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Possible wider implications and clinical value of commercially sponsored evaluations:

A discussion on research methodology in response to Guest, Singh, Rana and Vowden's report on an RCT evaluating treatment efficacy of an electroceutical device in non-healing venous leg ulcers

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Abstract

This paper is written in response to a publication in the Journal of Wound Care by Guest et al. The publication and subsequent analysis of the Guest paper provides a vehicle for a wider debate about the care of people with wounds; including who manages the wound, how resources are allocated and the use of supplement technologies. It also raises a further important issues regarding whether the outcomes from a single randomised control trial (RCT) provides a more reliable level of evidence than the findings of previous investigations involving observational trials.

This article analyses the results from the cited study comparing clinical outcomes from previous published studies and evaluates whether a conclusion may be reached as to the most appropriate and reliable method to assess the efficacy of such medical devices used in wound care. It discusses why the assessment of clinical evidence can be a problem when there is variance of outcomes in studies which use different research methodologies.

The hierarchy of evidence lies at the heart of the appraisal process; and within healthcare it is common that smaller commercial companies present small scale observational trials as evidence for the efficacy of the product they are promoting. This practice is commonly followed because these trials are relatively cheap in comparison to research involving more complex methodologies, have significantly shorter durations and commonly patients are selected by clinicians to produce a likely or desired outcome. Therefore, we question whether this level of data promoted as evidence for clinical efficacy should be dismissed?

Guest et al reported that in UK within wound care clinical practice is inconsistent with significant regional variations; therefore, unless clinical practice guidelines are strictly enforced in a study, which then may be unrepresentative of current clinical practice does it mean that any results produced could not be transferred to the current clinical environment? We discuss the conundrum.

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Conflict of interest statement.

There are no current conflicts of interest

Overview

This paper is written in response to a publication in the Journal of Wound Care, Vol 27, No 4, April 2018 authored by Guest, Singh, Rana, and Vowden¹. The contents of this article opens up a wider debate about the care of people with wounds; including who manages the wound, how resources are allocated and the use of supplement technologies. It also raises a further question regarding the outcomes from a single randomised control trial (RCT) and whether it is of more value than the findings of previous investigations.

Guest et al reported on the clinical efficacy and subsequent cost-effectiveness of an externally applied electroceutical (EAE) device, (Accel-Heal: Synapse Electroceutical Ltd, Westerham, U.K) for treating non-healing venous leg ulcers (VLUs)². Accel-Heal is promoted as an adjunct treatment to current clinical practice management; therefore, the control arm of the study was not tightly controlled because the aim of the study was to evaluate the whether the addition of the device or blinded placebo added to current treatment regimes resulted in a cost and clinical benefit.

The study method used in the reported study was a prospective, randomized, double-blind, placebo-controlled, multi-centre study of patient's aged over 18 years with a non-healing VLU. The definition of a non-healing VLU used for the study was one that following 28 days of best practice guidelines, delivered by a suitable qualified practitioner, had not reduced in size by a minimum of 20%. Patients were randomised in the ratio of 1:1 to receive six units of the EAE (consisting of a self-contained, programmed electric microcurrent generator and two skin contact pads) or an identical-looking placebo device over 12 consecutive days.

Patients were followed-up for 24 weeks from randomisation, during which time patients received wound care according to the local standard care pathway, completed health-related quality of life (HRQoL) instruments over twelve scheduled visits and health-care resource use was measured. The cost-effectiveness of the EAE device was estimated at 2015/16 prices in those patients who full filled the study's inclusion and exclusion criteria (economic analysis population).

At 24 weeks after randomisation, 34% of the VLUs in the EAE and 30% of the VLUs in placebo groups had healed; therefore, only 4% of the subjects in the active group showed any benefit over the placebo. Unsurprisingly there was no statistical difference between the active electroceutical device and the placebo.

The time-to-healing was a mean of 2.6 and 3.5 months in the EAE and placebo groups, respectively; again there was no statistical difference between the two groups.

Therefore, in summary the results highlighted that there were no significant differences in healing rates, healing time and healthcare resource use between the two groups. At first sight there appears, from the reported study results, to be no clinical or economic justification why the electroceutical device should be applied to a patient with a VLU or why it is included on the Drug Tariff for clinical prescribing by NHS Prescription Services when a prospective randomised, double blinded placebo study showed a placebo device to be just as effective. In **summary**, the cost of £240.00 for the device has no clinical or economic justification to be used when an empty casing with a flashing light has the same effect.

The question to ask following this study, **relevant to modifying clinical practice is**; can the results from one single study be relied upon and does an RCT effectively ‘trump’ the results of any previous investigations that came before it? In summary, does this study provide conclusive evidence that the electroceutical device **used in the study** is an ineffective clinical tool for treating poorly healing VLUs? This is an important question to ask, not only specifically for this particular device but for decision making based upon research study based evidence.

This particular study is being discussed because behind the headline results reported **by Guest and his colleagues** is a very revealing picture involving significant differences in clinical practice across study sites, unbalanced groupings following randomisation and disparity of study protocol adherence which may provide some explanation as to why when making important clinical decisions clinician’s should, to use a metaphor, be wise to take notice of more than simply the match result. To continue the metaphor, understanding how the game was played and what influenced the final result may be as important in order to reach a reliable conclusion.

Discussion

Purpose

The purpose of this response paper is to analyse in greater detail the results from this specific study using the study subject’s CRF data and compare the reported clinical outcomes from previous published studies using the same EAE device which has been tested using less robust methodologies, primarily observational studies where reported outcomes differ significantly from the RCT.

We evaluate whether a wider conclusion may be reached as to the most appropriate and reliable method to assess the efficacy of such medical devices in wound care and evaluate why the assessment of clinical evidence can be a problem when there is variance of outcomes in studies which use different methodologies.

Background

The use of an external electric current to promote healing of chronic wounds was first introduced more than 40 years ago³. Evidence that justifies investigation into its use as a treatment method in wound healing are a systematic review and meta-analysis, a study method at the top of the hierarchy triangle, citing 21 randomised controlled trials (RCTs) which concluded that electrical stimulation appears to increase the rate of healing in chronic leg ulcers and may be superior to standard care for these wounds⁴.

However, a more recent systematic review of three RCTs concluded that it was unclear whether electromagnetic therapy, a similar application influences the rate of healing of venous leg ulcers (VLUs)⁵. So how does the results of this RCT using the Accel-Heal device inform the debate and how does it fit with the two data reported from the systematic reviews?

Identified variants in the subject's CRF data

A thorough analysis of the data from the current study highlights that the outcomes were confounded primarily by unwarranted variation in patient management between study centres and between individual clinicians within each centre. These variables were outside of the control of the study management team and were only revealed after the study was completed and unblinded when a thorough analysis of the subject's CRF data was undertaken.

The following variants were identified; the significance and potential impact upon the outcomes will be discussed:

1. The area of the wounds that healed in the EAE group was nearly twice that of those in the placebo group (mean: 13.3 versus 7.7cm² per VLU). We know that wound size is a confounder to healing⁶
2. The pre-randomised duration of the wounds that healed in the EAE group was double that of those in the placebo group (mean: 2.6 versus 1.2 years per VLU). The literature reports that the length of time a wound is unhealed is a significant determinant on the possibility for future healing⁶
3. At the conclusion of the study the EAE-treated patients in comparison to the placebo group reported less pain, more social functioning and greater overall wellbeing satisfaction. However, none of these differences reached statistical significance but should they still be discounted given the variables identified?

In summary, were the two study groups, despite being blinded and randomised, unequal? If this is the case then the outcomes from the subjects in each group cannot be relied upon as an accurate representation and hence the study is of little help in judging the clinical and cost effectiveness of the device.

What study method should be applied in wound care?

The purpose of any research is to reflect as accurately as possible what is actually happening in a given situation. In medicine in particular this can prove to be difficult particularly when it involves human subjects as invariably it introduces an inordinate number of **potential** variables resulting in a situation significantly more complex than initially considered. It could be argued that the more these variables are controlled the further from everyday clinical practice a study moves.

Therefore, the method selected by a researcher will inevitable have a bearing on the rigor of a study and to an extent the subsequent outcome(s); as has been highlighted with this current study under discussion. In addition, truly independent research is a rarity particular when there are commercial considerations so should a reviewer of evidence be careful when considering results presented when there is a commercial sponsor sitting behind them?

Direct evidence comes from research that directly compares the interventions in which we are interested when applied to the populations in which we are interested and measures outcomes important to patients. Guyatt et al⁷ discussed that evidence can be indirect in one of four ways: the patients may differ from those of interest (the term applicability is often used for this form of indirectness), the intervention tested may differ from the intervention of interest, outcomes may differ from those of primary interest, for example, surrogate outcomes that are not themselves important, but measured in the presumption that changes in the surrogate reflect changes in an outcome important to patients and a fourth type of indirectness, conceptually different from the first three, occurs when clinicians must choose between interventions that have not been tested in head-to-head comparisons⁷.

If making comparisons between treatments under these circumstances will require specific statistical methods and will be rated down in quality depending on the extent of differences between the patient populations, co-interventions, measurements of the outcome and the methods of the trials of the candidate interventions.

Evidence, what evidence?

Evidence based medicine has been described as ‘the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients’⁸⁻¹⁰. In theory this involves evaluating the quality of the best available clinical research, by critically assessing techniques reported by researchers in their publications and integrating this with clinical expertise.

Although it has and still does provoke controversy, the hierarchy of evidence lies at the heart of the appraisal process. The hierarchy indicates the relative weight that can be attributed to a particular study design. Generally, the higher up a methodology is ranked, the more robust it is assumed to be. At the peak of the hierarchy triangle lies the meta-analysis, synthesizing the results of a number of similar trials to produce a result of higher statistical power. At the other base end of the spectrum lies observational studies, thought to provide the weakest level of evidence.

Within healthcare it is common that smaller commercial companies present small scale observational trials as evidence for the efficacy of the product they are promoting. This practice is often followed because these trials are relatively cheap in comparison to research involving more complex methodologies, have significantly shorter durations and commonly patients are selected by clinicians to produce a likely or desired outcome. Therefore, should this level of data put forward as evidence for clinical efficacy be simply be dismissed, particularly by clinical decision makers?

The answer we are proposing is no; so why? It could be argued that a well-conducted observational study may provide more compelling evidence about a treatment than a poorly conducted RCT, or indeed a well conducted RCT which has subjects with many variables such as changing comorbidities. Therefore, whilst the hierarchy focuses largely on quantitative methodologies it is again important to choose the most appropriate study design to answer the question.

At the heart of the debate about the hierarchy of study design concerns the ranking of evidence, versus its relevance to clinical practice. Techniques lower down the ranking are not always superfluous; for example, the link between smoking and lung cancer was first identified via cohort studies carried out in the 1950s⁹.

Although randomised studies are considered more robust, it would in many cases be unethical to perform an RCT evaluating risk factor exposure; a cohort deliberately exposed to, for example tobacco smoke or illicit drug use would not be acceptable. Therefore, a study method used will have to assess subjects exposed to it by chance or personal choice.

There is debate over the relative positions of different methodologies. For example, the RCT has been traditionally been regarded as the most objective method of removing bias and producing comparable groups, but the technique is often slow, expensive and produces results that are difficult to every day practice¹⁰⁻¹¹. We would cite wound care being a prime example of this.

Guest et al report that in UK in wound care clinical practice is inconsistent with significant regional variations so unless clinical practice guidelines are strictly enforced in a study, which then would be unrepresentative of current clinical practice, therefore, producing results that could not be transferred to the current clinical environment^{6,13}. This appears to be the case in this study under analysis with even variation between clinicians in the same centre¹⁴.

In addition, many subjects, particularly those presenting with chronic and complex ulcers commonly also present with co-morbidities which may be significant confounders to wound healing. Therefore the hierarchy is also not absolute. Therefore, the question for researcher considering appropriate study design surrounds inclusion and exclusion criteria for subject inclusion. The narrower the inclusion criteria and the more tightly grouped the subjects are in study groups can reduce the number of variables. However, this then may have the effect of moving the cohort away in terms of similarity from the everyday clinical practice scenario. For example, within wound care two significant confounders to healing are smoking and obesity. However, to exclude all patients who smoke or/and are obese would not reflect the make-up of the average wound care population.

It is important to understand distinctions between study designs. Some investigators argue that well-constructed observational studies lead to similar conclusions as RCTs¹⁵. However, others suggest that observational studies have a more significant potential to over or underestimate treatment effects. Examples of this can be found in medical and orthopedic surgical specialties which show that discrepant results can be found between randomized and nonrandomized trials¹⁶⁽²³⁾. One recent nonsurgical example of this is hormone replacement therapy in postmenopausal women¹⁷.

Previous observational studies suggested that there was a significant effect of hormone replacement therapy on bone density with a favorable risk profile. However, a recent large RCT found an increasing incidence of detrimental cardiac and other adverse events in those undergoing hormone replacement therapy, risks which had **hitherto** been underestimated by observational studies ^{ibid} ¹⁷. As a result of this the management of postmenopausal osteoporosis has undergone a shift in first-line therapy¹⁸.

Randomization

As randomization is the key to balancing prognostic variables, it is first necessary to determine how it was undertaken; the method used to randomize subjects from the cohort. The most important concepts of randomization are that allocation is concealed and that the allocation is truly random. If it is known to which group a patient will be randomized it may be possible to potentially influence their allocation¹⁷. Examples of this would include randomizing by chart number, birthdates or odd or even days for patients to present to clinic. This necessarily introduces a selection bias which negates the effect of randomization. This makes concealment of allocation a vital component of successful randomization. Allocation can be concealed by having offsite randomization centers, web-based or phone-based randomization.

In wound care ulcer size and wound duration could have been accounted for in the randomization process by grouping subjects wound size and duration before randomization so that the two arms of the study were more closely balanced. This could have produced a significant effect on measured outcomes in the two arms of the study.

Blinding

In surgical trials blinding is obviously not possible for some aspects of a trial. It is not possible or indeed ethical to blind a surgeon with respect to which patient is under his knife, nor is it usually possible to blind a patient to a particular treatment. However, there are other aspects of a trial where blinding can play a role. For instance, it is possible to blind outcome assessors, the data analysts and potentially other outcomes' adjudicators. Thus it is important to understand who is doing the data collecting and ask, are they independent and were they blinded to the treatment received? If not, possible influences, either subconscious or not, on the patient and subsequent results can happen.

In this current study it appears that clinician treating the subjects quickly guessed whether they were dealing with an active or placebo device despite the fact that the treatment produces no physical sensation to the patient. This was reported by some clinicians as the subject's pain levels drop significantly more quickly when using an active device. Therefore, when the same clinician in the study managed more than one subject they reported and interpreted it as a pattern emerging.

Beyond blinding to the doctor-patient relationship

Despite the array of controls put in place to ensure that a reliable, valid and stringent study is orchestrated to produce confidence in the results it produces, there remain several psychological elements that influence how clinicians might behave differently when treating patients who are a part of a clinical study. RCTs are seen as the gold standard when controlling for bias. However, in reality this is often easier said than done when doctor-patient relationships are highly complex interacting systems¹⁸.

Patient's perceptions are subjective and they themselves can influence study outcomes through a subjective bias that is influenced by their mental and physical status²⁰. These factors are left unaccounted in RCTs like the one reported here.

Confidence Interval

The confidence interval used in statistical calculations represents the accuracy or precision of an estimate of accuracy. A 95% confidence interval is a range of values that you can be 95% certain contains the true mean of the population. With large samples, it can be more accurately inferred that what is arrived at is with more precision than with a small sample; therefore, the confidence interval is quite narrow when computed from a large sample.

Commonly, when researchers present an estimate of confidence in a study they will put a confidence interval (CI) in place. The CI is a range of values, above and below a finding, in which the actual value is likely to fall. Guyatt, when discussing the Grade Guidelines²¹ suggests that examination of 95% confidence intervals (CIs) provides the optimal primary approach to decisions regarding imprecision. For practice guidelines, rating down the quality of evidence (i.e., confidence in estimates of effect) is required if clinical action would differ if the upper versus the lower boundary of the CI represented the truth.

An exception to this rule occurs when an effect is large, and consideration of CIs alone suggests a robust effect, but the total sample size is not large and the number of events is small. Under these circumstances, one should consider rating down for imprecision.

This is where decisions made about the weight of validity made from results of studies researchers and subsequent reviewers should consider the number of patients required for an adequately powered individual trial.

Guyatt et al propose that systematic reviews require a different approach given they are an analysis and collation of a number of related studies. If the 95% CI excludes a relative risk (RR) of 1.0, and the total number of events or patients exceeds the optimal information size criterion,(OIS) precision is adequate. If the 95% CI includes appreciable benefit or harm then a RR of under 0.75 or over 1.25 rating down for imprecision may be appropriate even if OIS criteria are met.

Conclusion

This article is primarily a discussion of the value of RCT and other methodologies in the evidence pyramid applied in wound healing studies rather than a specific analysis of whether the Accel-Heal therapy does or does not work for augmentation of healing in leg ulcers. However, the EAE study provided a vehicle for the discussion on that particular cited investigation to open a much wider debate whether treatment efficacy and cost-effectiveness has been demonstrated or not. Clinicians need to be able to make therapeutic choice decisions based upon evidence provided, so judging the quality and applicability of that evidence is very important.

We have discussed the potential inconsistency of relative, rather than absolute treatment effects in binary/dichotomous outcomes. In the Grade guidelines: 7 Rating the quality of evidence – inconsistency; Guyatt et al²¹ report that a body of evidence is not rated up in quality if studies yield consistent results, but may be rated down in quality if inconsistent. That specifically applies to the cited studies on the Accel-Heal device; an RCT demonstrating one finding in contrast to the outcomes reported in observational studies.

Guyatt et al state that the criteria for evaluating consistency include similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity. These authors suggest that to explore heterogeneity, systematic review authors should generate and test a small number of a priori hypotheses related to patients, interventions, outcomes, and methodology. When inconsistency is large and unexplained, rating down quality for inconsistency is appropriate, particularly if some studies suggest substantial benefit, and others no effect or harm rather than only large vs. small effects.

Evidence-based medicine requires the integration of clinical judgment, recommendations from the best available evidence and the patient's values. The phrase the *best available evidence* is used quite frequently to justify the use of one treatment over another.

In order to fully understand what this means one needs to have a clear knowledge of the hierarchy of evidence and how the integration of this evidence can be used to formulate a grade of recommendation²²⁻²⁴. It is necessary to place the available literature into the context of a hierarchy but see it through the lens of day-to-day clinical practice.

It is fair to say it would be unusual that a single study be relied upon to provide reliable conclusive evidence and a systematic review should be the baseline to establish a recommendation for practice. Evidence based medicine has been defined as the process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions²¹.

The practice of evidence-based medicine means integrating individual expertise with the best available external clinical evidence from systematic research. The best available external clinical evidence means clinically relevant research, often from the basic sciences of medicine, but especially from patient centered clinical research into the accuracy and precision of any diagnostic tests or therapy under scrutiny.

One of the driving forces behind the development of evidence based medicine has been the recognition of the gap between research evidence and clinical practice. Research literature is constantly changing and the volume of health information has increased rapidly making the sifting process considerably more difficult and arguably less reliable.

To conclude on the study under discussion which has facilitated the raising of some more generally applied points; Guest et al reported ^{ibid} that there was significant and considerable regional variation in treatment regimes and inconsistency in the clinical management of wounds. This study was designed as a placebo-controlled study in which patients were randomised in a 1:1 ratio to receive the EAE or an identical-looking placebo device. Complete certainty of the evidence provided is highly unlikely to be achieved. However, in terms of clinical decision making reviewers should identify what in the methodology applied and subsequent data generated undermines or compromises that certainty.

An issue that has been raised is the relevance of the sample size and the potential for the sample to have adequate power to detect a difference, should one exist, between the study groups. Returning to the Accel-study as an example, the study authors state that their sample size was based to detect a difference of approximately 25% (absolute values) between the two treatments with 90% power resulting in 50 patients recruited to each treatment arm. One could put forward an argument that if the standard of care applied to subjects in the study was good, then expecting a new treatment modality to improve outcomes by 25% is a large effect. However, if this calculation was based on previous data using the same device then the authors would have confidence that the calculation was correct. However, if, for possibly a number of different reasons, seen or unforeseen that 25% figure wasn't reached and the placebo group out performed their expected outcome the study would be short on subject numbers. Again in the case cited the device was reported as performing significantly less well than in observational studies and the placebo group performed better than anticipated.

The study reported no difference in outcomes between the treatment and placebo arm of the study; however, the study may not have been powered sufficiently to detect a difference, thus we don't actually know if there is actually no effect difference between the two treatment arms; it may just be that the study couldn't show that because of under powering.

There is one interesting aspect to this study and it concerns the recruitment of suitable subjects. The study did not reach the required sample size of 50 subjects in each arm; there were 43 in the EAE group and 47 in the placebo group which raises other questions about difficulty in recruitment.

Nevertheless, Guest et al ^{ibid} reports that in their opinion in many respects the Accel-Heal study was an observational study, conducted as an adjunct to each centre's normal clinical practice designed to evaluate the effect of introducing the EAE into the local standard care pathway of a group of hard-to-heal VLU's. Accordingly, apart from receiving six units of the EAE or placebo over a period of 12 days, and patients being asked to complete HRQoL instruments at the scheduled appointments, the clinicians were allowed to manage their patients according to their usual practice. Moreover, patients were managed by non-wound specialist practice nurses, district nurses and, on rare occasions, by health-care assistants who were not part of the clinical investigator's team, in addition to tissue viability nurses. This resulted in considerable variation in patient management and corresponding resource use, both between centres and between individual patients within the centres.

Furthermore, this was compounded by the fact that the sample sizes varied from eight patients at one centre to thirty five at another. Consequently, the inconsistencies in patient management at one centre potentially dominated the results of the study. Guest et al suggests that this possibly confounded the study's findings because management practices varied between the centres and wound care was often variable between patients, creating a degree of bias.

This imbalance was further compounded by the wound population having not been properly controlled by the randomisation design leading to an imbalance of patients between centres in terms of sample sizes, wound area and wound duration. Another issue around imprecision is the wide CI around the results, for example, we calculate an Odds Ratio (OR) of wound healing is OR: 2.14 (95% CI: 0.83 to 5.51), and the mean difference in ulcer area at the end of the study is MD: -6.00 (95% CI: -25.41 to 13.41). With such wide confidence intervals, the small sample size, the base line incomparability of ulcer size and the wide variation in application of standard care, the evidence presented would be downgraded to very low certainty. To put this into context, a clinical decision maker would be unlikely to consider using a treatment with a very low certainty evidence.

However, irrespective of the above and arguably of more significance was the unexplained variability in the use of compression and dressings which did not correlate directly with exudate levels. For example, large amounts of gauze were used and relatively little super absorbents and alginate dressings. It is difficult to understand why this type of clinical management was being used which is not consistent with current best practice procedure.

Additionally, there was a lack of clinical correlation between signs, symptoms and dressing type and compression therapy frequency which may reflect the fact that patients were, at times, managed in the community by practice nurses or district nurses.

To explore the why the healing rates in the EAE group were lower than expected and higher than expected in the placebo group as has been highlighted the rates also differed greatly from the results reported using the same device in single arm observational trails^{25,27}. Therefore, looking for reasons over and above methodological ones is often helpful in order to place different outcomes from different study methods measuring the same device or treatment. This can assist in planning future studies or placing the outcomes of studies into a correct context.

The healing rates in the EAE group were lower than expected and higher than expected in the placebo group. The rates also differed greatly from the results reported using the same device in single arm observational trails²²⁻²⁵. An explanation proposed for the cited Accel-Heal study does not involve statistics or research methods and demonstrates why researchers using particularly medical devices and pharmaceutical medications under review should ensure the basic underlying science is sound before engaging in clinical in-vivo studies. Accel-Heal uses generic off the shelf skin surface metallic electrodes on either side of a wound to deliver the electrical energy from the device. It is suggested that this can create a potential gradient across the wound causing a flow of ions through the wound tissue resulting in a flow of electric energy without the need for an electric micro-current generator. An explanation proposed is that two skin surface metallic electrodes on either side of a wound can create a potential gradient causing a flow of ions through wound tissue resulting in a flow of electric energy without the need for an electric micro-current generator.

Alternatively, Guest et al suggest that the EAE is only able to exert a therapeutic effect on those wounds where the body's own 'natural' electric current is absent or deficient²⁸ as may be the case in large wounds or wounds of long duration. Therefore, in this particular study, many of the wounds in both groups may have had an effective 'natural' electric current, and that would explain why the device was more effective in larger wounds and those of longer duration. This explanation may also explain why the EAE performed better in the previous clinical evaluations than in this study, where the wound duration before the start of treatment was a mean >2.0 years per patient.

Evaluating the published data on these aspects there is insufficient published evidence on the basic science on the application of EAE particularly with regards to dose allocation and the mode of action; the functional or anatomical change, at the cellular level which may be initiated by the application of the EAE device. Therefore, any clinical observations may be viewed with a high degree of skepticism.

This clearly warrants further investigation as the technology clearly shows an encouraging direction of travel in a clinical area where wholly effective and consistent treatments and the application of treatments appear to be lacking.

With regards to the study management it was reported that consistent monitoring of the study became challenging due to the clinical site's own patient management. Hence, there was poor or inaccurate completion of the CRFs on some occasions and inaccurate administration of SF36.

Additionally, it was reported ¹ *ibid* that the clinicians at the different centres interpreted the meaning of an adverse event differently and patients were managed by clinicians in the community who were not part of the clinical investigator's team at the centres. Furthermore, different centres documented resource use between the scheduled visits in different ways resulting in inconsistencies in documentation associated with unscheduled visits.

A significant limitation to the study was that the results were truncated at 24 weeks and excluded the costs and consequences of managing patients with an unhealed ulcer beyond this period. A follow up study would have been helpful to understand how the wound healing fared after 24 weeks.

To finish; this paper is intended to raise potential research methodology flaws and anomalies to provide consideration for reviewers when evaluating data presented a *clinical evidence*. It is not unusual to have reported, particularly by small commercial entities, that their particular technology or offering is *clinically proven*. As brief as this discussion paper is, we aimed to highlight that this is an extremely high bar to reach and if claimed a forensic evaluation of the research should be conducted before accepting that claim as credible.

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