WORLD UNION
OF
WOUND HEALING SOCIETIES

EVIDENCE IN WOUND CARE

Overview of evidence in wound care

Assessing level 1 evidence in wound care

Translation of evidence to practice into improve outcomes

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POSITION DOCUMENT

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108 Cannon Street
London EC4N 6EU, UK
Tel: +44 (0)203 735 8244
info@omniamed.com
www.woundsinternational.com

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Wound management research improves patient care and clinical outcomes by standardising assessment, planning and implementation of treatment. In the field of wound care, high-level evidence is possible, but it can be difficult to conduct due to the wide-ranging nature of wounds and patients.

Additionally, there is an ever-growing variety of products and devices available to practitioners to improve healing rates and patient outcomes. In many cases, these products have enabled practitioners to heal more complex wounds and manage more challenging and difficult cases. However, practitioners must be able to critically appraise evidence to make appropriate and effective evidence-based changes to practice.

The first article on page 4 titled 'Overview of evidence in wound care' sets the global scene of wound care research, as well as looking at the available study designs and their strengths and weaknesses. It provides a clear description of the levels of evidence available for wound care, the types of evidence available and their application to practice.

The second article on page 11, 'Assessing level 1 evidence in wound care', looks at what practitioners need to know to critically appraise level 1 evidence, especially randomised controlled trials, in order to evaluate their value and ascertain how the findings can be applied to practice.

The final paper starting on page 18, 'Translation of evidence to practice into improve outcomes', considers the steps required to achieve successful transition from research evidence to making changes in clinical practice, and the barriers that need to be overcome. The article guides practitioners on how to make evidence-based changes to their practice, with examples.

Authors

Joachim Dissemond, Professor, Dermatology and Venerology Consultant, Department of Dermatology, Venerology and Allergology, University of Essen, Germany

David G Armstrong, Professor of Surgery and Director, Southwestern Academic Limb Salvage Alliance (SALSA), Keck School of Medicine, University of Southern California (USC), Los Angeles, CA, USA

Andreas Stang, Professor, Center for Clinical Epidemiology, Department of Medical Informatics, Biometry and Epidemiology, University of Essen, Germany; Adjunct Professor, School of Public Health, Department of Epidemiology, Boston University, MA, USA

Dirk T Ubbink, MD, PhD, Professor, Department of Surgery, Amsterdam University Medical Centers, Amsterdam, The Netherlands

Hester Vermeulen, RN, PhD, Professor, Nursing Science, Department of IQ Healthcare, Radboud University Medical Center, Nijmegen; Faculty of Health and Social Studies, HAN University of Applied Sciences, Nijmegen, The Netherlands

Fran L Game, Honorary Professor, School of Medicine, University of Nottingham; Consultant Diabetologist, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK

William J Jeffcoate, Honorary Professor, School of Medicine, University of Nottingham; Former Consultant Diabetologist, Nottingham University Hospitals Trust, Nottingham, UK

Jeanette Milne, Chief Matron Community/Lead Nurse Tissue Viability, Northumbria Healthcare NHS Foundation Trust, Northumbria, UK

Gulnaz Tariq, Unit Manager for Wound Care, Sheikh Khalifa Medical City, Abu Dhabi, UAE

Reviewers: Chairs of the WUWHS International Scientific Committee

Afsaneh Alavi, Professor, Dermatologist, University of Toronto, Toronto, Canada

Dieter Mayer, Professor, Senior Consultant of Vascular Surgery and Head of Wound Care, Switzerland

Overview of evidence in wound care

Joachim Dissemond, Professor, Dermatology and Venerology Consultant, Department of Dermatology, Venerology and Allergology, University of Essen, Germany
David G Armstrong, Professor of Surgery and Director, Southwestern Academic Limb Salvage Alliance (SALSA), Keck School of Medicine, University of Southern California (USC), Los Angeles, CA, USA
Andreas Stang, Professor, Center for Clinical Epidemiology, Department of Medical Informatics, Biometry and Epidemiology, University of Essen, Germany; Adjunct Professor, School of Public Health, Department of Epidemiology, Boston University, MA, USA

Healthcare systems worldwide face increasing pressures from the public, from policy makers and from healthcare professionals, to deliver high-quality care within budgetary and resource constraints[1,2]. One approach to address the increasing pressures that emerged in the early 1990s is the growing use of research evidence, when making decisions around the adoption or continued use of procedures, practices and interventions[3].

EVIDENCE-BASED MEDICINE

Without research evidence, treatment decisions rest upon the expertise and experience of the clinician, influenced by patient's expectations[3]. The term evidence-based medicine (EBM) defines the process of integrating clinical expertise and patient expectations **alongside** research evidence to make decisions about the care of individual patients[4-6].

VALIDITY

Throughout the evolution of EBM; there has been a consistent view that not all evidence has equal weight[7]. Typically the quality of patient-orientated studies is influenced by the study design, and in particular by its validity (Box 1).

Box 1: Validity

Internal validity: The extent to which a piece of evidence supports a claim about cause and effect, within the context of a particular study.
External validity: The extent to which the conclusions of a scientific study can be applied outside the context of that study.

A study design with high internal validity provides confidence that the study results accurately reflect the relationship between the treatment and outcome, with limited possibility for the outcome to have been caused by extraneous factors, and not by the intended treatment. Internal validity is not solely a matter of study design, but it is also influenced by the capacity to conduct and report studies consistently. External validity refers to how generalisable the results are to other patient populations; a study with low internal validity is unlikely to be generalisable to other patient groups (low external validity)[8].

EVIDENCE PYRAMIDS

The evidence pyramid is a useful visual representation of the the internal validity of different study designs; designs of low internal validity are at the base of the pyramid and designs of high internal validity are at the top (Figure 1a). While the evidence pyramid is a useful guide, it is important to recognise it has limitations and should be viewed with careful consideration. An alternative perspective has been proposed that accounts for the role of meta-analyses and systematic reviews as a 'lens' through which to view all the available published data. In addition, the boundaries between study designs are depicted as wavy lines to represent that factors other than study design can influence the interpretation of evidence (Figure 1b).

The debate around evidence pyramids should also consider the goal of the research project: to understand the effects of treatment where high internal validity is a key requirement or to seek to make new discoveries and find explanations for the causes of disease[11]. Where the goal is to understand the disease aetiology, the traditional research pyramid may be reversed, with case reports and case series providing useful data to start an exploration of disease causation. This may be especially valid in the case of rare diseases or harms where there are few patients with the condition available for recruitment into high internal validity studies, such as randomised controlled trials (RCTs).

Regardless of the challenges described, the evidence pyramid provides a simple overview of study designs that may have high internal validity and, as such, may impact or change clinical practice where a clear relationship is found between a treatment and clinical outcome.

STUDY TYPES FEATURED IN THE EVIDENCE PYRAMID

SYSTEMATIC REVIEWS AND META-ANALYSES

While systematic reviews are regarded with the highest validity, they tend to identify weaknesses in individual wound healing RCTs. For example, in a Cochrane Review of local treatments for patients with venous leg ulcers, 51 of the 78 RCTs (65%) had a high or very high risk for bias; the remaining 27 RCTs had an unclear or low risk of bias[12]. RCTs may be summarised through systematic reviews or meta-analyses of the individual study data; systematic reviews or meta-analyses may provide consensus on the value of interventions and so inform healthcare policy.

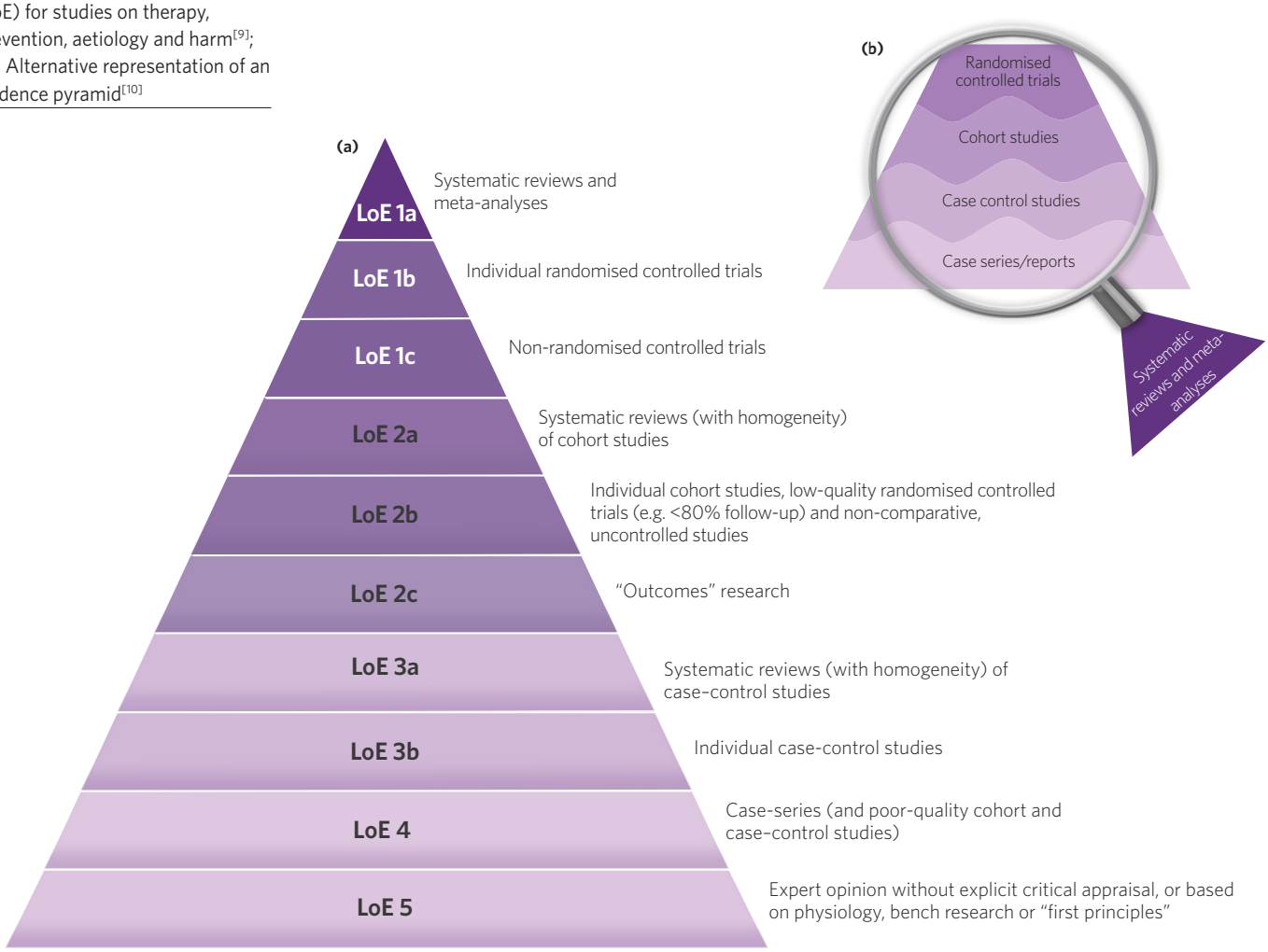

Figure 1: (a) Levels of evidence (LoE) for studies on therapy, prevention, aetiology and harm[9]; (b) Alternative representation of an evidence pyramid[10]

RANDOMISED CONTROLLED TRIALS

The RCT is usually viewed as the best study design to answer questions on whether a treatment affects clinical outcome[13]. An RCT is considered to have high internal validity, so reducing the likelihood of bias (flaws in the running of the study); this is discussed in greater detail in the second article within this document (page 11).

The strength of the RCT arises from five factors:

- Random allocation of patients to intervention and control groups, reducing systematic differences between the groups.
- Intervention groups are treated identically except for the experimental treatment.
- Patients and clinicians are ideally unaware of the treatment allocated. This double-blinding is viewed as part of the high internal validity of the RCT and can identify relationships between intervention and outcome. However, these studies are not frequently performed in wound research[14]. A major challenge lies in how clinicians and patients can be blinded to the treatments they provide and receive respectively; for example, in the case of negative pressure wound therapy (NPWT), the device itself precludes double-blind studies of NPWT and standard of care[15].
- Analysis of the data is performed for all patients who are allocated to the experimental and control treatments regardless of whether they received their intervention (intention-to-treat analysis).
- Analysis of the data is focused upon predetermined outcomes rather than searching the data to find statistically significant differences between the groups.

There are a number of factors to consider when interpreting an RCT, which include:

- RCTs are required to be appropriately powered; this requires the study to recruit sufficient participants to allow the primary endpoint to be compared between treatment groups (e.g. number of wounds healed). The power of a study reflects the ability of a study to detect a difference (should that difference exist) between the two compared interventions. In wound healing, it is customary to accept an 80% power, helping to keep studies small enough to be feasible, but accepting that there is a 20% probability the study will fail to detect a significant difference between interventions where that difference does exist.
- The point of entry of the patient into an RCT also deserves attention. A run-in period of 2–4 weeks after the initial patient screening, but before randomisation to treatment, is often used in diabetic foot ulcer (DFU) studies (e.g.[16-19]). Here, 'easy responders' can be identified from potential trial participants. These 'easy responders' show markedly reduced wound size over the run-in period due to standardisation of their wound treatment. While run-in periods may help to establish a population of truly 'hard-to-heal' wounds, the impact of run-in periods on both internal and external validity require consideration[20].
- RCTs represent the effect of an intervention under ideal conditions; however, the patient inclusion and exclusion criteria greatly impact upon the reported outcomes and the external validity of the study. There may be value in addressing 'real world' studies of wound healing with no inclusion or exclusion criteria to understand how wound interventions work in everyday practice (effectiveness research).

Box 2: Confounding

Confounding is caused by uncontrolled factors known as confounders and creates bias in the relationship between treatment and clinical outcome, e.g. wound size, number of co-morbidities and wound aetiology.

For example, in a non-randomised study of people with heel pressure ulcers, participants with good peripheral circulation of their lower leg may be more likely allocated to the novel treatment and participants with poor peripheral circulation of their lower leg may be more likely allocated to the standard treatment. As a result, ulcer healing may be a consequence of their adequate circulation rather than the intervention.

NON-RANDOMISED STUDIES

Non-randomised studies may indicate an association between a treatment and a clinical outcome, although their internal validity may be lower than that of a well-conducted RCT. The selection of patients in a non-randomised study may be determined by the researchers or jointly by the clinician and their patients[21]. The arbitrary selection of patients to receive the treatment may introduce imbalances in the risk factors for the studied outcome and result in confounding (Box 2).

While some of this imbalance may be addressed through statistical methods[21], it is unlikely that all bias due to confounding factors can be eliminated. Imbalance between treatment groups in non-

Box 3: Challenges of wound registries

- Expensive to collect data on the thousands of patients required to allow comparison between interventions.
- Infrequent assessments with gaps where patients did not attend for treatment.
- Loss to follow-up as patients' wound near closure[28].

randomised studies is likely to increase the apparent effect of treatment and always increases the uncertainty around the perceived effect of the intervention[21]. Non-randomised studies may face challenges when:

- Trying to standardise control interventions.
- Describing the method of treatment allocation.
- Choosing which data to collect (particularly around adverse and long-term outcomes).
- Establishing an *a-priori* statistical analysis plan prior to starting the study[22].
- Using historical controls (e.g.[23]): such studies are compromised by the lack of baseline comparability between cohorts, the use of adjunct therapies differing over time and different assessments of outcome.
- In a single-arm study that undertakes a before–after comparison, regression to the mean occurs where patients are enrolled due to extreme wound status (e.g. wound size, exudate production) and repeated measurements over time move closer to the mean rather than indicating progress or deterioration in the wound.

Management of confounders may be aided through case–control studies. This form of non-randomised study where patients who have experienced a specific clinical outcome (e.g. developed a chronic wound) known as 'cases' are matched to, and compared with, a second group of patients who did not experience the same clinical outcome, known as 'controls'.

Other non-randomised study designs include case reports and case series (which provide limited evidence linking treatment to outcome) and cohort studies (where groups of patients are followed until they develop a specified outcome). There has been considerable recent interest in large-scale cohort studies in wound healing with wound registries reported[24-27] although several challenges exist (Box 3).

DEVELOPING A MORE ROBUST EVIDENCE BASE FOR WOUND MANAGEMENT

Regardless of the study design selected to quantitatively answer wound healing questions, there are practical and methodological challenges that need to be addressed as wound healing research evolves.

Definition of chronicity: Chronic wounds are often defined in terms of their duration; wounds that persist anywhere from between 4 and 12 weeks have been labelled 'chronic'[29]. However, there are also definitions of chronicity that incorporate the underlying pathophysiology. For example, a DFU is described as chronic from the outset[30]. Given lack of consensus over the chronic wound definition, alternative definitions such as 'hard-to-heal' or 'therapy refractory' have come to the fore[31]. However, these alternative labels pose similar challenges to the term 'chronic' and also lack consensus agreement.

Definition of outcome measures: The outcome measures used to report wound progress or deterioration require standardisation so studies can collect clinically relevant indicators in a consistent manner. Protocols for systematic surveys of outcome measures in pressure ulcer management[32], pressure ulcer prevention studies[33] and outcome measures suitable for leg ulcer studies[34] have been developed. Such work requires expansion across other wound aetiologies before ideally condensing into a set of outcome measures relevant for all wounds.

Definition of study endpoints: Ideally, randomised and non-randomised studies would follow wounds until they are completely closed. The United States Food and Drug Administration (FDA) holds complete wound healing as the only recognised primary clinical trial endpoint[35]: "*100% reepithelialisation of the wound surface with no discernible exudate and without drainage or dressing, confirmed at two visits 2 weeks apart*[36]". Across 65 trial reports, only 40.6% (*n*=26) defined wound healing according to the FDA definition[36]. Without consensus over when a wound has healed, there will remain variation around trial outcome data.

For some trials, complete wound healing may not be the most appropriate study endpoint. Many interventions are used for only part of the wound healing journey; for example, silver antimicrobial dressings should only be used for a maximum of 4 weeks, with assessment at week 2[37]. Therefore, for silver antimicrobial therapy, the most appropriate study endpoint or outcome measure may be 'time to resolve infection'. Other endpoints or measures of healing include wound appearance, function, pain and patient quality of life[38]. At present, many of the tools to capture such endpoints are not fully validated.

Focus on medical statistics: Errors in selecting statistical tests, based on the distribution of the collected data, in statistical reporting[39] and in study planning, leading to an underpowered study[40], remain common. Statistical handling of data can affect both randomised and non-randomised studies; for example, inclusion of multiple wounds of one individual may lead to correlated observations being treated incorrectly as independent of one another. In any clinical study, a medical statistician should be involved from study design through data capture and analysis.

Funding: Since conducting clinical trials can be expensive, ideally this work could be publicly funded. Commercial funding remains important to maximise potential for research while allowing larger studies to be performed. A funding model whereby several industry partners come together to support high-quality research, rather than a single industry sponsor, could be explored, although this would be challenging.

Registering trials online: Study protocols of clinical studies should always be reviewed and registered and, in some countries, it is mandatory for industry sponsors to declare RCTs on public registries. Ideally all wound studies would be registered and the protocol available for review.

Registry-based data analyses: All patients with wounds, or as many as possible who receive treatment, should have their data recorded in a standardised way and give informed consent for their data to be included in a registry. A large international registry would enable the study of effect modifiers of treatments, including sex, social status and ethnicity*. Real-world effectiveness research through registries would also be important for interventions such as NPWT[41].

Evaluating remission: Studies evaluating techniques and technologies to extend time in remission are as important to public health, policy makers and patients as any single advance in tissue repair or wound healing[42,43]. For example, approximately 40% of people with diabetes will have a recurrent DFU following healing at 1 year, which increases to nearly 66% at 3 years and 75% at 5 years[44,45].

Smart monitoring of wound parameters: Smart dressings or objective monitoring instruments that enable the measurement and recording of various parameters repeatedly or continuously without removing dressings may be useful in trials[46]. For example, changes in pH values[47] and reactive oxygen species[48] in wound fluids are available, but not routinely used, to avoid unnecessary dressing change. Basic research is required to understand which parameters are the most useful to measure.

'Best should not become the enemy of the good': While we may wish for all wound healing questions to be answered by high internal validity studies, that will never be the case. Lower quality study designs will continue to provide some insights into the link between intervention and outcome (especially where attention is given to the impact of confounding factors).

*Ethnicity is not a permitted indicator by some ethics committees, but it is permitted in the USA.

CONCLUSION

The wound healing community requires standard definitions of basic parameters such as wound healing because, without a standard vocabulary, it is not possible accurately evaluate and synthesise the studies that are available. High-quality wound care studies are relatively scarce and often rely on real-world data and non-randomised study designs that have weak insights into the relationship between an intervention and clinical outcome; however, these studies do provide a platform upon which high validity studies may be based.

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Assessing level 1 evidence in wound care

Dirk T Ubbink, MD, PhD, Professor, Department of Surgery, Amsterdam University Medical Centers, Amsterdam, The Netherlands
Hester Vermeulen, RN, PhD, Professor, Nursing Science, Department of IQ Healthcare, Radboud University Medical Center, Nijmegen; Faculty of Health and Social Studies, HAN University of Applied Sciences, Nijmegen, The Netherlands
Fran L Game, Honorary Professor, School of Medicine, University of Nottingham; Consultant Diabetologist, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK
William J Jeffcoate, Honorary Professor, School of Medicine, University of Nottingham; Former Consultant Diabetologist, Nottingham University Hospitals Trust, Nottingham, UK

The design of the randomised controlled trial (RCT) compared to other research methodologies offers the clearest understanding of the relationship between an intervention and clinical outcome compared to other research methodologies[1]. The RCT, given its methodological rigour, is generally preferable over non-randomised or observational study designs, and forms the main source upon which systematic reviews of interventions are based. Recognising that there are sources of bias emphasises the need for full and transparent reporting of clinical trials, which will allow readers to assess the validity, strengths, and limitations of the research performed, and may protect clinicians from using biased results to inform their clinical decision-making.

HETEROGENEITY IN WOUND CARE: IMPACT ON THE EVIDENCE BASE

The quality of published controlled trials, not just RCTs, in the field of wound care, particularly diabetic foot ulcers, is inconsistent[2], with many being flawed by defects in design, conduct, analysis or reporting. It is therefore important for clinicians to understand the methodological flaws that lead to bias in RCTs. The presence of bias weakens our confidence that the results allow a true and valid conclusion to be reached regarding the chosen intervention's role in improving clinical outcome.

CONDUCT BIAS

Conduct bias refers to methodological flaws in a study design and conduct that lead to bias. While the RCT offers methodological rigour, failure to adhere to the study protocol can introduce bias and reduce the confidence of clinicians in the trial results and conclusions. It is generally believed that there are four key sources of bias that could be reduced by details of design of RCTs (Table 1).

Table 1. Sources of conduct bias within an RCT[3]

Type of bias	Stage of RCT	How it occurs
Selection bias	Group selection	Randomisation and allocation to treatment groups are flawed
Performance bias	Exposed or not exposed to the intervention	Blinding to treatment allocation does not occur A change in treatment occurs as current intervention is not considered to be working
Attrition or exclusion bias	Follow-up period	Numbers of patients lost to follow-up are high or different between the treatment arms
Detection bias	Assessment of outcomes	Outcome in one treatment arm is measured in a different way to the other arm

REPORTING BIAS

Reporting bias describes the bias that arises due to selective reporting of only the statistically significant study findings[3]. Reporting bias can be introduced if authors are tempted to overemphasise differences of marginal statistical significance (with perhaps limited clinical significance) and/or positive results of secondary analyses. Adverse outcomes of an intervention may be neglected or reported selectively by researchers, which will also exaggerate the beneficial outcome of the intervention[4].

Box 1: Three forms of negative study findings[5]

- **Conclusive negative results:** derived from well designed and conducted studies that show clear evidence of a neutral or negative effect (i.e. intervention is as good as the control, or even less effective than the control)
- **Exploratory negative results:** derived from well designed and conducted studies, with exploratory data analysis suggesting the intervention was less effective than the control
- **Inconclusive negative results:** poorly designed and conducted study, which is often too small to show the effect of the intervention.

PUBLICATION BIAS

Publication bias can occur when the outcome of a study influences the decision to publish or not[4,5]. Publication bias typically results in negative findings (Box 1) not being published as they are less likely to be of interest to journals seeking to maintain a high impact factor. In the case of exploratory or inconclusive findings, such journals tend to reject weak negative results and, for their career progression, researchers may choose to avoid publishing in less prestigious, low impact factor journals. Clinical trial registration on accessible databases was, in part, an initiative to help reduce the failure to publish exploratory or inconclusive negative findings[6]; however, selective reporting of trial outcomes remains common regardless of a trial's inclusion in an accessible registry[7].

GUIDE TO DETAILED STUDY APPRAISAL

Critical appraisal is intended to help readers establish the trustworthiness, value and relevance of a study by evaluating the following forms of validity:

1. Internal validity (risk of bias)
2. External validity (generalisability)[8].

During study appraisal, clinicians should consider for key areas:

- Where the research article sits in the evidence pyramid
- The authors of the article
- The prestige of the journal in which the work is published
- The source of funding of the research.

Clinicians must be able to critically appraise RCT evidence to evaluate the methodological quality and findings, and to determine how the findings should influence their decision-making in practice.

EVALUATION OF INTERNAL VALIDITY

Several questions are discussed below that consider the likely risk of bias within the study[9,10].

How was the control intervention selected?

Selection of the control intervention should ideally be based on a combination of the following four activities[9]:

- Systematic review of relevant literature
- Cumulative meta-analysis of completed trials
- Formal survey of expert clinical practitioners
- Publication of the trial's protocol to solicit critical appraisal.

One of the key guiding principles when justifying randomly exposing patients to interventions is the notion of clinical equipoise[11]: where there is genuine uncertainty as to whether the intervention or control is clinically superior. If no uncertainty exists and one intervention is generally considered superior, there is no justification to perform an RCT.

Box 2: Null and alternative hypotheses

- **Null hypothesis**: there is no difference statistically, or clinically, between the intervention and the control treatments[12
- **Alternative hypothesis**: there is a difference between the efficacy of the intervention and the control treatments.

Is the sample size adequate?

A key part of planning an RCT lies in the identification of the number of participants required to be able to confirm or reject the null hypothesis (Box 2). If too few participants are recruited, two errors can occur:

- Type-I error (alpha): the study concludes there is a difference between the efficacy of the intervention and control treatments where none really exists.
- Type-II error (beta): the study concludes there is no difference between the intervention and control treatments, but in reality there is.

Avoiding a Type-II error requires the study to have adequate power to detect a true difference between treatments. In wound healing studies, the power is conventionally set at 80%, indicating that there is a

20% (1 in 5) chance of not showing a true difference between treatments when there is. Setting a higher power substantially increases the number of participants required in a study[12]. Underpowered studies may have significant risk of bias but can still contribute to systematic reviews and meta-analyses where the data, from several studies are combined.

How are the outcome measures selected?

Each study should have one primary outcome measure that is used to calculate the overall result of the study[13], and the sample size should be calculated to avoid a Type-II error. When studies have multiple secondary outcomes, the study will not be powered to ensure Type-II errors are avoided when analysing the data to compare secondary outcome measures.

Both primary and secondary outcome measures should be patient-related, e.g. number of healed wounds, pain and quality of life[14]. The use of surrogate outcome measures in RCTs may be problematic; election of appropriate surrogate outcomes should be based on their demonstrated validity as predictors of a final patient-centred outcome[15].

Was the randomisation of participants truly random?

One of the most common approaches to randomisation is block randomisation[16]. Block randomisation is used to generate equal numbers of participants within each study group. As the block size increases, the number of permutations for which group the next participant will be allocated to also increases. However, there remains a risk that, if the clinician recruiting participants to a study knows the block size, then they will be able to predict the treatment group to which the next participant will be allocated; for example, if a block of two has been used, when one participant has been allocated to the control group, then the next participant will be known in advance to join the treatment group, defeating the purpose of randomisation and introducing bias to the study[16].

Was the allocation of participants to intervention adequately concealed?

It is generally recommended that multicentre trials should use a centralised randomisation facility to prevent investigators subverting the randomisation process. Adequate randomisation and allocation concealment are key to reducing selection bias in an RCT[17-18].

Were the groups similar at the start of the study?

If the randomisation has been conducted properly and the study is adequately powered, then the intervention and control groups will be similar at the start of the study. However, even where randomisation has been correctly performed and the number of participants is appropriate, there can be differences between groups at the start of the study, such as age or disease severity. These differences are known as chance bias[19]. Statistical correction can be completed for such baseline differences by means of covariance or regression analysis.

Were participants and practitioners providing care blinded, and outcome assessment blinded?

Ideally, the participant should not know the treatment they have received (single-blind), the practitioners should not know which treatment they have provided (double-blind) and the individuals making assessments of outcome should be unaware of which group received treatment or control interventions (triple-blind).

Traditional blinding in RCTs may be problematic in medical device studies given the visible differences between interventions[20]. Lack of double-blinding in wound healing RCTs is a key methodological weakness as non-blinded studies tend to over-estimate the effects of interventions by 7%[18]. However, blinded outcome assessment is feasible in wound healing studies[21] and should form part of the RCT methodology and be reported in study publications.

Was there minimal loss to follow-up and were all exclusions from the study explained?

All study participants will ideally progress through the RCT, so that the group sizes are the same at the start and end of the trial. Participants leave studies for a wide range of reasons such as personal preference, intolerance to the interventions, and mortality. If over 25% of participants leave the study (especially if this occurs in only one of the study arms), this presents a serious risk of attrition bias[22].

Was an intention-to-treat analysis performed?

If all participants remain in a study from start to end, then the data analysis would include all participants in both study groups, maintaining the power of the study to detect differences between intervention and control groups. Where participants leave the study early, there can be a temptation to include only those who completed the study (and have a complete data set) in the final analysis. This approach reduces the power of the study to detect differences between study groups[23]. If the participants who leave the study early are removed from the analysis, it may over-estimate the potentially positive effects of the trialled intervention.

An intention-to-treat analysis maintains the original randomisation by including all participants in the analysis regardless of whether they received the treatment, died or left the study for other reasons. This approach to RCT data analysis provides an unbiased estimate of treatment effect compared with only analysing those who received the treatment and completed the study (per-protocol analysis)[23].

EVALUATION OF EXTERNAL VALIDITY

The external validity of a trial is the extent to which the trial results can be generalised to other patient populations. There are many factors that can reduce the external validity of a trial, including the study participant inclusion and exclusion criteria[24]. Concerns over being allocated to the control arm[25], cultural factors and a willingness to participate in a research study can make it difficult to recruit a wide range of patients that is representative of the patient population[26] and impact or reduce the external validity of the study.

VALIDITY SCORING TOOLS

Some organisations specialising in the promotion of evidence-based practice offer simple validity checklists to assess internal and external validity (e.g. in the UK, the Centre for Evidence Based Medicine [CEBM][27], the Joanna Briggs Institute [JBI][28], and the Scottish Intercollegiate Guidelines Network [SIGN][29]). Beyond general RCT reporting requirements, such as the Consolidated Standards of Reporting Trials (CONSORT; a 25-question checklist of information to include in any publication reporting an RCT[30]), several authors have proposed both design and reporting criteria for trials in wound healing, for example[22,31,32].

Specific validity scoring tools for wound studies

A group representing both the European Wound Management Association (EWMA) and the International Working Group on the Diabetic Foot (IWGDF) published a 21-point score designed to assess the validity of intervention studies relating to diabetic foot ulcers (DFUs; Box 3)[22].

The scale is divided into four sections: study design, study conduct and analysis, study outcomes and study reporting. The items selected are based solely on the opinion of experts in the field who had themselves conducted a number of cohort studies, RCTs and systematic reviews[22]. Although no validation of this 21-point score has yet been published, it has the potential to be a very relevant scoring tool to evaluate the validity of studies reporting evidence on which to base wound, and specifically DFU, care. The intention was, that, if each of the 21 items scored 1 point, studies could be graded by aggregating the points.

Box 3. Required rationale and markers of quality: the 21-point scoring system for reports on clinical trials for the prevention and management of diseases of the foot in patients with diabetes[22]

Study design

1. Are adequate definitions included for the terms "ulcer," "healing," and all other required aspects of the population and the outcomes?
2. Was the choice of study population appropriate for the chosen intervention and the stated outcomes?
3. Was the control population managed at the same time as those in the intervention group?
4. Is the intervention sufficiently well described to enable another researcher to replicate the study?
5. Are the components of other aspects of care described for the intervention and comparator groups?
6. Were the participants randomised into intervention and comparator groups?
7. Were the participants randomised by an independent person or agency?
8. Was the number of participants studied in the trial based on an appropriate sample size calculation?
9. Was the chosen primary outcome of direct clinical relevance?
10. Was the person who assessed the primary outcome or outcomes blinded to group allocation?
11. Was either the clinical researcher who cared for the wound at research visits or the participant blinded to group allocation?

Rationale: study design

The intervention should be the only difference between study groups; there should be no difference between the baseline characteristics of the participants, other than those that may be the result of chance. It is also important that all participants otherwise receive defined good standard care. The importance of this is to ensure that any intervention being studied is the only difference between groups, which could account for any observed difference. The method of randomisation (ideally by an independent agency) should be described, together with a sample size calculation, blinding/masking (especially of the outcome observer) and a choice of an outcome measure that is clinically relevant.

Study conduct

12. Did the study complete recruitment?
13. Was it possible to document the primary outcome in 75% or more of those recruited?
14. Were the results analysed primarily by intention to treat?
15. Were the appropriate statistical methods used throughout?

Rationale: study conduct

The four questions relate to completion of recruitment and follow-up, as well as to statistical analysis.

Outcomes

16. Was the performance of the control group of the order that would be expected in routine clinical practice?
17. Are the results from all participating centres comparable? Answer "Yes" if the study was done in only one centre.

Rationale: study outcomes

Question 16 checks that the differences observed between groups are not the result of unusually poor performance in the control group, as has been the case in a number of published trials reporting apparent benefit of an intervention.

For question 17, as many multicentre studies have a core of high-recruiting centres and a majority in which recruitment was either moderate or low, it is important to ensure that the aggregate outcomes are not dominated by performance in a small number of high recruiting centres. For example, if usual care is different in different centres, any benefit could be by chance, but if randomisation is stratified by centre, then this could have less of an influence. While this can be minimised by randomising separately by study centre, this can increase the total number of participants needed.

Study reporting

18. Is the report free from errors of reporting, e.g. discrepancies between data reported in different parts of the same report?
19. Are the important strengths and weaknesses of the study discussed in a balanced way?
20. Are the conclusions supported by the findings?
21. Is the report free from any suggestion that the analyses or the conclusions could have been substantially influenced by people with commercial or other personal interests in the findings?

Rationale: study reporting

The four questions are designed to explore the possibility of reporting bias. Questions 19–21 aim to expose aspects of the report that reflect intentional or unintentional choice of words, which could either exaggerate or obscure some aspects of the findings.

The 21-point scale for studies on diabetic foot ulcers is reproduced from the Lancet Diabetes and Endocrinology with permission from Elsevier.

Note: Assessing systematic reviews

Systematic reviews and meta-analyses are becoming increasingly common and are often conducted as part of the preliminary work for higher degrees and/or in planning new trials. Existing systematic reviews are frequently updated at relatively short intervals. Readers need to exercise the same vigilance to identify bias when studying such reviews. This is of particular importance when the authors of a review are not themselves experts in the chosen clinical field (some groups undertake systematic reviews on a number of different topics). Reviewers who are not clinical experts may be unable to assess the significance of some findings; for example, the need to judge whether the outcome in the comparator group is what would be expected in clinical practice, and whether all participants received good standards of care. As with other study designs, checklists exist to help structure the critical appraisal of systematic reviews, for example PRISMA[33] and Critical Appraisal Skills Programme (CASP)[34].

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CONCLUSION

Recognising sources of bias in an RCT emphasises the need for full and transparent reporting of clinical trials, which will allow readers to assess the validity, strengths, and limitations of the research performed, and may protect clinicians from using biased results to inform their clinical decision-making.

There is no such thing as a 'perfect' clinical study; all RCT data will, to some extent, have bias that reduces confidence in the study results. It is unlikely that future RCTs will eliminate all bias; therefore, critical appraisal of all individual studies and systematic reviews is a skill set now required by all health professionals and researchers so that they can make informed clinical decisions.

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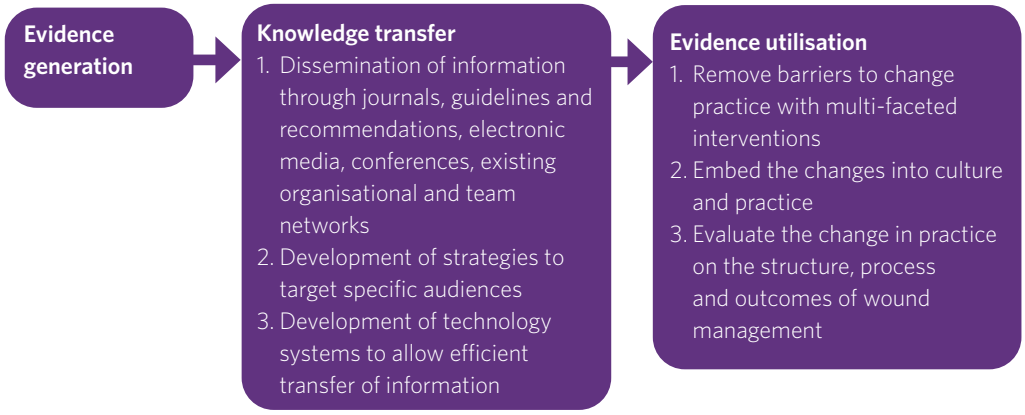
Translation of evidence into practice to improve outcomes

The generation of evidence on the efficacy of healthcare practices is the first step towards changing practice[1]. Evidence-based practice considers both the best available evidence and the context in which care is delivered, including patient preferences and practitioners' judgement[1]. Once evidence is generated, knowledge transfer and utilisation help to translate study results into everyday clinical practice and health decision-making (Figure 1), known as one part of translational research[2,3].

Figure 1: Understanding knowledge transfer and utilisation



In an ideal scenario, translational research should be based on strong clinical evidence. In wound management, it is well discussed that uncertainty and potential for bias exist in many studies[4-6] leading to the continued use of ineffective practices, variations in practice and the underuse of evidence-based care[7]. Translation of research and innovation into daily practice requires a complex interplay between human, organisational and performance factors (Box 1).

Box 1: Factors that facilitate or prevent translation of evidence[8-9]

- The quality of the research evidence
- The context in which the translation is to occur, including local culture and leadership of the organisation and staff
- How and by whom the process of translation is managed
- External environment, including market trends, knowledge of best practice and whether innovation provides a competitive advantage
- The role of 'top-down' and 'bottom-up' management of change and local performance evaluation of the new innovation, including user satisfaction, effectiveness and efficiency.

One important element to translate study data of new products or procedures into everyday practice lies in understanding the economics of health care, in particular, knowledge of both the costs incurred and benefits accrued.

Jeanette Milne, Chief Matron Community/Lead Nurse Tissue Viability, Northumbria Healthcare NHS Foundation Trust, Northumbria, UK
Gulnaz Tariq, Unit Manager for Wound Care, Sheikh Khalifa Medical City, Abu Dhabi, UAE

HOW HEALTH ECONOMICS CAN ASSIST WOUND MANAGEMENT TRANSLATIONAL RESEARCH

While the demand for high-quality wound management has been identified[10] and the number of interventions to aid wound healing continues to increase, there continue to be significant constraints on new resources[11-13].

Therefore, choices have to be made based on the costs and benefits associated with an intervention[14]. Health economics help to structure the assessment of cost and benefit through four different forms of economic evaluation (Table 1).

Table 1. Health economic evaluations

Method	Benefits and outcomes	Action
Cost-minimisation analysis	Outcomes from different wound interventions are equivalent	Select the intervention with lowest cost
Cost-effectiveness analysis	Benefit measured as a clinically relevant outcome (e.g. number of wounds healed)	Select the intervention that incurs the lowest cost to heal one additional wound
Cost-utility analysis	Benefit measured as quantity and quality of life	Compare wound management with other aspects of health care in terms of cost incurred to provide 1 year in perfect health
Cost-benefit analysis	Benefit measured in monetary terms	Consider how are non-monetary outcomes such as wound area reduction are priced?

Cost-utility analysis often uses Quality-Adjusted Life Years* (QALYs) to reflect the benefit gained from specific interventions[14,15]. The value of QALYs lies in the ability to directly compare alternative healthcare treatments (i.e. the cost to obtain 1 QALY directly through wound management or indirectly through diabetes care for those with diabetic foot ulcers [DFU]).

INTERPRETATION OF COST-EFFECTIVENESS AND COST-UTILITY STUDIES

Health economics can provide insights into whether a new intervention should be adopted, both at a strategic and a local level. However, the interpretation of cost-effectiveness and cost-utility studies is rarely straightforward[16], as a new intervention may provide greater clinical benefit but at a higher cost than current treatment.

In an economic evaluation, it should be clear what type of cost is under analysis: direct costs or productivity costs. Direct costs reflect the monetary burden of the medical care and non-medical care expenditures made in response to disease. Productivity costs take into account the societal perspective, and reflect the monetary value of the work lost due to death induced by disease or its treatment[16].

Cost-effectiveness and cost-utility analyses help to inform policy and strategic decisions but lack granularity to assess the impact of new technologies at a local department level. Identifying all the elements that contribute to the care of individual patients allows recognition of the processes that incur high costs and illustrates whether a care pathway is efficient.

New evaluations may be required to assess the level of investment and disinvestment that may occur when considering whether to adopt a new intervention into wound management; one such approach is time-driven activity-based costing (TDABC)[17]. TDABC records all the human and technology resources that contribute to a process of care (e.g. wound management) used to treat patients.

*One QALY is equal to 1 year of life in perfect health[18]; as health deteriorates, each year of life is weighted with a quality of life score (ranging from 0 to 1). A reduced quality of life score reflects an individual's inability to perform daily activities, along with the presence of pain and impaired mental health.

However, understanding the economic implications of new interventions forms only a part of the complex jigsaw that determines whether new products and procedures enter routine daily care[19]. The next part is whether there is the evidence to support its translation into practice.

Evidence generation

1. EVIDENCE GENERATION: EVIDENCE FOR OPTIMAL WOUND MANAGEMENT

While there is limited evidence in wound care to support practice, for the purpose of this article, three key examples of where research and evidence have changed clinical practice are explored.

Multidisciplinary teams

For over 20 years, the potential benefits of delivering wound care through multidisciplinary teams (MDTs) have been discussed[20-23]. While many of the studies that support MDT working in wound care are methodologically weak[24], there is a clear trend that improved wound management outcomes can be achieved. Where MDT working is performed, there can be reductions in the severity of amputation, mortality and length of hospital stay of people with DFUs[24]. In a multi-method study that compared the effectiveness of MDTs to 'usual care' for the treatment of pressure ulcers in long-term care facilities, there were similar reductions in pressure ulcer area, but there were reduced direct costs of USD$650 per long-term care resident with MDT working[25].

Compression for venous hypertension

Compression of the lower limb using bandages and hosiery is the primary treatment of venous hypertension, a key factor in the development of venous leg ulcers (VLUs)[26]. Multiple systematic reviews have highlighted the value of limb compression in both the healing and prevention of recurrence of VLUs[27-30]. However, significant variations in practice occur; for example, only 16% of patients with lower limb wounds had been assessed for their suitability for limb compression[11], while other reports suggest that only 6.3% of patients with VLUs had lower limb compression[31]. While limb compression is known to be effective, not all patients receive this intervention, highlighting the challenges to transforming research findings into daily care.

Technology Lipido-Colloid-Nano-Oligo Saccharide Factor (TLC-NOSF) dressings

Dressings that contain Technology Lipido-Colloid-Nano-Oligo Saccharide Factor (TLC-NOSF) inhibit matrix metalloproteinases and promote angiogenesis in the wound[34] (Box 2). Level 1 studies have reported the effect of these dressings with improved complete wound healing in neuro-ischaemic DFUs compared with the same dressing without sucrose octasulfate[33]. Over 20 weeks of treatment, complete wound healing occurred in 60/126 (48%) of the patients allocated the sucrose octasulfate dressing and in 34/114 (30%) of those who received the control dressing. This double-blind randomised controlled trial (RCT) had good internal validity and conformed to the proposed reporting requirements for DFU studies identified by Jeffcoate et al[35] (details on page 15). Secondary analyses of the RCT identified both that the sucrose octasulfate dressings were more likely to be effective when initiated at an early stage in wound treatment[36] and to be more cost-effective than the control dressing[37].

A second double-blind RCT compared sucrose octasulfate dressings against a control dressing when used in the treatment of VLUs[38]. Over 8 weeks of treatment, the VLUs reduced in area by 58.3% in the sucrose octasulfate dressing group and by only 31.6% in the control dressing group. A pooled-data analysis of observational studies conducted in France and Germany[39] evaluated chronic wound healing (pressure ulcers, VLUs and DFUs) when dressed with a sucrose octasulfate dressing and showed reduced healing times consistent with the results of the two key RCTs[33,38].

Box 2. Technology Lipido-Colloid-Nano-Oligo Saccharide Factor

Technology Lipido-Colloid-Nano-Oligo Saccharide Factor (TLC-NOSF) local treatment is indicated for DFUs, leg ulcers and pressure ulcers. The treatment is composed of a lipido-colloid TLC-NOSF Healing Matrix (NOSF impregnated in a TLC healing matrix). When in contact with wound exudate, the TLC-NOSF Healing Matrix forms a lipido-colloid gel, which creates and maintains a moist environment conducive to healing. The TLC-NOSF Healing Matrix acts locally in the wound on two key factors significantly impairing wound healing: inhibition of excess matrix metalloproteinases[32], and restoration of neovascularisation by reactivating vascular cells' proliferation and migration[32,33].

Knowledge transfer

2. KNOWLEDGE TRANSFER

The next step of translational research is knowledge transfer. Focusing on sucrose octasulfate dressings as an example, Edmonds et al[31] concluded that a "*sucrose octasulfate dressing is effective and safe, and its use is easy to implement by all health care professionals*". The evidence indicating the likely efficacy of the sucrose octasulfate dressing in the management of DFUs and VLUs has now translated into strong recommendations for use of the dressing by national and professional groups (Box 3).

Box 3. National and professional groups recommending the use of sucrose octasulfate dressings

- In the UK, National Institute for Health and Care Excellence (NICE) recommended use of sucrose octasulfate dressings in the treatment of both DFUs and VLUs[40].
- In France, similar recommendations have been made by the National Authority for Health[41]. Using a rating system to indicate likely benefit from using the sucrose octasulfate dressings, Haute Autorité de Santé (HAS) has rated the use of the dressing on leg ulcers at level 4 with a higher anticipated benefit for treatment of DFUs (level 3). All the other wound dressings have a level 5 rating, which marks the lowest anticipated benefit.
- The 2019 International Working Group on the Diabetic Foot Guidelines[42] on wound healing interventions have included a recommendation on the use of sucrose octasulfate dressings. This recommendation is one of 13 recommendations and the only one to support specific dressing use for DFUs: "*Consider the use of the sucrose octasulfate impregnated dressing in non-infected, neuro-ischaemic DFUs that are difficult to heal despite best standard of care*".

Evidence utilisation

3. KNOWLEDGE UTILISATION: EVIDENCE INTO PRACTICE

SERVICE EVALUATION EXAMPLE: NORTHUMBRIA HEALTHCARE NHS FOUNDATION TRUST, UK

Knowledge utilisation involves translating evidence and recommendations into routine clinical care. A 10-patient non-comparative case series from Northumbria Healthcare NHS Foundation Trust in the UK was conducted to evaluate the effectiveness of using dressings sequentially, including sucrose octasulfate dressing, to manage infection, deslough and reduce healing time (Box 4)[43].

Box 4. Summary of a 10-patient non-comparative case series from Northumbria Healthcare NHS Foundation Trust[43]

Baseline patient characteristics

- Gender: *n*=5 men, *n*=5 women
- Age (range): 66–89 years
- Ankle–Brachial Index (range): 0.66–1.07
- Wound aetiology: *n*=4 VLU, *n*=6 mixed aetiology
- Wound volume* (range): 72–12,500 cm^3
- Wound duration (range): 8–184 weeks (median 60 weeks)
- Patients who had compression applied before the start of the evaluation: *n*=9.

Care provided

- All patients received compression therapy as per best practice[27-30].
- The evaluation focused on the effectiveness of using dressings sequentially to manage infection, deslough and reduce healing time. At enrolment, UrgoClean was applied as a primary dressing to facilitate desloughing among patients with >30% slough (*n*=5); UrgoClean Ag was applied among patients who had signs of critical colonisation and devitalised tissue (*n*=5) for a maximum period of 4 weeks; UrgoStart was used among patients with <30% slough or after using UrgoClean Ag.
- Dressing change was determined by clinical need.

Results

- Healed before or at 12 weeks: *n*=4 (1 VLU and 3 mixed aetiology)
- >40% wound size reduction at 4 weeks: *n*=7
- >75% wound size reduction at 12 weeks: *n*=8
- Patients ending the study in UrgoStart: *n*=8
- The patients whose wounds had not healed at 12 weeks continued with the treatment plan
- No patient had systemic antibiotics during the 12-week evaluation.

Limitations

There was no control group.

*Wound volume reduction greater than 40% at 4 weeks has been reported to be a predictive indicator of healing[44,45]. Wound volume was used as a marker in this case series as some VLUs were deep. Wounds were measured by tape measure.

The evaluation and results prompted the development of a local pathway for a nursing team (Figure 2). The pathway included evidence-based information to guide decision-making that was easily accessible and inclusive of product-specific advice and signposting. Sucrose octasulfate dressing has been used for 16 months by the team and wound products expenditure is now £22,000 below budget (Figure 3).

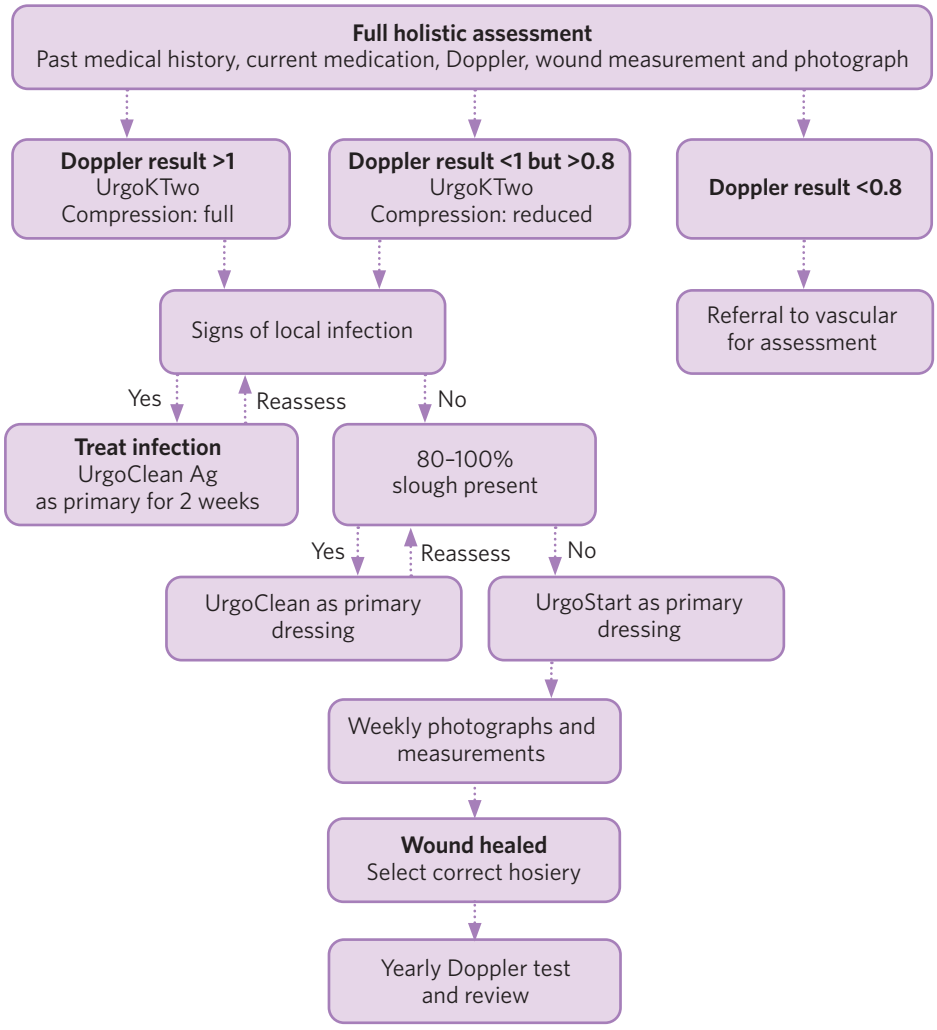


Figure 2: Local care pathway developed for a group of nurses at Northumbria Healthcare NHS Foundation Trust, UK

Compression: full: 40mmHg; reduced: 20mmHg
UrgoClean Ag: silver-containing dressing to resolve local signs of infection
UrgoClean: soft adherent dressing with poly-absorbent fibres to remove slough and manage wound exudate
UrgoStart: sucrose octasulfate dressing to promote angiogenesis and inhibit proteases
UrgoKTwo: two-layer compression system

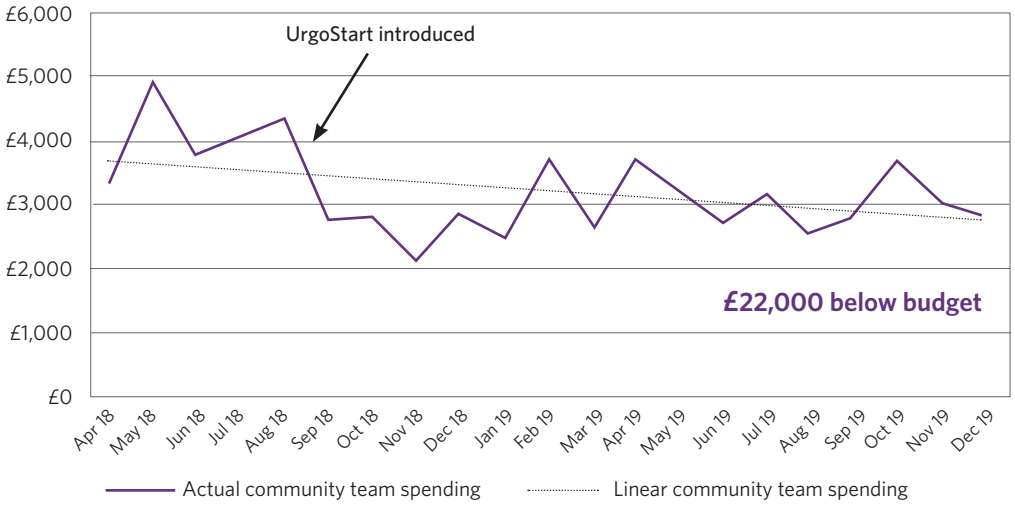


Figure 3: Reduction in expenditure (£) following implementation of the care pathway in one community nursing team

CONCLUSION

The generation of robust evidence of wound care interventions is a key part of evidence-based practice. Translating evidence into routine daily care is a complex, challenging multi-stage task. The non-comparative case series from the UK is an example of how evidence-based wound interventions with good evidence and recommendations from international and professional bodies can be translated into practice within a locally developed care pathway.

Locally developed care pathways that are adaptable have been shown to generate positive clinical outcomes and represent one approach to successful implementation of a product's use in routine care. Other approaches that support the translation of evidence into practice include providing adequate education, improving motivation for clinicians, as well as understanding the economics of health care and how practice affects cost. All of which offer the opportunity to ensure more appropriate use of healthcare resources and improve patient outcomes.

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