Health Economics and Outcomes Research of Wound Care: Overview of Methodology

Adrienne M. Gilligan*

Vector Oncology, Rosenberg, Texas.

Adrienne M. Gilligan, PhD

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*Correspondence: Vector Oncology, 7010
Belle Meadow Lane, Rosenberg, TX 77469
(e-mail: agilligan@vectoroncology.com).

Objective: To provide an overview of comparative effectiveness research (CER) methodology and discuss the challenges of health economics and outcomes research (HEOR) in wound care.

Approach: Narrative description of HEOR methodology with supporting references.

Results: With the increasing costs of clinical trials, the use of observational studies in a real-world setting will be essential. Wound care clinicians should understand the importance of proper methods for conducting CER studies. Propensity score methods and marginal structural modeling can create a “quasi-randomized” environment for measuring wound closure and can help drive informed decision-making. In wound care, a paucity of HEOR information is available with great reluctance to use this information by payers, the Food and Drug Administration, the Centers for Medicare & Medicaid Services, and other agencies. Furthermore, a limited amount of high-quality retrospective data to measure wound care outcomes exist. The U.S. Wound Registry is one of few data sources that accurately reports on outcomes for all wound types and is a Qualified Clinical Data Registry.

Innovation and Conclusions: Several CER approaches in observational studies provide sufficiently detailed information to help decision-makers make informed choices about wound care products regarding efficacy in the real-world setting. Using CER and cost-effectiveness studies succinctly needs to be incorporated if progress is to be made in improving wound care outcomes and reducing cost.

Keywords: health economics, outcomes research, comparative effectiveness, wound care

SCOPE AND SIGNIFICANCE

THE USE OF health economics and outcomes research (HEOR) in wound care has steadily increased over the past 5 years. Despite this, comparative effectiveness research (CER) is limited by the paucity of properly conducted observational studies and short-length clinical trials. In addition, obtaining proper data to measure outcomes (*i.e.*, granulation or closure), recurrence, infection, and amputation remains a challenge.

TRANSLATIONAL RELEVANCE

Concern about whether patients receive effective health care is increasing. With the United States transitioning from a volume-based payment system to a value-based payment system, it is essential that clinicians understand CER so they can (1) make informed decisions about the allocation of financial resources and (2) treat patients with the most efficacious therapy to improve clinical, economic, and humanistic outcomes.

CLINICAL RELEVANCE

Implementation of HEOR in wound care remains challenging due to the reluctance of the Centers for Medicare & Medicaid Services (CMS) to adapt and recognize other primary or surrogate endpoints aside from complete wound closure. Complete wound closure (*i.e.*, reepithelialization without drainage or dressing requirements) is currently the only Food and Drug Administration (FDA)-approved primary endpoint in clinical trials to demonstrate efficacy for wound care therapies. Consequently, no FDA-approved surrogate endpoints are currently available that may be more suitable for short-term outcomes, such as elimination of infection, wound granulation percentage, or reduction in wound surface area.

INTRODUCTION

With increasing utilization, access, and subsequent costs of health care, resources become scarce, and prioritization in health care becomes unavoidable. HEOR is a discipline used to complement clinical decision-making (*e.g.*, efficacy, safety, and quality) and to guide decision-makers regarding patient access to services and treatment.¹ Since the 1980s, HEOR has advanced considerably in methodology and can provide data to assist health care payers in determining if a treatment works (*e.g.*, effective) in the populations they serve, and how much of the treatment cost should be reimbursed by third-party payers and the CMS. The basic premise of HEOR is that choices between alternatives should be made to promote efficiency without compromising the quality of care.

The increased use of HEOR data can be expected in future decision-making processes as a key part of the request for comparative effectiveness evidence.^{2,3} In addition, a greater emphasis is now placed on involving the patient in health care decisions. The outcomes research in HEOR is increasing in importance, because it can provide data on specific populations and treatment combinations that are used in a “real-world” setting. Holtorf *et al.* examined the current use of HEOR data in health care decision-making in the United States and found that ~75% of health care providers use HEOR data regularly in their decision-making processes. However, most health care providers and stakeholders do not have a quality assurance process in place for reviewing HEOR data. For example, formulary drug placements show that the lowest-priced branded drugs are often not placed in a preferred tier, indicating that the role cost plays in the formulary decision-making process is complex.¹

In wound care, the use of HEOR has steadily increased over the past 5 years. Despite this, CER is limited by the paucity of properly conducted observational studies and short-length clinical trials. In addition, obtaining proper data to measure outcomes (*i.e.*, granulation or closure), recurrence, infection, and amputation remains a challenge. Therefore, the objective of this study was to provide an overview of CER methodology and discuss the challenges of HEOR in wound care.

CLINICAL PROBLEM ADDRESSED

Health care costs continue to increase substantially, particularly for managing chronic wounds which is estimated to cost Medicare at least \$28 billion annually.⁴ With the United States transitioning from a volume-based payment system to a value-based payment system, it is essential that clinicians understand CER so they can make informed decisions about the allocation of financial resources and can treat patients with the most efficacious therapy to improve clinical, economic, and humanistic outcomes. Since Carter previously published an article on cost-effectiveness (CE) in wound care,⁵ this article is intended to be an educational piece on CER methods, how they complement CE studies and how they can be applied to wound care research.

MATERIALS AND METHODS

For each section, the literature was searched for useful references to studies or resources that were relevant. PubMed was searched from 1970 to June 2018; retrieved only references in English and used the following keywords: health economics; outcomes research; wound care; wound care reimbursement; retrospective; and observational in combination with comparative effectiveness. Google was searched in June 2018 for references to comparative effectiveness methodology.

RESULTS

Comparative effectiveness research

Several definitions have been developed for CER, with the most relevant from the Institute of Medicine and U.S. Federal Coordinating Council, which defines CER as the generation of evidence that compares the benefits and harms of alternative methods or different interventions to prevent, diagnose, treat, and monitor health conditions in “real-world” settings to improve the delivery of care.^{6,7} The focus is on “real-world” settings as opposed to a laboratory setting where patients are

highly prescreened and comprised of select patient populations. Findings from CER should be highly generalizable to the overall population and to specific subpopulations, especially ones that are often excluded or marginalized from clinical trials. Older patients, women, racial, ethnic, or socioeconomic minorities, patients with complex comorbid conditions, patients who are immunocompromised, patients who have large wound surface areas, patients with a large amount of exudate, and patients with infection are examples in wound care.

To achieve these goals, different types of studies can constitute CER, including observational studies, systematic reviews, meta-analyses, and randomized clinical trials. Each type of study design has its strength and limitations; however, for the purposes of this article, the focus will be on observational studies (Fig. 1). Observational studies can address several limitations of clinical trials because they originate from clinical practice, which better reflects “real-world” conditions. For example, the U.S. Wound Registry (USWR) database comprises electronic medical records (EMRs) from over 100 hospital outpatient wound care provider-based departments in the United States and Puerto Rico.⁸ The USWR is certified to meet the Health Information Technology for Economic and Clinical Health Act (HITECH Act) standards, which include adherence to wound care quality measures developed for the USWR as a Qualified Clinical Data Registry and are nationally recognized by the CMS as part of the Physician Quality Report

System.^{8,9} All wound and ulcer types are included and are risk stratified for outcomes reporting using the Wound Healing Index. Specific outcomes measures include healing or wound closure, surgical closure, amputations, and death. With the increased use of EMR and claims data, vast amounts of real-world data are more accessible than in previous years.

The primary challenge in observational studies is confounding by indication (or channeling bias), especially when analyzing pharmaceuticals.¹⁰ In observational studies (unlike clinical trials where inclusion/exclusion criteria are stringent), a myriad of patient and physician factors influence who receives one therapy over another. For example, sicker patients may be more likely to receive a specific treatment compared to healthier patients. Therefore, even if the treatment is effective, the sicker patient may be more likely to experience an adverse event or die than the healthier patient, which may underestimate the true treatment effect. A way to reduce channeling bias is to exclude patients already taking the treatment of interest during the study period (*i.e.*, newly treated). Even though requiring patients to be newly treated can reduce sample size, it ensures that patients are observed at the time of treatment initiation, which allows for adjustment for severity of disease, comorbidities, or other confounders. Furthermore, advances in statistical methods have led to continued improvement in the ability to control for confounding in observational studies, some of which are reviewed below.

Figure 1. Strengths and limitations of clinical trials and observational studies.

Propensity score methods. Two types of propensity score methods are useful for assessing wound care outcomes: propensity score matching (PSM) and inverse probability of treatment weighting (IPTW). PSM allows a researcher to estimate the average treatment effect. The most common implementation of PSM is one-to-one matching, in which pairs of untreated (or control) and treated cohorts are created, such that matched subjects have similar values for their propensity score. Once a matched sample is formed, the treatment effect can be estimated by directly comparing (*e.g.*, apples to apples comparison) outcomes between treated and untreated (or control) subjects. This methodology has slowly increased over the past 5 years. For example, PSM was used to compare clostridial collagenase ointment to medicinal honey as an adjunct therapy to selective sharp debridement in patients with stage III/IV pressure ulcers, and to compare patients treated with acellular synthetic matrix plus standard care to standard care for patients with venous leg ulcers.^{11–13}

IPTW uses weights based on the propensity score to create a synthetic sample in which the distribution of measured baseline covariates is independent of treatment.¹⁴ Each individual in the cohort is assigned a weight based on the probability that they would be exposed to the treatment. In contrast to matching treated and untreated individuals, IPTW uses the entire cohort and can address many confounding variables. Given that most retrospective studies in wound care have a small sample size, the IPTW approach may be considered over PSM. When using either approach, it is essential to understand the patient population of interest so the appropriate matching covariates are selected. Table 1 provides an example of matching factors that were included in comparing clostridial collagenase ointment to medicinal honey for stage III/IV pressure ulcers.¹²

Historically, regression adjustment is used more frequently than propensity score methods for estimating the effects of treatment when using observational data. However, to create a quasi-randomized study, propensity score methods are more appropriate. These methods used in CER bridge the gap between randomized controlled trials (RCTs) and population-based studies. For CER, there are multiple reasons to use PSM over regression-based models. First, propensity score methods allow the researcher to separate the design of the study from its analysis.¹⁴ This is similar to a clinical trial, wherein the study is designed first and the effect of treatment on the outcome is estimated after. When using PSM, the

Table 1. List of matching factors included in the propensity score matching

Patient age	Wound age	Wound surface area
Arrival score	Number of concurrent wounds	Infection surrogate score
End-stage renal disease	Pressure ulcer stage	Patient paralyzed

propensity score is estimated and can be matched to a control cohort before assessing outcomes. However, when using multivariate regression, the outcome is contingent on the covariates selected for the model input and can be more easily manipulated to achieve a specific outcome.¹⁵ Second, increased flexibility allows researchers to use PSM over regression, particularly when outcomes (if dichotomous or time-to-event) are rare (*e.g.*, mortality) and treatment is common (*e.g.*, wound care dressings).¹⁶ If outcomes are dichotomous or time-to-event (*e.g.*, granulation or closure), prior research suggests that at least 10 events should be observed for every covariate entered into a regression model.^{17,18} If the occurrence of treated or untreated is more common than outcomes (*e.g.*, more dressings, biologics, or devices compared to patients reporting granulation or closure), the PSM may provide increased flexibility. Finally, the PSM allows easier assessment of the degree of overlap in the distribution of covariates between the two treatment groups. In multivariate regression, the degree of overlap between the two groups may be challenging to assess. In PSM, if substantial differences exist across treatment groups, the differences will be reflected by the small number of matched patients.

Marginal structural modeling. As mentioned above, treatment and outcome are often affected by other factors. For example, if the treatment is use of clostridial collagenase ointment and the outcome is 100% granulation of stage III/IV pressure ulcers, and the treated group is older than the untreated (or control) group, age may confound the relationship between treatment and outcome.¹² In addition, other variables may affect the relationship between treatment and/or outcome, such as wound age, wound surface area, infection, number of concurrent wounds, if the patient is immunocompromised, has end-stage renal disease, or has paralysis. In longitudinal studies with repeated measures of confounding, these complex relationships are frequently encountered. Over time the same variable may be a confounder (*i.e.*, time-varying confounder affected by previous treatment), and standard methods to address confounding will produce biased results.

Marginal structural models (MSM) appropriately control for the effects of time-varying confounders that are affected by prior treatment

(exposure).¹⁹ They are called marginal because they use the marginal distribution of the treatment (or exposure) variable at any time point to assess its relationship with the outcome and are called structural because models exploring causal relationships are referred to as structural in the econometric literature.²⁰ MSM can be useful in assessing wound care outcomes because, often-times, chronic wounds in patients take months or even years to achieve full closure (if they ever do), and are often treated with several therapies (sometimes concurrently), which can make measuring the true treatment effect, of one therapy, challenging. Several time-varying confounders can impact wound closure such as age, development of new comorbidities, development of new wounds, and multiple treatments on the same wound.

DISCUSSION

Concern about whether patients receive effective health care is increasing. While recent data from the Census Bureau have shown an increase in medical spending, there is little evidence between more effective care and the growth rate of medical spending.²¹ When the Affordable Care Act (ACA) was passed, the Patient-Centered Outcomes Research Institute (PCORI) was established to promote evidence-based treatment and to generate information on comparative effectiveness of competing therapies. However, just because a therapy is more efficacious does not imply that it has a lower net cost to society (including the cost offsets from improved health). Despite this, most physicians, policy makers, and the health care industry are reluctant to include costs in making recommendations about clinical decision-making.²² These concerns stem from fear of public distaste for “rationing health care,” potentially stifling innovation, and subjecting clinical decision-making to scrutiny based on cost. Because of these fears, under section 6301(c) of the ACA, PCORI “shall not develop or employ a dollars-per-quality adjusted life year...as a threshold to establish what type of health care is cost-effective or recommended.”²³

Glick *et al.* examined the Tufts Medical Center Cost-Effectiveness Analysis Registry (the largest known database to contain both CER and CE studies) to analyze how often disagreement occurs between the most effective treatment and the cost-effective treatment, and found disagreement between the two types of analyses only 19% of the time.²² Additional research is warranted on the subject, but these findings set the foundation for

establishing the importance of having both CER and CE in clinical decision-making.

Implementation of HEOR in to wound care remains challenging due to the reluctance of the CMS to adapt and recognize other primary or surrogate endpoints aside from complete wound closure. Complete wound closure (*i.e.*, reepithelialization without drainage or dressing requirements) is currently the only FDA-approved primary endpoint for clinical trials to demonstrate efficacy of wound care therapies.²⁴ Consequently, more suitable surrogate endpoints for short-term outcomes, such as elimination of infection, wound granulation percentage, or reduction in wound surface area, are currently not approved.

Despite the development of algorithms to model the kinetics of wound closure, acceptance remains limited among regulatory agencies and clinicians. Waycaster *et al.* used an exponential decay algorithm looking at cost per cm² reduction in wound surface area to indicate how the addition of becaplermin to diabetic foot ulcer standard treatment can reduce the total direct cost of care to the payer.²⁵ Use of an exponential decay model quantifies closure rates as coefficient estimates from a standard statistical test, allows for hypothesis testing on treatment efficacy, and avoids the limitations of a “hard” primary endpoint (closed or unclosed) at an arbitrary selected time point.²⁶ In addition, the exponential decay model is an easy-to-use application and does not require mathematical transformation of the actual wound measurements. Subsequently, this algorithm could be incorporated in to clinical decision-making at the bedside and can be implemented in to EMRs for health care providers.²⁶

As the United States transitions to a value-based payment system, valid and reliable data will be essential to conduct a proper CER study. Fife *et al.* compared real-world healing rates from the USWR with RCTs and publicly reported data and found that real-world data from the USWR and RCTs provide convincing evidence that the majority of patients (55–70%) do not achieve wound closure, in contrast to a mean publicly reported healing rate of 92%.²⁷ To achieve the only current CMS/FDA primary endpoint, criteria are needed to establish honest healing rates. Wound care researchers are actively working with the FDA to approve new appropriate clinical outcomes and patient-reported outcomes for wound care therapies.²⁸ The European Wound Management Association has published multiple guidance documents on how to improve the evaluation of new treatment strategies regarding outcomes measures in clinical studies

that will meet the requirements for evidence-based information in wound care management.^{29–31} Hopefully, these guidance documents will contribute to the development of global standards for wound care outcome measures and will result in more comparative effectiveness studies that drive reimbursement for wound care treatment.

INNOVATION

If HEOR in wound care wants to continue to improve and evolve, researchers and health economists should understand and execute the appropriate methodology used in CER studies. Failure to obtain high-quality data and to use proper CER methodology, when assessing wound care outcomes, result in inaccurate reporting. Until the FDA acknowledges more than one primary endpoint and adds recognized surrogate endpoints, outcomes research in wound care will continue to struggle. Furthermore, CER and CE studies must be used succinctly in decision-making if progress is to be made in improving outcomes and reducing cost.

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TAKE-HOME MESSAGES

- A limited amount of high-level CER studies exist in the wound care space.
- Several CER approaches in observational studies provide sufficiently detailed information to help wound care stakeholders make informed choices about wound care products regarding efficacy in the real-world setting.
- The use of observational studies and the appropriate methodology in a real-world setting will be essential as the costs of clinical trials continue to increase.
- Outcomes research in wound care will continue to struggle until the FDA acknowledges more than one primary endpoint or adds surrogate endpoints.
- CER and CE studies succinctly need to be adopted for HEOR to impact improving wound care outcomes and reducing cost.

author listed. No ghostwriters were used to write this article.

ABOUT THE AUTHOR

Adrienne M. Gilligan, PhD, is an Associate Director of HEOR at Vector Oncology. Previously, she was a Research Leader at Truven Health Analytics, where she led multidisciplinary teams to design and deliver real-world evidence and outcomes research studies for biopharmaceutical clients. Her research has resulted in multiple publications across a variety of therapeutic areas, including oncology, neurology, cardiology, and wound care. Dr. Gilligan previously served as a manager in health economics and outcomes research at Smith & Nephew and holds a PhD and master's degree in pharmaceutical economics, policy, and outcomes from the University of Arizona.

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Abbreviations and Acronyms

ACA	= Affordable Care Act
CE	= cost-effectiveness
CER	= comparative effectiveness research
CMS	= Centers for Medicare & Medicaid Services
EMR	= electronic medical record
FDA	= Food and Drug Administration
HEOR	= health economics and outcomes research
IPTW	= inverse probability of treatment weighting
MSM	= marginal structural models
PCORI	= Patient-Centered Outcomes Research Institute
PSM	= propensity score matching
RCT	= randomized controlled trial
USWR	= U.S. Wound Registry