indicated for individual types of wounds.

Health Outcomes

The most clinically important outcome in evaluating treatments for wound healing is the percent of patients that heal completely following a course of treatment. Time to complete healing is another important, objective outcome measure. Secondary outcomes that have some clinical relevance are the decrease in the size of a wound, pain associated with

a wound, and facilitation of surgical closure. Adverse outcomes with electrical stimulation and electromagnetic therapy are expected to be minimal, but may include discomfort and infection associated with the device.

Specific Assessment Questions

1. In patients with chronic skin wounds that have not healed with standard care, does the addition of electrostimulation to standard care improve outcomes?

2. In patients with chronic skin wounds that have not healed with standard care, does the addition of electromagnetic therapy to standard care improve outcomes?

Review of Evidence

A total of 15 studies enrolling 644 patients (816 wounds) met the inclusion criteria for this Assessment. A number of RCTs were excluded due to too few patients and/or duplicate data (See Table A, Appendix). Two additional studies that were classified by others as RCTs were determined to have nonrandomized patient assignment and were also excluded (Stefanovska et al. 1993; Franek et al. 2000). The evidence from the 15 included studies will be reviewed separately for the categories of electrical stimulation and electromagnetic therapy.

Electrical Stimulation

Ten studies enrolling 511 patients (683 wounds) compared electrical stimulation plus standard wound care to standard wound care alone (Table 2). Three studies treated pressure ulcers, 2 diabetic ulcers, one venous ulcers, and 3 included mixed ulcer types. All of these studies except for one (Carley and Wainapel 1985) were placebo-controlled trials that used a sham electrical stimulator in the control group. The majority (6 of 10) were double-blinded studies; 3 were single-blinded only (Baker et al. 1996; Lundeberg et al. 1992; Griffin et al. 1991) and the final study was unblinded (Carley and Wainapel 1985). Three of the studies were multicenter trials (Wood et al. 1993; Feedar et al. 1991; Gentzkow et al. 1991) and the remainder were single-site trials.

The trials were all of relatively small size, with total enrollment ranging from 20–80 patients. In the 2 studies enrolling 80 patients there were 4 study arms, resulting in only 20 patients per treatment arm (Baker et al. 1996; Baker et al. 1997). The study with the largest number of patients per study arm (Wood et al. 1993) had an average of 36 patients in each arm. Five of the 10 trials (Baker et al. 1997; Baker et al. 1996; Wood et al. 1993; Gentzkow et al. 1991; Feedar et al. 1991) used the wound as unit of analysis rather than the patient, thereby inflating their N for analysis of results.

Formal quality assessment for these studies was performed by the methods of Harris et al. (2001), with modifications for studies of wound healing according to the methods in a recent AHRQ evidence report (Samson et al. 2004). None of the studies met all of the quality indicators (Table 3), therefore, none of the included trials was judged to be of high quality. In fact, all of the trials had at least one fatal flaw that resulted in a poor quality rating. In each case, the fatal flaw was either lack of adequate randomization scheme combined with baseline imbalances on important cofounders, or a high overall dropout rate in combination with statistical analysis that did not attempt to account for dropouts.

Table 4 summarizes the outcomes reported by these studies. The percent of patients with complete healing, the most important clinical outcome, was reported by 5 of the studies. All 10 studies reported the rate of healing, expressed as the percent decrease in wound size at the end of the study, or provided data that allowed calculation of the percent decrease in wound size. Other outcomes were infrequent, with one study (Houghton et al. 2003) reporting a standardized method for scoring the appearance of wounds (PWAT score), and one study (Wood et al. 1993) reporting a response rate defined as at least 80% decrease in wound size.

Of the 5 studies that included the outcome of percent complete healing, 2 of the 5 reported a statistically significant improvement in the electrical stimulation group as compared to placebo (Wood et al. 1993; Lundeberg et al. 1992). In both of these trials, a substantially greater percentage of patients in the electrical stimulation group healed compared with placebo, with the absolute differences being 55% and 27%, respectively. Two additional studies showed numerical trends that favored the electrical stimulation group, but in one study (Peters et al. 2001), the difference did not reach statistical significance, and in the other study (Baker et al. 1996), statistical testing was not reported for this outcome.

Table 2. RCTs of Electrostimulation for Wound Healing – Study Characteristics

Study/yr	Population	Study Design	n (pts)	n (wounds)	Treatment Regimen	Outcomes
Houghton 2003	Pts with chronic LE ulcer(s): – vascular or diabetic origin – ≥3 mos. duration – Failure to heal with standard care – No steroid therapy, malignancy, osteomyelitis, cardiac conduction disturbances, DVT, pregnancy	– Double-blind RCT, with sham placebo device – 1–2 wk run-in period where all pts treated with standard care only	27	42	Pulsed, high-voltage ES: – EGS model 300 portable device: – 45-minute treatment period 3x/wk for 4 wks	– decrease in wound size – wound appearance by photographic wound assessment score (PWAT)
Peters 2001	Diabetic pts with foot ulcers: – Grade 1A-2A ulcers – TcO_2 >30 mmHg – No osteomyelitis, malignancy, cardiac conduction disorder	– Double-blind RCT, with sham placebo device	40	40	Pulsed, high-voltage ES: – Micro-Z™ device - Dacron mesh nylon stocking for 8-hr period with following cycle: – Dose 50V , 80 pulses/sec x 10 min, followed by 8 pulses/sec x 10 min, followed by 40 min rest	– % complete healing – time to healing – reduction in ulcer size
Baker 1997	Diabetic pts with open skin ulcers	– Double-blind RCT, with sham placebo device – Three treatment groups at different e-stim regimens	80	114	Asymmetric, biphasic AC ES: – UltraStim device with 3 delivery protocols – Three treatment sessions/day of 30 min each 5 d/wk for 28 d or until healing	– % complete healing – decrease in wound size
Baker 1996	Pts with spinal cord injuries and skin ulcers	– Single-blind RCT, with sham placebo device – Three treatment groups at different e-stim regimens	80	192	Asymmetric, biphasic AC ES: – UltraStim device with 3 delivery protocols – Three treatment sessions/day of 30 min each 5 d/wk for 28 d or until healing	– % complete healing – decrease in wound size

Table 2. RCTs of Electrostimulation for Wound Healing – Study Characteristics (cont'd)

Study/yr	Population	Study Design	n (pts)	n (wounds)	Treatment Regimen	Outcomes
Wood 1993	Pts with chronic skin ulcers: – ≥5 mos. duration – Lack of healing with standard care – No steroid therapy or other meds that interfere with wound healing	– Multicenter, double-blind RCT, with sham placebo device	71	74	Pulsed, low-intensity ES: – MEMS CS 600 device – 300μA alternating with 600μA at frequency of 0.8 Hz	– % complete healing – % response (≥80% reduction in size) – decrease in wound size
Lundeberg 1992	Pts with diabetic leg ulcers due to venous insufficiency: – No osteomyelitis, arterial disease, arthritis, trauma, allergy to standard treatment	– Single-blind RCT, with sham placebo device	64	64	Constant, AC ES: – Delft electrical nerve stimulation device – 80 Hz frequency	– % complete healing – decrease in wound size
Feedar 1991	Pts with chronic skin ulcers: – Stage II, III, or IV – Size 4–100 cm^2 – No pacemaker, osteomyelitis, PVD, thrombosis, pregnancy, or steroid therapy	– Multicenter, double-blind RCT, with sham placebo device	59	67	Pulsed ES: – Vara/Pulse® device – Regimen with amplitude of 29.2mA, duration 132μs – Two treatment sessions/day of 30 min each for 4 wks	– % complete healing – decrease in wound size
Griffin 1991	Male pts with spinal cord injury – Grade II–IV pelvic pressure ulcer – No cardiac disease, autonomic dysfunction	– Single-blind RCT, with sham placebo device	20	20	High voltage, pulsed ES: – Intelect 500 device – Sessions 1 hr/day for 20 days	– decrease in wound size
Gentzkow 1991	Pts with pressure ulcers: – Stage II, III, or IV – Size 4–100 cm^2	– Multicenter, double-blind RCT, with sham placebo device	NR	40	Pulsed ES: – DermaPulse device – Two treatment sessions/day of 30 min each for 4 wks	– % complete healing – decrease in wound size
Carley 1985	Inpatients with LE or sacral skin ulcers	– Unblinded RCT	30	30	Low-intensity, DC ES – Sessions 2 hr twice/day for 5 d/wk for 5 wks	– decrease in wound size

Table 3. Quality Ratings for RCTs of Electrical Stimulation

Study	Initial Assembly Comparable Groups: Adequate Randomization	Initial Assembly Comparable Groups: Equal Distribution of Confounders	Avoids High Overall Loss to Follow-up, or Important Differential Loss to Follow-up	Measurements Reliable, Valid, Equal: Clear Description Reproducible	Measurements Reliable, Valid, Equal: Blinded Outcome Assessment	Comparable, Clearly Defined Interventions	All Important Outcomes Considered	Appropriate Analysis of Results: Adjust for Confounders	Appropriate Analysis of Results: Intent-to-Treat Analysis	Overall Rating
Houghton 2003	NR	No Age – Yes Duration – No (35 mos. vs. 55 mos.) Size – Yes	Yes 2/29 (7%) total 2/13 (15%) Ctrl 0/14 (0%) ES	Yes	Yes	Yes	No	No	No	POOR Non-comparability of groups a fatal flaw
Peters 2001	NR	No Age – Yes Duration – Yes Size – No (3.5 cm^2 placebo, 1.6 cm^2 treatment)	Yes 4/40 (10%) total 2/20 (10%) Ctrl 2/20 (10%) ES	Yes	No	Yes	Yes	No	No	POOR Non-comparability of groups a fatal flaw
Baker 1997	NR	No Age – Yes Duration – No (59 vs. 109 vs. 74 vs. 54 d) Size – NR	No 28/114 (25%) total 3/25 (12%) Ctrl 8/33 (24%) ES1 12/28 (43%) ES2 5/28 (18%) ES3	Yes	Yes	No Standard treatment not well described	Yes	Yes Analysis by wound	No	POOR Non-comparability of groups a fatal flaw
Baker 1996	NR	No Age – No (33 vs. 34 vs. 40 vs. 36 yr) Duration – No (86 vs. 183 vs. 231 vs. 154 d) Size – No (8.6 vs. 6.6 vs. 2.4 vs. 8.5 cm^2)	Yes 27/192 6/25 (25%) Ctrl 7/67 (10%) ES1 8/58 (14%) ES2 6/42 (14%) ES3	Yes	Yes	No Standard treatment not well described	Yes	Yes Analysis by wound	No	POOR Non-comparability of groups a fatal flaw
Wood 1993	NR	No Age – Yes Duration – Yes Size – No (1.9 cm^2 placebo, 2.6 cm^2 treatment)	Yes	Yes	Yes	Yes	Yes	No Analysis by wound	No/NA No pts lost to f/u	POOR Non-comparability of groups a fatal flaw

Table 3. Quality Ratings for RCTs of Electrical Stimulation (cont'd)

Study	Initial Assembly Comparable Groups: Adequate Randomization	Initial Assembly Comparable Groups: Equal Distribution of Confounders	Avoids High Overall Loss to Follow-up, or Important Differential Loss to Follow-up	Measurements Reliable, Valid, Equal: Clear Description Reproducible	Measurements Reliable, Valid, Equal: Blinded Outcome Assessment	Comparable, Clearly Defined Interventions	All Important Outcomes Considered	Appropriate Analysis of Results: Adjust for Confounders	Appropriate Analysis of Results: Intent-to-Treat Analysis	Overall Rating
Lundeberg 1992	NR	NR Age – Yes Duration – NR Size – Yes	No 13/64 (20%) total 5/32 (16%) Ctrl 8/32 (25%) ES	Yes	No	Yes	Yes	No	No	POOR High overall loss to f/u and lack of analysis accounting for dropouts a fatal flaw
Gentzkow 1991	NR	No Age – Yes Duration – No (33% v 15% >1 yr) Size – No (12.5 cm^2 placebo, 19.2 cm^2 treatment)	Yes 9/49 (18%) total 5/24 (21%) Ctrl 4/25 (16%) ES	Yes	Yes	No Standard treatment not well described	Yes	Yes Analysis by wound	No	POOR Non-comparability of groups a fatal flaw
Griffin 1991	NR	No Age – Yes Duration – No (3.0 vs. 4.5 wk) Size – Yes	No 3/20 (15%) total NR by treatment group	Yes	No	Yes	No	No	No	POOR Non-comparability of groups a fatal flaw
Feedar 1991	NR	Yes Age – Yes Duration – Yes Size – Yes	No 12/59 pts (20%) 17/67 wounds (25%) NR by treatment group	Yes	Yes	Yes	No	Yes Analysis by wound	No	POOR High overall loss to f/u and lack of analysis accounting for dropouts a fatal flaw
Carley 1985	No Randomization by pairs not adequate method	No Age – Yes Duration – No (5.2 vs. 8.6 mos.) Size – Yes	NR	No	No	Yes	No	No	No	POOR Non-comparability of groups a fatal flaw

Table 4. Electrical Stimulation for Wound Healing – Outcomes

Study/yr	F/U	Group	N enr/ N eval	% Complete Healing	p-value	%↓ Ulcer Size	p-value	Other	p-value	Comments
Houghton 2003	8 wk							ΔPWAT score		
		E-stim	14/10			46 ± 13%	<0.05	-5	<0.05	
		Placebo	13/11			22 ± 6%		-1.6		
			15/							
Peters 2001	12 wk	E-stim	20/18	65% (13/20)	0.06	86.2%	NS			
		Placebo	20/18	35% (7/20)		71.4%				
Baker 1997	4 wk	E-stim1	33/25*	45% (15/33)	NR	27 ± 5**	NS			* number of wounds
		E-stim2	28/16	29% (8/28)		18 ± 6				** % decrease/wk
		E-stim3	28/23	36% (10/28)		11 ± 5				
		Placebo	25/22	48% (12/25)		14 ± 3				
Baker 1996	4 wk	E-stim1	67/60*	52% (35/67)	NR	36.4 ± 6.2*	NS			* number of wounds
		E-stim2	58/50	57% (33/58)		29.7 ± 5.1				** % decrease/wk
		E-stim3	42/36	43% (18/42)		23.3 ± 4.8				
		Placebo	25/19	24% (6/25)		32.7 ± 7.0				
Wood 1993	8 wk							% response**		* indicates increase in ulcer size
		E-stim	41/41	58% (25/43)	<0.0001	83%	<0.0001	73% (31/43)	<0.0001	** defined as ≥80% decrease in
		Placebo	30/30	3% (1/31)		-12%*		13% (4/31)		wound size
Lundeberg 1992	12 wk	E-stim	32/24	42% (10/24)	<0.05	61 ± 14	<0.05			
		Placebo	32/27	15% (4/27)		41 ± 11				
Feedar 1991	4 wk	E-stim	59/47*			56.1 ± 25.0	<0.02			* Total # pts, NR by treatment group
		Placebo				32.3 ± 47.3				
Griffin 1991	3 wk	E-stim	20/17*			63%	0.05			* Total # pts, NR by treatment group
		Placebo				14%				
Gentzkow 1991	4 wk	E-stim	25/21			50 ± 31	0.04			
		Placebo	24/19			23 ± 47				
Carley 1985	5 wk	E-stim	15/NR			89%	<0.01			
		Placebo	15/NR			45%				

All 10 studies reported the change in wound size, with 7 of the 10 studies reporting a statistically significant result favoring the electrical stimulation group. In the 3 remaining studies (Peters et al. 2001; Baker et al. 1997; Baker et al. 1996), numerical change in wound size favored the electrical stimulation group, but the differences did not meet statistical significance. Houghton et al. (2003) reported on the appearance of the wounds by a standardized measure (PWAT score) and reported a significantly improved appearance for the electrical stimulation group. Wood et al. (1993) reported percent response, defined as at least 80% decrease in wound size, with a statistically significant improvement in response for the electrical stimulation group and an absolute difference of 60%.

The most common methodologic limitation for these studies was failure to demonstrate comparability of groups at baseline. This indicator included the adequacy of randomization and demonstration of baseline comparability on 3 major confounding variables, age, wound size, and wound duration. No study met both criteria of adequate randomization and comparability on these 3 parameters. In 8 of the 10 studies, neither adequacy of randomization nor comparability of groups on baseline parameters was demonstrated. This combination resulted in a poor rating for these 8 studies. Feedar et al. (1991) was the only study to demonstrate baseline comparability on the major confounders; however, this study did not adequately describe the randomization methods used. Lundeberg et al. (1992) described an adequate randomization method, but did not report on all 3 baseline parameters.

Table 5 summarizes the direction of bias for the 10 electrical stimulation studies. Overall, the direction of bias is not in favor of the treatment group. More commonly, there is no clear direction of bias, or the direction of bias favors the control group.

Other common methodologic limitations of these studies were high dropout rates and a lack of appropriate statistical analysis. Eight of the 10 studies reported dropouts, with a range of 7–25%. The total number of wounds excluded in these 8 studies was 98 of 556, representing 18% of the total number of wounds enrolled. Six of these 8 studies reported dropouts by group, and in 4 of these studies, there was evidence for differential dropout by group. None of the studies used intention-to-treat or other forms of analysis to account for dropouts. In addition, 3 of the studies (Wood et al. 1993; Baker et al. 1996; Baker et al. 1997) used the wound as unit of analysis rather than the patient.

Treatment delivery varied considerably among these studies. There were differences in the type of electrical stimulation used (direct, pulsed, or alternating current); the intensity of the stimulation; the frequency of the treatment sessions (ranging from several times per day to several times per week); and the duration of treatment. This variability made it difficult to compare treatment "dose" across studies, and precluded any ability to evaluate a dose-response relationship.

Electromagnetic Therapy

Five studies enrolling 133 patients (133 wounds) compared electromagnetic therapy plus standard wound care to standard wound care alone (Table 6). Four of the 5 studies treated venous ulcers, and one enrolled patients with pressure ulcers (Salzberg et al. 1995b). All 5 studies were placebo-controlled trials that used a sham electrical stimulator in the control group. Four of 5 were double-blinded studies; one was single-blinded only (Kenkre et al. 1996). One of the studies was a multicenter trial (Stiller et al. 1992), and the remainder were single-site trials.

The electromagnetic therapy studies enrolled smaller sample sizes overall than the electrical stimulation studies; therefore, the minimum number of patients per arm for electromagnetic therapy was modified to 5 (as compared to 10 for electrical stimulation). The number of patients enrolled in the included electromagnetic therapy studies ranged from 19–44. The largest study (Ieran et al. 1990) enrolled approximately 20 patients per treatment arm.

Formal quality assessment for these studies was performed as for the electrical stimulation studies. None of the studies met all of the quality indicators (Table 7); therefore, none of the included trials was judged to be of high quality. All of the trials had at least one methodologic limitation, and the majority had one or more major limitations or fatal flaws that resulted in a poor quality rating.

The outcomes reported in these studies are summarized in Table 8. The percent of patients with complete healing was reported by 3 of the studies. All 5 studies reported the rate of

Table 5. Distribution of Major Confounders in Electrical Stimulation Studies

		Distribution of Major Confounders							
Study/Yr	Group	Age	% Difference*	Ulcer Size	% Difference	Ulcer Duration	% Difference	Baseline Comparability?	Direction of Bias
Houghton 2003	Ctrl	62.4 yr		5.5 cm^2		35 mos.		No	Favors control
	ES	66.3 yr	+1.0	6.4 cm^2	+16.0	55 mos.	+36		
Peters 2001	Ctrl	59.9 yr		3.5 cm^2		5.5 mos.		No	Favors ES
	ES	54.5 yr	-9.0	1.6 cm^2	-54.0	5.0 mos.			
Baker 1997	Ctrl	52 yr		NR		2.0 mos.		No	Favors control
	ES1	58 yr	+11.5	NR		3.6 mos.	+80		
	ES2	50 yr	-3.8	NR		2.5 mos.	+25		
	ES3	51 yr	-1.9	NR		1.8 mos.	-10		
Baker 1996	Ctrl	33 yr		8.6 cm^2		2.9 mos.		No	No clear direction
	ES1	34 yr	+3.0	6.6 cm^2	-23.3	6.1 mos.	+110		
	ES2	40 yr	+21.2	2.4 cm^2	-72.1	7.7 mos.	+131		
	ES3	36 yr	+9.0	8.5 cm^2	-1.1	5.1 mos.	+75.9		
Wood 1993	Ctrl	74.9 yr		1.9 cm^2		4.9 mos.		No	Favors control
	ES	75.6 yr	+1.0	2.6 cm^2	+36.8	5.5 mos.	+12.2		
Lundeberg 1992	Ctrl	66.0 yr		22.0 cm^2		NR		No/NR	No clear direction
	ES	67.5 yr	+2.3	24.2 cm^2	+10.0	NR			
Gentzkow 1991	Ctrl	62.2 yr		12.5 cm^2		33% > 12 mos.		No	No clear direction
	ES	63.3 yr	+1.8	19.2 cm^2	+34.9	15% > 12 mos.	-18**		
Griffin 1991	Ctrl	26.0 yr		2.7 cm^2		0.75 mos.		No	Favors control
	ES	32.5 yr	+25.0	2.3 cm^2	-14.8	1.5 mos.	+100%		
Feedar 1991	Ctrl	60.7 yr		16.9 cm^2		19% > 12 mos.		Yes	NA
	ES	66.6 yr	+9.7	14.6 cm^2	-13.6	20% > 12 mos.	+1.0**		
Carley 1985	Ctrl	73.6 yr		3.9 cm^2		5.2 mos.		No	Favors control
	ES	70.3 yr	-4.4	4.7 cm^2	+20.5	8.6 mos.	+65		

* defined as ((treatment – control)/control) × 100
** absolute difference in the percent of pts with ulcer duration >12 mos.

Table 6. RCTs of Electromagnetic Therapy for Wound Healing – Study Characteristics

Study/yr	Population	Study Design	n (pts)	n (wounds)	Treatment Regimen	Outcomes
Kenkre 1996	Pts with venous ulcers: – ≥1 mo. duration	Single-blind RCT with sham placebo device	19	19	Elmedostraal device: – Sessions 30 min/d, 5 d/wk for 4 wk, followed by 4-wk observation period	– % complete healing – reduction in ulcer size – reduction in pain score
Salzberg 1995b	Pts with spinal cord injury and pressure ulcer: – Stage II or III – No pts with multiple ulcers – No recent ulcer surgery, pacemaker, infection, joint replacement, terminal illness	Double-blind RCT, with sham placebo device	20	20	Diapulse device	
Stiller 1992	Pts with refractory venous ulcers: – ≥1 mo. duration – Failure to heal with standard therapy – Stable size in 2 wk prior to study – No arterial disease, heart disease, cerebrovascular disease, thrombosis, systemic disease	Multicenter, double-blind RCT, with sham placebo device	31	31	PELUT device – Sessions 3 hr/d for 8 wks or until healing	– reduction in ulcer size – reduction in pain score
Todd 1991	Pts with chronic venous ulcers	Double-blind, pseudo-randomized, with sham placebo device	19	19	Magnetoplus Standard ulcer care for 2 wks EM sessions 15 min 2x/wk for 5 wks	– reduction in ulcer size
Ieran 1990	Pts with venous ulcers: – ≥3 mos. duration – No steroid therapy, arterial disease or systemic diseases	Double-blind RCT, with sham placebo device	44	44	Dermagen device – Sessions 3-4 hr/day for 90 days or until healing	– % complete healing – time to healing – reduction in ulcer size

Table 7. Quality Ratings for RCTs of Electromagnetic Therapy

Study	Initial Assembly Comparable Groups: Adequate Randomization	Initial Assembly Comparable Groups: Equal Distribution of Confounders	Avoids High Overall Loss to Follow-up, or Important Differential Loss to Follow-up	Measurements Reliable, Valid, Equal: Clear Description Reproducible	Measurements Reliable, Valid, Equal: Blinded Outcome Assessment	Comparable, Clearly Defined Interventions	All Important Outcomes Considered	Appropriate Analysis of Results: Adjust for Confounders	Appropriate Analysis of Results: Intent-to-Treat Analysis	Overall Rating
Kenkre 1996	NR	No Age – Yes Duration – No (963 placebo vs. 324 wks treatment) Size – No (119 placebo vs. 72 mg treatment)	Yes 0 dropouts	No Unclear validity of method for measurement	No	No Standard treatment not well described	Yes	No	NA	POOR Non-comparability of groups a fatal flaw
Salzberg 1995b	NR	No Age – Yes Duration – NR Size – No (33 cm^2 placebo vs. 15 cm^2 treatment)	Yes 1/20 (5%) total 0/10 (0%) Ctrl 1/10 (10%) EM	Yes	Yes	NR	Yes	Yes	No	POOR Non-comparability of groups a fatal flaw
Stiller 1992	Yes	Yes	Yes 4/31 (13%) total 3/13 (23%) Ctrl 1/18 (6%) EM	Yes	No	Yes	No	No/NA	No	FAIR Does not meet all quality criteria but no fatal flaws
Todd 1991	No Pseudo-randomization – alternate treatment assignment	No Age – Yes Duration – No (3.6 yr(?) v. 18.3 yr) Size – No (8.4 cm^2 placebo, 5.4 cm^2 treatment)	No 2/19 (11%) total 0/9 (0%) Ctrl 2/10 (20%) EM	No	Yes	Yes	No	No	No	POOR Non-comparability of groups a fatal flaw
Ieran 1990	Yes	No Age – Yes Duration – No (23 mos. placebo vs. 30 mos. treatment) Size – No (17.9 cm^2 placebo vs. 11.3 cm^2 treatment)	Yes 7/44 (16%) total 3/22 (14%) Ctrl 4/22 (18%) EM	Yes	Yes	No Standard treatment unclear; compression stockings withheld	Yes	No	No	POOR Difference in baseline size and suboptimal standard care fatal flaws

Table 8. Electromagnetic Therapy for Wound Healing – Outcomes

Study/yr	F/U	Group	N enr/ N eval	% Complete Healing	p-value	%↓ Ulcer Size	p-value	Time to Healing	p-value	Other	p-value	Comments
Kenkre 1996	7 wks									↓ pain score		
		EM1	5	20% (1/5)	NR	-63*				72%	<0.05	Indicates increase
		EM2	5	20% (1/5)		63	<0.05			42%		in ulcer size
		Placebo	9	22% (2/9)		34				13%		
Salzberg 1995b	12 wks	EM	10/9	100% (9/9)	NS	84*	0.01	13.0 (med)	<0.001	Stage II		* % healing at 1 wk
		Placebo	10/10	100% (10/10)		40*		31.5 (med)				
		EM	5/5	60% (3/5)	NR	70.6	NR			Stage III		
		Placebo	5/5	0% (0/5)	NR	20.7	NR					
Stiller 1992	8 wks									↓ pain score		
		EM	18/17			47.1	<0.0002			0.6*	<0.001	*4-point pain scale
		Placebo	13/10			-48.7				0.15		
Todd 1991	5 wks	EM	10/8			22.0	NS					
		Placebo	9/9			9.1						
Ieran 1990	12 wks	EM	22/18	66.6	<0.02	47	NR	71 d	NR			
		Placebo	22/19	31.5		30		76 d				

healing, expressed as the percent decrease in wound size at the end of the study, or provided data that allowed calculation of the percent decrease in wound size. Two studies reported time to complete healing (Salzberg et al. 1995b; Ieran et al. 1990) and 2 studies (Kenkre et al. 1996; Stiller et al. 1992) reported changes in pain score.

One of the 5 studies (Ieran et al. 1990) reported a significantly greater rate of complete healing for the electromagnetic group, with an absolute difference of 35.1%. The two other studies did not report significant differences for this outcome (Salzberg et al. 1995b; Krenke et al. 1996). Three of the 5 studies reported a statistically significant benefit for the electromagnetic therapy group in the healing rate. In the 2 remaining studies (Todd et al. 1991; Ieran et al. 1990), numerical healing rates favored the electromagnetic therapy group, but the differences did not reach statistical significance. Salzberg et al. (1995b) reported a significantly shorter median time to healing, while Ieran et al. (1990) reported no difference in time to healing among groups. Both of the studies that included pain as an outcome (Kenkre et al. 1996; Stiller et al. 1992) reported a significantly greater decrease in pain scores for the electromagnetic therapy group.

The most common methodologic limitation for these studies was failure to demonstrate comparability of groups at baseline. Only one study (Stiller et al. 1992) demonstrated baseline comparability by adequately describing their randomization process and showing comparability between groups on major confounding factors. Ieran et al. (1990) described an adequate randomization scheme, but had substantial baseline differences in wound size and duration. In the remaining 3 studies, neither adequacy of randomization nor comparability of groups on baseline parameters was demonstrated. These 3 studies received a poor rating for failing both of these parameters.

A more detailed analysis of the baseline differences was done (Table 9). For these, the direction of bias in these baseline differences favors the electromagnetic therapy group. In the 4 studies that have baseline differences, 3 are biased toward electromagnetic therapy and the fourth does not have a clear direction of bias (Table 9).

Other common methodologic limitations of these studies were high dropout rates and a lack of appropriate statistical analysis. Dropouts ranged from 0–16%, and the total number of patients excluded in these 5 studies was 14 of 133, representing 11% of the total number of patients enrolled. None of the studies used intention-to-treat or other forms of analysis to account for dropouts. One study (Ieran et al. 1990) withheld some components of standard care in both groups (compression stockings); this study was rated poor for this flaw, combined with baseline differences in wound size and duration.

As with the electrical stimulation studies, treatment delivery varied among the electromagnetic therapy studies. There were differences in the type of device used; the energy intensity; the frequency of the treatment sessions (ranging from several times per day to several times per week); and the duration of treatment. This variability made it difficult to compare treatment "dose" across studies, and precluded any ability to evaluate a dose-response relationship.

Summary of Evidence and Discussion

There are numerous small RCTs included in the review of evidence; however; there is a lack of high-quality trials that allow conclusions on the efficacy of electrical stimulation and electromagnetic therapy for treatment of chronic wounds. The available evidence does not convincingly demonstrate that electrical stimulation or electromagnetic therapy leads to significant health outcome benefits on the most important clinical outcome, i.e., the percent of patients that heal completely.

For electrical stimulation, 5 studies report the outcome of complete healing, and 2 of these studies (Wood et al. 1993; Lundeberg et al. 1992) report statistically significant differences in favor of electrical stimulation. Wood et al. (1993) included patients with pressure ulcers from 4 long-term care facilities. The patients in these long-term facilities were characterized by poor functional status and impaired mental status. The authors reported a large difference in the percent of patients with complete healing in favor of the electrical stimulation group (58% vs. 3%, $p<0.0001$), but a number of factors limit confidence in these results. The population is not generalizable to a larger population

Table 9. Distribution of Major Confounders in Electromagnetic Studies

		Distribution of Major Confounders							
Study/Yr	Group	Age	% Difference*	Ulcer Size	% Difference	Ulcer Duration	% Difference	Baseline Comparability?	Direction of Bias
Kenkre 1996	Ctrl	73 yr		119 mg**		89.0 mos.		No	Favors EM
	EM1	59 yr	-19.0	63 mg	-47.1	9.8 mos.	-88.9		
	EM2	78 yr	+6.8	81 mg	-31.9	26.5 mos.	-70.2		
Salzberg 1995b	Ctrl	50 yr		33 cm^2		NR		No	Favors EM
	EM	58 yr	+16.0	15 cm^2	-54.5				
Stiller 1992	Ctrl	63.8 yr		7.7 cm^2		11.8 mos.		Yes	NA
	EM	63.0 yr	-1.3	7.3 cm^2	-5.2	9.8 mos.	-16.9		
Todd 1991	Ctrl	76.4 yr		83.5 cm^2		18.3 mos. (?)		No	Favors EM
	EM	72.2 yr	-5.5	53.9 cm^2	-35.4	3.6 mos. (?)	-80.3		
Ieran 1990	Ctrl	66 yr		17.9 cm^2		23 mos.		No	No clear direction
	EM	65 yr	-1.5	11.3 cm^2	-36.9	30 mos.	+30.4		

* defined as ((treatment – control)/control) × 100
** weight in mg of cutout of ulcer tracing

of all patients with chronic pressure ulcers. The rate of healing in the control group is lower than that seen in other trials (range 15–48%). This may be due to a standard care regimen that was of low intensity (most dressings, wound cleaning and whirlpool only) and to the poor physical status of the patients. The groups were comparable at baseline on age and wound duration, but not on wound size, with a larger mean size at baseline for the control group (2.6 vs. 1.9 cm^2). There were no patients lost to follow-up, but 6/71 patients died during the course of the 8-week trial, and it was unclear how these deaths were handled in the analysis. The analysis was performed by wound rather than by patient, and there were no adjustments for confounders in the analysis.

Lundeberg et al. (1992) enrolled 64 patients with diabetic ulcers, and also reported a large difference in complete healing in favor of the electrical stimulation group (42% vs. 15%, $p<0.05$). However, this study also had methodologic flaws that limit confidence in the results. This was a single-blinded trial, and the outcome assessment was not performed in an independent, blinded fashion. There was a 20% overall loss to follow-up, and there was neither full accounting for the dropouts, nor an intent-to-treat analysis performed. Peters et al. (2001) reported differences in complete healing that approached statistical significance (65% vs. 35%, $p=0.06$) in a small study of 40 patients with diabetic ulcers. This study had baseline imbalances on wound size, did not perform outcome assessment in an independent blinded fashion, and the authors did not adjust for confounders or perform an intent-to-treat analysis.

The final 2 studies reporting on complete healing were Baker et al. (1996), which included patients with pressure ulcers and Baker et al. (1997), which included patients with diabetic ulcers. These studies used 3 different electrical stimulation regimens and compared to a sham control. There were numerical differences on percent of patients with complete healing for some electrical stimulation groups but not for others, and no statistical testing was reported for these results. These 2 studies were also limited by baseline differences in wound size and duration, high overall loss to follow-up, and analysis that did not include adjustment for confounders or intent-to-treat approach.

For electromagnetic therapy, the evidence follows a similar pattern, with a lesser quantity of evidence. Of the 5 available studies, 3 report on the outcome of complete healing, and only one study (Ieran et al. 1990) reports statistically significant differences in favor of the electromagnetic therapy group. One of the 5 studies reports a shorter mean time to healing for the electromagnetic therapy group (Salzberg et al. 1995b). Three of the 5 studies report a larger decrease in wound size for the electromagnetic therapy group (Kenkre et al. 1996; Salzberg et al. 1995b, Stiller et al. 1992); and 2 studies report better pain scores for the electromagnetic therapy group (Kenkre et al. 1996; Stiller et al. 1992).

Wound healing treatment trials must show that an intervention has efficacy independent of the many confounding factors and the variable natural history of the disorder. High-quality trials of wound healing treatments will ideally have the following features: 1) enroll patients with one type of wound, 2) assess patients on a wide range of baseline characteristics, and demonstrate that potential confounders are equally distributed among groups, 3) use a double-blind design, with a sham placebo control, 4) ensure that optimal standard care is delivered to both treatment and control groups, 4) report on the percent of patients with complete healing, and/or time to complete healing, 5) assess outcomes in an independent, blinded fashion, and 6) follow patients for at least 3 months to assess complete healing and recurrences.

The available studies do not meet these recommended parameters. The most common limitation identified in these trials was baseline imbalances on major confounders, which were present in almost all cases. An analysis of the direction of bias for 3 major confounders (age, wound size, wound duration) revealed that, in most cases, the bias did not favor the treatment group. Therefore, it is unlikely that these baseline imbalances represent systematic bias in randomization by the researchers. More likely, the differences arise by chance as a result of the small size of these trials and the large variability in baseline variables such as wound size. In several instances, the researchers address this issue and report that outliers were present and may have skewed baseline values. The presence of baseline imbalances on these 3 major confounders also raises the possibility that the distribution of other confounders may be imbalanced. For example, patient comorbidities at baseline are seldom reported and it is not possible to determine

whether imbalances in these confounders may impact the reported results.

The studies also do not meet these study quality criteria on a number of other parameters. Studies often include populations of mixed wound types (5/15), do not use double-blind methodology (6/15), have a trial length of less than 12 weeks (11/15), do not report outcomes of complete healing (7/15), and do not assess outcomes in an independent, blinded fashion (6/15). These additional limitations compound the lack of baseline comparability on confounding variables, and further limit confidence in the results of these studies.

The results suggest that electrical stimulation and electromagnetic therapy may promote wound healing or some aspect(s) of wound healing, but considerable uncertainty remains as to whether these modalities lead to clinically significant health outcome benefits, given various flaws in how studies were conducted. To demonstrate efficacy for these treatments, larger, well-conducted, randomized, controlled trials are needed. These trials should focus on one type of wound, demonstrate baseline comparability on important confounders, and account fully for dropouts. Statistical analysis should include both multivariate approaches to controlling for confounders and methods to account for loss to follow-up. The outcome of complete healing should be the primary outcome in these studies, and follow-up should be long enough to assess recurrences.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Medical Advisory Panel made the following judgments about whether electrical stimulation or electromagnetic therapy as an adjunctive treatment for chronic skin wounds meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria:

1. **The technology must have final approval from the appropriate governmental regulatory bodies.**

No electrical stimulation device or electromagnetic therapy device is currently cleared or approved by the U.S. Food and Drug Administration (FDA) for the specific indication of wound healing. A number of devices have been cleared for marketing for other indications. Use of these devices for wound healing is an off-label indication.

2. **The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

The evidence is not sufficient to permit conclusions on the efficacy of electrical stimulation or electromagnetic therapy as adjunctive treatments for wound healing. The body of evidence for electrical stimulation and electromagnetic therapy consists of numerous small RCTs (n=10 for electrical stimulation; n=5 for electromagnetic therapy). To conclude that either of these technologies is an effective adjunctive treatment for wound healing, the body of evidence must have certain properties. Well-designed and well-conducted sham placebo-controlled RCTs are needed that consistently show better outcomes for active treatment over placebo, reflected in statistically and clinically significant results. The available evidence does not convincingly demonstrate that electrical stimulation or electromagnetic therapy results in clinically significant improvement in the most important outcome, i.e., the percent of patients that heal completely.

Wound healing treatment trials must show that an intervention has efficacy independent of the many confounding factors and the variable natural history of the disorder. Such trials will ideally have the following features: 1) enroll patients with one type of wound; 2) assess patients on a wide range of baseline characteristics, and demonstrate that potential confounders are equally distributed among groups; 3) use a double-blind design, with a sham placebo control; 4) ensure that optimal standard care is delivered to both treatment and control groups; 4) report on the percent of patients with complete healing, and/or time to complete healing; 5) assess outcomes in an independent, blinded fashion; and 6) follow up patients for at least 3 months to assess complete healing and recurrences.

Electrical Stimulation. Only 5 of 10 electrical stimulation studies report on the key health outcome, complete healing. The other 5 studies found statistically significant advantages for electrical stimulation in percent reduction in ulcer size, with follow-up periods ranging between 3 weeks and 8 weeks across studies.

While greater change in wound size suggests better healing with electrical stimulation, follow-up is generally short, and this outcome is not a substitute for measuring the incidence and timing of complete healing. Only 2 of the 5 studies that reported complete healing found results that significantly favored electrical stimulation. The strongest study included 71 patients, and there was confounding of baseline characteristics favoring the control group. Adjustment for confounders was not employed but the proportion of complete healing at 8 weeks was 58% in the electrical stimulation group and 3% in the placebo group ($p<0.0001$). The other study (n=64) achieving statistical significance had more significant flaws: confounding of unclear direction, no statistical adjustment, and high overall loss to follow-up (20%). At 12 weeks, 42% in the electrical stimulation group achieved complete healing, compared with 15% in the placebo group ($p<0.05$).

A study of 80 patients with 192 wounds showed a pattern of higher complete healing with electrical stimulation, but confounding of unclear direction was present and no statistical test results were given. The 2 remaining studies do not provide support for the efficacy of electrical stimulation. In both, confounding appeared to favor electrical stimulation, but neither found a statistically significant result. While some of the results from electrical stimulation trials are favorable, methodologic flaws were common, and statistical significance was achieved in only 2 studies reporting on the primary outcome of complete healing.

Electromagnetic Therapy. For electromagnetic therapy, the evidence follows a similar pattern, with a lesser quantity of evidence. Of the 5 available studies, 3 report on the outcome of complete healing, and only 1 study reports statistically significant differences in favor of the electromagnetic therapy group. One of the 5 studies reports a shorter mean time to healing for the electromagnetic therapy group. Three of the 5 studies report a larger decrease in wound size for the electromagnetic therapy group, and 2 studies report better pain scores for the electromagnetic therapy group.

The results suggest that electrical stimulation and electromagnetic therapy may promote wound healing or some aspect(s) of wound healing, but considerable uncertainty remains as to whether these modalities lead to clinically significant health outcome benefits, given various flaws in how studies were conducted. To demonstrate efficacy for these treatments, larger, well-conducted, randomized, controlled trials are needed. These trials should focus on one type of wound, demonstrate baseline comparability on important confounders, and account fully for dropouts. Statistical analysis should include both multivariate approaches to controlling for confounders and methods to account for loss to follow-up. The outcome of complete healing should be the primary outcome in these studies, and follow-up should be long enough to assess recurrences.

3. **The technology must improve the net health outcome; and**
4. **The technology must be as beneficial as any established alternatives.**

The evidence does not permit conclusions as to whether electrical stimulation or electromagnetic therapy as an adjunctive treatment for chronic skin wounds improves health outcomes or is as beneficial as established alternatives.

5. **The improvement must be attainable outside the investigational settings.**

Whether electrical stimulation or electromagnetic therapy as an adjunctive treatment for chronic skin wounds improves the net health outcome has not been established in the investigational settings.

Based on the above, electrical stimulation or electromagnetic therapy as an adjunctive treatment for chronic skin wounds does not meet the TEC criteria.

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Appendix

Table A. Excluded Articles

Study/Yr	Reason for Exclusion
Adegoke et al. 2001	<10 patients per study arm (ES)
Bentall and Eckstein (no date)	Not full-length, peer-reviewed publication
Cameron 1964	Published prior to 1980
Comorosan et al. 1993	Did not include relevant outcomes
Franek et al. 2000	Nonrandomized patient assignment
Gogia et al. 1992	<10 patients per study arm (ES)
Goldin et al. 1981	Not chronic skin wounds
Ionescu et al. 1982	Not full-length, peer-reviewed publication
Kaplan and Weinstock 1968	Not chronic skin wounds
Kloth and Feedar 1988	<10 patients per study arm (ES)
Lobell and Bobrow (no date)	Not full-length, peer-reviewed publication
Mulder 1991	Duplicate publication
Pennington et al. 1993	Not chronic skin wounds
Salzberg et al. 1995a	Duplicate publication
Sambasivan 1993	Not chronic skin wounds
Sherman et al. 1999	Not chronic skin wounds
Stefanovska et al. 1993	Nonrandomized patient assignment
Wilson 1972	Not chronic skin wounds

Table B. Key to Abbreviations in Tables

AC	alternating current
cm(s)	centimeter(s)
Ctrl	control
DC	direct current
DVT	deep venous thrombosis
EM	electromagnetic
ES	electrical stimulation
LE	lower extremity
mg	milligram
min(s)	minute(s)
mo(s).	month(s)
NS	not significant
PC	pulsed current
pt(s)	patient(s)
PVD	peripheral vascular disease
RCT(s)	randomized, controlled trial(s)
wk(s)	week(s)
yr(s)	year(s)

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