A methodology for evaluating wound care products in complex chronic wounds

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Abstract

Background: The question of whether particular methodologies can generate knowledge of a sufficiently rigorous and relevant standard to guide patients' interventions is regularly debated. This debate tends to be polarised between those who advocate the randomised controlled trial (RCT) as the ultimate scientific methodology and those who find RCTs wanting in terms of the information derived and their limited generalisability beyond the immediate trial population. This paper argues for a suite of methodologies that can evaluate wound care interventions; it also details a novel methodology for use in complex chronic and palliative wound care. *Aim:* To outline a methodology that can evaluate the clinical performance of wound care products in the context of complex treatment and care. *Methods:* The methodology is informed by the UK Medical Research Council framework for the design of complex evaluations, and is an N-of-1 design. *Results:* A novel methodology for evaluating the effectiveness of wound care technologies in complex chronic wound care and palliative wound care has been proposed. *Conclusion:* The methodology requires validation in prospective studies. The purpose of this paper is to open a constructive debate. *Conflict of interest:* None.

KEY WORDS

Complex chronic wounds
Palliative wound care
New methodologies
Wound debridement

The evidence base for chronic wound care interventions is weak. The field of wound care is dominated by the polarised debate around whether randomised controlled trials (RCTs) are the 'gold standard' of wound care evaluation (Gottrup, 2008). Given the heterogeneity of wounds and wound care interventions, the considerable variation in healing, 'hard to heal' and 'never to heal' wounds, together with individual patient experiences, is there not a case for a suite of methodologies and research designs for wound care? This paper offers a novel methodology for evaluating the effectiveness of wound care technologies in complex chronic wound care and palliative wound care. This methodology is underpinned by the UK Medical Research Council (MRC) framework for the design of complex interventions, and is an N-of-1 design (MRC, 2008).

The methodology provides clear predictions of the outcomes of a given intervention and generates in-depth information about individual responses, including differences between the responses of patients receiving the same intervention. In effect, the methodology enables us to answer the 'how', 'why', 'when' and 'when not' questions in order to guide clinical decision-making in relation to a particular intervention.

N-of-1 designs can satisfy the criteria of objectivity and internal validity without the need for large study samples (MRC, 2008). The validity and generalisability of the findings generated through N-of-1 designs can be confirmed and challenged through routine post-market surveillance, ideally using the same outcome measures.

Chronic wounds

Chronic wounds arise from a number of different aetiologies and conditions, which will direct treatment, care and local wound interventions. There are core, cross-cutting local wound problems for which wound care products play a critical management role. These include the presence of dead tissue, bacterial colonisation, exudate, odour, and peri-wound skin damage from exudate and dressing removal. These elements of chronic and palliative wound care can provide discrete and measurable end-points of an intervention, and the focus for N-of-1 studies and data collection (Brown et al, 2008; Grocott and Campling, 2009). For the purposes of this paper, wound debridement with larval therapy will be used as the working example.

Methodology, study design and methods

The methodology was developed from the WRAP study (Woundcare Research for Appropriate Products – Engineering and Physical Sciences Research Council [EPSRC] Grant Reference: GR/R39023/01; Cowley and Grocott, 2007), and the EPSRC Innovative Manufacturing Research Centre, MATCH (Multidisciplinary Assessment of

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Technology Centre for Healthcare). It is based on the MRC (2008) framework, which is recommended as good practice for complex clinical evaluations (*Figure 1*). Cost parameters can be measured alongside clinical outcomes with the involvement of a health economist (Cowley and Grocott, 2007). The clinical outcomes are measured in this proposed methodology using the TELER system, which will be described later in the paper (Grocott et al, 2007). Data analysis is quantitative and qualitative.

Qualitative reasoning and interpretation of the findings is performed to build explanations of wound care interventions in different patient situations. This includes the development of theoretical explanations with regard to how the particular product(s) being evaluated has performed optimally, or not, as the case may be. The explanations extend to making recommendations as to which patient groups might benefit from the technology and which may not. In effect, reasoned explanations of the strengths and limitations of the technology are drawn from the data and the analysis (Grocott and Cowley, 2001; Cowley and Grocott, 2007; Grocott and Campling, 2009).

Study design

The study design, informed by the stages of health technology assessment from the MRC (2008) framework, is outlined in *Figure 1*.

Pre-clinical

This is the phase in which the relevant theory for predicting the role and outcomes of the intervention is researched and documented. For example, the theory behind larval therapy is that the larvae will debride dead tissue by using it as their food source. The clinical relevance and expected outcome is debridement of dead tissue in a wound while sparing healthy tissue. This theory will be drawn from a number of sources. If the product is new, it will come from the manufacturer if it is not as yet in the literature. The theoretical basis/mode of action of the product will then guide the outcome measures selected to detect

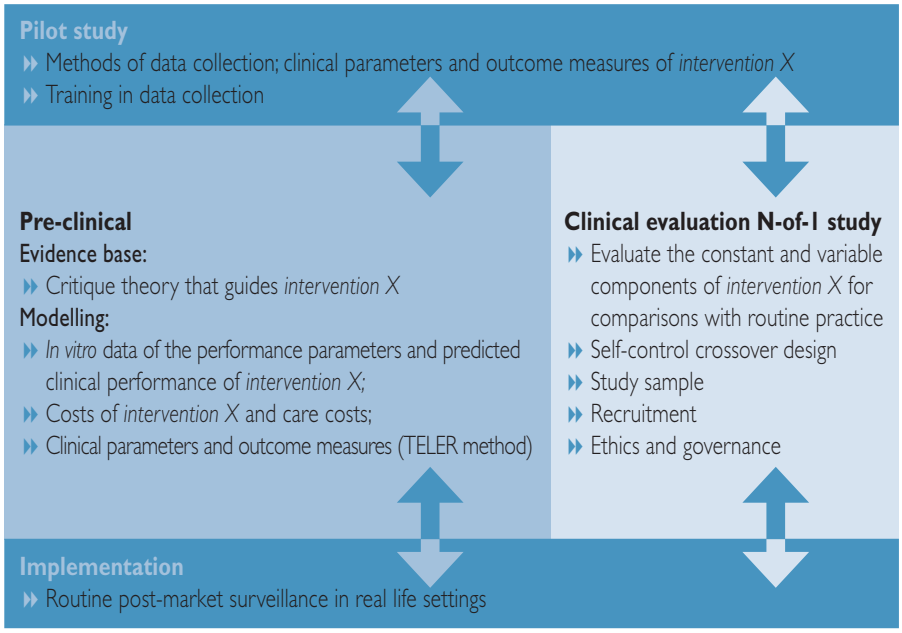


Figure 1. Study framework: iterative process of establishing the clinical and cost-effectiveness of intervention X adapted from MRC 2000; 2008 (Craig et al, 2008).

the performance of the product against the stated mode of action.

Variables that can affect the end-point, or the relationship between the intervention and outcome, are recorded in order that weak conclusions — improper inferences between an observed effect on the outcome variable and the intervention — are not drawn. For example, the manufacturers state that the larvae must be able to breathe or they will die; therefore, a breathable dressing system must be used in the protocol. Theorising also includes predicting the timeframe for achieving outcomes.

In a study evaluating the performance of larval therapy, end-points or outcomes would be determined by reading the literature on the therapy and consulting experienced practitioners and manufacturers. In addition, the use of bagged or loose larvae would need to be evaluated on the grounds that the dressing protocol and time to debridement is different in the two types (see: www.zoobiotic.co.uk/products-biofoam.htm; Jones and Thomas, 2000; Dumville et al, 2009). On this basis, the predictions outlined below are made for the bagged presentation of larvae — these predictions are defined in terms of

Table 1
Debridement of dead tissue

Code 5	No dead tissue
4	Yellow tissue in a thin patchy layer, wound bed showing
3	Yellow tissue in a thin layer with isolated thick patches of brown/yellow tissue
2	Yellow tissue in a thick layer, may include thick patches of brown tissue
1	Brown/yellow tissue in a thick layer, may include patches of black tissue
0	Black tissue which is dry and leathery and covers the wound

Table 2
Interventions required between routine dressing changes (dressings more frequent than weekly)

Code 5	No interventions* necessary
4	One intervention necessary
3	More than one intervention necessary
2	Complete dressing change within 13–23 hours of application
1	Complete dressing change within 6–12 hours of application
0	Complete dressing change within 0–5 hours of application

* Interventions: re-padding, mopping, re-taping to remove wet dressings and prevent soiling

Table 3
Dressing fit: components that define the scope of the patient problem

Code 5	Not experiencing any components
4	Experiencing one component
3	Experiencing two components
2	Experiencing three components
1	Experiencing four components
0	Experiencing five components

patient recorded outcome measures in the modelling phase.

Predicted outcomes of using bagged larvae on the clinical parameter of wound debridement:

- Wound appearance with regard to the presence of dead tissue: the manufacturer's recommendations are that the dressings can remain in situ for up to five days. Clinical signs of a reduction in dead tissue should be apparent within this timeframe
- Exudate: the mode of action of larval therapy comprises secretion of powerful proteolytic enzymes to break down and liquefy dead tissue. The larvae ingest a proportion of the liquefied tissue but the process involves an initial increase in exudate before it decreases, along with the reduction and clearance of dead tissue. The expected pattern of dressing change requirements will be at least daily at the outset, reducing in frequency as debridement is achieved. That said, at no point should the patient be embarrassed by soiling. Two indicators capture these important facets of treatment and patient outcomes — soiling and frequency of dressing changes/re-padding
- Peri-wound skin condition in relation to exudate: the proteolytic enzymes damage peri-wound skin unless it is protected. The manufacturer's recommendation is to protect the skin with a specified barrier cream and that the skin should remain intact, or recover from existing damage from exudate
- Dressing fit/seal: unless the dressing fits the wound and forms a seal around the bagged larvae the treatment can fail (Turkmen et al, 2009) — the exudate will leak and cause soiling and peri-wound damage. Dressing fit, together with the application of a breathable dressing, are therefore important variables which can explain failure to reach the predicted treatment outcomes
- Odour control: larval therapy generates a particular odour of its own. In addition, the wound may be malodorous because necrotic tissue supports the proliferation of proteolytic bacteria. The metabolic processes of these organisms result in the formation of volatile amines responsible for the unpleasant smell. By removing the necrotic material and the associated bacteria, the larvae reduce or eliminate wound odour. The predictions are that odour from the wound may increase before decreasing as the wound is debrided
- Pain: the application of larvae can reduce wound-related pain. This is presumed to take place when infection, which is responsible for the presence of inflammatory mediators that cause pain in the surrounding tissue, is eliminated. However, around the second or third day of therapy, pain may be increased by the presence of larvae. The reason for this is not certain, but pH changes within the wound may be implicated. In such situations, the manufacturer recommends that the larvae are removed after two days instead of three, and the patient's analgesia is reviewed
- Acceptability to the patient and their personal experiences: these experiences are individual and are not pre-judged. Rather, they are captured directly from the patients in this methodology and are a rich source of qualitative data.

Modelling

The modelling components include *in vitro* metrics and measurement, translation into clinical parameters and predictions of performance. Modelling refers here to translating the more abstract statements around the predicted performance of the product in the theory phase turning these into physical models that are tested *in vitro*. In addition, from the *in vitro* testing, the clinical parameters of performance and outcome measures can be defined. Predicted outcomes of using bagged larvae on the clinical parameter of wound debridement include the following and

are captured using TELER indicators illustrated in *Tables 1–3*. The physical outcomes of the larval therapy are captured using pre-defined hierarchical indicators (*Tables 1* and *2*). The patient's experiences are captured using the component indicators (*Table 3*). These comprise five statements which define the patient's main issues and concerns regarding aspects of larval therapy. These statements are generated with the patient and carer and are not pre-determined by researchers and clinicians.

The industrial modelling methods are specific to the performance parameter under scrutiny and generate *in vitro* test data. An example of industrial modelling of bagged larvae may involve animal testing. Patient and environmental factors that may influence real-life dressing performance also need to be predicted by reading relevant research and incorporating clinical experience in the modelling phase. An example would be the occlusive effects of clothing and bedding, and the steps taken to minimise such effects documented in the patient's wound care protocol.

The TELER system of clinical note-making and patient-recorded outcome measurements, TELER indicators, are adopted in this methodology. The indicators specify the intervention and incorporate the predictive performance of the intervention into observable outcomes on specific parameters (Le Roux, 1983). In addition, the individual patient context is defined, i.e. their medical history, condition, whether they are doing their own dressing changes or have a carer to help, together with his or her personal experience of the intervention (see *Tables 1–3* for examples of TELER indicators).

Pilot study

During this phase, the methods of data collection are validated and there is training in data capture (with the TELER system, TELER Limited undertake the training). The methods include free text data (comments or qualifications that are relevant to the study and the data), photographs for illustrative and measurement purposes, and quantitative patient-recorded outcome measures (*Table 4*). In addition, the TELER indicator measures changes in the amount of dead tissue in the wound and the wound's size can be strengthened by incorporating existing and new wound measurement systems (e.g. Visitrak, Smith and Nephew Ltd, Eykona Technologies Ltd).

Table 4
Methods of data collection and analysis

Data collection methods	Data analysis
Free text data ▸▸ Demographics ▸▸ Diagnostics ▸▸ Treatment and care ▸▸ Dressing protocol ▸▸ Comments on dressing usage, performance Visual images ▸▸ Digital images of the wounds Numerical data ▸▸ TELER clinical indicators	Qualitative and numerical data analysis Visual inspection of: 1. Graphic displays of numerical data 2. Automated calculation of two indices: - patient outcome index - duality of care index System of reasoning: to develop explanations of dressing performance against predicted performance in the context of patient and treatment variables (Toulmin et al, 1984; Grocott and Cowley, 2001)

Data collection series

Research methods

As stated earlier, this methodology utilises qualitative and quasi-experimental research methods (*Table 4*). The data can be recorded manually or electronically via a digital data capture system (Tablet PC; digital pen and paper), into the clinical note-making software (TELER software) for analysis.

Data recorded on the TELER clinical note-making system should comprise:

- Clinical-free text data (demographics, diagnoses, wound history, medical treatment and care, history of dressing usage, wound dressing protocol) recorded at data point 1 and updated as changes occur
- Digital images of the wounds and dressings in situ, for illustrative and measurement purposes, recorded at data point 1 and repeated at every dressing change
- Numerical outcome measures within a clinical note-making system to evaluate intervention X (which in the example given in this paper would be bagged larval therapy for debridement) against standard dressings. The clinical note-making system has been validated in WRAP (Browne et al, 2004). The validity of the TELER indicators is predicated on the use of sound clinical knowledge and evidence to underpin the definitions of the indicators. Ensuring validity of the indicators is ongoing. With new knowledge the indicators are revised. Patients' experiences are captured from their own perspectives. The reliability of the data collected depends on training, accurate assessment and data recording skills.

The methodology comprises a self-control crossover design with a timed and/or randomised crossover from standard dressings to intervention X to enable case and cross-case comparisons on the parameter of interest. For example, wound debridement where the intervention is bagged larval therapy which is being compared with a standard debriding agent such as a hydrogel dressing. The intervention can be randomised as long as the principle of equipoise is followed, meaning that there is genuine uncertainty over whether or not the intervention will be beneficial.

The methodology takes into account the recommended objectives of clinical

investigations into a medical device, as set out in the Medical Devices Regulations (SI 2002 No 618) (available online at: www.mhra.gov.uk/home/groups/es-era/documents/publication/con007504.pdf). These stress that evaluations of medical devices should verify that, under normal conditions of use, the performance characteristics of the device are those intended by the manufacturer. In addition, the aim is to determine any undesirable side-effects and to assess whether these constitute risks when weighed against the intended performance of the device (Medicines and Healthcare products Regulatory Agency [MHRA], 2008).

With regard to patient sampling, the proposal is that study samples comprise groups of patients whose wounds are considered suitable for a given intervention by externally agreed assessment criteria. The intervention is introduced in a randomised or non-randomised self-control crossover model: the patients serve as their own controls (MHRA, 2008). The key question to be answered for the entire study sample is whether or not the product reached the clinically significant improvement that was specified at the outset, e.g. clearance of dead tissue.

Sequence of data collection

Dressing performance is measured using an ABC design, where A denotes the base period when the standard dressing continues to be used; B denotes the intervention period when the new dressing is to be used; and C denotes the post-market surveillance, or follow-up period (*Figure 2*). As stated, randomisation can be adopted as appropriate to the intervention and study group.

Clinical outcomes are predicated on improvement or lack of improvement in patient outcomes for the predicted dressing performance, determined by core TELER indicators against baseline indicator scores. The intervention is more effective than the standard dressing if its performance is two or more clinically significant improvements on the standard intervention. The baseline period consists of five dressing changes. The intervention period needs to be tailored to the intervention and the individual patient. For wound debridement using bagged larval therapy, studies to date indicate a range of intervention periods may be necessary. For example, dressings may be in situ for 3–4 days and 2–6 cycles may be required for complete debridement (Dumville et al, 2009).

The difference in performance between two interventions is measured by subtracting the mode for the base period from the mode for the intervention period, which provides the outcome for the intervention as 'more effective' or 'not more effective'. This may be regarded as a valid outcome when no confounding patient effect, such as the dressing being applied incorrectly, occurred in either the base or intervention period.

The group level outcome for the intervention is the percentage of patients for whom the intervention was more effective. The intervention is considered more effective if the percentage is larger than 50%, and the lower limit of the 95% confidence interval for the percentage is larger than 50%. In addition, qualitative explanations of effectiveness, using a system of reasoning outlined below, will add to the understanding of the intervention and future clinical applications (Grocott and Campling, 2009).

Therefore, taking the debridement example, core indicators for larval therapy would include clearance of dead tissue, leakage and odour. Code 5 denotes optimum performance. If the baseline codes for an individual participant are low (codes 0, 1), the participant is crossed over to intervention X, post-intervention codes are incrementally 2, 3, 4 and 5 and if the performance is sustained at codes 4 or 5 for four further interventions, the outcomes may be regarded as clinically significant.

Sample size will depend on the study in question, particularly the predicted timeframe for achieving the desired patient outcomes. As already indicated, predicted outcomes in relation to an intervention, for example debridement, will take a number of days, whereas some aspects of device performance can be achieved within one data point, e.g. absence of soiling. The timeframe of the data collection series needs to take account of any requirement to change the intervention on clinical grounds. For example, a clean wound bed in a debridement study marks the end of the study period. These parameters need to be worked up in the pre-clinical and modelling phase of the study framework and built into the sampling plan. Overall, the expectation with the proposed methodology is that sample sizes and sampling timeframes will be smaller than those required for parallel group designs with time to healing end-points (MRC, 2008).

Data analysis

For the TELER data, the analysis comprises automated calculation of patient-specific outcome indices as follows:

- Deficit index: the scale of the problems as they present
- Improvement index: the scale of improvement relative to the deficit
- Maintenance index: the patient's condition relative to the potential for deterioration
- Effectiveness of care index: the extent to which treatment and care are delivered in a therapeutic process.

Group level indices are also calculated on the basis of the level of the deficit the patient entered the study on, and the extent to which the deficit has resolved with the treatment and care they have received:

- Health deficit index
- Health gain index.

B^1 B^2 B^3 B^4 B^5	X^6 X^7 X^8 X^9 X^{10} X^{11} X^{12} X^{13} X^{14}	p^1 p^2 p^2 p^{14} p^5 p^6 p^7 p^8
Base mode (B)	Intervention mode (X)	Post-market surveillance mode (P)

Figure 2. Data collection series.

The qualitative component of the analysis involves the development of theoretical explanations and generalisations of the findings using a system of reasoning (*Figure 3*). It involves drawing conclusions from factual study data, backing the conclusions with reasons and evidence (*in vitro* test data, research studies) and challenging them with rebuttals (confounding variables that pose alternative conclusions). A detailed explanation of the qualitative component of data analysis is found elsewhere (Grocott and Cowley, 2001).

Post-market surveillance

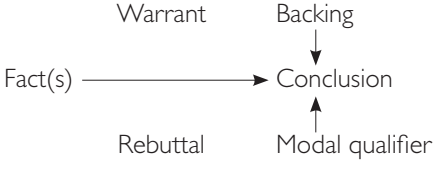
The purpose of this phase is to determine the long-term stability, effectiveness and generalisability of interventions via routine data capture using the clinical note-making system.

Conclusion

This paper has argued for a suite of methodologies and research designs for wound care because of the heterogeneity of wounds and wound care interventions, the considerable variation in healing 'hard to heal' and 'never to heal' wounds, together with individual patient experiences.

A novel methodology for evaluating the effectiveness of wound care technologies in complex chronic wound care and palliative wound care has been proposed. It is underpinned by the MRC framework for the design of complex interventions, and is an N-of-1 design.

The findings from studies using this design can be strengthened with rigorous routine post-market/post-study surveillance in real-life settings, ideally using the same data capture tool as is used in the study. This methodology is being piloted, and more field testing and critical review are required. WUK



- Warrant — provides a rationale for, and explains the step from fact to conclusion
- Backing — justification for conclusion
- Modal qualifier — expresses confidence/doubt in conclusion
- Rebuttal — challenges the conclusion with an alternative explanation

Figure 3. System of reasoning (adapted from Toulmin et al, 1984).

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Key points

- A suite of methodologies and research designs are needed to generate an evidence base for wound care practice.
- The MRC framework for the design of complex interventions provides guidance and examples of methodologies that may be applicable to wound care research.
- One such methodology, an N-of-1 design, is proposed for the evaluation of wound care technologies in the context of treatment and care.
- The N-of-1 design needs to be tested in prospective studies to determine the quality and utility of the evidence generated.

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