The future of evidence for wound management products: should the gates be widened?

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Wound care is, indisputably, a dynamic field of research and clinical activity. Clinical practice is shaped in part or wholly by guidelines which, in turn, are developed from the repository of available evidence. In the quest for clinical practice established upon the principles of evidence-based medicine, we are led in search of "best available evidence". We thus need to examine what exactly does 'best-available evidence' consist of? For example, one school of thought considers that "A Cochrane Review is a systematic review of research in health care and health policy that is published in the Cochrane Database of Systematic Reviews." (Cochrane Library, nd). Systematic reviews are used to inform clinical decision making and this approach has been adopted by a number of organisations and journals around the world (Cochrane Back and Neck, nd). A systematic review is not a research methodology but an attempt to distil the available evidence into 'conclusive conclusion' by means of statistical meta-analysis, provided that there are clinically relevant conclusions to be drawn. The putative gold standard for research methodology is that of the randomised controlled trial (RCT) which tends to be the only form of evidence that is accepted by Cochrane Review panels, and then only after the application of qualifying restrictions arbitrarily imposed on the available evidence. We have been unable to find any Systematic Reviews relating to wound care that contain any evidence other than the RCT. The reason for the predominance of the RCT as the evidence cornerstone seems to centre around the need to avoid bias in the reporting of trial results but the achievement of this goal in itself has been challenged under the collective banner of 'evidence-biased medicine'. In addition, this approach provides a clear limitation in the gathering of evidence and excludes valuable 'patient-centred' lines of inquiry which evaluate, amongst other forms of evidence, quality of life. We, therefore, need to ask the question, should the evidence scrutinised for use in wound care and wound care products consist only of RCT evidence or include a much broader "all-inclusive" approach, whereby other sources of evidence are incorporated into the equation? At this time, we should remind ourselves, that no formal, robust evidence exists that places the RCT at the top of an evidence pyramid or indeed if an evidence pyramid exists at all. In reality, what we have is a variety of evidence sources that have been stratified according to an arbitrary value, again, not validated by robust methodology.
Keith Cutting and Richard White

1. From your personal/professional perspective what value do you attach to Cochrane Reviews in wound care?

UA: I discovered the Cochrane wound care reviews quite early in my tissue viability career. As a busy clinician swamped with information, I was mostly trying to work out 'what works'? Such 'questions of effectiveness' are ideally answered through good quality systematic reviews of RCTs but finding and critiquing research is a skilled, time-consuming task. Cochrane reviews do the hard work for me and give me information I can trust upon which to base my practice. Unfortunately, Cochrane reviews too often reveal the lack of valid and reliable evidence but that has value in identifying what we know and what we don't know. Cochrane reviews are usually good quality but the Cochrane Wounds Group has especially high standards, so I regard the Cochrane Reviews in wound care as very valuable.

CB: I think Cochrane reviews tend to work well when there is a large evidence base of high-quality evidence that requires synthesis into a summarised set of data. The methods used are ideal for condensing a lot of high-quality data into a few meaningful parameters that can be used to make informed treatment decisions. I think they tend to be less valuable and even possibly misleading if the evidence base is more fragmented or spread down the evidence hierarchy, rather than across the top layers where the methods struggle to synthesise and evidence tends to be omitted by default. So you really have to question what the evidence base looks like with wound care in terms of understanding how useful Cochrane reviews are, and I think it is beyond any doubt that the majority of the evidence

is quite low down that evidence hierarchy. The use of such reviews is, therefore, limited, not that they are poor *per se*, but rather that it is dangerous to completely rely on these results without reflecting on the totality of the evidence.

NC: Obviously I do not have an unbiased opinion as I established Cochrane Wounds in 1995 and have been Coordinating Editor (now Joint Coordinating Editor with Jo Dumville) since then. Healthcare practitioners are faced with an enormous volume of literature, including marketing material, about the effects of wound products and individuals cannot possibly keep on top of it. We strive to produce and publish high-quality, independent, systematic reviews about the effects of wounds-related interventions. We also conduct reviews on wound prognosis and diagnosis. Cochrane is an international collaboration, producing reviews across all healthcare topics and all reviewers are required to follow the same, internationally accepted methods irrespective of the topic. The high methodological standards in Cochrane have propelled it to being the premier source of reliable information about the effects of healthcare worldwide. Our aim is to ensure that Cochrane Wounds reviews are highly valuable to decision-makers and we receive a lot of feedback telling us they are. Crucially our reviews are produced with and by clinicians on prioritised topics. The hard evidence of the value of Cochrane Reviews in wound care comes from the download statistics; there are 53 Cochrane Review Groups and during 2017 there were only three groups whose reviews were downloaded more frequently from the Cochrane Library than those of the Wounds Group (Cullum, 2018).

SJ: No clinical insight is required in order to perform a Cochrane review. Cochrane reviews in wound care are usually dangerous. Dangerous because they typically will only look at evidence from RCTs and will completely ignore every other kind of evidence. This approach is fine for some areas, such as drug trials, but is completely inappropriate for wound care as it is so difficult to perform an RCT.

One example of the danger of this approach when they stated that there is little or no evidence to support the idea that antimicrobial dressings are of value in treating burn patients. Nowhere in this statement was a warning that only RCTs have been included as evidence, and that every other form of evidence was ignored. This statement empowered managers to try to prevent clinicians using antimicrobial dressings for burn injuries. Luckily for our patients, the clinicians were able to win this battle, but it makes our lives harder.

2. Is there a valid 'evidence hierarchy' or should we opt for a 'horses-for-courses' approach?

UA: The most important thing is that the research design should be capable of answering the research question, so a 'horses-for-courses' approach is sensible. Having said that, the 'evidence hierarchy' is useful when considering designs for questions of effectiveness ('What works?') but only if applied appropriately. It is not relevant for other types of questions such as 'What is it like to experience…' which would need a qualitative approach. Even for 'what works' questions, the evidence hierarchy should not be rigidly applied. For example, a well-designed RCT may provide more valid and reliable data than a poorly-designed systematic review. In some situations where it is not possible to recruit an adequate sample size or too expensive to justify an RCT, a well-designed cohort study may be the highest level of evidence achievable.

CB: We have to deal with the reality of what evidence we have, whilst recognising that what we say we will accept might affect what data is generated. For example, I suppose you could argue that if we say we will accept small observational studies as evidence, then we may destroy the incentive for producers to fund large RCTs. But that isn't the case here, as decision makers have generally reiterated the need for better studies to little avail. So given the persistence of the low quality of the evidence base, I think we would be better served by a more rigorous assessment of what we have, rather than insisting on better quality. But this doesn't just mean applying RCT methods of evaluation to what is less robust and also possibly 'commercialised' evidence. Instead we need to critically, robustly and maybe even slightly cynically assess the extent to which imperfect data may hinder our understanding of the impact of treatments and how important this may be. If we persist with taking the high ground on evidence quality, a likely consequence is that cost-effective treatments are not adopted and it will be patients who ultimately miss out. It might also mean that treatments which are not cost-effective are adopted. But we need to understand the balance of these outcomes and an informed evaluation of the imperfect evidence base is almost certainly more informative than an approach that only accepts a non-existent perfect evidence base.

NC: The evidence hierarchy people refer to most concerns casual relationships ('Does this treatment cause this effect?') but that is only one type of clinical question. The evidence to answer a particular clinical question depends on the nature of the question. There is not just one 'evidence hierarchy' — there is one for every type of clinical question and therefore an inherent contradiction in this question — there *has* to be a horses-for courses approach. However, the courses are not 'wound care' or 'stroke medicine' — the courses are the type of clinical question or uncertainty.

Our reviews, asking questions about the effects of interventions, privilege RCTS because, when well conducted, they are most likely to disentangle the effects of interventions from the effects of bias and confounding. In other words, any apparent

treatment effect is more likely to be really due to the treatment, rather than a fundamental difference in the people making up the groups being compared, or a bias in the way a study was conducted. This is just science.

So, if you want to be more likely to draw the right conclusion about whether an intervention works, you should only look at RCTs and, even then, only listen to the results of the well-conducted, adequately sized ones. There is absolutely nothing about wounds that makes the conduct of RCTs particularly difficult and there are now plenty of examples demonstrating this.

On the other hand if your question is about prognosis, e.g. 'Do levels of protease activity predict wound healing?', then well conducted cohort studies are the best source of evidence. Similarly, if your question is about the performance of a particular diagnostic test, you need to look at diagnostic test accuracy studies.

SJ: When evaluating the evidence for wound care, I prefer to use the 'GRADE' system (http://www.gradeworkinggroup.org/), as endorsed by National Institute of Health and Care Excellence (NICE), the BMJ and the World Health Organization amongst others.

This system also classifies evidence as high, moderate or low quality, but 'high'-quality evidence will include not only RCTs without important limitations, but also will include overwhelming evidence from observational studies. This is more useful in a subject area such as wound healing, where RCTs are uncommon. Of course, truly evidence-based medicine will recognise not only the best research evidence, but also will take into account patient concerns and clinical expertise.

3. If the patient truly lies at the centre of care, and bearing in mind the regulatory perspective, should patient-reported outcome measures (PROMs), audits and post-marketing surveillance studies, feature significantly in the collation of best available evidence?

UA: There is a strong moral argument for using outcome measures that are informed by patients' views, so PROMs are a logical extension of this philosophy. Audits are a valuable form of evidence for measuring performance against an agreed set of standards and post-marketing surveillance studies also play a valuable role in monitoring the safety of a drug or device. So it makes sense for such studies to be included as part of the evidence base for informing clinical practice. However, the most important questions are whether a wound care intervention is clinically and cost-effective and whether it is acceptable to the patient. Such questions need appropriately designed research studies that use patient-relevant core outcome measures and which are capable of providing valid and reliable or trustworthy results (such as RCTs, cohort studies and qualitative studies). We are only truly putting the patient at the centre of care, if we use the appropriate science to derive valid and reliable or trustworthy answers.

CB: Unquestionably yes and I would argue for a greater use of these sources of information in all disease areas and not just wound care. Even if the evidence were to be improved substantially, it is unlikely to address all the areas of concern. For example as providing a bench mark for the long-term modelling of the costs and health outcomes of wounds that have failed to heal within the time limits of a trail. Understanding the recurrence rates etc. The other important use of such data may be that it allows us to revisit decisions made on earlier uncertain evidence. It might be optimal to provisionally say yes to something on the grounds that current evidence suggests it is cost-effective, but to insist on coverage with evidence development in order to revisit decisions.

NC: Best available evidence for what and whom? The nature of the question or uncertainty drives the identification of the appropriate evidence to answer it.

The patient is definitely at the centre of care, so that means listening to patients, understanding their goals of treatment and providing the treatment that is most likely to help meet that goal. I think PROMs and patient-centred outcomes are widely confused. PROMs are completed by patients and measure their health status or health-related quality of life at a point in time. They are of huge value to health services and may be distinct from those outcomes that are prioritised by patients themselves but not necessarily reported by them. We have shown that complete wound healing is the outcome most highly valued by people with chronic wounds, but this outcome is not usually reported by patients.

Audits are very valuable as tools to identify inappropriate variations in care and when audit results are fedback, they can be effective in improving professional performance. Post-marketing surveillance is usually used to identify adverse events, see the "Yellow Card Scheme" (Yellow Card, nd). It is true, however, that large scale, high-quality, routinely collected and prospective (rather than cross-sectional) data can give us insights into product usage and outcomes — even signals as to the effects of treatments — but the data need to be robust, accurate and subject to careful analysis and interpretation.

SJ: Companies spend a lot of time and effort gathering evidence about the safety and efficacy of their various products, which is required by the various regulatory bodies to get licensing for their products. In the wound care sector, these are very seldomly RCTs and, as such, this wealth of evidence is not looked at, certainly not by the Cochrane group. Most of this evidence never even gets published, so is not accessible to most clinicians. Perhaps the evidence that the companies provide to notifiable bodies should be made available on the company website.

4. What evidential value do you ascribe to the NICE technology assessment process?

UA: The NICE technology assessments do cause confusion amongst clinicians as many seem to ascribe them the same level of importance as NICE clinical guidelines. It can't be helpful for industry either, as different regulatory bodies seem to require different levels of evidence. I would not want to see good-quality products withheld from patient care, but we do need to raise the evidence bar for products that claim to have an active impact on healing. Topical interventions are unlikely to cause physical harm to patients but expensive but ineffective interventions cause harm to the NHS purse and, ultimately, the tax payer. Unfortunately, very few wound care products are supported by robust evidence that their use has a meaningful impact on improving healing (compression therapy for venous leg ulceration is one exception). We need to find a way to reduce the over-use of ineffective products and increase the use of effective products.

CB: As a health economist, I'm unsurprisingly generally favourable of the NICE approach. However, I think it fails in wound care in two areas. Firstly, the standard models used to assess the economic evaluation of wound care products are, by focussing on healed and unhealed wounds, are just too simple. Unhealed wounds vary from seriously deteriorating to actively healing and they have very different cost and quality of life implications. Models which ignore these distinctions and have a consolidated 'unhealed' state are not making the most of the limited evidence base available to them and may miss the true incremental differences in costs and quality of life between treatments. This is especially significant when the evidence follow-up time is limited and a substantial proportion of wounds are unhealed — a common criticism of the evidence base. Secondly, health economists have always struggled with the concept of uncertainty and how that should be incorporated into decision making. This is reflected by the vague implementation of dealing with uncertainty in the NICE guide to the methods of technology assessment (NICE, 2013). This is even more important when the evidence base is such that the uncertainty isn't wholly captured by a standard error in a difference of means! Fortunately, there have been substantial and award-winning developments in the health economics literature about incorporating uncertainty directly into decision making in a genuinely informative manner (Claxton et al, 2016). Such nuanced thinking has yet to be introduced to the NICE methods but its application could lead to a break-through in the current impasse in wound care. In fact, I struggle to see a clinical area in which it could have a bigger and better impact.

NC: The key issue here is that there are several NICE assessment processes and they are regularly confused. We would ascribe high value to NICE clinical practice guidelines and NICE technology appraisals because they are based on independent, rigorous systematic review of the clinical and economic evidence.

SJ: I have been involved in these appraisals for several years. In contrast with the Cochrane approach, a NICE technology appraisal is based on a review of clinical and economic evidence, mainly provided by the company, supported by testimonies from patients, healthcare professionals and commissioners. Clinical evidence shows how well the technology works — the health benefits. The evidence includes the impact on quality of life (for example, pain and disability), and the likely effects on mortality. Economic evidence shows how well the technology works in relation to how much it costs the NHS and whether it represents value for money. This appraisal is very useful to us in the NHS, as when NICE recommends a treatment 'as an option', the NHS must make sure it is available within 3 months of its date of publication. Five categories of commendation are used: recommended, optimised, only in research, not recommended and recommended for use in the Cancer Drug Fund (not very relevant for wounds!). WUK

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