Article Category: Perspective Article

A New Approach to Clinical Research: Integrating Clinical Care, Quality Reporting, and Research Using a Wound Care Network-Based Learning Healthcare System

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Running Head: A Wound Care Network-Based Learning Healthcare System

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Sources of funding: This study was funded by the SerenaGroup®.

Abstract

The disparity between ideal evidence from randomized controlled trials and real-world evidence in medical research has prompted the United States Food and Drug Administration to consider the use of real-world data to better understand safety and effectiveness of new devices for a broader patient population and to prioritize real-world data in regulatory decision making. As the healthcare system transitions from volume- to value-based care, there is a growing need to harness the power of real-world data to change the paradigm for wound care clinical research and enable more generalizable clinical trials. This paper describes the implementation of a network-based learning healthcare system by a for-profit consortium of wound care clinics that integrates wound care management, quality improvement, and comparative effectiveness research, by harnessing structured real-world data within a purpose-built electronic health record at the point of care. Centers participating in the consortium submit their clinical data and quality measures to a qualified clinical data registry for wound care, enabling benchmarking of their data across this national network. The common definitional framework of the purpose-built electronic health record and the 21 wound-specific quality measures help to standardize the potential sources of bias in real-world data, making the consortium data useful for comparative effectiveness research. This consortium can transform wound care clinical research and raise the standards of care, while helping physicians achieve success with the Merit-Based Incentive Payment System.

Keywords: Learning Healthcare System, Real-world Data, Quality Improvement, Outcomes Research, Evidence-based Medicine

Introduction

The demand for randomized controlled trials (RCTs) in the wound care industry has never been greater, as technological advances spur innovations in wound healing science. However, these prospective trials demonstrate efficacy under ideal conditions, with exclusion criteria that target sicker patients, deeming more than half of the patient population with chronic wounds ineligible to be enrolled in the majority of RCTs.[1] Consequently, trials for potential therapies compete for a small and highly unrepresentative pool of subjects, excluding a large population of patients of wound care with complex comorbid conditions. Payers then deny coverage of new therapies to real-world patients, because data demonstrating their *effectiveness* among such compromised individuals are lacking.

The disparity between ideal RCT evidence and real-world evidence in medical research has prompted the United States (US) Food and Drug Administration (FDA) to draft guidance on the use of real-world data (RWD) in regulatory decision making.[2] RWD refers to data sourced outside of clinical trials. The use of big data, real-world evidence, patient input, and precision medicine is among the FDA's 10 regulatory science priorities of 2017.[3] Prior to the advent of widespread electronic health record (EHR) adoption, harnessing RWD for any aspect of regulatory decision making would have been improbable.

In 2009, the Health Information Technology for Economic and Clinical Heath Act established national standards for healthcare data exchange ("interoperability") as part of the larger initiative of healthcare payment reform.[4] At the core of the paradigm shift towards value-based and patient-centered care is the Learning Healthcare System (LHS), a concept introduced in 2007 by the Health and Medicine Division (HMD), when it was then known as the Institute of Medicine, that integrates clinical care, patient participation, quality improvement (QI), and

comparative effectiveness research (CER). In a LHS, knowledge is obtained continuously through routine clinical documentation at the point of care (POC) and turned into guidance through clinical decision support (CDS), with a resulting vast repository of data on treatment *effectiveness* to enhance RCTs and evidence-based medicine.[5-10] The transition of the healthcare system from volume-based reimbursement to one based on value provides an opportunity to advance wound care research. Although there has been a surge in new approaches to the use of EHRs in the creation of a LHS,[11] the LHS envisioned by the HMD has remained largely unrealized due to the challenges of interoperability created by heterogeneous EHRs, a diversity of users and organizations, and a lack of implementation standards.[7,10] A recent systematic review on LHS implementation identified only 13 publications of actual LHS implementation processes.[10] None of the articles covered all of the 3 main issues that are a focus of a LHS: clinical data reuse, collaborative learning, and patient reported outcomes (PRO), most of which will be necessary to control the various sources of bias that currently limit the use of RWD. Theoretical LHS examples abound, but what is most needed are publications describing *specific* operational models.[8,10]

The creation of a LHS is even more challenging for wound care, because the field is not recognized as a medical specialty (which affects collaboration, advocacy, and policy), and because federal funding for research on the clinical care of patients with chronic wounds is alarmingly insufficient. In the absence of the leadership usually afforded by a medical specialty society, 2 of our authors (TES and CEF) collaborated with 25 wound care experts and representatives of major wound care organizations in September 2015 on a 24-point action plan to improve clinical research in the area of leg ulcers.[12] Participants in the consensus meeting strongly supported the creation of a clinical research network for wound care. However, given

the lack of funding and wound care's organizational and infrastructural challenges, such a network was deemed a long-term goal without any clear path to realization.

As an alternative to federal funding, for-profit research can help lay the foundation of a LHS, provided that improved clinical operations and patient outcomes are integrated into the investigation.[8] We created a network of wound clinics that gains efficiencies from centralized research coordination and uses contracted research as a revenue stream. We developed a LHS that links these research centers to a wound care–specific EHR that offers CDS relevant to wound care, quality measure implementation, quality reporting, and remote quality monitoring, all of which have improved adherence to standardized wound care.[13-15] These evidence-based reminders within the EHR are linked to quality measures for which clinicians receive quality reporting credit under federally mandated programs, providing additional incentive to standardize optimal clinical care. We describe the implementation of a network-based LHS by a consortium of wound care clinics that integrates wound care management and QI, harnessing structured data within a purpose-built EHR to change the paradigm for wound care clinical research and enable more generalizable wound care trials. Additionally, clinical data reuse by documentation at the POC as captured by a purpose-built EHR, PRO quality measures made available by a wound registry linked to the EHR, and collaborative learning through CER within our research consortium are discussed. Lazarus et al. effectively describe the theoretical framework needed to establish a LHS in wound care;[12] herein we present an already operational example for wound care that is both practical and reproducible.

Network Infrastructure

While the concept of an independent research network is appealing, we were unable to secure ongoing grant funding to ensure the network's long term viability. It was not possible to

hire staff without a secure funding model, and the majority of staff time was consumed exploring ways to fund the network rather than performing wound care research. Federal funding for wound care research is not commensurate with the amount of Medicare dollars expended on this issue, and the level of awareness relating to wound care as a healthcare priority is low. In contrast, private equity has made significant investments in the wound care industry, and new products have been developed at a rapid pace, all of which need to be evaluated in clinical trials. Given the absence of federal funding and the demand for contract research, we developed a private research network, which has seen rapid, year-on-year growth.

The SerenaGroup® (Cambridge, MA)[16] was founded 2 decades ago in 1997 to meet the need for wound care services. The research program was added in 2005 with a vision to advance research and establish best clinical practices. The organization has conducted over 100 clinical trials on growth factors, gene therapy, bioengineered skin products, and novel pharmaceuticals. The group's research efforts have produced over 130 abstracts, 100 manuscripts, and over 300 presentations worldwide. There are currently 23 participating facilities in 10 states, including 22 wound care clinics and a new research institute in Pittsburgh, PA.

More than 60 advanced practitioners, including physicians, podiatrists, nurse practitioners, advanced practice registered nurses, and certified nurses in wound care, work within our network. The clinical research consortium within the network offers a list of services, including research contracting, research negotiations, investigator training, employment of site monitors, the provision of the network EHR for clinical research, and quality reporting services. Currently, 12 facilities in 9 states have adopted the consortium's network EHR, with new clinics in the process of doing so. The other facilities in the network utilize their hospital's EHR, which is not used for research purposes. Approximately 47 physicians and 4 advanced practice

registered nurses also participate in the consortium, with advanced practitioner oversight provided by an average of approximately 4 per facility. Most clinicians are in private practice; some are university employees. All clinicians must agree to take and maintain investigator training in Good Clinical Practice (GCP), clinical trials regulations and conduct, and research procedures.[16] All facilities are hospital-based outpatient clinics owned by hospitals.

Clinics are motivated by a variety of factors to participate in the research network, including: (1) the use of clinical trial income to compensate for revenue lost because of healthcare reform market forces, (2) the possibility of additional patient volume driven by research trial advertisements, (3) the staff development and training that is associated with research activities, and (4) the wound clinic management services that are provided in conjunction with research network management.

Transition to a network, purpose-built EHR

As the network grew, we observed operational barriers that hindered the quality of the research process that could be solved with better data analytics: busy clinicians unintentionally overlooked potential patients for trial enrollment, there was a need to perform some monitoring from a central location, and there was a need to identify which sites were better suited for specific trials due to unique differences in the types of patients they saw. At the same time, as part of healthcare reform, there was increasing pressure from the Centers for Medicare and Medicaid Services (CMS) for quality reporting. The Physician Quality Reporting System (PQRS) moved from the bonus to the penalty phase, causing practitioners who were not submitting quality data to experience a negative adjustment of their Medicare Part B payments. Additionally, practitioners who were not submitting data to a "specialty registry" experienced separate financial penalties under the Meaningful Use (MU) program.[17] Although nationwide

exchange of health information was the primary motivation for universal EHR adoption, another major impetus was to improve evidence-based care with tools like CDS that could provide reminders at the POC, often linked to relevant clinical quality measures. Although our clinical trials were successful, significant effort and thus expense were required to standardize the usual care of the patients in the control groups [e.g. venous leg ulcer (VLU) compression, diabetic foot ulcer (DFU) offloading, and vascular screening]. Furthermore, independent hospital EHRs rarely collect discrete data with regard to wound appearance or treatment, usually providing only areas for the use of "free text." Moreover, hospital EHRs have no decision support that is relevant to wound care, nor are there wound care relevant measures in PQRS. Our network was in need of a wound care–specific EHR that ensured that all patients could be efficiently evaluated for clinical trial participation, had remote monitoring capabilities, fulfilled MU and quality reporting requirements, and used structured language to facilitate RWD capture.

Figure 1 illustrates how we achieved a LHS through our consortium. We selected a purpose-built EHR (Intellicure, Inc., The Woodlands, TX) for wound care documentation that continuously generates real-world evidence for use in wound care research, by efficiently collecting all patient data at POC using structured programming without relying on "free text", and provides wound-specific clinical practice suggestions that standardize usual care. Research-related patient and wound data elements are embedded in the data collection framework of the EHR.

Clinicians document structured data at POC within an EHR primarily using drop-down menus and decision trees. Multiple data dictionaries are used within the common definitional framework. Diagnoses are collected via ICD-10 (International Classification of Diseases, version 10)[18] coded encounters, which the EHR further embellishes by asking the precise body location

and side (left vs right) for all wounds, so that clinicians are presented with the same series of choices for every wound or ulcer type, even when the ICD-10 does not require it. The proprietary mechanism by which clinicians determine the diagnosis code for a wound is based on a series of carefully crafted sequential "decisions", each of which narrows the list of applicable codes. This is a powerful research tool, because it ensures that the process of classifying a specific wound happens at the same way at each facility participating in the consortium. Procedures are reported via Current Procedural Terminology[19] codes. Other standardized coding language include: LOINC (Logical Observation Identifiers Names and Codes)[20] for laboratory values, RxNorm[21] for medications, and SNOMED CT (Systematized Nomenclature of Medicine—Clinical Terms)[22] for wound and outcome related information, which is based on wound outcomes commonly reported in the literature. Clinicians must commit to POC documentation, which reduces inefficiencies, decreases the probability of documentation errors, promotes information transfer, and makes CDS possible.[7,23]

The EHR assesses for GCP for various wound types based on quality measure performance. Clinical practice suggestions, developed using the Wound Healing Society clinical practice guidelines,[24] guide clinicians in their decision making processes and drive success with quality measure performance. The clinical suggestions link to a suite of wound care quality measures, which encapsulate all key aspects of GCP and were developed by the US Wound Registry (USWR), a qualified clinical data registry, for which our practitioners can receive PQRS credit. These quality measures can be downloaded at no cost by the public for immediate installation in any certified EHR (http://www.uswoundregistry.com/Specifications.aspx)].[25] Importantly, there are also 2 PRO measures, which are provided with CDS: patient reported quality of life (QOL) and patient reported wound outcome. For effectiveness studies to be

possible, we must control the areas of care that represent GCP, such as offloading, vascular screening, moist wound care, and debridement of devitalized tissue. The wound care quality measures of the USWR standardize usual care so that the comparative effectiveness studies of advanced therapeutics are possible.

The EHR internally audits the chart to calculate both the physician and the facility level of service so that human coders are not needed.[26-28] Photographs can also be archived in a manner compliant with the Health Insurance Portability and Accountability Act (HIPAA), and they can be automatically appended to follow-up letters. Because data are collected in a structured format, quality reports are simple to generate. The structured language can be leveraged to produce reports regarding any specific type of patient, wound, or combination of variables that may be needed for clinical trials (e.g. wound size, Wagner grade, diabetes, etc.). The clinical practice suggestions also enable reports that reveal variations in care. As a result, we are able to identify whether there are physicians in the consortium whose practice standards indicate they would not make adequate research investigators. Similarly, programming can also be created that actively alerts the physician at the POC that a patient may be appropriate for a currently open trial.

Clinicians are incentivized to provide complete documentation and follow CDS, because the internal auditing mechanism is linked to reimbursement and because of the regular quality and benchmarking reports provided to them. Furthermore, clinicians fulfill the participation requirements of PQRS (and now the Merit-Based Incentive Payment System) by submitting electronic quality data to the USWR. The USWR staff provide remote monitoring of data completeness and cross-check data validity, which also further improves adherence to clinical practice guidelines.[15] Missing data are addressed in reports identifying specific patients by name

who lack EHR documentation of certain vital testing or interventions. Reports show the specific quality performance of each provider. In analytic datasets derived from EHR data, missing data are handled by usual statistical means, such as specific imputation algorithms, imputation using maximum likelihood algorithms, and/or outcomes handled as right censored observations.

The network EHR also provides validated tools to assess activities of daily living, alcohol use, nutritional screening, pain, and several other assessments commonly needed and/or used in wound research. Additionally, the Wound Healing Index (WHI) is embedded in the EHR, which allows risk stratification of ulcers so that matched cohorts can be created for either prospective or retrospective research.[29-31] Therefore, consortium clinics can use the WHI to work together as their own network to perform real-world studies. Furthermore, risk prediction models like the WHI estimate the healing likelihood of a patient's wound, which provides additional CDS.[32]

EHR data are transmitted nightly to the vendor's computing cloud, where they are archived and moved to the USWR server to be used for quality reporting, benchmarking, and CER. There is growing interest in the use of registry data for CER and a general agreement that it can enhance RCT data and fill in the knowledge gaps for clinical decision making, provided that the sources of bias can be controlled.[3,23,33] The FDA mentions multiple important variables that must be controlled to ensure RWD data are reliable for CER: data sources, data accrual methods, data completeness, data assurance, data adequacy and relevancy, data analysis methods, timeliness of data entry and their availability, a common definitional framework, and bias.[2,3] Table 1 lists the RWD reliability variables of the FDA and demonstrates how our consortium, by using the purpose-built EHR, fulfills the requirements for reliable data. These variables can be controlled in a LHS by implementing a comprehensive direct-from-EHR strategy that allows for POC electronic documentation using structured language, which

eliminates the data errors that can result from manual data entry and from data entered at a time distant from care, and that incorporates precision medicine with appropriate statistical analytical tools.[7,23,32,34,35] Smart analytic tools, models, and infrastructure are needed to not only extract data at POC, but to make these data useful to clinicians, help guide their decision making processes, and generate more evidence to improve the overall clinical care process.[3,36] The network EHR used by the consortium clinics controls sources of bias by standardizing the way the diagnosis is identified, standardizing usual care through quality measures, removing patient selection bias by collecting 100% of patients and 100% of ulcers, preventing post hoc vetting of outcomes, and risk stratifying patients with the WHI (Table 1). The use of this network EHR provides the necessary architecture to implement a comprehensive LHS for CER, quality reporting, and clinical care improvement. Aggregated consortium data are shared with the participating clinics in the form of benchmarking reports, which evaluate their clinicians' adherence to quality measures. Any investigator can also access registry data by submitting a research project plan to the Woodlands IRB for review and approval.

We began to network our facilities together with this purpose-built EHR, despite reluctance from some hospitals. The current hospital EHRs do not have the necessary features to collect sufficiently structured data, risk stratify patients, naturally incorporate CDS that is specific enough for use in practice and to populate patient registries. Hospital EHRs that provide more advanced programming are still not able to network facilities together. We continue to work with facilities to guide their transition process to the consortium EHR, so that they too can begin to benefit from participation in our LHS and the USWR.

Impact of a Network-based EHR, RWD vs RCT data

Before the consortium, hospital EHRs were not able to collect data sufficiently structured to be able to provide us with useful patient and wound information for something as simple as trying to understand how many patients in our network had diabetic foot ulcers (DFUs). Therefore, we were not able to use the hospital EHRs for research. All of our trials were performed with traditional study techniques using paper or electronic Case Report Forms. Among the recent RCTs performed by the network,[37-42] a total of 196 subjects with VLUs were enrolled in 2 trials, which ultimately treated 165 subjects.[37,38] A total of 271 subjects with DFUs were in 4 trials, which ultimately treated 244 subjects.[39-42] Only 1 wound per patient was studied in these trials, and many common comorbid conditions and severe wounds were excluded. These nongeneralizable trials are small and contrast drastically with the RWD from the consortium, in which all patients and all wounds are included in the dataset, regardless of comorbid conditions and severity of wounds.

Table 2 compares the trial data of a recent VLU RCT[37] evaluating an allograft and its retrospective follow-up study[43] with the RWD from the consortium. There are 856 patients in the consortium with 1,943 VLUs. Patients with VLUs have the highest mean number of wounds per patients (of all wound type), with 5.3 wounds. Additionally, some of these patients have many small ulcers, which are registered using free text as “multiple” or “scattered”, but we have become skilled at removing any questionable ulcers from the VLU dataset, and the EHR enforces the convention of linking both wounds and ulcers to a “related to” diagnosis, which is mandated by CMS for wounds. The RCT enrolled only 84 subjects, but more startling is the fact that it only studied 4.3% of the number of VLUs counted in the consortium (84 vs 1,943 VLUs). The patients in the consortium are an average of 8-11.6 years older than those who were enrolled in the trial, with the majority of them (68.5%, n = 586) being 65 years or older, compared to

39.3% in the RCT. In the consortium, 14.1% of patients have peripheral arterial disease or atherosclerosis, and 15.5% have congestive heart failure, conditions which were excluded in the RCT. Astoundingly, the mean size of the consortium VLUs are more than 5 times the size of the RCT VLUs, which excluded VLU ≥20 cm^2. We used the trial exclusion criteria and the wound severity to estimate the mean WHI among subjects in the RCTs and found they were more likely to heal than the patients in the consortium (WHI scores: 75.9 vs 69.3). Surprisingly, although the consortium dataset reflects an older and sicker patient population with lower WHI scores, the healing rates at 4 weeks and 24 weeks are higher than the RCT subjects' healing rates. This might be due to the fact that only 44 out of 84 patients (52.4%) participated in the retrospective follow-up study to the RCT and had healing rates for their index VLU reported at 24 weeks.[43] Therefore, the healing rate of the subjects at 24 weeks likely does not reflect the entire RCT population.

Table 3 compares RWD of patients in the consortium to trial data of a recent DFU RCT that analyzed the safety and efficacy of an allograft vs a bioengineered skin substitute.[41] The number of DFUs studied in this RCT (n = 100) represents only 3.8% of the DFUs available in the consortium (n = 2,634). However, this large repository of consortium patients (n = 1,047) is generally not eligible for RCTs, because our real-world patients fall within the exclusion criteria, including renal failure (12.2%), and a significantly higher number of total wounds per patient (4.3), which impacts healing likelihood. In contrast to the Wagner 1 or 2 ulcers enrolled in the RCT, nearly 43.6% of real-world patients have ulcers worse than a Wagner 2, and their initial wound surface area is 3 times larger than the DFUs enrolled in RCTs. Real-world patients take a significantly longer mean time to heal than the patients enrolled in RCTs (most likely because their wounds are so much bigger). The estimated mean WHI of the subjects enrolled in the RCT

was very high when compared to the mean WHI of the patients in the consortium (88.1 vs 68.6), demonstrating how skewed trial circumstances are for real-world applicability.

For now, our growing consortium represents a small subset of patients of wound care. However, our patients' data (Tables 2 and 3) contrast strikingly with RCT data and demonstrate that a real-world population of patients are older and sicker, with common comorbidities, and thus do not meet the idealized inclusion criteria of RCTs. The result is that real-world patients are subsequently denied access to the new therapies entering the market via the argument by payers that their effectiveness among compromised patients is unproven. The RWD of our consortium are more generalizable than RCTs, because they are all inclusive, making it possible to evaluate the effectiveness on the vulnerable individuals prohibited from participating in controlled trials. As more clinics join the consortium, an even larger population of patients with chronic wounds will further increase the generalizability of consortium data.

Discussion

The Research Network of the Patient-Centered Outcomes Research Institute (PCORI) is among the most important LHS enterprises to date, with 11 clinical data research networks (CDRNs) and 18 patient-driven research networks that provide EHR data analysis on common and rare conditions and genetic disorders.[9,44] PCORI denied the application of one of our authors (CEF) to support an already established CDRN tracking DFUs and unusual leg ulcers (e.g. sickle cell anemia ulcers), because [DFUs and nonhealing wounds] were "not a healthcare priority." The outlook for federal funding sufficient to implement a wound care research network is bleak, despite the staggering costs associated with wounds. Alternative solutions are needed. The use of the purpose-built EHR in our consortium is an example of a growing LHS that leverages

available technology to perform clinical data reuse of all patient data, including wound-specific PROs, to carry out collaborative learning through real-world trials.

Patients in the US receive appropriate, evidence-based care only 55% of the time, regardless of their race, socioeconomic status, education, or health insurance.[45,46] The situation is even worse for patients with chronic nonhealing wounds; only 6%-17% of them receive evidence-based care at each visit.[47] The impetus on the part of the FDA to utilize RWD is an opportunity for the wound care community to overcome the barriers that have, until now, prevented the creation of a LHS focused on wound care. We have been caught in a vicious cycle wherein RCTs exclude real-world patients,[1] with the result being that the evidence base derived from these studies that does not apply to real-world patients.[1,12] Consequently, clinicians, patients, and payers are hindered in their decision making, because limited evidence is available to determine the best treatment for a chronic wound.[12,48] Currently, the most logical way out of this is to use EHRs to facilitate registry participation and generate RWD. As Califf and Sherman cautioned, data are meaningless without the critical context and analysis that transforms information into the evidence that can facilitate clinical decision making.[49] RWD reflect all patient experiences, but they can also contain bias. In Table 1, we demonstrate how the use of a purpose-built EHR controls for the potential sources of bias to ensure that RWD generated by the clinics and shared through collaborative learning is of the highest possible quality.

In Tables 2 and 3, counts of VLUs and DFUs documented in the consortium EHR since adoption began are provided, along with their average WHI scores. The difference in the number of real-world patients seen compared to the subjects enrolled in our various trials and the difference in their relative severity is noteworthy. Furthermore, when looking at recent and ongoing RCTs done in our consortium, the mean screening failure rate is 26.3%, which increases

to 39.4% for VLU trials. These RWD confirm the nongeneralizable nature of prospective trials and indicate how much larger trial enrollment could be if a more representative population of patients were enrolled. Larger trials are needed in wound care. Lazarus et al found that among 63 prospective VLU trials, the median number of participants was a trifling 37.[12] Recent RCTs from our research network show higher enrollment numbers, with more than 80 patients enrolled,[37,38] but these enrollment numbers make up less than 10% of the number of patients with VLUs in the consortium (Table 2). More importantly, these patients in the consortium have on average more than 5 wounds, whereas the RCTs only targeted 1 index wound, which resulted in further selection bias. The small size of prospective trials is due to the restrictive criteria of their design, the end result of which is a chronically limited level of evidence for the field of wound care. Wound healing is a slow process, and only about two thirds of patients can ever be expected to heal.[50] In order to adequately power studies to find significant differences between treatments, sample sizes of over 400 patients might be necessary.[12]

Publications abound with prediction models, but these tools are rarely used in clinical practice.[32] With EHRs, they have become more user friendly and can automatically calculate risks and healing likelihoods for clinicians to use at POC. With the WHI, clinicians participating in our consortium and the USWR are not yet provided the score at POC, as further dialogue is needed to be certain what the effect of the WHI would be on clinical practice.[51] Furthermore probabilistic estimations need to be useful to improve decision making.[32] In wound care, the ability to predict which wounds will heal requires further attention. For now, the WHI risk stratifies patients and can be used to facilitate effectiveness trials with RWD.

With regards to the recent call by leaders of the wound care community to improve wound care research and establish a wound care clinical trials network,[12] we kindly request our

colleagues to consider our alternative network model (Figure 1) that has already been successfully implemented and which harnesses a wound care–specific EHR to generate real-world evidence by RWD data collection. An action point from that meeting is the collection of clinical research data of leg ulcers on a standard template.[12] The purpose-built EHR used by our consortium integrates a common definitional framework with multiple data dictionaries, including SNOMED, to collect data throughout the entire patient care process and transmit it automatically to the USWR for CER. The action plan calls for the adoption and validation of QOL tools and advocates for patient-centered outcomes,[12] which we can provide to the wound research community via the PRO quality measures of the USWR. We look forward to the day that independent funding for wound care research reflects the size and scope of this problem. Until then, we invite our wound care colleagues to consider creating sustainable models similar to ours which harness the requirement for quality reporting in order to standardize care and generate the data needed for CER, by meeting the demand for commercial research.[12] Given that there is currently no federal funding available for a wound care clinical trials network, our research network model provides a mechanism to strengthen the wound research community. Industry pays for wound care research, and, for now, a for-profit model such as ours can ensure sustainability of a research network. Funding is, however, needed to develop and implement more quality measures in wound care, strategic activities already being undertaken by the USWR.

Our growing LHS relies in part on previously collected data and allows the consortium to perform for the first time clinical data reuse on all the RWD collected from on all the patients for CER. More generalizable, real-world effectiveness trials can now be performed by our network with the consortium RWD. These effectiveness trials should include patients with renal disease,

DFUs with Wagner grades >2, much larger wounds, patients with multiple wounds, and more diverse patients. Our LHS is unique to wound care in that it not only integrates the LHS tenets of clinical care, QI, patient-based value, and CER, but it is also scalable. By participating in the consortium, clinics contribute their RWD data to the USWR, in which 130 clinics in 34 states and Puerto Rico participate. All facilities agree to report the same quality measures submitted by the USWR on their behalf and use the same practice suggestions, allowing for the benchmarking of their data across this national network. The common definitional framework of the purpose-built EHR controls for bias, and the 21 wound-specific quality measures help to standardize the potential sources of bias, making these RWD applicable to CER. By submitting their structured POC data documentation to the registry, these facilities are paving the way for a new era in wound care clinical research that shifts the paradigm from traditional nongeneralizable RCTs to the increased generation of improved real-world evidence.

Our consortium model is not without its limitations. As previously described, the patients in the consortium represent a small subset of the total population of patients with chronic wounds. However, these patients also represent the challenging realities of real-world clinical care, by suffering from conditions which are excluded from RCTs. The exclusion of older and sicker patients from RCTs ultimately limits the coverage indications of new therapies and technologies. The issue of screening failure rates deserves further study.

While it is true that, traditionally, RCTs have provided the evidence base for FDA clearance of new therapies and coverage and reimbursement policies by payers, the FDA now recognizes the possible value of real-world evidence generated from the care of real-world patients to assist in their regulatory decision making process.[2,3] Therefore, RWD, such as data from our consortium, will be increasingly important for the expansion of FDA cleared

indications and in support of payer coverage policy. Unlike RCTs, real-world outcome data are based on treatments that are neither blinded nor randomly assigned. However, the value of real-world evidence is that it incorporates the complex decision making that occurs between the provider and the patient, in addition to the variability inherent in clinical practice. Evidence generated by this consortium can advance wound care research by providing a solid evidence base for CER that targets the treatment and care of all patients, which is currently not possible in controlled trials.

As we are in the process of linking our entire research network to the purpose-built EHR, our paradigm shift for wound care clinical research will allow us to centralize access to research data, standardize usual care for the control patients, and help clinicians make a smooth transition to Medicare's new Quality Payment Program. This will allow us to raise the standards of both usual care and help physicians achieve success with Merit-Based Incentive Payment, the new framework for payment that is part of the Medicare Access and CHIP Reauthorization Act, by which CMS hopes to reward "better" care and not just "more" care.[52,53]

Acknowledgments

Sources of funding: This study was funded by the SerenaGroup® and the US Wound Registry.

Conflicts of Interest: TES: CEO of SerenaGroup; CEF: Chief Medical Officer of Intellicure and shareholder, Executive Director of the USWR (uncompensated); KAE: paid consultant of Strategic Solutions, Inc, RAY: none; MJC: paid consultant to this study.

List of Abbreviations

BSS = bioengineered skin substitute; CDRN = clinical data research network; CDS = clinical decision support; CER = comparative effectiveness research; Electronic Health Record = electronic health record; DFU = diabetic foot ulcer; FDA = Food and Drug Administration; GCP = Good Clinical Practice; HMD = Health and Medicine Division; ICD-10 = International Classification of Diseases, Version 10; IRB =institutional review board; LHS = learning healthcare system; LOINC = Logical Observations Identifiers Name and Codes; MU = meaningful use; NA = not available; PAD = peripheral arterial disease; PCORI = Patient-Centered Outcomes Research Institute; POC = point of care; PQRS = Physician Quality Reporting System; PRO = patient reported outcomes; QI = quality improvement; QOL= quality of life; RCT = randomized controlled trial; RWD = real-world data; SAP = statistical analysis plan; SNOMED CT= Systematized Nomenclature of Medicine Clinical Term; US = United States; SWC = standard wound care; USWR = US Wound Registry; VLU = venous leg ulcer; WHI = Wound Healing Index

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Figure Legend

Figure 1: A learning healthcare system implemented for wound care

CDS = clinical decision support; CER = Comparative Effectiveness Research; CMS = The Centers for Medicare & Medicaid; CPIA = clinical practice improvement activities; EHR = electronic health record; MIPS = Merit-based Incentive Payment System; QCDR = qualified clinical data registry; QMs = quality measures; USWR = The US Wound Registry

A= Point-of-care clinical documentation in a wound care–specific EHR incorporates evidence-based CDS, linked to specific QMs the provider will report to CMS as part of MIPS.

B= The Research Consortium, which consists of 12 clinics in the United State, with 51 providers using the same wound care–specific EHR, transmits structured clinical data to the USWR.

C= The USWR calculates QMs for the provider and facilitates CPIA. Provider performance reports compare the provider to the aggregate Consortium provider performance.

D= Performance reports and information gleaned from CER are learning opportunities, which help the provider improve quality of care. CER findings are used to improve the CDS within the wound care–specific EHR enabling patients to benefit from knowledge gained.

E = The USWR as a QCDR transmits to CMS the information necessary for the provider to succeed with MIPS, including QM data and CPIA, activities which demonstrate success with Advancing Care Information (formerly known as the Meaningful Use of an EHR).

F= As a result of QCDR participation, the provider is successful with MIPS and eligible for a positive adjustment to his/her billed Part B Medicare revenue.

G= The USWR deidentifies registry data and prepares analytical datasets for clinical research.

H = Real-world patient data are used for market research.

I = Real-world patient data are used for CER.

In this way, a learning healthcare system has been realized, thanks to the collection of structured data within a wound care–specific EHR.

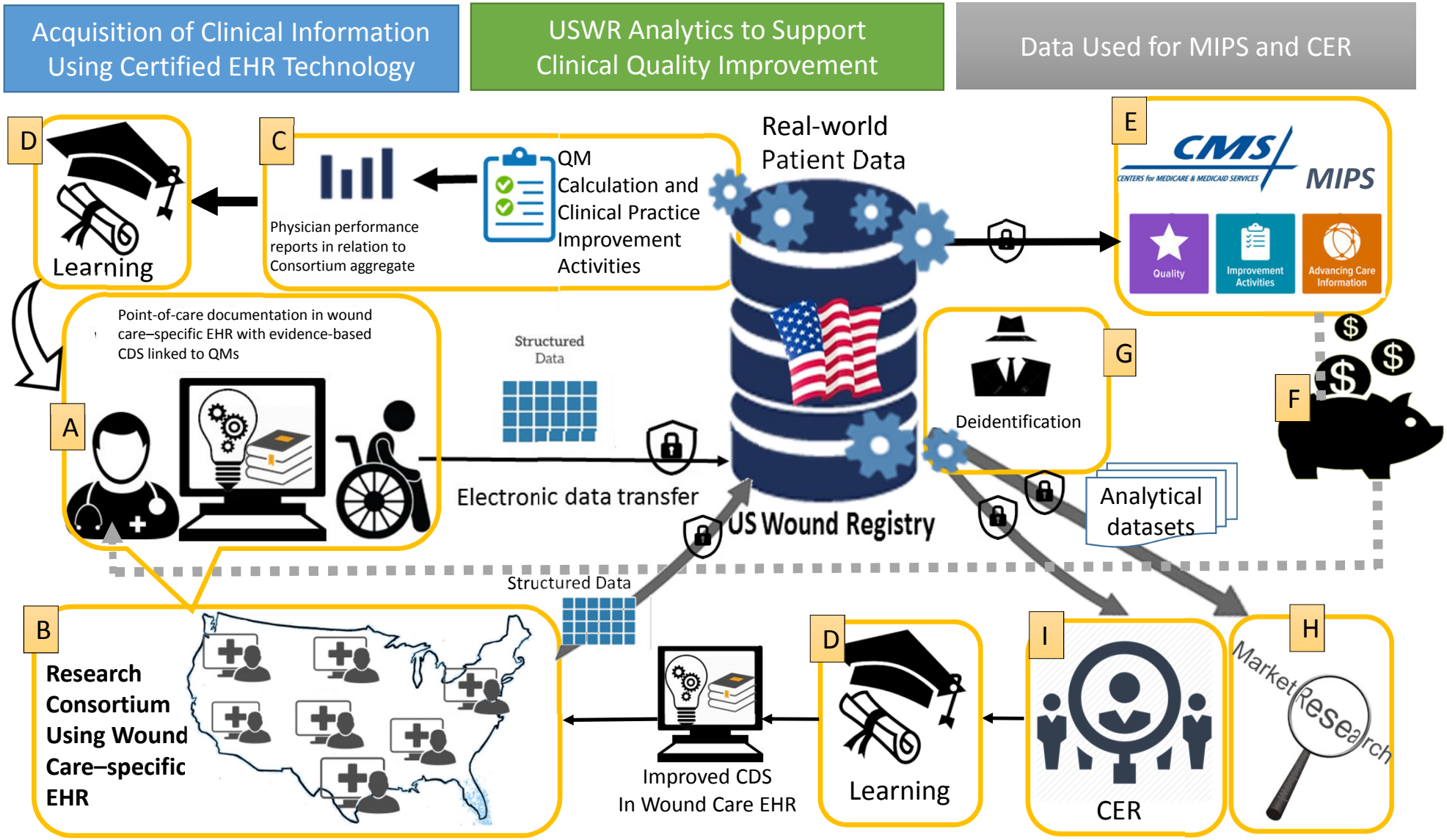

Table 1. The use of real-world data collected by a purpose-built electronic health record in a wound care-specific research consortium to fulfill the requirements of the United States Food and Drug Administration.[2]

Data Accrual		Data Assurance	
FDA Factor Needed	**EHR Feature**	**FDA Factor Needed**	**Consortium Feature**
• Individual sites prepared to completely and accurately collect data	• Sites must meet a minimum standard for data completeness prior to using EHR	• Data quality assessments	• Monitoring/remote monitoring by USWR; facility level reports monitor the data elements' completion rate
• Common data capture form	• Data captured direct from EHR	• Data completeness	• Data are as complete and accurate as the patient's EHR
• Common definitional framework	• Structured data used (no free text); multiple data dictionaries used over entire course of patient care, beginning with diagnosis	• Source verification, data collection, and recording procedures followed	• Structured data accrual direct from EHR at POC is the only way data can be collected and transmitted to USWR
• Common temporal framework	• All data documented at POC	• Long-term data consistent across sites	• Only sites using the structured, purpose-built EHR can participate in consortium, ensuring data are consistent over the long-term
• Bias minimized by patient	• All patients and all wounds	• Evaluation of sites' ongoing	• Monitoring provided by USWR;

Data Accrual		Data Assurance	
FDA Factor Needed	**EHR Feature**	**FDA Factor Needed**	**Consortium Feature**
selection and enrollment criteria	included	training, use of data dictionaries at sites, and sites/data monitoring practices	quality reports for each provider include all patients and all wounds and compare to consortium benchmarks
• Sources and technical methods for data element capture	• Direct-from-EHR data accrual integrated at POC and transmitted to USWR with linkages to billing, benchmarking reports, and quality reporting	• Audit mechanism in place	Internal auditing mechanism in EHR determines physician and facility billed level of service and is an incentive for complete and accurate and data documentation
• Timeliness of data entry, transmission, and availability	• All data documented at POC and transmitted to USWR for immediate use		
• Data collection procedures, evaluation protocol, and SAP relative to data evaluation	• Complete SAPs used; the WHI risk stratifies patients and creates matched cohorts for retrospective/prospective research		
• Whether data collection	SNOMED-CT data dictionary used		

Data Accrual		Data Assurance	
FDA Factor Needed	**EHR Feature**	**FDA Factor Needed**	**Consortium Feature**
impacts the determination of treatment outcomes	for all wound and outcome related information; no post-hoc vetting of data and outcomes; as part of PQRS, healing outcome is reported in relation to WHI score rather than using the common practice of removing patients with poor outcomes from the denominator		
• Adequate patient protections in place	• USWR independent IRB reviews projects and considers informed consent determination; notifications in each facility welcome patients to the "LHS" and explain how they can opt out of registry participation; reports run of time to sign off charts for clinicians, charts are locked after 48 hours; all data deidentified prior to use in research; the WHI is		

Data Accrual		Data Assurance	
FDA Factor Needed	**EHR Feature**	**FDA Factor Needed**	**Consortium Feature**
	not visible to providers so that they are not aware of predicted risk of healing		

EHR = electronic health record; FDA = United States Food and Drug Administration; IRB = institutional review board; LHS = Learning Healthcare System POC = point of care; PQRS = Physician Quality Reporting System; RWD = real-world data; SAP = statistical analysis plan; SNOMED CT: Systematized Nomenclature of Medicine – Clinical Terms;[22] USWR = US Wound Registry; WHI = Wound Healing Index

Table 2. An in-depth comparison of patient demographic and clinical characteristics of a venous leg ulcer randomized controlled trial[37,43] of a wound-case specific research network vs. the real-world patient dataset in the network's internal consortium of clinics.

Variable	VLU RCT Dataset			Consortium Dataset (n = 856)
	Allograft (n = 53)	SWC (n = 31)	Total (n = 84)	
Total number of VLUs, n	53	31	84	1,943
Mean age, years	59.0	62.6	NA	70.6
≥65 years, n (%)	21 (39.6%)	11 (35.5%)	33 (39.3%)	586 (68.5%)
Race/ethnicity, n (%)				
White	NA	NA	39 (88.6%)[a]	705 (82.4%)
Black/African American	NA	NA	NA	34 (4.0%)
Hispanic ethnicity	NA	NA	NA	2 (0.2%)
PAD or atherosclerosis n (%)	Excluded	Excluded	Excluded	121 (14.1%)
Congestive heart failure, n (%)	Excluded	Excluded	Excluded	133 (15.5%)
Mean no. of wounds per patient, n	Unknown	Unknown	Unknown	5.3[c]
Mean wound duration, weeks	58.4	56	NA	8.6
Mean initial wound area, cm^2	6.0	6.3	NA	31.3
Initial wound area ≥20 cm^2, n (%)				
No. of patients with VLUs ≥20 cm^2	Excluded	Excluded	Excluded	308 (35.9%)
No. of VLUs ≥20 cm^2				509 (26.2%)

No. of VLUs with reduction in wound size by ≥40% at 4 weeks, n, %	33 (62.3%)	10 (32.3%)	43 (51.2%)	1,613 (83.4%)[d]
Mean reduction in wound size at 4 weeks, %	48.1%	19%	NA	-46.3%[e]
No. outcomed as healed at 24 weeks,[f] n (%)				
No. of patients outcomed as healed	NA	NA	24 (54.5%)[a]	605 (70.7%)
No. of VLUs outcomed as healed	NA	NA	24 (54.5%)[a]	1,427 (73.4%)
Mean time to heal, weeks	NA	NA	NA	18.6
Mean weeks in service[g]	4	4	4	20.4
Mean Wound Healing Index score	75.9[h]	75.9[h]	75.9[h]	69.3

NA = not available; PAD = peripheral arterial disease; RCT = randomized controlled trial; SWC = standard wound care; VLU = venous leg ulcer

[a]Data from 44 participants of original RCT who participated in a follow-up study[43]; [b]based on an ankle brachial index >0.75; [c]includes all wound types; [d]data available for 1,933 VLUs; [e]18 VLUs increased in size over 10-fold; [f]defined as complete epithelialization; [g]for RCT only, follow-up retrospective study looked at 24 weeks for 44 patients from the RCT;[43] [h]estimated.

Table 3. An in-depth comparison of patient demographic and clinical characteristics of a diabetic foot ulcer randomized controlled trial[41] in wound care-specific research network vs the real-world patient dataset in the network's consortium of clinics.

Variable	DFU RCT Dataset				Consortium (n = 1,047)
	BSS (n = 33)	Allograft (n = 32)	SWC (n = 35)	Total (n = 100)	
Total number of DFUs	33	32	35	100	2,634
Mean age, years	63.8	63.3	60.6	NA	64.3
Race/ethnicity, n (%)					
White	30 (90.9%)	30 (93.8%)	31 (88.6%)	91 (91.0%)	794 (75.8%)[a]
Black/African American	3 (9.1%)	2 (6.2%)	3 (8.6%)	8 (8.0%)	49 (4.7%)[a]
Hispanic ethnicity	NA	NA	NA	NA	10 (1.0%)[a]
History of chronic renal disease,[b] n (%)	Excluded	Excluded	Excluded	Excluded	128 (12.2%)[c]
Autoimmune connective tissue disease n (%)	Excluded	Excluded	Excluded	Excluded	21 (2.0%)
Mean no. of wounds per patient	Unknown	Unknown	Unknown	Unknown	4.3[d]
Wounds of Wagner Grade ≥3, n (%)					
No. of patients with DFUs graded ≥3	Excluded	Excluded	Excluded	Excluded	457 (43.6%)
No. of wounds graded ≥3					452 (28.6%)[e]
Wound duration >52 weeks, n (%)					
No. of patients with DFUs >52 weeks	Excluded	Excluded	Excluded	Excluded	69 (6.6%)
No. of DFUs >52 weeks					87 (3.3%)

Mean initial wound area, cm^2	2.7	2.6	3.1	NA	8.5
Initial wound area ≥25 cm^2					
No. of patients with DFUs ≥25 cm^2	Excluded	Excluded	Excluded	Excluded	157 (15.0%)
No. of DFUs ≥25 cm^2					220 (8.4%)[f]
No. outcomed as healed at 12 weeks[g], n (%)					
No. of patients outcomed as healed	24 (72.7%)	31 (96.9%)	18 (51.4%)	73 (73%)	816 (77.9%)
No. of DFUs outcomed as healed	24 (72.7%)	31 (96.9%)	18 (51.4%)	73 (73%)	1872 (71.1%)
Mean time to heal, weeks	6.8	3.4	8.2	NA	10.1
Mean Wound Healing Index score	88.1[h]	88.1[h]	88.1[h]	88.1[h]	68.6

BSS = bioengineered skin substitutes; DFU = diabetic foot ulcer; NA = not available; RCT = randomized controlled trial; SWC = standard wound care

[a]Based on data from 652 patients; [b]based on a serum creatinine level >3/0 mg/dl; [c]includes dialysis and transplant; [d]based on data available for 1,580 DFUs; [e]based on data available for 2,619 DFUs; [f]defined as complete reepithelialization at 12 weeks; [g]includes all wound types; [h]estimated.