MEDICAL DEVICE PARTNERING PROGRAM

TECHNICAL REPORT

WOUND HEALING DEVICE

December 2020

This report was prepared for:

SIS Manufacturing

4/20 Clarendon Street,

Frankston, VIC 3199

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This work has been supported by:

launchvic via MEDICAL DEVICE PARTNERING PROGRAM

CONTENTS

1 EXECUTIVE SUMMARY

1.1 KEY FINDINGS

The aim of this initiative was to undertake a literature review on the use of electric stimulation (ES) in wound healing. The review collated and summarised the evidence as it pertained to evidence regarding clinical and cost effectiveness, safety of the intervention, and the populations in which ES has been used and found to have optimal effectiveness.

To enhance the rigor of the review, a systematic searching protocol was developed and implemented. A database search strategy was designed in consultation with wound experts and a senior librarian. A title/abstract and full text screening process was employed using Covidence software. This approach was utilised to optimise confidence that the final result identified and included all relevant research papers, and these were, therefore, incorporated into the key findings which informed the recommendations.

This review determined the following key findings:

1. Published evidence from *in vivo* research including several meta-analyses indicate a consistent positive effect of ES treatments/devices on the number of wounds healed and the wound healing rate compared to no ES.
    a. All studies examined suggested a positive effect of ES from both equivalent and non-equivalent treatments/ devices.
    b. Large standard deviations/ 95% confidence level ranges arising from this research impacts the ability to identify with confidence the size of the effect associated with ES.
    c. The positive effects observed with *in vivo* research were substantiated by a considerable and consistent foundation of *in vitro* research in which positive wound healing outcomes were observed while markers of cellular response that underpin positive wound healing were also noted.
2. There is *in-vivo* evidence supporting the effectiveness of ES for a variety of wound aetiologies and populations including chronic wounds (venous, arterial, mixed, neurotrophic), pressure injuries, diabetes related foot ulcers, burns, surgical wounds, acute wounds and fractures with no chronic underlying conditions, painful wounds, infected wounds, recurrent wounds, and among people of all ages (over the age of 18).
    a. There was a suggestion by the Gardner et al. (1999) meta-analysis of equivalent treatments/ devices that ES was more effective when treating pressure injuries compared to other wounds; however, this finding requires corroboration with more recent evidence, and is not consistent with another more recent systematic review of non-equivalent treatments/devices (Barnes et al., 2014).
    b. The area in which ES has experienced the most apparent translation of evidence to clinical practice guidelines is in relation to pressure injuries.
3. There is limited, dated, inconsistent, and contradictory *in vivo* evidence and meta-analyses regarding the effectiveness of different types of ES including direct, pulsed, alternating currents, or electrode placement, to guide treatment protocols. Recent meta-analyses, both classified as involving non-equivalent treatments/devices, suggest the following:
    a. There is no difference between monophasic and biphasic waveforms in the treatment of diabetes related foot ulcers (Chen et al., 2020).
    b. Unidirectional ES is more effective than bi-directional ES for varied wound aetiologies (Koel & Houghton, 2015).

4. Cost effectiveness evaluations have been an overlooked aspect in the published evidence with respect to ES treatments/devices. There is promising evidence from one study to suggest an equivalent form of ES could reduce health service costs and primary nurse visits (Taylor et al., 2011).
5. Few studies specifically reported data pertaining to safety concerns, adverse events or serious adverse events associated with ES. When safety was mentioned, no serious adverse events were identified. Adverse events that were mentioned were either consistent with events that occur for wounds regardless of intervention and during usual wound healing (i.e., infection, increased wound exudate, hypergranulation, and pain). These adverse events were infrequent and were especially minor and less commonly for equivalent treatments/devices. A list of some adverse events noted in the studies is provided below categorised by equivalence to the SIS product/treatment:

Equivalent studies

a. No discomfort experienced (Ramadhinara & Poulas, 2013) and no safety concerns were observed (Hampton & King, 2005).
b. A burning feeling or redness surrounding tissues of short duration was noted and did not require treatment (the use of wireless treatment where the limb was exposed to the treatment) (Wirsing et al., 2015).
c. Painless redness without complication and unknown if related to treatment (Griffin, 2013).

Non-equivalent studies

d. Tolerability was good/ very good for three quarters of participants (Herberger et al., 2012).
e. Treatment was ceased (n=2) when the treatment involved a heated room (Lawson & Petrofsky, 2007).
f. Excessive granulation of treated wounds (Adunsky et al., 2005).
g. Local irritation (possible effect of the DDCT on the silver ions contained in the topical sulphadiazine ointment) (Adunsky et al., 2005).
h. Sensation of tingling/ prickling sensation, discomfort (Mulder, 1991) and pain (n=1) at wound edge where the wound was exposed to the dispersive electrode (Herberger et al., 2012).
i. Maceration (Herberger et al., 2012) and exudation (Mulder, 1991).

1.2 RECOMMENDATIONS

1. There is merit in the use of ES to facilitate wound healing outcomes and further exploration of this intervention in practice is warranted.
2. ES has been used safety with human participants with only minor adverse events that represent usual occurrences in wound healing and are treatable. As these events are especially mild in severity and less common among equivalent ES, the current product aligns with technology that could be considered safe for in vivo use.
3. Due to the limited reports of evidence regarding safety, the following cautions for future research are recommended:
    a. The adverse events noted in executive summary item 5 should be actively monitored in future studies.
    b. Safety assessment and monitoring is required for any participants with limited sensation or peripheral neuropathy, for example, people with spinal cord injuries or diabetes related foot ulcers, for whom the capacity to monitor protective sensation may be reduced.
    c. Use of hypo-allergenic electrodes may be considered to protect the skin while assessment and monitoring of the skin and consideration of electrode placement is necessary in this patient cohort to avoid the risk of skin damage or degradation.
    d. Research protocols should incorporate basic bio-engineering training of the team implementing future studies with access to further consultation of treatment experts to enhance patient safety when implementing the treatments/devices.
4. To address the considerable methodological variability and limitations evident in the published literature, future studies would benefit from undertaking research involving a randomised controlled trial design that includes appropriate randomisation processes, blinding, and standardised wound care, with a sample size informed and justified by an appropriate power analysis. Furthermore:
    a. The use of a standardised definition of a chronic wound is encouraged.
    b. Future studies would benefit from justification of ES treatment protocols.
    c. Close monitoring of reasons for attrition is recommended from research trials as the attrition from some research studies when reported was at or exceeded preferred thresholds (i.e., the CONSORT Statement) for retention (for example, Asadi et al., 2017; Adunsky et al., 2005).
    d. Feasibility studies are encouraged upon which a program of robust clinical trials can be established to optimise translation of the research to practice, address gaps in current studies such as cost analysis and reporting of participant safety, and to examine and mitigate the high attrition rates observed in some studies.
        i. Specifically, factors that hinder the uptake of the ES treatments/devices is a gap in the literature and qualitative exploration of the experiences and perspectives of stakeholders, i.e., treating clinicians, clinic managers, and wound care experts with regards to factors affecting their decision in prescribing/suggesting the ES treatments/devices for eligible patients, as well as the consumer experience is recommended.
5. The following exclusions from research have been repeatedly identified in the published literature and warrant *consideration* as exclusions / contraindications in addition to contraindications noted for the SIS product; people with implanted electrical devices, pregnant or breastfeeding women, people with active neoplasms or malignancy, people

with acute cardiac concerns, people with severe infection or acute inflammation, people with kidney or liver failure, other skin diseases, people with severe chronic disorders (e.g., blood disorders), treatment involving metal ions i.e., silver dressings, and people under the age of 18 years,

a. It is recommended that the impact of these exclusion and contraindications is considered for the ramifications for the size of the market as well as when determining study eligibility criteria and recruitment timeframes.

2 BACKGROUND

Electric Stimulation (ES) has been reported for decades as a therapeutic method/treatment to aid and promote wound healing. As early as 1968, in-vivo preclinical studies on ES therapy were conducted, followed by numerous animal and clinical studies to support its application. Studies on cutaneous wound healing in animal models became more prevalent in the 1990s. In 2002, the American Food and Drug Administration granted premarket approval for the clinical use of ES devices to treat certain chronic wounds (in particular, diabetes related foot ulcers, Stage III or IV pressure injuries (PIs), and arterial ulcers) that had failed to respond to standard conventional wound therapies [1]. Recent advances in research of this 'electrical phenomena' in wound management have created an interest in the utility of this modality within the clinical setting [2, 3].

Undamaged human skin has an endogenous electrical potential and a transcutaneous current potential of 20–50 mV [4]. This is generated by the movement of sodium ions through Na+/K+ ATPase pumps in the epidermis. Following an injury to the skin, a flow of current through the wound pathway generates a lateral electrical field (through epithelial disruption) termed the "current of injury" or the "skin battery" effect. Therefore, the current of injury is thought to be significant in initiating repair.

ES is defined as the application of electrical current through electrodes placed on the skin either near or directly on the wound [5]; with a variety of methods of electrode placement noted in ES [6-8]. However, the majority of trials apply the electrodes directly onto the skin or directly onto the wound. The electrodes are then connected to a stimulator that is designed to create a small electrical charge in the tissue. ES replaces the current that would be produced naturally when the tissue is broken [9].

Several different applications as well as ES modalities (electrical waveforms and currents) exist, including direct current (DC), alternating current (AC), and pulse current (PC), and electro-biofeedback ES. Additionally, mono- or bipolar and bi- or tri-electrodes are used. Direct current involves unidirectional continuous flow of current for longer than 1 second [10]. Pulsed current involves the brief uni-directional or bi-directional flow of electrons or ions in which each pulse is separated by a longer off period with no current flow [10]. No single form of ES has been advocated as the most 'optimal' for the treatment of cutaneous wound healing. A challenge to the field is that,

as per all medical treatments and indeed the wound healing process itself, ES requirements of the wound are dynamic.

When ES is applied to a wound surface, beneficial effects are produced throughout the three phases of cutaneous wound healing: inflammation, proliferation and remodelling phases. During the inflammatory phase, ES increases blood flow and tissue oxygenation secondary to vasodilation, and stimulates fibroblasts whilst simultaneously reducing oedema and providing an increased antibacterial effect. During the proliferative phase, ES increases keratinocyte proliferation, membrane transport, collagen matrix organisation, wound contraction, and the stimulation of DNA and protein synthesis. Finally, during the remodelling phase, ES increases epidermal cell proliferation and migration as well as stimulation of fibroblasts, thus enabling enhanced wound closure [11, 12].

Although the use of ES to assist wound healing has been studied for several decades and various types of ES devices have been applied in clinical practice and trials, many questions remain about the effect, underlying mechanisms and the intensity and time at which ES should be applied to achieve the most optimal effect for wound closure. The aim of this initiative was to undertake a literature review on the use of electric stimulation in wound healing. A systematic approach to the review was employed to achieve a rigorous and comprehensive report that would enhance reviewer confidence in the findings and recommendations.

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3 METHODS

La Trobe University was contracted by Swinburne University of Technology as part of the Medical Device Partnering Program (MDPP) in 2020, to undertake a literature review on the use of electric stimulation in wound healing. The literature review would provide a broad and general overview of electric stimulation applications in wound healing. The review will be restricted to the specific electric stimulation parameters (e.g., current, voltage) employed by the device under consideration and would further categorised evidence for its equivalence to the manufacturer's product (see Appendix B).

A literature review was undertaken as per an agreed database search strategy developed in consultation with and implemented by La Trobe University library services (see Appendix A for the full search strategy and results). A single reviewer title/ abstract and full text screening process was conducted to increase confidence that the final product included a thorough and replicable screening process of database resources. Covidence software was utilised to manage the title /abstract and full text search. A PRISMA of the results was generated with reasons for exclusion from the full text screening detailed. Quality appraisal and meta-analysis of the papers were outside the scope of this brief.

To complement the database searching, an online search of relevant devices as used in wound care, and information about identified devices in the public domain was sourced and summarised. Further searches for guidelines that address the concept of electric stimulation in wound healing were undertaken.

During the project period, several meetings were convened between the La Trobe University, SIS manufacturers, and the MDPP team employed by Swinburne University of Technology to review progress, clarify search parameters including a review of the draft search strategy, the draft reporting template, and the equivalence categorisation of in vivo evidence.

Reported herein is a narrative summary of the literature supplemented with tables of studies as they relate to the following topic areas:

- Patient population
    - Most common patient population type in the publications

- Most benefit in which patient population type
- Patient setting (hospital, care home etc)
- Patient journey, at what point are devices generally used

- Safety
  - Most common adverse events occurred
  - Any patient types recommended as contraindicated or precautions taken – such as pacemaker patients or certain comorbidities
  - Overall safety review of publications and recommendation on how much can be leveraged for the SIS device
- Cost
  - Overview of articles demonstrate cost saving in terms of bed days in hospital for example
- Efficacy
  - Publications that may demonstrate reduction in the use of antibiotics in patients who used devices vs not
  - Overall recommendation of which articles best describe efficacy of such devices. Class A evidence etc.

3.1.1.1 Concept 1 Population (wound types)	*3.1.1.2 Concept 2* Intervention (Electrical stimulation)
Burn*	**Electric stimulation (MeSH)** [1]
Wound*	**Electric stimulation therapy (MeSH)** [1]
Venous leg ulcer*	Electric*adj 2 stimula* [1]
Lower leg ulcer*	Low intensity direct current
Surgical wound*	LIDC
Diabetic ulcer	NOT TENS which targets nerves
Diabetic foot ulcer	NOT surg* implant*
Diabetic leg ulcer	NOT electromagn*
Amputation wound*	NOT PEMF pulsed magnetic field
Laceration	NOT EMS which targets muscle
Pressure injur*	NOT Interferential
Pressure ulcer*	NOT NMES muscle/nerve targets
Venous stasis ulcer	
Soft tissue injur*	

Arterial ulcer* Bed sore* Decubitus ulcer* Chronic adj2 wound* Acute adj2 wound* Infect* adj2 wound*	

3.1.2 Inclusion Criteria	3.1.3 Exclusion Criteria
- Wounds that involve a break in the skin and can include chronic and acute wounds (inclusion can be but are not limited to chronic lower leg ulcers such as VLU, Mixed, Lymphodema), diabetes related wounds, pressure injuries, surgical wounds) - Any papers including treatment of wounds with electrical stimulation to the wound bed, wound edge, or surrounding tissue. - Papers with any study design including literature reviews, case studies, and opinion or commentary citations.	- Any study where the only electrical stimulation application involves electrical stimulation that is seeking to stimulate the muscle or nerve (NMES or EMS), interferential treatment (IF), or pulsed magnetic field (PEMF), or high voltage pulsed current (HVPC). - Any study involving only patients with neoplastic illness (i.e., with malignancy associated with the wound or with other systemic malignancy) - Any study involving only patients with a primary or systematic acute/ severe cardiovascular presentation - Any study where the skin is intact or is a dermatological condition - Any study that is not written in English - Any study for which an abstract / full text cannot be sourced - Any study including lesions arising from Pyoderma gangrenosum or from any other unknown aetiology - Did not address a wound healing outcome - Any study including patients with severe renal disease

	- Conference abstracts only available

3.1.4 Other Information

3.1.5 Databases - MEDLINE - CINAHL - EMBASE

4 RESULTS & DISCUSSION

4.1 PRISMA SCREENING RESULTS

As described in Figure 1, the search identified 3497 articles of which 835 were identified as duplicates by the Covidence software. The research team undertook title/abstract screening of 2662 articles of which 2157 were excluded as not matching the eligibility criteria. The full text of 505 were reviewed and 160 papers were included in the final analysis. The PRISMA chart representing the screening process is provided in **Figure 1**.

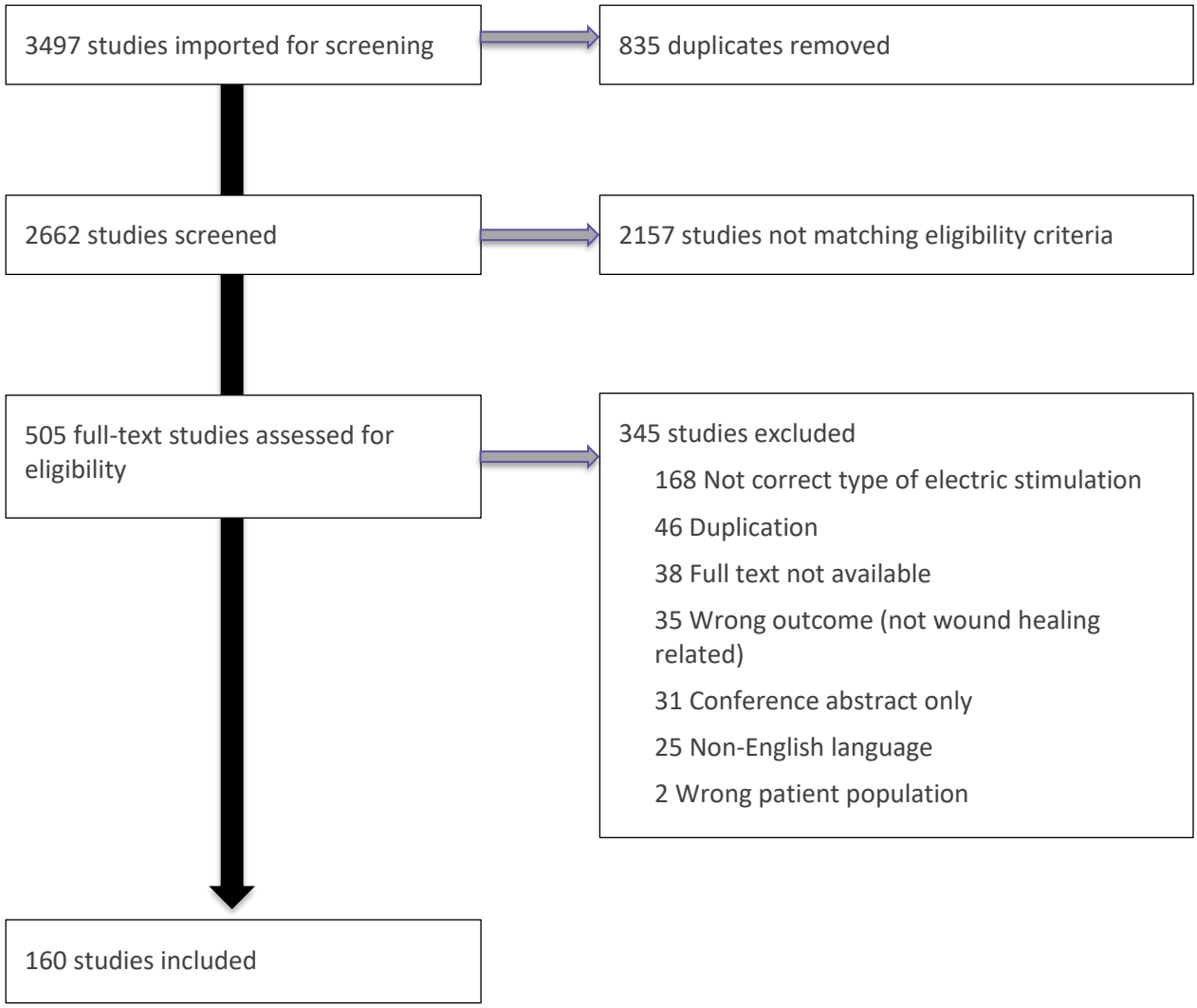

Figure 1. PRISMA flow chart of article screening

4.2 PRIMARY *IN-VIVO* EVIDENCE

Thirty-four *in-vivo* manuscripts were identified and accessed in the search. All 34 in-vivo articles reported results in favour of the ES treatments/devices albeit with great variation in effect size as well as substantial methodological constraints (small sample size, potential conflict of interest, potential confounding/bias, or large standard deviations/range of 95% confidence level). Few reported treatment/device-related safety outcomes (Griffin, 2013; Hampton & King, 2005; Wirsing et al., 2015) while only one study conducted a cost analysis model (Taylor et al., 2011). In most of these reviewed studies, no rationale was provided in relation to the dosage/duration of the treatment. Based on the best information available in the full texts, documentation regarding the SIS treatment modes (Appendix B), and further consultations with the SIS manufacturer, articles were categorised according to the potential equivalence (or otherwise) of the reviewed electrical stimulations to SIS's treatments/devices. It is noted that the categorisation was not always straightforward due to complex electrical engineering designs of the treatments/devices and/or limited description of the intervention.

4.2.1 3.1.1. Partial/Potential equivalence

No studies were identified where the ES treatments/devices investigated in the reviewed articles were exclusively equivalent to the SIS's treatment mode including modality (current type), current parameters (intensity, voltage intensity, frequency), and electrode arrangement. However, potential, or partial equivalence between some of reviewed ES treatments/devices and SIS's low-intensity devices was found in 19 of the 34 *in-vivo* articles (see **Table 1**). Of these 19 articles, five investigated Accel-Heal treatments/devices, seven investigated low-intensity direct current (LIDC), two investigated wireless micro current simulation, four investigated low-intensity pulsed current/waveform, and two investigated other devices.

4.2.1.1 Low-intensity direct current

In six of the studies that investigated the effectiveness of the LIDC with current intensity of 1mA or less, it was often that only one of the three ES parameters (current, voltage or frequency) that was in an equivalent range with the SIS LIDC device; remaining parameters were often much higher values in comparison. The arrangement of electrodes for SIS's devices appeared to be most similar to that in the work of Karba et al. (1997). The research populations included in these articles were both healthy volunteers and patients with complex comorbidities, ≥ 18 years of age (ranging from 18 to 80s) and from a variety of settings, and most had chronic wounds. In terms of efficacy, the reviewed LIDCs were reported to significantly improve up-regulation of angiogenesis in subcutaneous acute wounds (Ud-Din et al., 2015), or the general healing rate in all chronic wounds (Gardner et al., 1999; Karba et al., 1997). Statistically non-significant improvement in growth factors was also found (Dias Ismiarto et al., 2021). Also reporting postive results using the LIDC modality, the study by Gault and Gatens (1976) was, however, subject to bias due to a small sample size and lack of rigour. Patient safety while using the ES treatments/devices and cost were not explored or mentioned in any of these six articles.

4.2.1.2 Accel-Heal

All five studies (mainly case studies or small scale clinical trial) investigated low-intensity Accel-Heal devices on middle-aged or elderly patients with chronic, hard-to-heal, or recurrent wounds (Griffin, 2013; Ovens, 2017a; Ovens, 2017b; Taylor et al., 2011; Young et al., 2011). These devices were potentially equivalent to SIS' devices in terms of low intensity, although in only one of the five studies did the authors specify that the pulsed-direct-current modality of 40 microamperes was employed for this device (Young et al., 2011). The treatment was reported to have achieved

pain relief, kickstarted the healing process, inflammation reduction and subsequently wounds healed in case studies (Griffin, 2013; Ovens, 2017a; Ovens, 2017b). The use of this treatment in combination with compression also showed immediate and long-term effects on oedema-reduction (Young et al., 2011) and improvement in wound healing outcomes compared to non-ES-treatment group (Taylor et al., 2011). There was no information patient safety in any of the five articles. In terms of cost effectiveness, based on the positive outcomes of a small-scale trial, Taylor et al. (2011) estimated that the use of Accel-Heal would save approximately 15% of the UK National Health Services cost and 26% of number of nurse visit (equivalent to approximately £6.7 million) in five months. This is the only cost evaluation study in this review.

4.2.1.3 Wireless micro current stimulation

The wireless micro current stimulation treatment was in the same output current range with that of SIS's devices albeit with differences in modality (Ramadhinara & Poulas, 2013; Wirsing et al., 2015). This contactless type of treatment transferred a small current by using electron motions to facilitate cellular metabolisms. The operational mechanisms of this treatment remained under-investigated as according to Kambouris et al. (2017). The efficacy of the treatment on middle-aged and elderly patients with (mostly) chronic wound healing was inconclusive due to small sample sizes and the lack of a control group (Wirsing et al., 2015). Contraindications, treatment-related adverse events and nil improvement when indwelling fibrin layers was used were reported (Wirsing et al., 2015), raising questions about the applicability of the treatment.

4.2.1.4 Low-intensity pulsed current/waveform and other treatments/devices

Limited by small sample sizes, six remaining studies reported statistically non-significant positive outcomes in favour of ES treatments/devices, with an exception of one study reporting

significant outcomes albeit with large 95% confidence intervals (Ud-Din et al., 2015). These outcomes included: (1) improved up-regulation of angiogenesis (Ud-Din et al., 2015), (2) increased vascular endothelial growth factor and (3) reduced inflammation (Sebastian et al., 2011) among young healthy participants with acute wounds (punched biopsy wound sites); (4) improved wound healing (Wood et al., 1993), (5) pain relief (Fraccalvieri et al., 2015) among middle-aged or elderly patients with chronic wounds; and (6) stimulated epithelialisation of a painful infected leg ulcer among an elderly patient (Hampton & King, 2005). Exploring the use of microcurrent stimulation on young patients with burn injuries, Ibrahim et al.'s (2019) research was, however, subject to methodological concerns due to baseline differences between the study groups at baseline. None of these studies reported aspects related to patient safety and cost effectiveness. It is noted that Ud-Din et al. (2015) is the only study in this reviewed shared the same current output (4 microamperes) with SIS's low-intensity device although their output voltage and frequency were not equivalent. On the other hand, the treatment/device investigated by Wood et al. (1993) is found to shared similar waveform outputs, and the one studied by Fraccalvieri et al. (2015) had similar electrode arrangements with that of SIS's devices.

Table 1. Reviewed articles of potential/partial equivalence to SIS' devices.

Author	Design	Electrical Treatment/ Device	Population	Safety	Equivalence	Cost	Efficacy
	Low-intensity direct current						
1. Gardner et al. (1999)	• Meta-analysis N= 15 RCT Studies of 4 types of electronic stimulations (LIDC, HVPC, TENS, AC) • Objective: "To quantify the effect of ES as an adjunctive therapy for chronic wound healing and to explore the influence that the type of ES and type of wound may have on the effectiveness of ES." • Measurement: percentage healing per week	4 types of electronic stimulations (LIDC, HVPC, TENS, AC) • LIDC = 20-200 microampere, <8V, delivered through wound tissues • HVPC = 80-100 pulses/s, 2.5 microamperes, 75-200V, delivered through wound tissues • AC = alternating current, symmetrical biphasic pulses, low voltage milliamperes • TENS = 15-20 microamperes, 150 microsec pulse, 85 Hz.	• Type: older people with chronic wounds • Settings: varied • Patient journey: chronic healing ES sample: -N = 18 -Mean age: 58.8 ± 18.5 -Post treatment follow-up = 6.4 weeks ± 3.0 -Mean wound size at baseline = 8.8cm^2 ± 6.8 Control sample -N = 13 -Mean age = 58.8 ± 18.0 -Post treatment follow-up = 6.2 weeks ± 2.7 -Mean wound size at baseline = 9.2cm^2 ± 6.4.	Nil report	LIDC is potentially equivalent to SIS LIDC although the output current is much higher. AC is potentially equivalent to SIS AC (although no exact information was provided).	Nil report	• ES (including all types) led to a significant increase 144% of healing rate as compared to control treatment. • ES most effective in treating pressure ulcers. • Inconclusive difference of different types of ES due to potential of sampling error • Significant improvement of chronic wound healings after use of ES although the difference between different types of ES on different wound types was inconclusive.
2. Cukjati et al. (2001)	• Retrospective data analysis based on 4 study groups in 1989, "Wounds were randomly assigned to four treatment groups" p.544. ➢ conservative treatment (CO, n = 54 wounds, 65 patients): ➢ sham treatment (SH, n = 23 wounds, 23 patients) ➢ biphasic-current stimulation (AC, n = 181, 178 patients) ➢ direct-current stimulation (DC, n = 42, 42 patients). • Objective: "To determine the effects of wound, patient and treatment attributes on the wound healing rate and to propose a system for wound healing rate prediction." P.542 • Measurement: ➢ wound healing determined by wound area, perimeter and width-to-length ratio periodically ➢ "wound extent was described by wound length,	➢ Conservative treatment: selective debridement + standard dressing + broad-spectrum antibiotics when required. ➢ Sham treatment: Disconnected machine to deliver no current. ➢ Biphasic-[pulsed] current stimulation: Dosage ranged 0.5-2 hours/daily. Electrodes placed on two sides of the wound. Pulse duration: 0.25ms, repetition rate: 40 Hz. Alternated stimulation trains or pauses of 4s. Adjustable current range: 15-25mA. ➢ Direct-current stimulation: Dosage ranged 0.5-2 hours/daily. 0.6mA. Positive electrode placed over the wound surface, negative electrode placed on the intact skin around the wound, or both placed on	• N = 214 patients with 300 wound cases >1cm^2, at least 4 weeks duration • Age range: 23-82 years • Wound type: chronic ulcers (pressure, arterial, vascular, neurotrophic, traumatic) • Settings: nil information • Patient journey: chronic healing Significant difference between groups at baseline in terms of wound aetiology, wound diagnosis and treatment duration.	Nil report	Biphasic-current stimulation: unclear of equivalence to SIS AC DC: Equivalent modality but unsure of output voltage.	Nil report	• No difference in terms of healing time (days) • Significant difference in terms of healing rate per day: fastest among AC, followed by DC and CO. • The best prognostic factors are weekly follow-up measurements of wound area after at least 4 weeks monitoring • Treatment type is only one of the predictors to wound healing (not as strong as wound and patient related factors) • "Arranged in order of decreasing prediction capability, prognostic factors are: wound size, patient's age, elapsed time from wound appearance to the beginning of the treatment, width-to-length ratio, location and type of treatment."p.542

Author	Design	Electrical Treatment/ Device	Population	Safety	Equivalence	Cost	Efficacy
	width, depth, and grade" (by using the four-stage Shea grading system)	the healthy skin at the wound edge.					
3. Karba et al. (1997)	• A cutaneous wound model and double blinded clinical trial involving 3 groups: ➢ Group 1: (DC +, N = 16) "positive stimulation electrode overlaid the ulcer" ➢ Group 2: (DC +/-, N = 18) same electrical stimulation programme to treatment 1, but different electrode placement. ➢ Group 3: sham treatment (N = 16) • Objective: To evaluate the effectiveness of constant direct current stimulation on wound healing • Measurement: wound areas	• Constant direct current stimulation • Treatment 1: positive stimulation electrode (Encore TM Plus, Axelgaard Manufacturing Co., Ltd.), 0.6 mA. 1 electrode placed over and 4 around the wound to ensure even current distribution. • Treatment 2: Similar to treatment 1 but involving 2 electrodes placed on two edges of the wound. • Treatment on wound model: 0-66mV, 0.6mA. • Dosage: 2 hours/day (unclear for how many weeks)	• N = 50 spinal cord injured patients with pressure ulcers	Nil report	Treatment 2 equivalent to SIS LIDC's voltage although the current was much higher.	Nil report	• Relative healing rate per date was significantly highest among group 1 (DC +), followed by group 2 (DC +/-) • Wound modelling showed non-significant healing effect on intact skin although different distribution of the current was observed.
4. Gault & Gatens (1976)	• Clinical trial & case presentations • Clinical trial: Patients had bilateral ulcers, one receiving treatment and the other considered as control. • Objective: to investigate the effectiveness of low intensity direct current (LIDC) in ischemic skin ulcers. • Measurement: wound size	• Low intensity direct current • Output current: 200-1000 microamperes • Output voltage: 9V • Negative electrodes placed onto the ulcer; positive ones positioned around 25cm from the lesion. Electrodes avoided at umbilicus position. • The current customised to patient level, between bloody exudation and copious draining. • Dosage/duration: 6 hours/ day (2 hours treatment + 4 hours rest) x 7 days/week	• Type: N = 6 patients with bilateral ulcers • Age/wound type/ patient journey: unclear 2 Case presentations: • Type: elderly women with comorbidities • Setting: hospital • Wound type: Ulcer, unclear of aetiology and healing journey.	Nil report	Equivalent modality to SIS LIDC but not equivalent in output current and voltage. Output voltage (not current) can be equivalent when the treatment was adjusted to patient's individual level.	Nil report	• Higher percentage of overall healing and weekly healing in treated wounds as compared to controlled wounds. • 98% of wound healing in case presentation 1 after 6 weeks. • 97% of wound healed in case presentation 2. Unclear of treatment period.
5. Dias Ismiarto et al. (2021)	• RCT • Control group: Antibiotics use only • Treatment group: Antibiotics and LIDC • Objective: "To explore the effects of a molecular pathway from the application of low-intensity direct current (LIDC) for wound healing through the	• Electromagnetic Low-intensity direct current (stimulation ITO 320) • 500uA • Dose/Duration: 2 hours • Electrode arrangement: unclear	• Type: N = 32 in-patients, Indonesia • Age: unspecified • Wound type: infected, open fracture • Exclusion: pregnant/ breastfeeding patients, or those with severe chronic disorders (diabetes mellitus, dyslipidaemia disorders, blood clotting disorders, immunocompromised disorders, and autoimmune disorders).	Nil report	Equivalent to SIS LIDC modality although the current is much higher	Nil report	Stimulation of growth factor: Substantial wound contraction an increase in growth factor in the treatment group as compared to control group

Author	Design	Electrical Treatment/ Device	Population	Safety	Equivalence	Cost	Efficacy
	pathway signalling growth factor and initiation of fibroblast activation." • Measurement: Biomarkers and wound area (using digital calliper)						
6. Mohajeri-Tehrani et al. (2014)	• RCT • Control group: sham treatment LIDC (n=10) • Treatment group: LIDC (n=10) • Objective: to evaluate "the effect of low-intensity cathodal direct current on the release of plasma vascular endothelial growth factor (VEGF) and nitric oxide (NO) in diabetic foot ulceration" • Measurement: Wound surface, skin temperature and biomarkers.	• LIDC (The BTL-5000 series (BTL Industries, Ltd; Staffordshire, United Kingdom) • 1.48 ± 0.98 mA • Dosage/Duration: 1 h/day x 3 days/week x 4 weeks (12 sessions) Electrode arrangement: 1 near wound edge and another one proximally far from the wound (Arrangement based on previous study)	• Type: N = 20 diabetic patients with mild to moderate diabetic neuropathy, ankle-brachial index >0.7, • Age: 40-60 years • Wound type: Diabetic foot ulcer, wound surface area (WSA) >1.5 cm^2 • Setting: home environment • Patient journey: Chronic wound healing • Exclusion: Fracture in a lower limb, severe infection, malignancy, kidney failure, skin diseases, osteomyelitis, pregnancy, any drug administration or therapeutic device that could enhance wound healing (within the last 30 days), or medical condition for which ES is contraindicated.	Nil report although strategies were in place to reduce risk of burns among diabetic patients (using sensory threshold)	Equivalent to SIS LIDC modality although the current is much higher	Nil report	Stimulation of growth factor and healing process: • Significant increase in growth factor (VEGF) and biomarker indictor of wound healing (NO) in the treatment group as compared to control group • Insignificant change in wound area.
	Accel-Heal						
7. Ovens (2017a)	• Case study • Patient: 50-year-old woman • Wound type: recurrent infected venous malleolus ulceration (7.5cm x 7.5cm wound size, 0.75cm deep, 10% slough + 90% granulation) • Wound duration: 3 weeks • Pain score: 10/10 • Medication: Pain relief + broad spectrum antibiotics	• Electroceutical treatment (Accel-Heal) • Electrodes were applied next to the wound edge. • Treatment duration: 2 weeks	• Type: middle-aged • Wound type: recurrent, chronic & painful • Setting: outpatient • Patient journey: prolonged healing	Nil report	Insufficient information to make informed judgement Potential equivalence as per advice by SIS manufacturer	Nil report	• Contributing to "physiological change that amends the impaired biological functions in the wound, kick-starting the healing process in the wound" • Pain relief • Wound reduced in size & exudation • Would healed
8. Ovens (2017b)	• Case study • Patient: 80-year-old male • Wound type: recurrent venous leg ulcer (left malleolus) while using class II compression hosiery. • Wound characteristics: 27cm2 (20% granulation, 50% slough, 30% maceration). Pain 7/10. ABPI: 1.3 bilaterally. Some episodes of infection. • Medical history: atrial fibrillation, hypertension, enlarged prostate and osteoarthritis neck and back	• Accel-Heal® • Electrode placed opposite each other, avoiding any broken or cellulitic skin. Changed every 48 hours. • Duration: 12 days • Intensity according to patient tolerance	• Type: elderly • Wound type: recurrent & chronic • Setting: unclear • Patient journey: chronic wound healing	Nil report	Insufficient information to make informed judgement Potential equivalence as per advice by SIS manufacturer	Nil report	Kickstarted the healing process: • Wound appearance improved 3 weeks after treatment. • Pain gradually subsided. • Inflammation reduced. • Wound eventually healed.

Author	Design	Electrical Treatment/ Device	Population	Safety	Equivalence	Cost	Efficacy
9. Griffin (2013)	• Case series involving patients with long histories of leg ulcers and multiple comorbidities: • Patient 1: Female, "50-year history of venous problems", history of multiple chronic conditions including heart arterial disease. Mixed aetiology ulcer of 8 years on lower leg. Refused ABPI measurement. • Patient 2: Diabetic male patient, BMI>30 kg/m^2. History of varicose vein and angioplasty. Ulcers on both leg for more than 1 year. ABPI = 1.11 (right) and 0.61 (left). • Patient 3: Male patient with history of severe cardiac diseases, obesity, poor mobilisation, and smoking, BMI = 43 kg/m2. ABPI = 0.64 (Right) and 1.03 (left). Open ulcers, unclear of duration, required of topical antibiotics.	• Accel-Heal (Synapse Micro-Current Ltd) • "uses micro-currents [bio-current] to support tissue repair by interacting with biological processes" • Treatment duration: 48 consecutive hours (single unit) x 6 (= 12 days) • "The electrode pads are placed on healthy skin either side of the wound during a primary dressing change. The electrode wires are threaded through the standard dressing and are connected to the device, which is then activated via an on/off switch and tucked into the external dressing"	• Type: patients with multiple comorbidities • Wound type: chronic, hard to heal, varied aetiologies • Setting: unclear • Patient journey: chronic wound healing	Painless redness without complication – unknow if related to the treatment in patient 2.	Insufficient information to make an informed judgement Potential equivalence as per advice by SIS manufacturer	Estimation rather than actual evaluation "the potential to save the NHS up to 15% of costs, and up to a 27% reduction in the number of nurse visits, over a 5-month treatment period"	• Patient 1: Wound reduction by 28.9% and subsequently healed (unclear of days-to-healing) • Patient 2: Wound increased in size although the level of slough and granulation improved significantly. • Patient 3: Wound area reduction of 31.3%, granulation, level of slough, and epithelisation improved when combined with 2 layers of compression.
10. Taylor et al. (2011)	• Cost evaluation using 5-month Markov model at 2008–2009 prices ➢ Patients observed over 3 to 5 months. ➢ Group 1: 3 units of electric stimulation + two-layer compression + secondary dressing if required (n = 21) ➢ Group 2: compression and dressing only (unclear of sample size) • Objective: "to estimate the cost-effectiveness of using electric stimulation (ES) therapy (Accel-Heal) plus dressings and compression bandaging compared with dressings and compression bandaging alone in treating chronic, non-healing venous leg ulcers (VlUs) of > 6 months' duration from the perspective of the national Health Service (NHS) in the UK." P.464 • Measurement: Wound size & cost of resources	• Accel-Heal (Synapse Microcurrent Ltd.) "registered class IIA medical device, developed as a disposable, one-time use dressing" p.464 • Low-intensity electrical current pulses (unclear how low) • Electrodes placed on intact skin, on opposite borders of the wound. • Maximum wearing time: 72 hours • Dosage/Duration: 3 active units of ES therapy	• Type: "> 18 years of age and have a chronic, nonhealing VLU of > 6 months' duration, which did not have an ankle brachial pressure index (ABPI) < 0.8." • Mean age: 69.2 years (95% CI: 64.4; 74.0 • Exclusion: Moribund patients, ABPI <0.8, rheumatoid arthritis, or pyoderma gangrenosum • Wound type: chronic non-healing wound. Mean size 8.9cm^2 (95% CI: 4.9; 13.0). • Wound duration: 2 years (95% CI: 1.1; 2.9)	Nil report	Insufficient information to make an informed judgement Potential equivalence as per advice by SIS manufacturer	Total treatment (ES + compression + dressing) cost £748.94 as compared to £879.90 (compression + dressing only). Estimate of saving over the first 5 months of treatment: 15% reduction in NHS costs (£6.1 million) and 26% reduction in the number of nurse visits (0.6 million).	• Higher percentage of wound healed or improved in treatment group. • Higher mean health status in treatment group.
11. Young et al., (2011)	• Clinical trial • Objective: "to evaluate the efficacy of a medical device, accel-Heal, which generates a	• Compression AND low intensity pulsed current (Synapse Accel-Heal, class IIA device, under the	• Type: N = 30 Outpatients, monitored for 30 days, UK • Mean age: 72.7, range 46-95 years	Nil report	Potentially equivalent to SIS LIDC in terms of current intensity	Nil report	Significant reduction in periwound oedema immediately after treatment (44%) and after 20-90 days post treatment (67%).

Author	Design	Electrical Treatment/ Device	Population	Safety	Equivalence	Cost	Efficacy
	low-intensity pulsed direct current, on the management of oedema in chronic leg ulcers, using high-frequency diagnostic ultrasound." • Measurement: oedema level using high-frequency diagnostic ultrasound at baseline and post treatment duration x 3 positions (centre of the wound, peri wound, and uninjured skin near wound edge). • Conflict of interest declared (funder: Synapse micro-current ltd)	medical directive 93/42/EEC) • Working current: 40µA, with a rectified ramp waveform • Electrode arrangement: on intact skin near wound edge • Dosage/duration: continuous use over 10 days (except when changing dressing). • Compression continued post treatment	• Wound type: chronic, non-healing oedemic ulcers from venous and mixed aetiologies • Wound duration: 2-96 months • 5 loss to follow-up Exclusion: • Current corticosteroid therapy, radiation therapy or chemotherapy • Presence of ventricular arrhythmia, Atrial fibrillation or cardiac pacemaker • Metal implants near the area of treatment. • Setting: Outpatient, under close monitoring of GPs • Patient journey: chronic wound healing		(although much higher than SIS's) Not equivalent to current type (pulsed direct vs direct current)		
	Wireless micro current stimulation						
12. Wirsing et al. (2015)	• Clinical trial on 2 wound centres from Germany and Switzerland • Objective: To evaluate the effectiveness of WMCS on chronic wound healing • Measurement: digital wound area measurement of wound area • Check-up: baseline, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 12 weeks and longer.	• Wireless micro current stimulation (WMCS), "transfer current wirelessly to the wound by using oxygen's and nitrogen's ability to donate electrons", 1.5 – 4 microamperes, 45 minutes per session, "treatment surface covered is about 400cm2" • Necrotic tissues, fibrin and coverings were removed prior to treatment • Mean duration of treatment: 45 days	• Type: 47 outpatients with multiple comorbidities • Mean age: 72 years (range 39-91) • Wound types: chronic venous, arterial, mixed leg ulcers; diabetic foot lesions; pressure ulcers; posttraumatic lesions; decubitus; pyoderma; vasculitis and ulcer Martorell. • Wound duration: 10 months (range: 3 months – 11 years) • Settings: varied • Patient journey: chronic healing • Contradictions: people with acute inflammation or severe infection on wounds, pregnancy, implanted electrical device, malignancy close to the wound, epilepsy or other neuro-excitatory diseases, overshoot-granulation (rough) tissue of the wound or treatment with metal ion-containing wound-care products.	• Serious adverse events: nil • Adverse events: burn filling, or redness of surrounding tissues. All short duration and not required treatment. • Withdrawals of treatment: n=2 due to pre-existing severe infections. • No improvement observed among 3 patients with unremovable fibrin layer.	Equivalent to the SIS device's LIDC output parameters for infection treatment Non-equivalent to SIS devices in terms of type of contact (contact vs non-contact current transfer)	Nil report	• Efficacy on wound area reduction after using treatment: 41.1±27.3% (P =0.0215) per month (As compared to 17·1±19·4% before the trial) • Efficacy on wound area reduction after 8 weeks using treatment was 95% (unclear of sample, mean and standard deviation).
13. Ramadhinara & Poulas (2013)	2 case studies (treatment followed by standard wound care) Case study 1: • 70-year-old Indonesian man with diabetic. Currently having normal blood glucose level, well-controlled diet, and stable blood pressure.	• Wireless microcurrent stimulation (WMCS) (WetlingEUApS, Fredensborg, Denmark) • Current 1.5 microampere • Dosage: 1 hour/day until wound healed.	• Type: Middle-aged and elderly people with diabetic and other comorbidities • Wound type: acute and chronic • Patient journey: both acute and chronic wound healing	No discomfort reported	Equivalent to the SIS device's LIDC output parameters for infection treatment Non-equivalent to SIS devices in terms of type of contact (contact vs non-contact current transfer)	Nil report	Wound healed after 45 days (case study 1) or 4 days (Case study 2).

Author	Design	Electrical Treatment/ Device	Population	Safety	Equivalence	Cost	Efficacy
	• Medical history: foot amputation due to complication of diabetic foot ulcer. • Wound type: chronic ulcer due to unhealed amputation site Case study 2: • 47-year-old woman with type 2 diabetes, current use of insulin and oral antidiabetic medication. • Medical history: neuropathy, surgeries • Wound type: acute wound						
	Waveforms/pulsed current						
14. Fraccalvieri et al. (2015)	• Clinical trial ➢ Group 1: "Patients with wounds that were not responding to conventional therapies for at least 3 months. This group was evaluated for the wound healing" (n=21) ➢ Group 2: "patients with severe pain [with Visual Number Scale (VNS)>8] greatly impairing their quality of life or requiring a heavy use of painkillers. This group was evaluated for the effect of electric therapy on pain control" (n=11) • Objective: To evaluate "a particular type of ES, based on the recent application of a different type of waveform, corresponding to the principle of stochastic resonance introduced in this type of treatment."	• Bioelectrical signal therapy (BST) device (LifeWave, Petach Tiqwa, Israel • Two electrodes placed surrounding the wound. • Stochastic waveform component originates from a digital precursor that is a white signal (i.e. the same intensity range exists along the frequency spectrum). The output of the stochastic signal has a maximum amplitude of 7·5±0·5V, duration of 0·246 seconds with 80% of energy in the bandwidth of 0–1300 Hz, along this bandwidth the signal exhibits a stochastic white waveform. The output of the rectangular pulse train is a periodic biphasic pulse which has maximum amplitude of 12±1V and pulse duration of 4 millisecond"	• Type: "patients with chronic wounds not responding to traditional dressings, surgery or negative pressure therapies (NWPT)" • Age range: 34-88 • Wound type: Chronic wounds from varied aetiology, prolonged healing (or extreme pain) • Setting: Outpatient • Patient journey: Chronic wound healing ➢ Exclusion: Patients with arrhythmia, active pacemaker or defibrillator, kidney failure, liver failure, severe anaemia or sepsis, pregnancy or breastfeeding; wounds at chest level or above; neoplastic lesions or silver dressings.	Nil report	Equivalence to the waveform output part of the SIS device, as per advice by SIS manufacturer	Nil report	• Reduction in wound size and pain. • 10% of patients in group 1 did not respond to treatment.
15. Sebastian et al. (2011)	• Clinical trial • Punch biopsy was taken from the upper arms of 20 volunteers on day 0 and repeated on day 14. Treatment was applied every other day after repeated biopsies. Comparison was made between arms with treatment and arms without treatment • Objective: "demonstrate the effect of DW in vivo by comparing cutaneous wound healing in human volunteers	• Electrical stimulation (ES) waveform, degenerate wave (DW) • Non-invasive transcutaneous electrical stimulation device called Fenzian11,12 (CE approved and US FDA 510k registered) • Rationale of treatment: "promoting the migration of keratinocytes and macrophages, enhancing	• Population: 20 healthy Caucasian volunteers in UK • Aged 23 +/- 4, • Wound type: 5mm punch biopsy sites and 6-mm repeated punch biopsy sites • Setting: unclear	Nil report	Equivalent to treatments/devices in Griffin et al. (2013), as per advice by SIS manufacturer	Nil report	Reduced inflammation, improve up-regulation angiogenesis, and vascular endothelial growth factor

Author	Design	Electrical Treatment/ Device	Population	Safety	Equivalence	Cost	Efficacy
	undergoing temporal punch biopsies with and without ES" p.694 • Measurement: RNA isolation, cDNA synthesis, qRT-PCR, and DNA gel electrophoresis, Immunohistochemistry	Angio-triphosphate and protein synthesis". P.693					
16. Wood et al. (1993)	• RCT ➢ Control group: Sham treatment (n=30 patients, 31 ulcers) ➢ Treatment group: Pulsed low-intensity direct current (n=41 patients, 43 ulcers) • Objective: "to test this electrotherapeutic device in a multicentre double-blind placebo protocol on a statistically significant number of indolent chronic decubitus ulcers in stages II and III" • Measurement: wound areas by tracing and photographs	• Pulsed low-intensity direct current (MEMS CS 600, Harbor Medical Inc, Minneapolis, Minn) • "12-V battery and contains a feedback loop ensuring a current, 300uA followed by treatment at 600uA." • Frequency of 0.8Hz • Electrode arrangement: 2 electrodes on in-tact skin near wound edge. 1 additional electrode for larger ulcers (unclear how large). • Dosage/duration: 3 times/week	• N = 71 patients • Wound type: stage II and stage III chronic decubitus ulcers (no significant improvement in 5 weeks) • Mean age: 75.6 years (treatment group), 74.9 (control group) • Duration: 5.5 months (treatment group), 4.9 month (control group)	Nil report	Potential equivalence (in terms of intensity range and electrode arrangement) as per advice by SIS manufacturer	Nil report	More wounds in the treatment group improved as compared to control group
17. Ud-Din et al., (2015)	• RCT ➢ Group 1: Electrical Stimulation ➢ Group 2: secondary intention wound healing • Objective: "To evaluate the role of ES in affecting angiogenesis during the acute phase of cutaneous wound healing over multiple time points to identify if the enhanced effect occurred earlier than day 14." • Measurement: Biomarkers	Electronic Stimulation • Transcutaneous low intensity device – the Fenzian system (Fenzian Ltd, Hungerford, UK) • 4 microamps, 20–80V, default frequency of 60Hz • Impulses last approximately six-hundredth of a second • Applied on 4 occasions (not parallel in 2 groups) • Treatment of 30 minutes, applied near wound sites.	• Type: N = 40 healthy young adult Caucasians -BMI: 20-45 -Age: 18-30 • Wound type: punched biopsy wound sites • Setting: research setting • Patient journey: acute wound healing	Nil report	Output current is equivalent to SIS LIDC but much higher in output voltage (20-80V)	Nil report	Improved up-regulation of angiogenesis reflected through: ➢ Significant improvement in wound healing (wound surface, wound volume, wound diameter, wound depth, electrical field, blood flow, granulation tissue) in multiple data collection points post treatments [based on markers vascular endothelial growth factor-A (VEGF-A) & Placental growth factor (PLGF)]. Timepoint of significance: Day 7,10, and 14 post treatment.
Other device/treatment							
18. Hampton & King (2005)	• Case study	• Bio-electrical stimulation therapy using a specially designed dressing (POSiFECT). • "In the POSiFECT dressing, an electrode system is provided that generates a current flow that envelops and permeates an entire wound site" p.S31 • Electrode arrangement: on top of the wound. • Treatment duration: 7 weeks: 3 weeks on, 1 week	• Type: 70-year-old female with previous knee replacement • Wound type: non-healing, painful leg ulcers for 12 months. Wound odour, excessive exudation with evidence of colonisation of Pseudomonas. • Setting: Unclear • Patient journey: chronic nonhealing wound	No skin damage by the battery	Potential equivalence (in terms of intensity range and electrode arrangement) as per advice by SIS manufacturer	Nil report	Stimulate wound epithelialisation to promote healing: • Wound appearance improved by week 4. • Wound granulation improved by week 8 • Wound size reduced by 33.3% by week 8 (when the treatment stopped) • Wound healed by 2 months after the treatment stopped.

Author	Design	Electrical Treatment/ Device	Population	Safety	Equivalence	Cost	Efficacy
		off, 2 weeks on and 1 week off.					
19. Ibrahim et al. (2019)	• Clinical trial involving 3 groups: ➢ Group 1: negative pressure wound therapy (NPWT) ➢ Group 2: microcurrent electrical stimulation (MES) ➢ Group 3: Control Objective: "to compare the efficacy of NPWT and MES in accelerating healing of partial thickness burn wounds."	• NPWT & MES • MES purpose: "to mirror the body's own natural current as the used currents are similar to those produced by the body through tissue repair", to "regenerate the internal bioelectrical activity of injured tissues" p.214	• Type: N = 45 "Patients with thermal dermal burn injuries covering 25–40% of total body surface area" • Age range: 20s • Average length of stay until the enrolment to this study was highest in the control group. • Settings: Hospital • Patient journey: prolonged healing	Nil report	Potential equivalence (in terms of intensity range) as per advice by SIS manufacturer	Nil report	• MES and NPWT showed reduction in length of stay and bacterial growth. • MES was superior in percentage of wound surface reduction. NPWT was most effective in reducing colony count.

4.2.2 3.1.2. Non-equivalence

Fifteen of the reviewed studies investigated some ES modalities that, to our best knowledge and upon consultation by the manufacturer, were not equivalent to the parameters of SIS's devices. Please see **Table 2** for details of each of these studies.

Table 2. Reviewed articles of potential non-equivalence to SIS's devices.

Author	Design	Electrical Treatment/ Device	Population	Safety	Equivalence	Cost	Efficacy
1. Mulder (1991)	• Randomized double blind multi-centre study ➢ Control group: Sham treatment ➢ Treatment group: Electrical stimulation ➢ Having a cross-over period: treatment, cross over of sham treatment to actual treatment, & monitoring • Objectives: "(1) to compare the healing of open-skin wounds treated with electric stimulation with the healing of similar wounds treated with sham stimulation and, (2) to evaluate patient tolerance to the therapeutic regimen." • Measurement: Wound healing (percentage of wound reduction)	• Electric stimulator: self-contained (Dermapulse) • low-intensity, portable unit pulsed, direct current powered by a six-volt battery. • Three intensity levels were used: 30, 35, and 40mA, with a pulse width of 140psec and a charge per pulse of 4.2, 4.9 and 5.6 Microcoulombs, respectively. Frequencies of 64 and 128pps were used. • Dosage/Duration: 30 minutes/session x 2 sessions/day x 14 weeks • Duration: 14 weeks • Electrode placed at least 12 inches from the wound site.	• Type: 59 participants • Wound type: open wounds of pressure, vascular and surgical aetiology (including infected wounds). Size: 4-100cm^2 • Setting: 9 centres • Exclusion: ➢ Cancerous wounds near the eyes, larynx. ➢ Wounds in area where electric stimulation is not safe. ➢ Wounds with occlusion or risk of haemorrhage ➢ Patients with peripheral vascular problems, severe systemic diseases, pregnancy, cardiac pacemaker, obesity, long term steroid use, chemo/radiation therapy. • Patient journey: chronic wound healing	• Treatment-related adverse events: ➢ Exudation from a necrotic ulcer ➢ Discomfort ➢ Complaints of tingling/prickly sensation • Treatment-not-related adverse events: Skin irritation	Non-equivalent (different modality and high amplitude)	Nil report	Improved wound healing (due to improved tensile strength and reepithelization, reduced bacterial burden): • 56% wound size reduced in treatment group as compared to 33% in control group. • 92% response favoured treatment group, as opposed to 54% in control group. (analysis of only 47 participants included due to inconsistency/ protocol violation)
2. Baker et al. (1997)	• Prospective comparative study: ➢ Treatment A: Asymmetric biphasic square-wave pulse (patients in this group were older, longer wound duration and higher number of wounds, higher compliance rate than the 3 other groups, (n=21) ➢ Treatment B: Symmetric biphasic square-wave pulse (n=20) ➢ Control group 1: Very low stimulation current (n=19) ➢ Control group 2: No electrical stimulation (n=20) • Objective: To compare 2 stimulation waveforms on diabetic patients with open ulcers • Measurement: wound perimeter	• Treatment A: Asymmetric biphasic square-wave pulse • Treatment B: Symmetric biphasic square-wave pulse • "Amplitudes were set to activate intact peripheral nerves in the skin". • Control group 1: Very low stimulation current • Treatment durations: 30 minutes/session x 3 sessions/day x 5days/week (not sure for how many weeks) • Maximum duration = compliance • At least 1/3 of maximum duration = semi=compliance	• 80 diabetic patients, LA, USA • Setting: outpatient	• Nil report	Treatment A and B non-equivalent (different modality and high amplitude) Not enough information to make judgement regarding control group 1	Nil report	• Non-significant highest healing rate in group A, followed by group B as compared to 2 control groups.
3. Lawson & Petrofsky (2007)	• Clinical trial • Objective: "to compare healing rates and skin blood flow of chronic stage III and IV wounds in people with diabetes (D) and those without diabetes (WD) using a warm room and electrical stimulation." • Measurement: skin blood flow by Laser Doppler Imager	• Biphasic waveform electrical stimulation, (MP 100, Biopac Systems, Goleta, CA) • 30 Hz, pulse width 200 micro seconds and a current of 20 milliamps. • 5 volt output of the Biopac system converted to a current controlled stimulus • Treatment setting: 32°C room • Dosage/duration: 20 minutes/session x 3 sessions/week x 4 weeks	• Type: 10 diabetic & 10 non-diabetic outpatients, referred by physicians/ physical therapists • Exclusion criteria: patients with cardiac pacemaker, peripheral vascular disease disposing them to thrombosis, active osteomyelitis, or were receiving long term radiation therapy, steroid therapy, or chemotherapy, or pregnant. • Age: ≥ 40 years	• 2 stopped treatment due to adverse events related to heated room	Non-equivalent (different modality and high amplitude)	Nil report	• Blood flow outside of the wound increased before and during the electrical stimulation. • No increase in skin blood flow in the centre of the wound. • Healing rates over four weeks of up to 70% were seen in subjects with diabetes using biphasic current.

			• Wound type: chronic stage III and IV wounds • Setting: outpatient clinics, USA • Patient journey: chronic healing				
4. Petrofsky et al., (2005)	• In vivo experimental design • Objective: "comparing the response of normal skin to that of a variety of wounds with similar levels of non-noxious stimulation to examine the blood flow response 5 minutes of electrical stimulation." • Measurement: skin blood flow in the centre of the wound, wound edge and outside of the wound (by Doppler flow imager)	• Biphasic square wave, balanced current pulse at 250 usec pulse width, frequency of 30 Hertz, maximum current of 20 milliamperes. • Device: Challenge 8000, Tustin, California • Dosage/duration: 5 minutes	• N = 10 males and females with non-healing wounds for at least 3 months • Age: 31.4±4.3 • Wound types: finger wounds and calf wounds • Settings: Clinic • Patient journey: Chronic wound healing	Nil report	Non-equivalent (different modality and high amplitude)	Nil report	Improved blood flow in both control and treatment group (both at centre and wound border).
5. Petrofsky et al., (2010)	• Clinical trial ➢ Treatment 1: Local dry heat using infrared lamp (37°C; n = 10) ➢ Treatment 2: local dry heat + Electrical stimulation (n = 10) • Objective: "to deduce the individual roles of heat and ES in the healing of chronic wounds." • Measurement: skin blood flow inside and outside the wound (by Doppler flow imager)	• Biphasic sine wave stimulation (30 Hz, pulse width 250 ls, current approximately 20 mA). • Device: Challenge 8000A (MPTS, Tustin, CA, USA). "Using the three-channel electrical stimulator, current flows simultaneously from an active electrode (source) to the other two reference electrodes (receivers). The designated active electrode is rotated every second in sequence, allowing the current to create two pathways at any time during three-channel ES." • Dosage/Duration: 30 minutes/session x 3 sessions/week x 4 weeks	• N = 20 diabetic patients • Mean age: 48.4 ± 14.6 years • Wound type: non-healing diabetic foot ulcers Wound duration: 38.9 ± 23.7 months	Nil report	Non-equivalent (different modality and high amplitude)	Nil report	Significant improved blood flow (152.3 ± 23.4%) and significant decreased of wound size (68.4 ± 28.6%) and volume (69.3 ± 27.1%) in treatment 2 group as compared to treatment 1 group.
6. Koel & Houghton 2015	• Systematic review and meta-analysis • Meta-analysis included 15 RCTs that compared low frequency electrostimulation plus standard wound care with standard-wound-care-only.	• Low frequency electrostimulation (<1000Hz) • "two electrodes are attached to the body to realize an electric circuit leading to an internal electric field (EF) with physiological responses of the body" p.118 • "The placement of the electrodes is often one in the wound and the other one opposite to it or with both electrodes just around the wound" p.118	• Varied populations and wound types	Nil report	Likely not equivalent as most of the treatments included had high currents or voltages (based on brief review of references included in the meta-analysis)	Nil report	• "[T]he application of additional ES increases wound reduction at week 4 by an extra 27.7%" (95% CI 15.6, 37.8)" • "[T]he results of unidirectional ES (extra PAR4= 30.8%; 95% confidence interval [CI] 20.9, 40.6) are clearly better than for bidirectional ES (extra PAR4= 18.3%; 95% CI - 7.1, 43.7)." • "Unidirectional ES in combination with standard wound care improved wound healing effect in pressure ulcers by 42.7% after 4 weeks of treatment (95% CI 32.0, 53.3)."
7. Franek et al. (2001)	• RCT that included 3 groups: ➢ Group A: high voltage stimulation (HVS) in combination with compression	• Current stimulator Ionoson, made in Germany • High voltage stimulation (HVS): doubled-peak monophasic	• Type: N = 79 Patients with chronic venous insufficiency (such as oedema, hyperpigmentation and lipo-dermatosclerosis of the affected	Nil report	Not equivalent (high voltage low current)	Nil report	• Stimulation of granulation tissue and epidermisation" • Wound area changes and pus cleansing and granulation level were significantly highest in group A.

	stock, and cathode stimulation. (n = 33). ➢ Group B: topically applied medicine (n=32) (no compression) ➢ Group C: Unna's boot – control group (n=14) (no compression) • Objective: "to evaluate the effect of high voltage stimulation (HVS) on the process of healing of chronic ulceration" • Measurement: ➢ Wound healing: "percentage change of the suppurate area and the weekly rate of this change" ➢ Wound granulation: the granulation index	impulses of a total duration of 0.1 ms and frequency of 100 Hz. • "The voltage was around 100 V and depended on patient response. Stimulation was performed with a current which produced no motion effects, only a tingling sensation. • Electrode arrangement: "active electrode …on the saline soaked gauze which was in direct contact with the wound. The passive electrode was positioned above the knee joint, on the anterior surface of the patient's thigh". • Dosage/Duration: 50minutes/section x 1/day x 6 days/weeks.	limb) and other chronic conditions. Most had ABPI >=0.8 • Age: in their 60s • Wound type: chronic venous ulceration • Setting: unclear • Patient journey: Chronic wound healing				
8. Recio et al. (2012)	• Retrospective case series • Objective: "To demonstrate the effectiveness of ES in the treatment of recalcitrant pressure ulcers."	• High-voltage electrical stimulation • Treatment characteristics: 100 milliamperes, 100 pulses/second. • "Polarity was negative initially and was switched weekly. The amplitude and wave form were maintained throughout." • Dosage/Duration: 60 minutes/session, 3–5 times/week (unclear for how many weeks)	• Adult patients with spinal cord injury (SCI) and recalcitrant pressure ulcers from 10-14 months. • A: 49-year-old man with stage IV heel pressure • B: 29-year-old man with left ischial wound • C: 51-year-old man with stage III pressure ulcer • Setting: Outpatient • Patient journey: Chronic and hard-to-heal wound healing	Nil report	Not equivalent (high intensity and voltage)	Nil report	• Reduced wound surrounding areas due to enhanced tissue wound healing
	Direct current – not equivalent						
9. Adunsky et al. (2005)	• Multicentre, double-blind, randomized, placebo-controlled study • Objectives: to investigate "the decubitus direct current treatment (DDCT) electrostimulation treatment of pressure sores stage 3 degree, with respect to rates of ulcer closure and wound area reduction."	• Decubitus direct current treatment • Treatment duration: 8 weeks + 12 weeks follow-up	• Type: N = 63 geriatric in-patients (many were paraplegic) • Settings: "11 departments of geriatric and rehabilitation medicine" • Mean age: 71.1 ±18.8 • Wound type: stage 3 degree non-diabetic pressure ulcers lasting ≥30 days, size between 1 and 50 cm2, no recent history (minimum of 30 days) of growth factors or vacuum-assisted treatment. • Exclusion: those with high liver function enzyme level, renal failure or pacemakers, medical disorders, recent use of steroids, chemotherapy, or other 33 immune-compromising drugs	• 25 withdrawals: 10 due to personal medical reasons + 15 due to non-treatment related adverse effect • 2 treatment related adverse-effects [occurred in multiple patients – not just 2]: • Excessive granulation of the treated wounds • Local irritation (possible effect of the DDCT on the silver ions contained in the topical sulphadiazine ointment that	Not enough information to make an informed judgement	Self-acclaimed Potential saving in time-course	• General outcome: Insignificant higher ulcer area reduction, complete healing rate, and speed of wound closure in treatment group compared to placebo group. • Per-protocol outcome after adjusting large withdrawals (n=25): Significant shorter healing time in treatment group (102 +/- 10 days and 67 +/-9 days, respectively, p = 0.0329).

				patients were treated with).			
10. Adegoke & Badmos (2001)	• Single blinded RCT design ➢ Group 1: routine care + interrupted direct current (IDC) (n=4) ➢ Group 2: routine care + placebo (n=3) • Objective: to evaluate the effectiveness of IDC in patients with spinal cord injuries (SCI) and pressured ulcers. • Measurement: percentage of wound surface change	• IDC (Dufield Mk7 by Duffied Medical Equipment Ltd, Derbys). • Rectangular waveform, frequency of 30Hz. • Dosage/duration: 45 minutes/session x 3 times/weeks x 4 weeks • Electrode placed over the wound through a saline soaked gauge	• Type: N = 7 in-patients with spinal cord injuries (SCI) • Mean age: 52.7 ± 8.1 (group 1), 35 ± 13.5 (group 2), range 21-60 years. • Wound type: grade IV pressured ulcers. • 1 withdrawal from treatment due to discharge from hospital • Setting: hospital • Patient journey: chronic wound healing	Nil report	Unclear Note that the intensity of the treatment was adjusted "to a level just below that capable of producing muscle contraction".	Nil report	Wound surface reduction 22.2% in treatment group as compared to placebo group (2.6%)
11. Asadi et al. (2017)	• Single-blind RCT (control group vs low-intensity cathodal direct current) • Objective: To investigate the effect of low-intensity cathodal direct current on angiogenesis in ischemic diabetic foot ulcers (DFUs). • Measurement: Wound surface area; HIF-1a (stimulator of several angiogenic factors), NO (critical mediator of normal wound healing), VEGF (vascular endothelial growth factor), and sVEGFR-2 (soluble VEGF receptor-2 inducing angiogenesis) collected from wound fluid after debridement at first and last treatment session.	• Low-intensity cathodal direct current (LICDC) – stimulator BTL-5000 series (BTL Industries, Ltd., Staffordshire, United Kingdom) • Treatment duration: 1 h/day x 3 days/week x 4 weeks (12 sessions) • Sensory threshold intensity from the other arm/leg and rechecked every week (3.36 ± 0.58 mA) to prevent skin burns • ES with CDC was applied to the wound site through the active electrode (carbon rubber electrode, 2 3cm2) placed near the proximal edge of the ulcer, over intact skin	• Type: N=30 Type-2 diabetes patients in Iran (n=15 in each group) • Mean age: 50s to 60s. • Wound types: ischemic foot ulcerations, >2cm^2, light neuropathy (based on the UK scale), and a Wagner foot classification of 2. • Exclusion: osteomyelitis, a cardiac pacemaker, angioplasty, severe infection, cancer, kidney failure, other skin diseases, or any medical conditions for which electronic stimulation is contraindicated, such as pemphigoid. • 6 withdrawals from both groups due to medical/personal reasons.	Nil report regarding safety to patients during the treatment although cautionary approach regarding preventing burns due to reduced sensory sensitivity was applied.	Equivalent to SIS LIDC	Nil report	Potential in improving angiogenesis in ischemic DFUs as two of the four markers were significantly improved in treatment group (HIF-1a and VEGF). Percentage of decrease in wound surface areas were also significantly higher in treatment group (59.49% vs 27.07%).
	Other device/treatment						
12. Herberger et al. (2012)	• Multicentred, retrospective, noncontrolled study • Objective: "to determine effectiveness, tolerability, and safety of electrical stimulation therapy (EST) using an electrical stimulation device to treat wounds under hospitalized and routine ambulatory conditions." • Measurement: Wound size reduction, wound status, and global therapeutic result (Patient Global Assessment) of efficacy and tolerability of treatment.	• "The woundEL® system (Gerromed, Hamburg, Germany) consists of a dressing electrode (consisting hydrogel), a dispersive electrode (changed every 3-4 days), and the stimulation device" • Dosage & duration: 30 minutes/session x 2 times/day x 7 days/week x 8-12 weeks • Intensity depending on patient sensitivity (until a slight stinging sensation felt)	• Type: N = 95 hospitalised patients in Germany • Mean age: 69.1 ± 12.6 years • Wound types: refractory acute and chronic wounds (65.3% vascular, 14.6% diabetic foot ulcers, 2.1% pressure ulcers, 17.9% postoperative) • Average wound duration: 13.7 months • Patient journey: acute and chronic healing • Exclusion: "wound infection requiring treatment, osteomyelitis, malignant neoplasia in the wound region, or other serious underlying disease, such as a neoplasm currently requiring treatment, coronary heart disease, heart failure, and hepatic or renal disease"	Treatment-related adverse events: • Maceration (n=4) • Pain (n=1) at the wound edge, where the wound was exposed to the dispersive electrode Non-treatment related adverse events leading to exclusion from treatment: • Wound status deteriorated (n= 4) • "Surgery, mainly second amputations or debridement" (n=7) among seriously ill patients	High intensity – non-equivalent as per advice by SIS manufacturer	Nil report	Wound healing improved: - 44.7% wound size decreased - 30.4% complete granulation - 80.4% epithelialization (full or partial) increased Perceived tolerability: good (77.2%) or very good (78.5%).

			• Contraindications: "patients with an allergy to components of the wound dressings, or patients with a cardiac pacemaker or metallic implant in the immediate vicinity of the wound, and for those undergoing therapy with a high-frequency surgical device."	Treatment-non-related Serious adverse events: 2 deaths, 1 amputation, 1 hospitalization, 1 allergic reaction Other adverse events – unspecified if related to the treatment.			
Meta-analysis							
13. Lala et al. (2016)	• Systematic review (15 studies) & meta-analysis (5-8 studies) • Treatments included: ➢ Low intensity direct current (LIDC) (<1mA). ➢ Monophasic pulsed current (MPC) (most common: high-voltage pulsed current). ➢ Biphasic pulsed current (BPC). ➢ Microcurrent (MC): including MPC or BPC that provides current at a subsensory level. • Studies with indwelling electrodes excluded.	LIDC, MPC, HVPC, BPC and MC	• Type: Patients with spinal cord injury • Wound type: pressure ulcer • Settings: Varied • Patient journey: Chronic wound healing	Nil report	Potential non-equivalence as per advice by SIS manufacturer	Mentioned in passing	• Reduction in wound size & increase likelihood to heal: ➢ "EST significantly decreased the ulcer size by 1·32%/day [95% confidence interval (CI): 0·58–2·05, P<0·001] compared to standard wound care (SWC) or sham EST. ➢ EST increased risk of wound healing by 1·55 times compared with standard wound care or sham EST (95% CI: 1·12 to 2·15, P<0·0001)".
14. Chen et al. (2020)	• Meta-analysis using a random-effects model. N = 7 RCTs that compared ES with standard wound care (SWC). • Objective: "to evaluate the effectiveness of electric stimulation (ES) for diabetic foot ulcer (DFU) treatment" • Selection criteria: ➢ *In vivo* RCTs ➢ Population: Patients with type 2 diabetes and DFU ➢ Treatment group: ES and SWC, control group: SWC alone ➢ Outcome: percentage decrease in ulcer area at 4 weeks (4w-PDUA). ➢ Wagner classification: ≥ grade 2; ABPI > 0.5 ➢ Wound duration: ≥ 4 weeks. • Measurement: percentage decrease in ulcer area at 4 weeks (4w-PDUA) healing rate at 12 weeks	• ES applied in this article: "the application of an electric current of tolerable intensity (without generation of perceptible heat) to stimulate ulcer healing" p.609 • Two types of ES: Biphasic & Monophasic • Duration: varied from 4-12 weeks • Dosage: varied from 40 minutes/day to 8hour-50minutes/day. • Characteristics of current: varied	• N = 274 patients from 7 RCTs. (ranging from 10 to 41 each study) • Mean age: ranging from 48.4 – 66 • Wound type: Diabetic foot ulcer • Settings: Varied • Patient journey: chronic healing • Exclusion: osteomyelitis or severe soft tissue infection,	Nil report	Only one of the reviewed articles in the meta-analysis was equivalent (included in table 1) Potential non-equivalence as per advice by SIS manufacturer	Nil report	• Significant reduction in percentage of change in ulcer area in ES+SWC group as compare to SWC group (standardized mean difference, 1.09; 95% CI, 0.62-1.57; P<0.001). • Significant faster healing rate in the ES group at 12 weeks (risk difference, 0.19; 95% CI, 0.06–0.32; P= .005). • Analysis showed potential publication bias at week 4. • Inconclusive results of nil difference between monophasic and biphasic waveforms.
15. Barnes et al. 2014	• Systematic review and meta-analysis (n=21 RCTs published before 2013) • Objectives: ➢ "to investigate the effect of electrical stimulation on ulcer healing compared to	• Direct current (n = 2 RCTs) • Pulse current (high & low voltage) (n = 14 RCTs) • Alternating current (5 RCTs)	• 866 patients • Mean age: 29.25 • Unclear of setting and patient journey	Nil report	The results regarding pulse current may be not applicable to SIS devices as it included both high and low voltage treatments.	Nil report	• Significant increase in percentage of changes in ulcer size over the total study period with no heterogeneity: ➢ All electrical stimulation: 24.62%, 95% CI 19.98–29.27, P < 0.00001 ➢ Pulsed current: 28.31%, 95% CI 22.08–34.54, P < 0.00001

	usual treatment and/or sham stimulation". ➢ "to investigate the effect of different types of electrical stimulation on ulcer size reduction."				Potential non-equivalence as per advice by SIS manufacturer		➢ Alternating current: 20%, 95% CI 13.03–26.97, P < 0.00001 • Insignificant change in percentage of changes in weekly ulcer size with significant heterogeneity: ➢ All electrical stimulation: (increase) 1.64%, 95% CI 3.81 to 7.09, P = 0.56 ➢ Pulse current: (increase) 5.11%, 95% CI 4.26 to 14.47, P = 0.28 ➢ Alternating current: (decrease) 0.21%, 95% CI 7.59 to 7.16, P = 0.96 • Significant decrease in ulcer size with significant heterogeneity: ➢ All electrical stimulation: 2.42 cm^2, 95% CI 1.66–3.17, P < 0.00001 ➢ Pulsed current: 2.53 cm^2, 95% CI 1.51–3.54, P < 0.00001 ➢ Direct current: 2.53 cm^2, 95% CI 2.28–2.79, P < 0.00001

4.3. PRIMARY *IN-VITRO* EVIDENCE

In-vitro evidence with respect to research on direct current would appear to be more prevalent in the literature, followed by pulsed current treatments/devices. Only a few studies explored alternating current modalities while many studies did not provide sufficient information about ES modalities or parameters to categorise the study. Regardless of ES modalities, the vast majority of the reviewed articles reported positive outcomes in favour of the ES treatments/devices. There was no negative effect recorded and very few studies reported no differences in wound outcomes between study groups (Dueland et al., 1978; Jercinovic et al., 1996). Research subjects in these studies included rabbits, mice, pigs, guinea pigs, wound models of donated human skins/tissues, wound models of animals, peri dish, and human biofilms.

Positive effects of low-intensity direct current (i.e., ranging from 10 microamperes to 0.6 milliamperes, or, from 0 to 200mV/mm) included: (1) improved re-epithelisation and reduced dermal fibrosis (Chu et al., 1990), (2) earlier adherence in skin graft (Chu et al., 1991), (3) improved cell density (Wang et al., 2020), (4) improved general wound healing (Harding et al., 2012; Jang et al., 2018; Park et al., 2015; Reger et al., 1999), (5) improved fibroblast growth (Jang et al., 2018; Rouabhia et al., 2013), (6) increased amount of wound healing gene (Park et al., 2015), (7) improved proliferation of human keratinocytes (Rouabhia et al., 2020), (8) improved migration of human keratinocytes (Fang et al., 1998), and (9), increased [3H]thymidine incorporation (Cheng & Goldman, 1998).

Positive effects of low-intensity pulsed current included: (1) reduced collagen (Thawer & Houghton, 2001), (2) improved fibroblast intensity (Sari et al., 2019), (3) improved keratinocytes (Ren et al., 2019), (4) improved growth factors (Sari et al., 2019), (5) improved re-epithelisation (Sari et al., 2019), (6) reduced inflammation (Sari et al., 2019), (7) improved wound healing (Hajizadeh et al., 1996), (8) improved calcium flux in epidermis (Wood et al., 1993), and (9) improved epidermal healing (Sebastian et al., 2015).

In all studies where the effectiveness of multiple low-intensity ES types was compared, nil statistical significance in overall outcomes was achieved (Asadi et al., 2013; Fang et al., 1998; Hajizadeh et al., 1996; Reger et al., 1999; Snyder et al., 2017; Thawer & Houghton, 2001). It is, however, noted that different outcomes at different dosages (Sari et al., 2019) or intensities (Rouabhia et al., 2020) might be achieved.

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4.4. CLINICAL GUIDELINES

The area in which ES has experienced the most apparent translation of evidence to clinical practice guidelines is in relation to pressure injuries. The Registered Nurses' Association of Ontario [1], the Australian Wound Management Association [2], the US's National Pressure Ulcer Advisory Panel [3], and the US Institute for Clinical Systems Improvement suggest providing ES to promote healing in non-responsive Stage II PIs and in Stages III and IV PIs.

Regan et al. [4] conducted a systematic review of preventive and therapeutic interventions for PIs after spinal cord injury, and identified ES as an intervention for both PI prevention and treatment in the spinal cord injury population. Furthermore, the US Department of Health and Human Services' Agency for Healthcare Research and Quality (AHRQ) guidelines state that "*ES is the only adjunctive therapy with*

sufficient supporting evidence to warrant recommendation by the panel to be used for enhancing the healing rate Stage I or III PIs that have been unresponsive to conventional therapy" [5] (p 55). It was based on compelling clinical research [45-51] that the Agency for Health Care Policy and Research recommended the use of ES for the treatment of chronic PIs that failed to heal by conventional treatment [6].

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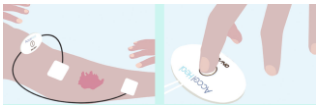
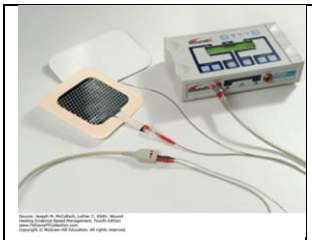
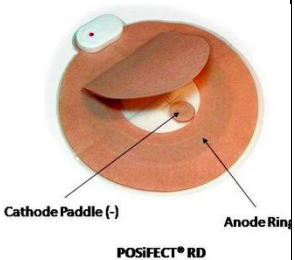
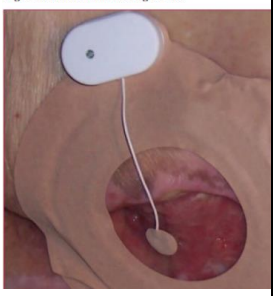
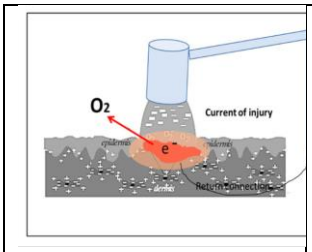
4.5. COMPARABLE ES TECHNOLOGY AND BRANDS

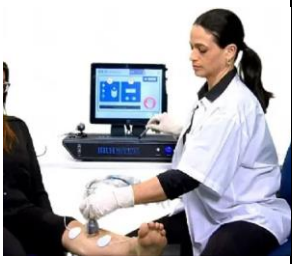
A list of ES technologies and brands were identified from the lietrature as well as a general search of the world wide web. Not all brands remain currently accessible. They are listed below with indications and actions noted. The number of products that have been available for use in healthcare supports the safe application of ES in vivo.

Brand & Company/ manufacturer	Delivery	Indications	Action

Dermapulse® Gerromed, Hamburg, Germany (Biofisica LLC, Atlanta, GA)-supplier	Delivers low frequency pulsed electrical current. Dermapulse® stimulator device is powered by a six-volt battery with a capacity of 20Ah. The device delivers current at pulse rate/pulse duration settings between 2 pps/350 microsec. to 128 pps/150 microsec. The intensity settings are between 0 and 150 mA., and in either positive or negative polarity.	Leg ulcers – chronic wounds	It has a maximum of four treatment electrodes and two dispersive electrodes that can be connected to the unit at one time. The sterile disposable treatment electrodes consist of 10.7cm x 10.7cm highly conductive carbon filled silicon rubber sheet. The non woven rayon/polyester fabric cover is non adhesive. The dispersion electrode has a surface area of 13.3 x 17.8 cm and consists of silver ink on carbon filled vinyl. Hydrogel glue is used as skin contact medium It has an automatic timer that shuts off the current at the end of the 30-minute treatment. Treatments are given twice per day for 30 minutes each, with a minimum of four and a maximum of eight hours between treatments. The ulcer bed is flushed with saline solution before each treatment and kept moist with saline solution between treatments. To enhance conduction of electricity to the wound, clean 4 x 4 gauze pads moistened with saline solution are placed directly over or into the ulcer. The electrode pads are composed of a carbon silicone rubber, covered with a cellulose sponge with an active contact area of 58 cm2. The electrode pad is saturated with saline, placed on top of the gauze pads and secured into place. A large non-treatment or return electrode is wet and placed on a large muscle group at a minimum distance of 12 inches from the ulcer and secured with velcro belts.
Accel -Heal® Accel-Heal Technologies Ltd. Hever Business Centre, The Old Station, Hever, United Kingdom www.accelheal.com https://www.hrhealthcare.co.uk/portfolio/accel-heal/  	Non-sterile single use micro current stimulation. Delivers a pre-set automated programme of subsensory electrical pulses to the wound. Delivers pulsed electrical stimulation with current varying from 40 – 500µA. The pulses are below the threshold for sensory stimulation. Delivers between 250 – 500 micro Coulombs per second (µC/s)	Relieves pain and stimulates healing in multiple wound types. Hard to heal wounds and painful wounds	Uses a 12 -day treatment period. Consists of six 48-hour disposable devices connected to electrode pads. Two electrode pads applied to intact skin on either side of the wound then connected to the Accel-Heal device. Once the dressing has been applied, the device is switched on and remains on for 48 hours. After each 48 hours of the 12-day treatment period, the device will automatically turn itself off. The old device is disposed of and a new device is then attached to the electrodes. Every 48 hrs during the 12-day treatment period the Accel -Heal device is changed for a new device. 
WoundEL LVMPC device (Go¨teborg, Sweden)	A monophasic pulsed direct current and low frequency generated by an electrical console.	Developed to kick-start /accelerate healing processes and reduce wound-related pain.	The electrodes can stay in place up to 4 days.

	There is a dressing electrode and a disperser electrode. Electrical current is evenly spread over the Dressing Electrode which also maintains a moist wound healing environment.	Hard-to-heal chronic wounds: Necrotic angiodermatitis, Venous leg ulcers and arterial, pressure ulcers, diabetic foot ulcers	
Decubitus direct current treatment (DDCT) electrostimulation treatment	The DDCT waveform has been processed from electrical activity. It provides both direct and alternating currents.	Pressure ulcers	The DDCT is a mains-powered stand-alone device, connected to a computer with a software to file such information as patient database and photographs of the ulcer at different points of time, During DDCT treatment, electrical currents are transferred to the healthy skin surrounding the necrotic wound area, through the use of soft external electrodes placed on the healthy skin surrounding the wound.
PosiFect RD DC BioFiscia, Odiham, Hampshire, United Kingdom   Figure 2. POSiFECT® RD with centre flap raised (it has a centre flap to allow inspection of the wound to facilitate placement of the central cathode paddle. The circular anode is embedded in hydrogel on underside of the dressing).  	Bioelectric wound dressing The dressing contains a miniature electric circuit that will deliver a microcurrent to the wound bed for a minimum of 48 hours. The current is derived from two lithium non-rechargeable coin cell batteries. The two-electrode system delivers bioelectrical stimulation. The first electrode, the anode, is a soft metal ring set into a hydrogel in the dressing. The second electrode is a small cathode paddle, which sits on the wound bed. *Figure 1. POSiFECT dressing in situ.* 	Chronic wounds when conventional therapies have failed. Venous leg ulcers, pressure ulcers, and diabetic foot ulcers. Can be used in conjunction with compression bandaging for treatment of venous leg ulcers.	Provides a bio-electric stimulation therapy in a single-use dressing that is applied directly to the wound. The dressing remains on the wound for 48 hours and is then replaced with a new dressing. The dressing has a black pull tab which is removed to confirm that the red light is flashing. If the red light is not flashing, the dressing should not be used. Using the tabs of the protective liner to facilitate aseptic application, the protective liner should be removed. The adhesive side of the dressing, which looks like a ring, should then be placed onto the non-wounded skin around the wound and pressed firmly. The lid should then be opened and the protective liner removed from the centre electrode (cathode paddle). The centre electrode is then placed directly onto the wound itself, ensuring contact with the wounded tissue at or near the centre of the wound or wound bed. As an optional step, if desired, the wound can be lightly packed with a suitable packing material to absorb excess exudate. The POSiFECT is placed over the central electrode taking care not to disturb the contact the electrode is making with the wound. Finally, the protective liner is removed from the lid and the lid closed, sealing it to the dressing and covering any packing material and the central electrode. The red light should not be flashing. The dressing should be changed as needed to maintain a moist, clean wound.
WMCS W200 Wetling, Fredensborg, Denmark	The WMCS has no direct contact to the wound. It generates tissue currents and voltages as a conventional electrode-	Chronic wounds, pressure ulcers, VLU, arterial ulcers, burns 1st, 2nd and 3rd degree, soft tissue	The WMCS device utilises the current-carrying capacity of air gases such as the ability of oxygen and nitrogen to accept or donate electrons, respectively. Negatively charged oxygen ions are "sprayed" onto the wound. When reaching the surface of the skin, these ions discharged their

	based electrostimulation device. The WMCS device produces a direct current at a very low intensity of 0.5 – 4.0µA	injuries and surgical wounds	extra electron to the damaged tissue. A single electrode, attached to the patient far from the treatment site, closes the circuit without physical contact to the wound.
Procellera DC device (Vomaris Innovations, Chandler, AZ) https://vomaris.com/tech/	Bioelectric wound dressing. Employs embedded microcell batteries that generate an electric field designed to mimic the body's physiologic electric field. It produces a low voltage of 2 -10mV by micro batteries of Ag and Zn metals which are inside a woven material and is activated by the moisture in the wound. It delivers 0.6 -0.7V at 10 micoramps.	Sustained broad spectrum antimicrobial impact for up to seven days. Partial to full thickness wounds Against gram-positive and gram-negative pathogens	V.Dox™ Technology employs a matrix of embedded microcell batteries comprised of elemental silver and elemental zinc. When in direct contact with a conductive medium, wound moisture, chemical reactions occur involving the transfer of electrons from the zinc to the silver in a process known as oxidation-reduction or REDOX reaction. This generates an electric field on the dressing surface.
GV350 High volt pulsed stimulator BioMedical Life Systems Inc www.bmls.com 	A two-channel device that delivers full-powered twin peak stimulation with alternating or continuous coordination between active outputs. Pulsed field. High voltage pulsed current. Waveform: Twin peak monophasic. Pulse rate: 1-100Hz. Pulse Width: Interpulse intervals of 100 microseconds, 5 microseconds. Stimulation: continuous or alternating. Output voltage: 0 -30 volts adjustable. Intensity: 0 -700mA peak. Powered by batteries or wall adapter	Adjunct treatment to medical diseases and conditions	Timer for desired treatment periods and fully adjusted pulse rate. Delivers full powered twin peak stimulation -alternating or continuous stimulation. Limited information was available about this device.
MicroPlus™ BioMedical Life Systems Inc www.bmls.com	Two channel analog device with three polarity settings: positive, negative or bipolar. The device has adjustable pulse rate 0.5-120Hz, pulse duration 1 -3 s, and micro/milliamp control. The unit is powered by one 9-volt battery. Waveform: Symmetrical square biphasic. Pulse	Used in veterinary aid for healing wounds in animal	Limited information was available about this device.

	Rate: 0.5 – 120Hz. Carrier Frequency: 14,000Hz. Output current: 0-5mA adjustable, 0-1,000µA. Output voltage: 0-2.5 Volts peak to peak.		
BRH-A2 Wound Healing System BRH Medical https://www.brhmedical.com/wound-healing/ 	Combines ultrasound and electrical stimulation and modulates them both individually or in combination during the treatment period. An interferential current is applied, meaning a lower voltage can be used to produce a therapeutic effect. The device includes software for patient record storage, wound photos, wound measurement, location, wound type.	Not specified	The mode of action is to create a "micro-circulation" effect, a massage like process within the tissues and blood vessels. To increase the blood flow to increase the healing rate. There are two - four electrodes that are placed close to the wound but not touching the wound edges. Duration of treatment is between 15 – 40minutes. An evaluation study applied the BRH-A2 device twice a week for 12 weeks or until wound healed. Four electrodes were placed around the wound and ultrasound was applied simultaneously with the electrostimulation for 13 minutes.
E-QURE Electric Quick Ulcer Remedy https://www.e-qure.com/images/docs/UserManual_8.2.16.pdf 	The BST device generates bi-phase, symmetrical electric pulses of 2Hz and pulse with of 4ms. Maximum output current: 6.5mA. Power source depends on the model either 120V, 60Hz, 02.A or 230V, 50Hz, 0.1A. The E-QURE consists of two components: the BST device (stimulator) and the E-QURE BST electrodes.	For the treatment of chronic hard to heal wounds	Treatment sessions 3 x 30minutes per day per wound. Electrodes are attached to healthy skin on opposite sides of the wound approx. 1.5 – 2cm away from the edge of the wound. Limited information was available about this device.

4.6. SECONDARY EVIDENCE PUBLICATIONS

A list of publications reporting secondary evidence such as literature reviews or narrative systematic reviews (that didn't involve a meta-analysis) from *in-vivo* studies is listed in chronological order below.

1. Arora, M.; Harvey, L. A.; Glinsky, J. V.; Nier, L.; Lavrencic, L.; Kifley, A.; Cameron, I. D. Electrical stimulation for treating pressure ulcers. Cochrane Database of Systematic Reviews 2020;2020(1):CD012196
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3. Palmieri, Beniamino; Vadalà, Maria; Laurino, Carmen. Electromedical devices in wound healing management: a narrative review. Journal of Wound Care 2020;29(7):408-418
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APPENDIX A: SEARCH STRATEGY AND OUTPUTS

Research Partnership Team, Library
La Trobe University
October 2020

TABLE OF CONTENTS

5 1. OVERVIEW

Customised Search for:

Name: Charne Miller

Email: c.miller@latrobe.edu.au

Contact Number:

Department: Nursing & Midwifery

Due Date: October 2020

Background information

Background information

The research team will generate a literature review that will be underpinned by an agreed database search strategy developed in consultation with and implemented by La Trobe University library services. A single reviewer title/ abstract and full text screening process will be conducted to increase confidence that the final product included a thorough and replicable screening process of database resources. The final product of the review will be narrative summary of the literature supplemented with tables of studies as they relate to the topic areas identified in the brief (as listed below). Quality appraisal and meta analysis of the papers are outside the scope of this brief. To complement the database searching, an online search of relevant devices as used in wound care, and information about identified devices in the public domain will be sourced and summarised.

The final report will be divided into the following areas included in the literature review brief:

- Patient population
    - Most common patient population type in the publications
    - Most benefit in which patient population type?
    - Patient setting (hospital, care home etc)
    - Patient journey, at what point are devices generally used?
- Safety
    - Most common adverse events occurred
    - Any patient types recommended as contraindicated or precautions taken – such as pacemaker patients or certain comorbidities
    - Overall safety review of publications and recommendation on how much can be leveraged for the SIS device
- Equivalence
    - Most useful publications that can be leveraged for likeness to the client's device
- Cost
    - Overview of articles demonstrate cost saving in terms of bed days in hospital for example
- Efficacy
    - Publications that may demonstrate reduction in the use of antibiotics in patients who used devices vs not
    - Overall recommendation of which articles best describe efficacy of such devices. Class A evidence etc.

Contact details for person who conducted the search:

Name: Sue Gilbert

Email: s.gilbert@latrobe.edu.au

Contact Number: 9763

6 2. SEARCH STRATEGY

6.1.1 Research Question

Aim: To undertake a literature review on the use of electric stimulation in wound healing.

6.1.1.1 Concept 1 Population (wound types)	*6.1.1.2 Concept 2* Intervention (Electrical stimulation)
Burn*	**Electric stimulation (MeSH)** [1]
Wound*	**Electric stimulation therapy (MeSH)** [1]
Venous leg ulcer*	Electric*adj 2 stimula* [1]
Lower leg ulcer*	Low intensity direct current
Surgical wound*	LIDC
Diabetic ulcer	NOT TENS which targets nerves
Diabetic foot ulcer	NOT surg* implant*
Diabetic leg ulcer	NOT electromagn*
Amputation wound*	NOT PEMF pulsed magnetic field
Laceration	NOT EMS which targets muscle
Pressure injur*	NOT Interferential
Pressure ulcer*	NOT NMES muscle/nerve targets
Venous stasis ulcer	
Soft tissue injur*	
Arterial ulcer*	
Bed sore*	
Decubitus ulcer*	
Chronic adj2 wound*	
Acute adj2 wound*	
Infect* adj2 wound*	

6.1.2 Inclusion Criteria	6.1.3 Exclusion Criteria
- Wounds that involve a break in the skin and can include chronic and acute wounds (inclusion can be but are not limited to chronic lower leg ulcers such as VLU, Mixed, Lymphodema), diabetes related wounds, pressure injuries, surgical wounds) - Any papers including treatment of wounds with electrical stimulation to the wound bed, wound edge, or surrounding tissue. - Papers with any study design including literature reviews, case studies, and opinion or commentary citations.	- Any study where the only electrical stimulation application involves electrical stimulation that is seeking to stimulate the muscle or nerve (NMES or EMS), interferential treatment (IF), or pulsed magnetic field (PEMF), or high voltage pulsed current (HVPC). - Any study involving only patients with neoplastic illness (i.e., with malignancy associated with the wound or with other systemic malignancy) - Any study involving only patients with a primary or systematic acute/ severe cardiovascular presentation - Any study where the skin is intact or is a dermatological condition - Any study that is not written in English - Any study for which an abstract / full text cannot be sourced - Any study including lesions arising from Pyoderma gangrenosum or from any other unknown aetiology - Did not address a wound healing outcome - Any study including patients with severe renal disease - Conference abstracts only available

6.1.4 Other Information

6.1.5 Databases

- MEDLINE
- CINAHL
- EMBASE

Notes about search:

7 3. DATABASE SEARCH

7.1 SUMMARY OF SEARCH

7.1.1 Database	7.1.2 Total articles
MEDLINE	1658
CINAHL	685
EMBASE	1154
Total before duplicates removed	**3497**

7.2 MEDLINE

22/10/10

7.2.1 Search Strategy:

Search ID#	Search Terms	Search Notes	Results
S1	burn* or wound* or venous leg ulcer* or surgical wound* or diabetic ulcer* or diabetic foot ulcer* or diabetic leg ulcer* or amputation wound or laceration or pressure injur* or venous stasis ulcer* or soft tissue injur* or arterial ulcer* or bed sore* or decubitus ulcer or chronic adj2 wound* or acute adj2 wound* or infect* adj2 wound*	Details about search	395224
S2	exp Electric Stimulation/		126893
S3	exp Electric Stimulation Therapy/		80975
S4	electric* adj2 stimula* or low intensity direct current or LIDC not TENS not surg* implant* not electromagn* not PEMF not EMS not interferential not NMES		156340
S5	2 or 3 or 4		226855
S6	1 AND 5		1658

7.3 CINAHL

22/10/20

7.3.1 Search Strategy:

Search ID#	Search Terms	Search Notes	Results
S1	burn* or wound* or venous leg ulcer* or surgical wound* or diabetic ulcer* or diabetic foot ulcer* or diabetic leg ulcer* or amputation wound or laceration or pressure injur* or venous stasis ulcer* or soft tissue injur* or arterial ulcer* or bed sore* or decubitus ulcer or chronic N2 wound* or acute N2 wound* or infect* N2 wound*	Details about search	166698
S2	MH "Electric Stimulation+"		18454
S3	electric* N2 stimula* or low intensity direct current or LIDC not TENS not surg* implant* not electromagn* not PEMF not EMS not interferential not NMES		17885

S4	2 or 3		21717
S5	1 AND 4		685

7.4 EMBASE

22/10/20

7.4.1 Search Strategy:

Search ID#	Search Terms	Search Notes	Results
S1	burn* or wound* or venous leg ulcer* or surgical wound* or diabetic ulcer* or diabetic foot ulcer* or diabetic leg ulcer* or amputation wound or laceration or pressure injur* or venous stasis ulcer* or soft tissue injur* or arterial ulcer* or bed sore* or decubitus ulcer or chronic adj2 wound* or acute adj2 wound* or infect* adj2 wound*	Details about search	408795
S2	electrostimulation		90171
S3	electric* adj2 stimula* or low intensity direct current or LIDC not TENS not surg* implant* not electromagn* not PEMF not EMS not interferential not NMES		87280
S5	2 or 3		132090
S6	1 AND 4		1154

APPENDIX B: SIS SIMULATION MODES TABLE

TABLE 1. SIS WOUND HEALING DEVICE – STIMULATION MODES AND EFFECTS						
	Electrical Stimulation (ES) Parameters					
	Output Voltage	**Output Current**	**Frequency**			
Units for ES parameters	Volts	Microamperes	Hertz			
Stimulation Mode				**Therapeutic Effect**	**Mechanisms of Action (MOA)**	**Supporting Literature**
Low Intensity Direct Current (LIDC)	0 - 5	discrete, 2.5, 7.5	-	Bacterial and viral infection treatment	https://siselectromed.com/research/#lidc	See Note 5
DC Voltage	0 - 1	dependent on total circuit resistance (R)	-	Cell phenotype modification (tissue regeneration↑)	https://pubmed.ncbi.nlm.nih.gov/5235589	https://patents.google.com/patent/US5814094A/en
DC Voltage Reverse Polarity	0 - 1	dependent on total circuit resistance (R)	-	Wound transepidermal potential difference 'current of injury' supplementation or replacement (initiate or accelerate cell migration and wound healing)	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5404801/figure/f4-jmdh-10-179	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5404801/#b83-jmdh-10-179
Alternating Current (AC)	0 - 1	2.5 - 5	4000	Small diameter sensory and efferent nerve fiber function blocking (pain↓, arteriole circulation↑)	https://www.practicalpainmanagement.com/pain/spine/radiculopathy/blocking-out-pain	See Note 5
Amplitude Modulated AC	0 - 1	2.5 - 5	Carrier: 4000, Signal: 10, 20, 25	Second messenger and growth factor up-regulation (multiple effects, see MOA)	https://siselectromed.com/research/#cyclic-amp	https://siselectromed.com/research/#cyclic-amp

Notes to Table 1:

1. Modes of action are not separated from given mechanisms of action.
2. SIS device can treat wounds and ulcers.

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