Cost-effectiveness Research in Wound Care: Definitions, Approaches, and Limitations

Marissa J. Carter, MA, PhD

Abstract
The value of cost-effectiveness research in all areas of healthcare, including wound care, is increasing. The purpose of this narrative review is to discuss and critically examine economic analysis methods and determine how current knowledge should be applied to wound care. Unlike evidence-based medicine, there is less agreement on how to conduct economic analyses in healthcare and universal guidelines for reporting these studies are lacking. A review of the literature shows that, in wound care, economic analysis is mostly limited to cost-benefit analysis with a limited time horizon; several examples specific to venous ulcers are presented. In addition, most analyses are models based on prospective studies; this is an especially important consideration because chronic wounds may take a long time to heal and/or recur. Other economic analyses that may be very useful to evaluate include those based on “real world” or practice-based studies, which provide results for all wound care populations and can be compared to facilitate development of cost-effective strategies for wound care treatment. Currently available cost-effectiveness study results may help healthcare providers devise cost-effectiveness strategies to embed in clinical practice guidelines that will save costs and improve patient quality of life.

Key Words: cost-benefit, cost-effectiveness, cost-utility, venous leg ulcers, diabetic foot ulcers

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Potential Conflicts of Interest: none disclosed

Debate in the US following the passage of major healthcare reform legislation has not waned, and the Obama administration continues to focus on cost savings and creating more efficient healthcare systems. Substantial cost savings in medicine can be achieved when we understand what works, how well it works, whether it is cost-effective, and if this information can be satisfactorily applied to healthcare systems. Despite ongoing examination and discussion regarding rating schemes, evidence levels, and the effects of its implementation, evidence-based medicine (EBM) can help evaluate the “what works” piece of the puzzle.

The American Recovery and Reinvestment Act (ARRA) emphasizes the importance of comparative effectiveness under the National Institutes of Health (NIH) Challenge Grants in Health and Science Research. In the broadest of definitions, according to a 2007 Congressional Budget Office (CBO) white paper, comparative effectiveness is “generating evidence that compares treatments.” The CBO also indicates that comparative effectiveness includes comparative economic analysis (see Table 1), as well as treatment outcomes research.

What form should comparative economic analysis take? Although the CBO white paper indicates that cost-effectiveness studies are extremely important, no particular guidance is given. Similar to the pyramid of study evidence in EBM in which randomized controlled trails (RCTs) are considered the highest level of evidence, cost utility (CU) (see Table 1) often is considered the desirable gold standard by which treatment cost effectiveness should be measured. However, there is no standard approach to CU with regard to modeling complexities. Moreover, other approaches may be helpful in comparing treatments in terms of economic costs and benefits or in generating data to input into more sophisticated CU models. In addition, many unresolved methodological issues in cost-effectiveness, particularly in wound care, remain.

The goal of this review is to: 1) discuss the strengths and weaknesses of different cost-effectiveness approaches with reference to wound care, 2) consider the assumptions, supposi-
tions, and parameters that affect cost-effectiveness calculations, and 3) provide examples of integrating evidence in cost effectiveness into comparative effectiveness in wound care.

**Methods**

The literature for this narrative review was obtained by searching for relevant papers published in English since 1990. Editorials and letters were not excluded if they provided useful information. Criteria for selection included lucidity, relevance to topic, and lack of bias. Studies on VLUs were cited as illustrations of cost-effective wound care models; other types of wound models were used to illustrate different types of economic analysis. PubMed, Scopus, and Google Scholar were the primary databases searched to obtain cost-effectiveness definitions and details of parameters used in cost-effectiveness studies — search terms included: cost-effectiveness + discount rate; cost-effectiveness + utility; cost benefit + wound; cost utility + medicine; cost-effectiveness + diabetic ulcer; cost utility + venous ulcer; cost + heal + diabetic ulcer; cost + wound + heal. Further searches concentrated on current approaches and projects that assess comparative effectiveness in healthcare in general and in wound care in particular and on illustrations of cost-effectiveness aspects in the wound care literature.

**Definitions**

**Types of studies.** Healthcare economics covers a multitude of methodologies to answer a variety of questions (see Table 1). The following will be considered: cost minimization, cost benefit, cost effectiveness, cost utility, and comparative effectiveness.

**Cost minimization.** Cost minimization is “an economic evaluation in which consequences of competing interventions are the same and in which only ... costs are taken into consideration.” Simply put, if the outcomes of two different treatments are the same, the analysis focuses on whether the costs are different. Such an analysis is not often conducted because the clinical outcomes of even relatively similar treatments are rarely the same in given populations. An example of cost minimization from the wound care literature involved determining from the societal perspective the cost efficient of three methods to repair pediatric facial lacerations: nondissolving sutures, dissolving sutures, or a tissue adhesive. This cross-sectional study, conducted in a tertiary-care pediatric emergency department, surveyed a convenience sample of 30 parents who ranked their preferences and willingness to pay for the three methods of wound closure in which all differential costs relevant to equipment utilization, pharmaceutical use, healthcare worker time, and parental loss of income for follow-up visits were calculated. In this instance, the investigators found that switching from standard nondissolving sutures to dissolving sutures saved $37.90 CAN per patient, but an even greater cost savings of $49.60 CAN could be realized when switching to tissue adhesive. This is a straightforward result because such a switch would result in the most efficient use of resources. Moreover, the choice of tissue adhesive also was preferred by the majority of parents.

**Cost benefit.** A cost benefit analysis (CBA) compares the cost of a treatment for a measurable benefit. The benefit can be quantified in a variety of ways. For example, in wound care, a common CBA involves the cost to heal a wound. So, dressing A would be considered more cost-effective than dressing B if the cost to heal was $100 compared to $250. Another wound

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**Table 1. Common study types used in healthcare economics**

<table>
<thead>
<tr>
<th>Study type</th>
<th>Measurement</th>
<th>Question asked</th>
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<tbody>
<tr>
<td>Cost minimization</td>
<td>Assumption that benefits of approach are equivalent; determine costs of approaches</td>
<td>What is the most efficient way of achieving the same goal?</td>
</tr>
<tr>
<td>Cost benefit</td>
<td>Define unit of benefit then the costs of the benefit</td>
<td>To what extent should a particular goal be pursued?</td>
</tr>
<tr>
<td>Cost effectiveness</td>
<td>Define units, such as life-years gained, then determine costs associated with defined unit(s)</td>
<td>Given a budget for a healthcare item, what is the most efficient way of spending it among several approaches?</td>
</tr>
<tr>
<td>Cost utility</td>
<td>Define units (QALYs or healthy years equivalent), then calculate units gained and associated costs</td>
<td>Given a budget for a healthcare item, what is the most efficient way of spending it among several approaches?</td>
</tr>
<tr>
<td>Comparative</td>
<td>Determine costs of the approaches and associated units of the benefits</td>
<td>How can outcomes of healthcare treatment be maximized while costs are minimized?</td>
</tr>
</tbody>
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**Key Points**

- The question of whether an existing or new treatment works and if it is better than something else is usually followed by: “What is the difference in cost?”
- As the author describes, this question is easier to ask than to answer.
- Using examples from the wound care literature, the author describes commonly used health economic analyses methods.
care CBA might involve calculating the cost to prevent a lower extremity amputation. For example, Guo et al\textsuperscript{10} modeled a hypothetical cohort of 1,000 patients 60 years of age with severe diabetic foot ulcers (defined as greater than or equal to Wagner 3 grade) using outcomes of healed, minor lower extremity amputation (LEA), major LEA, and death in two groups, one of which received adjunctive hyperbaric oxygen therapy (HBOT) and the other standard care (see Figure 1). Using the incremental cost of HBOT (total cost: $1,370,965 for HBOT treatment + cost of additional minor LEAs – cost of fewer major LEAs) and the result that 155 major LEAs are averted with an additional 45 cases of minor LEAs, the cost per major LEA averted is $8,845. If these results were confirmed and costs extrapolated to include all diabetes-related LEAs performed in the US on an annual basis (approximately 71,000\textsuperscript{11}), costs savings would be $630 million. These costs do not include those incurred beyond 1 year for amputees nor the potential effects of the reduced survival rate of amputees.\textsuperscript{12,13}

Cost effectiveness and cost utility. CBAs can be helpful but often lack critical information, such as the length of time the benefit endures, the objective presence of a disease, the subjective experience of the disease from the patient’s point of view — aka, quality of life\textsuperscript{14} — comorbidities, and mortality. Most importantly, one cannot compare CBAs outside of a specific condition; the cost to heal a wound obviously cannot be compared to the cost to debride a wound nor can unhealed wounds be factored into the calculation.

The objective of any cost-effectiveness analysis is to illustrate how the health benefits can be maximized for a given amount of resources.\textsuperscript{15} One approach is to use the concept of utility. Utility is a health state scale in which 1 represents perfect health and 0 represents death (see Table 2; see other commonly used cost-effectiveness terms in this table). Using this scale, Redekop et al\textsuperscript{19} found that patients with diabetes have a utility of 0.84 but at a patient with a noninfected diabetic foot ulcer has a utility of 0.75. In addition to reflecting multiple comorbidities, utility can help quantify changes in a health state. For example, using the data from Redekop et al,\textsuperscript{15} it can be seen when a patient with a diabetic foot ulcer heals, her utility increases from 0.75 to 0.84. However, to quantify change in utility over time, the quality adjusted life year (QALY) (see Table 2) is used.\textsuperscript{14} If one assumes the patient in the previous example has a life expectancy of 10 years and after her wound is healed she has no more health problems, healing the ulcer will increase her quality of life by 0.9 QALYs (0.84–0.75 [change in utility value] x 10 [her life expectancy in years]). By including the cost to heal the ulcer (for example $5,000), the cost utility of ulcer healing can be quantified as $5,000/0.9 = $5,556/QALY. These kinds of results are well understood by health economists but less so by individuals without training in healthcare economics. So, to paraphrase in simple terms, the patient’s quality of life has been improved by 12% at a cost to society of $5,000.

Although knowing the cost utility or cost effectiveness of a given treatment or intervention is useful, knowing how an additional or new treatment changes the cost utility of a conventional treatment, often referred to in wound care as “usual or standard care” with or without exact definitions is of far more value. This parameter, known as the incremental cost-effectiveness ratio (ICER) (see Table 2), is generally calculated as the cost of treatment of A – the cost of treatment B/success treatment A – success treatment B, where A can be considered the “new” treatment; for cost-utility cases, QALYs are substituted for “success.” One example is Flack et al,\textsuperscript{17} who created a Markov model of 1,000 hypothetical patients with diabetic foot ulcers over a 1-year period using data from the literature to derive transitional probabilities (see Table 2). In wound care, a Markov model involves iteratively modeling certain events, such as dressing changes, device application, or recurrence of a problem, such as infection or reappearance of a "healed" ulcer. Transition probability to the probability of moving from one health state to another, such as unhealed ulcer to healed ulcer. The health states used in the model were uninfected ulcer, infected ulcer, infected ulcer post-amputation, healed, healed post-amputation, amputation, and death. Patients initially treated with negative pres-
sure wound therapy (NPWT) were switched to an advanced dressing after 3 months of treatment if their wound remained unhealed, whereas patients treated with either traditional or advanced dressings were assumed to continue with their treatment for 12 months if they remained unhealed. The authors concluded that the ICER of NPWT versus advanced wound dressings over a time horizon of 1 year was a savings of $892,700 per QALY gained. This sounds like a bizarre result, until one looks at the data for the equation, which is: (C1-C2) = \( \frac{52,830 - 61,757}{0.54 - 0.53} \). In other words, NPWT saved $8,927 for a gain of 0.01 QALYs. There was very little gain in quality of life over the time period studied, but there were some useful cost savings.

Another illustration of an ICER comes from the work of Redkop et al., who used a Markov-based simulation model to compare the costs and effects of Apligraf® (Organogenesis, Canton, MA) plus good wound care (GWC) versus GWC alone in diabetic foot ulcers over a period of 1 year using data from an RCT published in 2001 in which 112 patients received Apligraf® and 96 patients received saline-moistened gauze. The results showed ICER savings of 427 Euros (1999 prices) per ulcer-free month in favor of GWC plus the bioengineered skin product. Because bioengineered skin use increased the amount of ulcer-free time by 1.5 months, the average cost savings would be about 850 Euros and a patient who received this product would have a better quality of life for about 6 weeks.

How does one know how to generally interpret an ICER? The answer is to look at both the cost and effectiveness changes in a quadrant (Q) system (see Figure 2). When the new intervention costs less and provides more effectiveness compared to the old or existing intervention, it falls into quadrant 1, which is dominant (see Table 2) — ie, it should be adopted. Conversely, when the new intervention is more costly and less effective, it should be rejected, because it is inferior (see quadrant 3; Figure 2; Table 2). However, when the new inter-

<table>
<thead>
<tr>
<th>Term</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>Acceptability curve</td>
<td>Cost-effectiveness graph in which willingness to pay for an intervention (cost) is plotted against the probability that the intervention will be cost effective</td>
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<tr>
<td>Benchmark</td>
<td>Cost per QALY that is considered to be cost-effective in varying degrees</td>
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<tr>
<td>Direct cost</td>
<td>Costs incurred by the healthcare provider</td>
</tr>
<tr>
<td>Direct method (utility)</td>
<td>Method used to directly elicit utility values from study participants, such as the standard gamble or time trade-off method</td>
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<tr>
<td>Discounting</td>
<td>Technique to calculate accrual of present values of costs and benefits in the future</td>
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<tr>
<td>Discount rate</td>
<td>Rate at which costs and benefits are discounted when either or both extend into the future beyond 1 year</td>
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<tr>
<td>Dominant (cost effectiveness)</td>
<td>Cost-effectiveness study that demonstrates cost savings and gain in benefits</td>
</tr>
<tr>
<td>Incremental cost-effectiveness ratio (ICER)</td>
<td>Difference in costs and benefits between a new intervention and the current or designated intervention</td>
</tr>
<tr>
<td>Indirect cost</td>
<td>Costs incurred by the patient, his or her family, as well as other costs to society</td>
</tr>
<tr>
<td>Indirect method (utility)</td>
<td>Method used to calculate utility values through use of a self-administered quality-of-life instrument</td>
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<tr>
<td>Inferior (cost effectiveness)</td>
<td>Cost-effectiveness study that demonstrates no cost savings and no gain in benefits</td>
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<tr>
<td>Markov model (cost effectiveness)</td>
<td>Model in which events are modeled iteratively</td>
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<tr>
<td>Perspective</td>
<td>Point of view from which a cost-effectiveness study is considered (societal or third party payor)</td>
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<tr>
<td>Quality-adjusted life year (QALY)</td>
<td>Unit of measurement used in cost utility studies</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Method by which parameters are varied in a cost-effectiveness study to determine their effect on economic outcomes</td>
</tr>
<tr>
<td>(Time) horizon</td>
<td>Period of time during which a cost-effectiveness study applies</td>
</tr>
<tr>
<td>Utility</td>
<td>Health quality scale ranging from 0 (death) to 1 (perfect health)</td>
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that return marginal results (meaning they are not dominant be adopted.  In the final analysis, cost-effectiveness studies of treatments that prohibit the use of cost utility studies in comparative ef-

Comparative effectiveness. No universal definition exists for comparative effectiveness. Although it can be characterized as “generating evidence that compares treatments,” the Agency for Healthcare Research and Quality (AHRQ) states that comparative effectiveness research requires the “development, expansion, and use of a variety of data sources and methods to conduct timely and relevant research and disseminate the results in a form that is quickly usable by clinicians, patients, policymakers, and health care providers.” However, recently passed US healthcare legislation embodies language that prohibits the use of cost utility studies in comparative effectiveness research, whereas many other countries insist that cost-utility data be a part of any coverage decision making. For example, the National Institute for Health and Clinical Excellence (NICE) in the UK requires cost-effectiveness analyses of certain medical technologies, especially drugs, as part of the basis for their coverage recommendations to the National Health Service in England and Wales. It applies a criterion of ≤£30,000 per QALY, meaning that if the cost utility exceeds this figure, the technology will not be widely adopted.

Parameters Used in Cost-effectiveness Analysis
Direct and indirect costs (see Table 2). Direct costs include any costs involved in diagnosis, evaluation, treatment, and long-term facility care or care at home by an agency and are usually the costs considered by the healthcare provider. Thus, in the example of a diabetic foot ulcer, this might be the cost of offloading and dressings, as well as the cost of assessment and treatment visits. Indirect costs include such items as lost productivity of the patient; the cost of caring for the patient by friends, family, or even relatives; and the lost productivity, travel, and out-of-pocket costs incurred by the patient and any disability payments paid by a government or insurance company.

Perspective. Two perspectives need to be considered (see Table 2): the third party payor (generally the medical insurance company or government healthcare system, such as Medicare) and societal. The societal perspective includes both direct and indirect costs; third-party perspective includes only direct costs.

The US Panel on Cost-Effectiveness in Health and Medicine recommends use of the societal perspective as the reference case for cost-effectiveness analysis because it considers everyone affected by the intervention and all health effects and costs that flow from it are counted, regardless of who experiences them. Health effects in this context also include both benefits and harms, even when these occur in people who are
The advantage of the self-assessment (indirect) and the time trade-off (TTO) approach, have become derived from direct methods. Such instruments include the EuroQol, and approaches grounded in risk theory (direct methods), showed that direct methods elicited higher utility values than their indirect counterparts: SG (0.81), TTO (0.77), EQ-5D (0.59), SF-6D (0.63), HUI-2 (0.75), and HUI-3 (0.68). These results have clear implications for healthcare policy makers. First, if indirect methods are used, consideration should be given to converting utility values to values obtained by direct methods, although such adjustments should only be considered as approximate. Second, a sensitivity analysis should be conducted in which values obtained by indirect methods are used to populate the lower limits of an analysis. Third, methods for making different decisions should not be mixed. Last, reviews, mathematical analyses, and experimental

Discounting. Because a dollar invested today is generally worth more than a dollar tomorrow, costs need to be discounted (see Table 2). For example, if someone pays $10,000 to heal a wound in 2010, it would cost $11,593 in 2015 to heal the same wound, assuming a constant annual inflation rate of 3% and an investment rate of 6% (discount rate = investment rate – inflation rate). Thus, costs projected in the future beyond a period of 1 year are discounted by some percentage; in this illustration, the discounted cost would be $8,587. However, present and continuing controversy exists regarding whether benefits also should be discounted, how discount rates for both costs and benefits should be determined, and whether they should be identical.27,28 On one hand, it can be argued that health, unlike wealth, cannot be invested to produce future gains29 (although putting an individual back to work seems to contradict this statement); on the other hand, people seem to value current health benefits more highly than future benefits and consequently future health gains ought to be discounted more than future wealth gains.30

Discount rates have varied considerably in cost-effectiveness analyses over the last 20 years. The UK’s NICE currently recommends a discount rate of 3.5% for both costs and benefits;31 the US Panel on Cost-Effectiveness in Health and Medicine recommends 3% for both cases.5 Whatever discount percentages are selected for a given analysis, it is incumbent on researchers to explore the effects of changing the discount rates via a sensitivity analysis. If the overall result changes when the discount rate is changed (eg, in Figure 2 the result moves into a different quadrant), the decision to adopt a new intervention may be difficult because of uncertainty. However, if the overall result stays the same regardless of the discount rate, the analysis is said to be robust and the adoption decision will be much easier. Studies that do not incorporate discounting should be used cautiously in any healthcare decision-making.

Estimating utility. In cost-utility analyses, estimating the utility for a given condition or disease state is challenging. Two main approaches have been used to map preferences to the utility scale: self-assessment scales (known as indirect methods) and approaches grounded in risk theory (direct methods) (see Table 2).

Self-assessment instruments to determine generic quality of life are common in medicine. However, only a few have been successfully translated to utility values using weights derived from direct methods. Such instruments include the European quality of life 5 dimensions (EQ-5D),32 the short form 6 dimensions (SF-6D),33 and the health utilities index (HUI-2/HUI-3).34 The advantage of the self-assessment (indirect) approach is that it is easy to administer; however, many researchers suspect the method results in lower utility values in comparison to direct methods. For example, utility values were reported consistently lower over a period of 1 year in rheumatoid arthritis patients who were given the SF-6D form compared to direct methods.35 Moreover, issues of adaptability, scales of reference, and age have surfaced, requiring corrective procedures in some instances.36,37

The direct approach has its roots in risk theory in terms of games and economic behavior developed by von Neumann and Morgenstern38 during World War II. The gold standard is the standard gamble (SG) in which a person is asked what risk of death he or she is willing to accept before declining treatment in a scenario in which treatment either succeeds completely (perfect health) or yields death, albeit instantly and painlessly (under anesthesia, for example).39,40 So, if an individual accepts a risk of death of 20% (ie, a probability of 0.2), the utility value would be 1.0 – 0.2 = 0.8. However, the SG has been criticized as too cognitively demanding and overestimating risk aversion.41,42 Subsequent modifications to the SG method, such as the healthy year equivalent instead of the QALY and the time trade-off (TTO) approach, have become widely accepted. In the TTO method, a subject first is asked how many years he or she is expected to live, and second, how many of those years he or she would be willing to trade in return for perfect health. Thus, if someone indicates that he expects to live 20 years and is willing to trade five of them, his utility would be 1.0 – 5/20 (0.75). In general, the TTO method appears to be more accepted by healthcare economic researchers of all the direct methods — it is easier to administer to subjects and it consistently elicits utility values that fall between those measured by the SG method and the VAS (visual analogue scale) method.43 However, it too has been criticized, due to the fact that it does not meet the original utility criteria stated by von Neumann and Morgenstern,38 which relate to decision-making theory in the presence of uncertainty.44 Moreover, it is difficult to separate longevity and quality of life from the finding that the longer the life expectancy, the less a subject will change years of life to be traded.45

What approach should be used to estimate utilities? Indirect methods are more popular because unlike direct methods, they do not require a trained interviewer. Although no definitive data exist from which to base a decision, elegant work conducted by Arnold et al,46 in which 32 studies were analyzed in respect of head-to-head comparison of direct and indirect methods, showed that direct methods elicited higher utility values than their indirect counterparts: SG (0.81), TTO (0.77), EQ-5D (0.59), SF-6D (0.63), HUI-2 (0.75), and HUI-3 (0.68). These results have clear implications for healthcare policy makers. First, if indirect methods are used, consideration should be given to converting utility values to values obtained by direct methods, although such adjustments should only be considered as approximate. Second, a sensitivity analysis should be conducted in which values obtained by indirect methods are used to populate the lower limits of an analysis. Third, methods for making different decisions should not be mixed. Last, reviews, mathematical analyses, and experimental
studies have shown that using indirect methods will favor allocation of healthcare resources away from interventions that prevent or delay death in favor of those that alleviate nonfatal conditions.49

Perhaps the most important question that remains is what group should be used to elicit utility values. Kassirer50 has argued that patient data are preferable because patients determine what is important to them. However, the US Panel on Cost-effectiveness in Health and Medicine recommends a community-based approach,3 which means preferences elicited from a representative section of society should be considered rather than simply patients with regard to allocating social resources.

Beneath these differences of opinion are further levels of complexity. In theory, health utilities can be estimated for any given patient population and because the judgment the person is asked to make is the same for all populations, health utility has the same meaning for all populations. Consequently, health utilities of different populations can be compared using the same index.51 The problem is that the estimated health utility of a population with diabetic foot ulcers (for example) will not necessarily represent the health utility of diabetic foot ulcers in general because many patients will have other diseases or health conditions even though they are asked not to consider these issues. Furthermore, how does one estimate the health utility of an individual with multiple medical problems? If the patient with an infected diabetic foot ulcer has severe cardiovascular disease, we might assume we could multiply the health utilities from these individual conditions15,52 to arrive at an overall health utility as follows: 0.70 (infected diabetic foot ulcer) x 0.77 (cardiovascular disease) = 0.54. Although this simple multiplicative estimator method performs better than others using different types of calculation, it still provides results that can be quite different from health utility estimates obtained for multiple conditions using preferences elicited through standard direct or indirect methods.53-56 Finally, researchers should be aware that specific subgroups may have very different preferences that can affect mean and variance heterogeneity—ie, some groups judge their quality of life to be very different from others.

If cost-utility analyses are used in any healthcare coverage or policy decision making, it is important to understand how the utilities were estimated, as well as any limitations imposed by the methods used to elicit utility numbers, rather than to blindly accept them.

**Benchmarks.** Benchmarking is only possible when used in the context of a common way to express health states and cost, such as cost per QALY. The concept behind benchmarking is to suggest what is acceptable (eg, a willingness to pay on the part of the healthcare provider) and what is not in terms of cost to obtain a gain in health over a period of time. In the 1980s, some round figures were suggested as a means of differentiating what is an acceptable cost to a provider or society for a gain in health. These figures were published in the early 1990s. Laupacis et al58,59 suggested that interventions costing $100,000 or less per QALY gained should be considered cost effective and interventions costing $20,000 per QALY gained extremely cost-effective; others suggested $50,000 per QALY gained as a cost-effectiveness benchmark.80 It is important to understand these figures were not derived from modeling or other economic considerations. Other countries have adopted more stringent benchmarks. For example, the UK’s NICE of £30,000 per QALY gained (about $45,000 in 2010) determines whether the NHS will pay for a given treatment, although in recent years evidence shows this figure is being used more as a guideline; and for certain conditions, this figure can be exceeded when the treatment in question is life-saving, the illness under consideration is extremely severe, or the intervention would prevent more harm in the future.61

In developing countries, some of these benchmarks would be meaningless. The World Health Organization has suggested that when the cost-effectiveness figure is below the gross domestic product (GDP) per capita, the intervention can be considered very cost-effective. Figures of one to three times the GDP also can be considered cost effective; figures more than three times the GDP should not be considered cost-effective. Consider the cost utility of healing a diabetic foot ulcer based on a time horizon of 10 years with no discounting: In the US (a developed country), it would be approximately $5,800/QALY based on the Medicare population costs described by Harrington et al63 and accounting for inflation64 versus $7,200/QALY for Iran (a developing country) based on a cost to heal of $6,500.65 Per recent GDP per capita data (US: $46 400; Iran: $12,90066), the intervention can be considered extremely cost effective in both countries.

Because benchmarks are arbitrary, they should only be used as guidelines in health policymaking in the context of the resources available to pay for specific treatments, not as absolute references for yes/no coverage decisions.

**The Role of Cost Effectiveness and Comparative Effectiveness**

How useful are cost-effectiveness studies? Do they really make a difference in terms of policy making, decision making, and coverage? Should cost effectiveness in some shape or form be obligatory? There are no easy answers to these questions. In the US, the Center for Medicare and Medicaid Services (CMS) has not traditionally used cost effectiveness as part of its coverage decision making, but there has been precedent. For example, on December 8, 2009 the CMS decided to cover screening for human immunodeficiency virus (HIV) infection for Medicare beneficiaries at increased risk.67 The reviewers included cost and cost-effectiveness studies as part of the evidence review, citing the Medicare Improvements for Patients and Providers Act (MIPPA) of 2008 as their authorization.68 For private insurers, who do not always reveal their methods for determining coverage of certain treatments, cost effectiveness is already starting to play a role, and in Australia, Canada,
and most of Western Europe, cost-effectiveness and cost-util-
ity data are already part of coverage decision making.69-71

The rancorous political debate over the passage of the re-
cent healthcare legislation in the US and the popular but er-
roneous citation of “death panels” and healthcare rationing
has frightened many individuals who know nothing about
cost-effectiveness methodology and are afraid this will mean
the end of healthcare as they know it. However, people also
want to receive a treatment that is effective. Although these
concerns are not without foundation, the reality is that health-
care is already rationed because there is a relatively finite pot
of money for individuals who cannot pay for all available
treatments regardless of cost. Thus, a better question to ask
might be whether cost-effectiveness methodology can be used
to guide more rational decision-making when it comes to
treatment — ie, development of preferred strategies. In
wound care, this can be explored using the venous leg ulcer
model as an example.

Cost-effectiveness of VLU treatments. The standard or
“usual care” treatment for VLU is compression using mul-
tilayered elastic bandages unless the patient has severe periph-
eral arterial disease or uncompensated congestive heart
failure.72,73 As such, direct provider cost would include the cost
of materials (including primary dressings as well as compres-
sion bandaging), the cost of changing the dressings, and cost
of initial and follow-up visits, along with debridement when
required. Franks and Posnett74 conducted a cost-effectiveness
analysis using a Markov model following a cohort of 100 pa-
tients over 1 year in which one group received high-compres-
sion therapy (four-layer bandaging) and the other usual care
lacking a systematic approach to the delivery or use of high
compression. Patients in both groups received care from com-
munity nurses at their home. The results showed that average
cost per patient was 1,205 Euros in the high-compression
group versus 2,135 Euros in the usual care group. Cost per
ulcer healed (excluding recurrences) was 1,697 Euros and
3,558 Euros, respectively. In another Markov cost-utility model study conducted in Ontario, Canada, Shannon75 also
found dramatically lower costs associated with the annual ex-
pected cost per patient when best practice (including effective
compression therapy) versus standard community care was
used to heal VLUs: $1,492 CAN versus $5,554 CAN. McGuckin et al76 also noted in a retrospective study conducted in
the US and the UK (N = 80) that patients were 6.5 and two
times, respectively, more likely to heal if a guideline was fol-
lowed, leading to lower costs. Finally, an economic analysis of
the VenUS trial, an RCT testing the efficacy of high compres-
sion (four-layer) versus short-stretch (lower compression)
bandages to heal VLUs conducted by Igleisas et al,77 reported an
ICER of -£11,366 per QALY (a cost savings of £227 with an
increase of 0.02 QALYs) over 1 year.

Based on 36 RCTs, Kerstein et al78 calculated that at 2000
prices, the costs to heal a VLU at 12 weeks ranged from $1,873
using hydrocolloid D primary dressings (Duoderm®, Conva-
Tec, Skillman, NJ) compared to $15,053 using a human skin
construct dressing (Apligraf®, Organogenesis, Mansfield, MA).
Based on a meta-analysis of studies published before 2000, it
also was calculated that only 39% of the VLUs would heal
using saline gauze at 12 weeks compared to 51% of hydrocol-
loid and 45% of human skin construct dressed VLUs. These
outcomes are similar to the venous stasis ulcer wound trajec-
tory data published by Steed et al79 involving 232 patients
treated in eight clinical trials at two independent wound care/research centers. It was determined that 60% of patients
will heal with moist wound care and compression at 20 weeks.
The large difference in cost between the hydrocolloid and
human skin construct dressings in terms of cost to heal a VLU
has been confirmed by others.80,81 However, the authors of a
Canadian analytical prediction model based on 293 patients
calculated that the incremental cost per ulcer day averted (a
rather awkward cost-benefit measure) was $26 CAN when compres-
sion and human skin construct were used and $22 CAN when the same combination was utilized for hard-to-
heal ulcers.82 Using outcome results and a 3-month horizon,
Sibbald et al83 found that using the human skin construct and
four-layer compression bandaging cost $14 per ulcer day
averted compared to four-layer compression bandaging alone.
Finally, Schonfeld et al84 employed a semi-Markov model to
describe the pattern of ulcer treatment, healing, and recur-
rence among patients with VLUs. The human skin construct
dressing plus a single layer of Coban bandaging (3M, St. Paul,
MN, USA) was compared to an Unna’s boot for a 12-month
period from the perspective of a commercial health plan. The
annual medical cost of managing patients with hard-to-heal
VLUs was $20,041 for the human skin construct versus
$27,493 for Unna’s boot.

In reviewing the above cost-effectiveness data, Langer and
Rogowski85 noted various methodological problems and con-
cluded: “The economic evidence suggests that despite their
high initial costs, tissue-engineered wound care products may
be cost effective or even cost saving if their use is restricted to
such ulcers that are unresponsive to healing” (author’s italics)
(eg, quadrant 2, Figure 2). This suggests a possible strategy for
more rational decision-making. In order to further refine that
strategy, some of the issues associated with these economic
studies need to be examined.

Issues Associated with Cost-effectiveness Studies

As mentioned previously, cost-benefit studies are limited in
application because the units of benefit are not the same;
costs per ulcer day averted are very different to cost per healed
wound. Moreover, the benefit unit healed wound can consid-
erably under- or overestimate costs. If the time horizon over
which the study is modeled is too short, a large proportion of
wounds will remain unhealed. Cost-effectiveness studies of
VLUs to date that compared Apligraf® to some kind of moist
wound care have used very short time horizons, typically 3 to
6 months — too short a time to allow all wounds to heal.
For example, in a large retrospective case series study of a typical wound care population, Fife et al found that of 807 VLUs, only 58.6% healed after 8.8 months. How are the costs of those unhealed wounds captured in such a model? This is important, because costs will continue to accrue until the wound is healed or a patient may die or undergo a lower extremity amputation. In addition, another ulcer may occur in another location or the wound may recur, which could be regarded as a failure of treatment and/or a consequence of venous disease. Although these kinds of outcomes are sometimes a part of a decision tree involved in creating a cost-effectiveness model, it can be difficult to decide how detailed they should be for a specific scenario, largely because of the complexities involved in modeling but also because it is not certain whether sufficient data exist that can be used to generate values for parameters within the model.

The time horizon for a cost-effectiveness study is also an important parameter. In the VLU cost-effectiveness studies, the time was very short. If costs and benefits are spread out over years instead of a few short months, cost effectiveness of a given treatment can become more favorable. The guiding principle here is to determine the time over which the benefit will endure, but in wound care this is not always obvious. Not all patients with a given condition will be the same in terms of comorbidities, immunocompetence, age, or risk for developing more serious sequits of the given condition. Robust cost-effectiveness studies should take these factors into account where possible to avoid categorizing the probabilistic response of a patient to a given treatment as identical in all instances. This is an issue that mirrors outcomes of RCTs in which analysis of subgroups can help a clinician decide if his or her patient is more like one of the subgroups rather than the “average” patient. For example, the elderly can have different responses to wound care treatments than younger individuals and immunocompromised patients (such as those taking long-term steroids or immunosuppressive drugs or those with diabetes or ischemia) and are more likely to have an impaired wound healing response.

Encapsulating these points suggests that only studies with a time horizon of at least 1 year and preferably much longer (5 years, 10 years, or longer) and which are robust in terms of their conclusions, should be used when formulating healthcare decisions and policy. Discussion here has been limited to VLUs but there are just as many issues with diabetic foot ulcer studies.

**Determining Priorities in Treatment Strategies for Venous Leg Ulcers**

One advantage of cost-utility models is that outcomes can be compared directly because they are in the same units — ie, cost per QALY. That is not to say that cost-benefit studies or studies that investigate costs and cost drivers for particular wound care models are not useful; they are. However, such data often can have less generalizable applicability.

Returning to the model of VLUs, the most basic strategy would be to ensure that all VLUs receive adequate compression. Unfortunately, compression is far from universally used. Fife et al’s retrospective observational study involving 2,139 patients with 4,364 VLUs found that only 17% received adequate compression. It was suggested that compression is not adequately reimbursed because it requires considerable time and expertise; thus, there is little incentive to do it. By comparison, for bioengineered skin, which is comparatively easy to apply, adequate reimbursement mechanisms exist. Moreover, patient adherence to compression bandaging recommendations is poor. The experience reported by Bolton et al appears to corroborate this finding; they noted, “Survey respondents and Task Force members reported that their facilities were cited and forced to pay fines for using evidence-based sustained, graduated, high-elastic compression modalities to manage VU patients…. Reimbursement varied widely among payors and was usually insufficient for and/or inconsistent with evidence-based VU care…. Four of the five respondents who provided comments said they may have to close their facility due to lost revenue while providing high-quality, evidence-based VU care.” Given the observed cost savings and improvement in quality of life documented in cost-effectiveness studies reviewed, the message from third party payors should be clear — Make sure that adequate compression is part of your guideline in treating VLUs — and as clear as the message from healthcare providers to third party payors — Pay us if you expect us to perform compression bandaging.

At the same time, as mentioned, the use of more advanced wound care products may be cost-effective for wounds that fail to heal using good standard care. In general, where good evidence exists (at least two well conducted cost-effectiveness studies) it would behoove healthcare providers to examine their clinical practice guidelines to determine not only if they are based on EBM, but also if they take into account that specified treatments are cost-effective and are included when they are cost-effective.

**Standards for Reporting Cost-Effectiveness Studies**

Unlike the Consort criteria for reporting randomized controlled trials, at this time no universally accepted specific reporting criteria exist for cost-effectiveness studies, although several journals have them for prospective authors and sometimes referees. How are studies determined to be good?

First, the study design should be described so the reader is aware of the type and perspective (societal or provider) of the economic analysis presented. If the model investigates recurrent phenomena, such as recurrence of an ulcer, the investigative method should be described.

Second, the sources and methods by which costs were obtained should be explicit, including any assumptions. The year in which costs apply should be stated (including whether costs were inflated from previous years) using some specific
mechanism, such as the US consumer price index, as well as any methods to convert currency. The currency in which costs are reported also should be stated. Costs should be discounted at 3% or 3.5% and a sensitivity analysis conducted to explore the effect of changing the discount rate. Although data are often limited, study authors should endeavor to estimate all direct costs and, where possible, calculate indirect costs so societal as well as healthcare provider perspectives can be presented.

Third, the source of the outcomes data used in the study should be identified and clearly described for all health economic studies. Generally, outcomes from RCTs are preferable, but if the quality of such trials is poor or RCTs have not been conducted, high quality observational data can be used.99 When several sources of outcomes are available, the study authors should explain how they were used — whether a meta-analysis was conducted or some weighting scheme.

Fourth, a decision tree showing probability of outcomes should be constructed and displayed in the article.99 A rationale for including or not including particular outcomes should accompany the description of the decision tree in order to understand the limitations of the analysis. For cost-utility analyses, the utility values for each health state also should be present in the decision tree and sources for utility values or methods used to their estimation should be identified.

Fifth, the time horizon(s) chosen should match the objectives of the study and the decision-making process by which the times were chosen should be elucidated.99 Sensitivity analyses also should explore varying the horizon time to demonstrate the effect on cost-effectiveness outputs.

Sixth, outputs should be reported in terms of ICERs, comparing the new treatment or intervention against standard or alternative treatments.97–99 Where standard treatments are not available, the comparison group could be placebo or a situation in which no intervention takes place — sometimes a “case of doing nothing.”94 The uncertainty of ICER estimates should be approximated where possible. A popular method for accomplishing this is to use bootstrap analysis — a method to simultaneously resample both cost and effectiveness parameter distributions that result in expanded 95% confidence intervals. The results can be plotted into a quadrant diagram, such as Figure 2, summed in terms of mean and 95% confidence intervals, or repackaged into a cost-effectiveness acceptability curve in which a range of willingness-to-pay thresholds are displayed on the x axis and the probability that the new therapy is cost-effective is plotted on the y axis (see Figure 3). From this graph, it can be seen that in order to achieve a probability of about 70% cost-effectiveness, the cost would be just under $5,000.

Finally, study authors should vary the important parameters in a sensitivity analysis15,97,98 to determine if any major conclusions would be substantially altered. Studies that do not provide sensitivity analyses (however done) can be misleading in terms of their conclusions.

In summary, cost-effectiveness studies that fail to report all relevant parameters and do not explore the results of changing various parameters should be used very cautiously in the context of making healthcare decisions.

Conclusions

Unlike EBM, there is less agreement on how to conduct economic analyses in healthcare; the field lacks universal guidelines for reporting studies. Combining treatment outcomes with cost-effectiveness analysis under the umbrella of comparative effectiveness provides information on not only what works and how well it works, but also whether it is economical to implement. Properly comparing effective treatments in economic terms can help healthcare providers determine which treatments might be better for different settings or different kinds of wounds. In wound care, economic analysis is mostly limited to cost-benefit analysis, which, unlike cost-utility studies, lacks common outcome units; thus, making comparisons among studies is difficult. In addition, more detailed studies are needed to help fill in the gaps that will enable better strategies to be developed in concert with EBM. Nevertheless, currently available study results may help healthcare providers devise cost-effectiveness strategies to embed in clinical practice guidelines that will save costs and improve patient quality of life.

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