Appropriate methodologies in wound care research

DAVID CHAPMAN-JONES
Chief Scientific Officer, Synapse Electroceutical

This article is based on a symposium held at the Wounds UK annual conference in Harrogate, UK, on 10 November 2015. The aim of the symposium was to define the current state of play in wound care research, and to discuss how we can combine traditional theories with practical evidence in order to use research in the most useful way.

THE PURPOSE OF RESEARCH

Research is only useful if it is relevant. Addressing delegates at the Wounds UK annual conference, David Chapman-Jones explained that, just as conducting research is vital to extending our knowledge, so is reading that research and establishing whether the research is relevant. Considering the purpose of research is a key element of establishing this: 'Why are we doing this? What do we want to know?'

This was explained using the analogy of a football crowd — it can be difficult to ascertain from such a large group exactly who the work is aimed at and what this audience wants. 'Lumping' an audience together into one homogenous group in this way can be a flaw in research, because the group is made up of individuals and it is important to acknowledge that everyone is different. It is unfeasible to look at such a large cohort; as a starting point, it is more helpful to break the audience down into specific groups.

The aim of research should be to present 'what is happening', as opposed to 'what you think is happening' — or 'what you would like to happen'. This inspires the question: if research is sponsored, is it loaded?

This argument can be applied to elements involved in any research; the researchers' own knowledge and prejudices mean that there is a danger of them 'knowing' the outcome of the study before it has even been conducted. David noted that this does not only apply in the scientific or medical community — research conducted by the Government can be 'a classic example' of this.

SENSITIVITY VERSUS SPECIFICITY

This brought us on to the topic of 'sensitivity versus specificity'. The invention of the magnetic resonance imaging scan is a key example to illustrate this dichotomy: this advance represented fantastic progress and enabled doctors to 'see everything'. However, this created problems of its own — for instance, if a patient presented with back pain and was then sent for a magnetic resonance image, this would throw up positive results that were not necessarily relevant to ascertaining a diagnosis. All patients over the age of 40 are likely to have some degree of degenerative disc disease, so establishing this is not helpful. This demonstrates that the

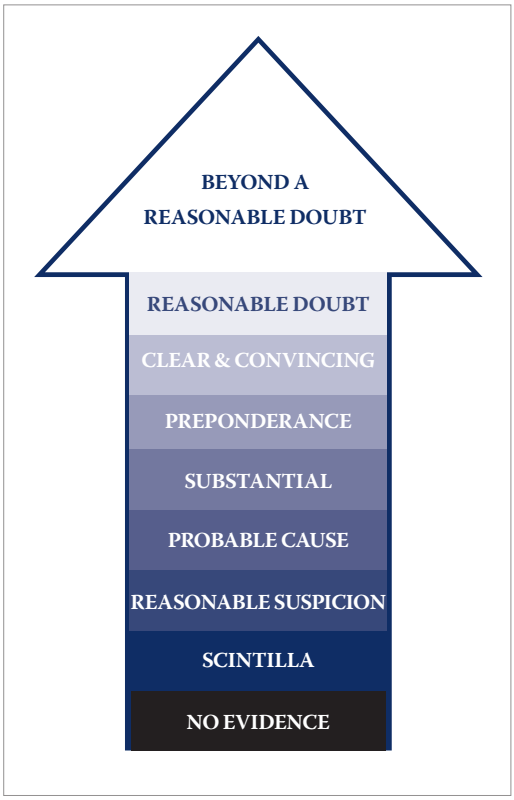

Figure 1. Levels of proof

magnetic resonance image is very sensitive but not specific.

The same theory applies to research, as 'you need to know what you are looking for' and this needs to be specific, rather than generic criteria. In wound care, this means looking at different wounds in this way — for example, if research is looking at non-healing ulcers, it would be more useful to investigate whether there is a common factor to these wounds that is causing them to be non-healing (e.g. patients being malnourished, or all being smokers). Investigating the reasons behind the facts in this way means that a solution may be found.

ATTRIBUTING OUTCOMES TO INTERVENTION

In any research study, the sample size needs to be appropriate in order for the resulting research to be useful. It is also vital to achieve the appropriate level of 'proof', which can be a subjective term (*Figure 1*). Comparing this to the legal world, in which proof must be 'beyond a reasonable doubt', the situation regarding scientific research can be different. In medicine, can anything be proven 'beyond reasonable doubt'? No matter how rigorous the research, it is unlikely that this will ever be achieved, as it is not possible to achieve that same level of certainty.

STUDY METHODS

The methodology is key to achieving the appropriate and relevant outcome. There are many different types of studies (*Figure 2*), and all methods have their advantages and their disadvantages.

In science, 'we are wedded to the double-blind RCT' (randomised controlled trial). However, in wound care, it is very difficult to get the outcome you expect in a randomised trial.

David explained that Synapse have undertaken a multicentre, triple-blind RCT, looking at venous leg ulcers. He highlighted that although this is considered 'the gold standard' method in research, it is more important to pick the most accurate method.

With this in mind, the cohort was broken down and investigated further. In this case, dealing with non-healing venous leg ulcers, the patients have had these wounds for very different periods of time. Therefore, it is more important to find the biggest factors in wounds not healing — e.g. whether patients may be obese or smokers.

The difficulty is that these factors may be — by chance — affecting the outcome of the trial. These are factors that cannot be influenced by the researchers — otherwise the trial is not 'random' — but it may affect the results. As David said, 'you have to look behind the obvious'.

This raises the question: 'Is the RCT as good as you can get for a wound care study?' In reality, people want to try a new product or treatment themselves and practical experience is key. However, this is anecdotal evidence that does not necessarily provide enough of a solid evidence base by 'traditional' research standards. The individual's own particular prejudices will always have an influence.

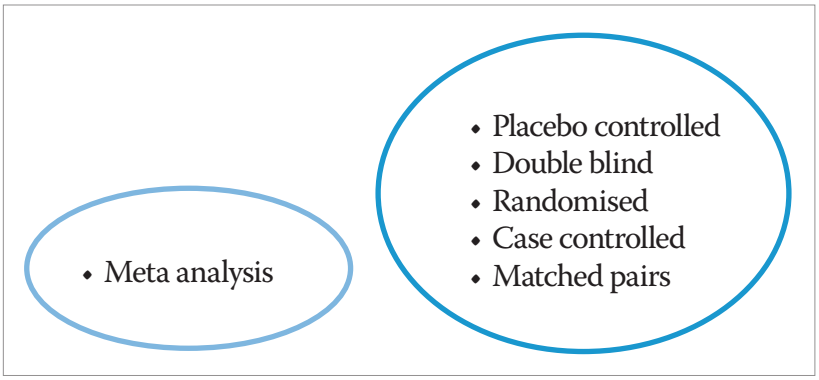

Figure 2. Study methods

$$n = \frac{p1 \times (100 - p1) + p2 \times (100 - p2)}{(p2 - p1)^2} \times f(a\beta)$$

Where:
p1 = response to current treatment
p2 = response to new treatment
aβ = significance and power of the study

For example: new treatment 40% respond, current treatment 30% respond: 10% difference
Assume 80% power and 5% significance; therefore f = 7.9 (0.2 x 0.5)

$$n = \frac{p1\ 30 \times (70) + p2\ 40 \times (60)}{(40 - 30)^2} \qquad \frac{X\ f(a\beta)}{100} \qquad n = 2100 + 2400$$

$= 45 \times 7.9 = 356$ subjects per group

Change the rates to 25 and 75 and the required number of subjects drops dramatically
$25 \times 75 + 75 \times 25/50^2\ 3750/2500$
$= 1.5 \times 7.9$
=12 subjects per group

Figure 3. Calculating study size using the method of Pocock and Stuart (1983)

Does practical experience count as 'research'? The issue is that if you use a product for long enough, it is likely that in some cases it will have an effect. For example, in the news it was reported that a malaria drug was found to work on patients with bowel cancer: of 11 patients, six showed some improvement, compared to two in the placebo group. David asked the audience: 'Would this have happened anyway? Can it be coincidence?' The key is that study size is important.

This question is addressed by Pocock and Stuart (1983). Their method (*Figure 3*) addresses the question, 'how many patients do I need in my study to make the results reliable?' and the more critical question, 'would I get the same result with, for example, 50 patients as with 11?'.

It is vital to define the outcome from the outset. This could be complete healing or wound closure — e.g. predicting that 40% patients will achieve wound closure. The predicted outcome may only be a small percentage difference between the old treatment and new treatment. Pocock and Stuart's theory can be used to calculate this reliability.

Using this method is useful, as David explained: 'Overestimating or being overconfident about a new treatment can be a very dangerous route to go down', as this can affect the reliability of statistics.

It is also important to consider how filtered the patients included in the study are, examining the inclusion and exclusion criteria, as this may determine the outcome. It is easy to skew a study in this way, as research may not apply in real life in the same way it does a filtered patient group. Particularly in wound care, there should be 'a wide entry gate', otherwise research will not be relevant to patients.

The example of 'the man on the bus' can be used as a useful barometer for this. This analogy illustrates how subjective viewpoints can be and that everyone reads facts through their own views and prejudices. An example was given of a case in which a group of men took part in consensual 'branding'. As this act was consensual, it was technically legal; however, in this case there was considered to be a moral element involved, as per the view of the hypothetical 'man on the bus'. Even in medicine, this issue of subjectivity is an important factor.

HOW WELL ARE WE DOING, AND WHY?

Collecting data in real time is often the only way that we can gauge 'how we are doing'. Tracking patients and their outcomes is the way to use data to change practice.

However, not all of this useful data is always given proper consideration, as the dominant trial remains the RCT, which is not always practical in wound care. As David explained, 'the RCT still completely dictates our data'. In order to use all relevant research and data in practice, how can we change organisations like the National Institute for Health and Care Excellence, who only deal with RCTs?

The average time to change from evidence is said to be 17 years, so seeking innovations in trials and their methodologies may be a better way forward. David highlighted that there can be 'laziness when it comes to trials — ticking boxes rather than thinking about whether the research produced is actually appropriate and relevant'. In wound care in particular, there are often many comorbidities and complex aetiologies involved that can make conducting RCTs difficult.

A solution may be to move away from prescribed care pathways, moving towards outcome-based rather than activity-based care. For example, if a patient has pain levels over 7, reducing their pain levels will also potentially make the patient more mobile. Unless these unexpected outcomes can be captured, this can skew research that does not take the full picture into account.

In summary, it is vital to capture real-time data — including how patients change and what is actually happening. Many factors are involved and affect research outcomes — it is therefore critical to track patients and capture data 'in a broader sense'. WUK

The workshop and report were supported by Synapse Electroceutical Limited.