Ms. Leslie Kux
Associate Commissioner for Policy
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

October 25, 2016

Re: FDA 2016-D-2153 "Use of Real World Evidence to Support Regulatory Decision-making for Medical Devices"

Dear Associate Commissioner Kux,

The Chronic Disease Registry (d/b/a The US Wound Registry), a 501 (c)(3) non-profit organization, appreciates the opportunity to provide written comments pertaining to the use of real world evidence to support regulatory decision-making, particularly as it pertains to medical devices used in the treatment of non-healing wounds.

USWR Questions Regarding the Guidance Document

We understand that the FDA cannot craft a guidance document that will address all possible scenarios relating to the use of real world evidence. Since we see the world through the lens of our registry, we would like to use examples from it to ask for clarification on specific points where we are not sure we understand your meaning. We hope you will find specific examples helpful as you craft your answers. We also wish to know whether the FDA is willing to comment on the approach we have taken to address the various sources of bias about which FDA expressed concern in the guidance document. In other words, because the use of real world data (RWD) regulatory decision making is still relatively new, we want to "get it right" when it comes to registry data collection and management. We would like to know if we have met your expectations and if not, what we need to work on so that our RWD might be considered by the FDA in decision making.

Who we are

The Chronic Disease Registry (d/b/a) the US Wound Registry (USWR) has been a patient registry for more than a decade, starting in 2005. Originally called the Intellicure Research Consortium, we provided a report to the FDA in 2007 on the safety of "the VAC" in comparison to moist wound care among outpatients (at the request of the FDA to evaluate the safety of this technology for home use).

Because patients taking anticoagulants were excluded from all negative pressure wound therapy (NPWT) *prospective* trials, registry data were needed to assess the safety of NPWT among these patients. This report, now nearly a decade old, was our first opportunity to offer real world evidence in support of a decision making process.

In 2008, the USWR was among the first registries recognized by CMS for reporting PQRI/PQRS data on behalf of eligible providers (EPs), and in 2014 we were among the first registries recognized by CMS as a Qualified Clinical Data Registry (QCDR). We develop quality measures relevant to wound care and currently have 21 measures approved by CMS including high value measures such as patient reported wound outcome and patient reported wound quality of life. Wound care practitioners can report relevant quality metrics for usual and customary care including diabetic foot ulcer off-loading, venous ulcer compression and vascular screening only through our QCDR since there are no wound related measures in PQRS.

To fairly report outcomes, we also developed the Wound Healing Index in conjunction with the Institute for Clinical Outcomes Research (ICOR), which is a series of mathematical models that enable us to predict the likelihood that a wound of a given type will heal, based on both wound and patient factors. **The WHI allows us to create matched cohorts for comparative effectiveness research (CER).** We also act as a specialty registry for practitioners involved in wound care who can satisfy the requirement for specialty registry data submission. More than 2000 EPs are engaged in transmitting to the registry the Continuity of Care Documents (CCDs) from all of the patients in their EHR.

The Responsibilities of the USWR:

- Operate numerous "specialty" registries (e.g. podiatry, hyperbaric oxygen, cellular products)
- Develop quality measures for wound care
- Report quality data on behalf of EPs participating in PQRS
- Acts as a specialty registry to satisfy Meaningful Use requirements (direct from EHR)
- Provide data for comparative effectiveness research using the WHI to risk stratify patients

Our Real World Data Repository

The bulk of the discreet data in our massive wound data repository derives from the longitudinal records of approximately 130 hospital based outpatient wound centers utilizing an electronic health record (EHR) purpose built for wound care documentation that agree to share their EHR data in exchange for national benchmarking. Data are collected almost exclusively in structured language (e.g. ICD-10-CM, SNOMED, RxNORM) and at the point of care, in the room with the patient, by the physician and the nurse. All wound treatments are collected including dressings by category and brand (**including antimicrobial dressings and the response of the wound**), negative pressure wound therapy and cellular and/or tissue based products (CTPs). It is important to know that there is no secondary data entry and that all the data in the USWR is obtained as a direct transmission from the electronic health record.

Practically, the USWR:

- Receives the electronically transmitted data of consecutive patients at hospital based clinics in 34 states
    - Receives 100% of patients in every clinic by direct-to-EHR data submission

    - Receives 100% of wounds in all patients by direct-to-EHR data submission
- Receives the electronically transmitted data of patients in whom quality measures are reported as part of PQRS by many different EPs
- Receives the electronically transmitted data from EPs engaged in MU registry participation who transmit Continuity of Care documents on 100% of patients
- Contains treatment data collected in the course of usual, routine care
- Collects quality measure data for PQRS reporting, outcome reporting, and quality improvement activities on real world procedures and patients
- Collects data in a way that does not alter the normal clinical care of the patient or affect treatment decisions
- Has an independent IRB to review data use

We have more than 2 million wound visits in more than 200,000 patients from only the past 2 years (although data collection began in 2005), making the USWR the largest repository of structured wound data that has ever existed.

Why we need Real World Evidence: Wound Care RCTs are non-generalizable

Real world patients with non-healing wounds have an average of 6 serious co-morbid conditions and take an average of 10 medications. The fundamental problem is that non healing wounds are a SYMPTOM of a disease, but we perform research on them as if the wound were the disease. Patients develop non healing wounds because they have an underlying medical problem (e.g. vascular disease, diabetic neuropathy, auto-immune disease requiring prednisone, malnutrition, immobility, etc.). Patients with chronic wounds are also likely to be members of vulnerable populations which, as the FDA has noted, are difficult to enroll in clinical trials (e.g. suffering from dementia, paralyzed, or at the extremes of age). Yet, these are the very conditions which comprise the *exclusion criteria* from every major wound healing RCT of the past decade that brought a new device or drug to market. When the exclusion criteria of all these RCTs were compared to more than 6,000 actual patients with chronic wounds, about 75% of them would have been excluded simply on the basis of their co-morbid conditions, medications, or the size or severity of their wound. In fact, using utility scoring, our analysis demonstrated that 3/4 of the most pivotal wound healing trials in the past decade enrolled subjects healthier than the average “man on the street.”

Even more frustrating, virtually all of the diabetic foot ulcer (DFU) trials involving cellular products have enrolled DFUs of such low grade severity that, in most studies, the majority of the *control s*ubjects healed with usual and customary care in only a few weeks. After these new products or devices are cleared by the FDA, the various Medicare Administrative Carriers (MACs) then craft coverage policy that mirrors the exclusion criteria of the trial, based on the Kafkaesque but irrefutable logic that the effectiveness of these products in more severe DFUs has not been demonstrated. We have provided an example of this situation in the table below.

Table 1. Diabetic foot ulcer “snapshot”: an in-depth comparison of patient demographic and clinical characteristics of a cellular product randomized controlled trial vs the USWR real world patient dataset obtained from the very same clinics that participated in the RCT. The majority of real world patients have wounds of a higher Wagner grade and their wounds are more than twice as large, 12% have chronic renal failure, and their wounds take much longer to heal. These real world DFUs are prohibited

from receiving cellular products by Medicare coverage policy, but clinicians treat them with CTPs and thus data accrue in the USWR in these more severe wounds.

Variable	BSS RCT (n = 33)		USWR real world patients in same sites (n = 1,047)	
	No.	%	No.	%
Total number of DFUs	33	—	2,634	—
Mean age, years	63.8	—	64.3	—
White	30	90.9%	494[c]	75.8%
Black/African American	3	9.1%	31[c]	4.7%
Hispanic ethnicity	NA	—	7[c]	1.0%
History of chronic renal disease	excluded	—	128[d]	12.2%
Autoimmune connective tissue disease	excluded	—	21	2.0%
Mean no. of wounds per patient	1	—	4.3[e]	—
Wounds of Wagner Grade ≥2	excluded	—		
No. of patients with DFUs graded ≥2			711	67.9%
No. of wounds graded ≥2			1,154	43.8%
Wound duration >52 weeks	excluded	—		
No. of patients with DFUs >52 weeks			69	6.6%
No. of DFUs >52 weeks			87	3.3%
Mean initial wound area, cm^2	2.7	—	8.5	—
Initial wound area ≥25 cm^2	excluded	—		
No. of patients with DFUs ≥25 cm^2			157	15.0%
No. of DFUs ≥25 cm^2			221	8.4%
No. of patients outcomed as healed	24	72.7%	816	77.9%
No. of DFUs outcomed as healed	24	72.7%	1,875	71.1%
Mean time to heal, weeks	6.8	—	10.1	—

BSS = bioengineered skin substitutes; DFU = diabetic foot ulcer; NA = not available; — = not applicable
[a]Based on a serum creatinine level >3/0 mg/dl; [b]defined as complete reepithelialization; [c]not documented for 62.3% of patients; data are from 652 patients; [d]includes dialysis and transplant; [e]includes all wound types; [f]estimated.

The sad fact is that we perform prospective clinical trials to demonstrate the efficacy of devices on wounds that could heal without these devices, so that we can deny Medicare coverage to the patients who do need treatment with them. As FDA Commissioner Califf commented on the FDA website, " . . .the data gathered from such studies may not actually depict the "real world" that many patients and care providers will experience—and this could lead to important limitations in our understanding of the effectiveness and safety of medical treatments."

We agree that if the FDA wishes to obtain data on the effectiveness or the safety of wound care products, the best (and perhaps the only) mechanism will be through registry reporting of real world data. We heartily support the FDA's movement in this direction and applaud the guidance document for tackling the challenges that the use of real world data (RWD) present. There are some specific points where we could use clarification. We are providing specific examples from our experience in the hope this additional detail helps you focus your answers:

1) Regarding the issue of investigational device exemption (IDE):

Example: Cellular product trials were primarily performed in Wagner 1 ulcers (see Table 1 above). However, the MAJORITY of diabetic foot ulcers seen in the real world are Wagner 2 or higher. Thus, at least half (but perhaps more) of the cellular and/or tissue based products (CTPs) applied to DFUs are actually applied in wounds of greater severity than the RCTs, and that data accrues in the USWR.

As we understand the guidance document, even though it is clear that some of our clinicians are using devices like cellular products outside of their FDA clearance, they are doing this in the routine practice of medicine and thus, no IDE is necessary for the general data collection activities of the registry, because it collects data on all uses of otherwise approved medical devices. Do we understand you correctly regarding your guidance on IDEs?

Example: Hyperbaric chambers are Class II devices cleared for the treatment of a variety of conditions. However, in the routine care of patients, clinicians may make case by case decisions to treat conditions that are not part of the investigational device authorization for hyperbaric chambers.

As we understand the guidance document, even though it is clear that some of our clinicians are using devices outside of their FDA clearance, they are doing this in the routine practice of medicine and thus, no IDE is necessary for the general data collection activities of the registry, because it collects data on all uses of otherwise approved medical devices. As further clarification, data on consecutive patients is transmitted to the USWR so there is no bias towards data collection for on-label or off-label use.

2) Clarification regarding informed consent (IC) with regard to real world evidence:

USWR data are primarily obtained via the direct transmission of electronic health records from hospital based outpatient wound centers. Clinical observations are entered at the point of care by both physician and the nurses who are documenting routine wound care interventions in the course of usual care. Patients sign a consent for medical treatment and they are notified that they are part of a "Learning Healthcare System" and that they have the right to "opt out" of participation in the registry.

Example: It is not possible to envision all of the potential questions which may arise in the future for which real world evidence can be of value. For example, USWR data has already been used to understand the safety of the VAC among patients on anticoagulants, and to understand the pattern of use of antimicrobial dressings, to name only 2 of many projects not envisioned when the registry was created. Thus, ***PROSPECTIVE informed consent is not possible for RWE****, because the point of real world data is that it is collected in the course of the usual clinical care of patients and that additional procedures such as special consents are NOT performed, otherwise the data does not represent the "real world".*

We would like to confirm that the FDA understands that it is not possible to have PROSPECTIVE informed consent for specific projects in the scenario of real world evidence because the "real world" we are documenting is the daily clinical care among patients who are NOT participating in a specific clinical trial. We want to ensure that the lack of prospective informed consent will not prevent real world registry data from <u>potentially</u> being able to be used by the FDA for purposes such as the expansion of coverage indication, assuming the data are compelling. USWR patients are protected by IRB review as discussed below.

3) Clarification regarding IRB approval:

We understand that the **prospective enrollment of new patients into a clinical trial** using the registry infrastructure meets the definition of a Clinical Investigation and is subject to 21 CFR 50 (Informed Consent) and 21 CFR 56 (IRB Review). Additionally, if the prospective enrollment is considered significant risk and is being used to determine safety and effectiveness of a medical device, an IDE approval will be required.

Example: The USWR receives periodic requests for RETROSPECTIVE analyses of data collected that was collected in the course of usual care. The analysis has no impact on care that was previously rendered and patient identifiers are removed prior to analysis. Once a data project is identified, a written request is submitted to the independent IRB of the USWR (The Woodlands IRB) which oversees the use of data and evaluates each project, to ensure that PHI is protected and that the projects meet the criteria for wavier of informed consent.

We would like confirmation from the FDA that this process is what you hand in mind in the guidance document.

4) Clarification regarding our approach to meeting the FDA's recommendations and the possible use of registry data in expansion of labeling

The FDA guidance document has stated that in some circumstances where real-world use of a device is in a broader patient population or wider set of circumstances than described in the device labeling, it may be possible *to use existing systematically collected real-world data to expand the labeling*. We think that is vitally important for the field of wound care if the patients most in needed of new technology are ever going to have access to it.

The guidance document discussed a number of factors affecting data relevance and reliability (e.g. data accrual, data completeness, adequacy, methods to minimize bias, data assurance, the source of data, etc.), as well as site preparedness, personnel training, data definitional framework, patient selection, linkage to claims, timeliness of data entry, and whether necessary and adequate patient protections were in place (e.g., de-identified data, maintenance of privacy, and need for informed consent as determined by the reviewing IRB and in compliance with FDA regulations). In Table 2 below, we explain how the USWR meets each of the FDA requirements. We have provided a third table (Table 3, appendix) which details the systematic way in which we approached possible areas of bias and the USWR publications in peer reviewed journals which demonstrate how we have minimized bias.

We would like confirmation from the FDA that these processes are what you had in mind in the guidance document. Our larger question is whether we can reasonably perform research that would lead to any of the following using USWR data (assuming the results were compelling):

- ***Expansion of coverage indications for approved devices***
- ***Post marketing surveillance (522)***
- ***Use of the WHI for the creation of matched cohorts***

Table 2. How the real world data of the USWR fulfills the FDA requirements

Data Accrual		Data Assurance	
FDA Factor Needed	**EHR Feature**	**FDA Factor Needed**	**Registry 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 registry, ensuring data are consistent over the long-term
Bias minimized by patient selection and enrollment criteria	All patients and all wounds included	Evaluation of sites' ongoing training, use of data dictionaries at sites, and sites/data monitoring practices	Monitoring provided by USWR; quality reports for each provider include all patients and all wounds and compare to network 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 impacts the determination of treatment outcomes	SNOMED-CT data dictionary used 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 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; USWR = US Wound Registry; WHI = Wound Healing Index

5) *Clarification regarding how the FDA will make determinations as to whether data elements fulfill a regulatory purpose*

The guidance document acknowledges that the data elements for existing RWD sources are primarily chosen for non-regulatory purposes such as clinical documentation and billing, quality reporting, quality assurance (QA) and quality improvement (QI). The guidance document states that in the case of clinical care registries), FDA will assess whether the individual data elements contained within the existing RWD source are sufficient (i.e., complete, well-defined, and appropriate in scope and timing) to fulfill a regulatory purpose. ***We would like to know the process by which FDA will perform that assessment and when that happens. Is that an assessment that only occurs if we perform an analysis that might provide data to expand a coverage indication? How is that performed?***

We applaud the FDA for its willingness to consider real world evidence in the regulatory process. Based on an analysis of the 5% Medicare Claims dataset (manuscript under preparation), more than $90 Billion was spent on the care of patients with chronic wounds in 2014, and they affect 15% of the Medicare population. Yet, federal investment in wound care research is almost non-existent. The USWR is anxious to utilize the vast repository of data to which we have access in order to improve the lives of patients. We would like to work proactively with the FDA to make this possible.

Yours Sincerely,

Caroline E. Fife, MD
Executive Director, USWR

Appendix: Table 3: A review of the evidence of currently available functions and features of the US Wound Registry and the bias they avoid**.**

Bias(es) Addressed	Registry Function	USWR Study Topic	Evidence from the USWR	Significance/Impact of Evidence	REF
Selection bias, recall bias, interviewer bias, systematic error from secondary data entry	Assess prognostic and quality of life factors	Impact of Medicare carriers' decision that patients should perform self-bandaging for compression.	55% of patients (301/547) needed assistance with ADLs, many of whom would be most likely unable to self-bandage.	Point-of-care documentation revealed that the decision to drop compression coverage in favor of self-bandaging was not supported by real world ADL evidence extracted from EHR data and could negatively affect the QOL and prognosis of patients with VLUs.	I
Selection bias, information bias, systematic error from secondary data entry, interpretative/ analytical bias	Assess quality of care, quality improvement, and adherence to CPG and standards	Adherence to basic wound care (offloading of DFUs and compression of VLUs)	• 6% of patients with DFUs received TCC • 17% of patients with VLUs had adequate compression.	There was a need for quality measures and clinical suggestions with the EHR to drive adherence to basic wound care.	J
		Retrospective analysis of the gap between the evidence and practice of DFU offloading	• Among 25,114 DFUs of 11,784 patients over a 6-year period, only 2.2% of 221,192 visits documented offloading. • Only 16.0% used the gold standard of TCC, although 96.3% of DFUs were TCC-eligible.	There was a need for clinical practice suggestions and quality measures to drive the offloading practice standard forward.	F
		Use of real-time performance in CPG implementation as measured by EHR data extraction to drive practitioner salary incentives and performance reviews.	• DFU offloading rates improved from 11.7% to 69.2%. • VLU compression rates improved from 27.9% to 79.7% • Both adherence to CPG and efficiency of care greatly improved.	This study justified the need for quality measures in wound care. The EHR can be used to drive practitioner quality of care, quality improvement, and adherence to CPG.	M,K
		Retrospective analysis of the use of antimicrobial dressings in clinical practice	Based on data from 3,084 wounds, it was observed that clinicians tended to use antimicrobial dressings for up to 4 weeks on patients with multiple comorbidities ($p = 0.001$), who were on antibiotics ($p < 0002$) and had an infected ($p < .00001$), refractory wound ($p < 0.00001$).	In the absence of CPG on the use of antimicrobial dressings, structured data collection of 3,084 wounds in the USWR revealed the practice patterns and decision making processes of clinicians.	G
		Use of remote quality monitoring/telemedicine to improve physician performance and adherence to CPG	For 3 years, a physician preceptor remotely monitored 6 physicians working in 5 wound centers in 2 states for 3 years. All physicians improved their	The feasibility of the purpose built EHR for remote quality monitoring in a field with limited training options and for the	N

			performance, with a significant improvement in documentation error rate.	purpose of an organized quality management program was demonstrated. Improved adherence to CPG using this EHR was confirmed.	
		The threat of lack of wound care quality measures to the field of wound care in the wake of the transition to value-based reimbursement	The USWR is a qualified patient registry that features PQRS reporting, measure assessments, and future registry submission requirements and is vital to reimbursement and federal quality initiatives.	The feasibility of the development of per visit process measures needed to address the gap between practice and CPG and/or standards of care was confirmed.	20
Selection bias, information bias, systematic error from secondary data entry, interpretative/ analytical bias, confounding by indication	Assess clinical effectiveness/ outcomes, including for benchmarking and quality reporting purposes.	Evaluation of wound care effectiveness in a real world patient population	• Almost two thirds of wounds healed (4,671/7,099) • Mean time to heal was 15 weeks • 10% of wounds healed in 33 weeks or more.	This study supports the use of the EHR data for CER, given that data are inclusive of patients who would be excluded from RCTs.	P
		Exclusion of real world patients from wound care RCTs	29.8% to 99.6% of 3,201 patients in 18 wound centers participating in the USWR would have not have met the inclusion criteria of 17 wound care RCTs.	RCTs are not able to evaluate the effectiveness of a wound care product or intervention, when more than half of patients are excluded from participation, greatly diminishing the applicability of RCT results to real world populations and evidence based medicine.	7
		Development of a validated risk-stratification model (WHI) to predict the healing likelihood of wounds	Based on EHR data collected from 50,967 wounds, significant predictors of healing among all wounds were wound size, wound duration, number of wounds, evidence of bioburden, tissue type exposed, being nonambulatory, and requiring hospitalization.	The use of structured data collection among a real world patient population (with no selection bias and based on true healing rates) in a risk stratification model can be used for CER to identify patients needing advanced therapy.	47
		Development of a validated risk-stratification model (WHI) to predict the healing likelihood of patients with PUs	• 4,300/6,640 body PUs healed (64.8%). • 1,240/1,909 heel PUs healed (65.0%). • Among clinicians who treated ≤30 PUs, for body PUs, 14.9% healed <33%, 45.3% healed 33%-67%, and 74.0% healed >67% of body PUs; for heel PUs, the corresponding rates	The use of structured data collection in a risk stratification model revealed real world PU healing rates among 8,549 wounds and demonstrated that clinicians treating a greater number of PUs had better outcomes, which can be used for benchmarking purposes.	48

			were 29.2%, 54.5%, and 76.7%. • Among clinicians who treated >30 PUs, for body PUs, 27.5% healed <33%, 55.3% healed 33%-67%, and 82.3% healed >67% of body PUs; for heel PUs, the corresponding rates were 38.1%, 54.6%, and 79.7%.		
		Development of a validated risk-stratification model (WHI) to predict the healing likelihood of patients with DFUs	66.1% (3,462/5,239) of DFUs registered in the USWR healed.	The use of structured data collection in a risk stratification model revealed real world DFU healing rates among 5,239 wounds. Results from this model can be used for quality reporting.	49
		Effectiveness of clostridial collagenase ointment when applied adjunctively with selective debridement on stage IV PUs compared with selective debridement alone	The proportion of closed wounds was twice as much and time to heal was significantly faster for PUs treated with clostridial collagenase ointment compared to those treated with debridement alone.	This study of clinical effectiveness revealed physician practice patterns in terms of how many debridements occur, what dressings are used, and whether an adjunctive therapy is prescribed.	R
Selection bias, information bias, interpretative/ analytical bias, systematic error from secondary data entry	Assess safety	Assessment of safety of NPWT on DFUs in terms of adverse events and complications on a real world patient population	Based on 72 DFUs treated with NPWT vs 1,299 DFUs not treated with NPWT, the rate of adverse events or complications was not statistically different, and NPWT was safe.	This early study demonstrated how a registry can assess safety among a real world patient population, which included patients taking anticoagulants, who would have been excluded from RCTs on NPWT (because anticoagulants were an exclusion criteria).	59
Selection bias, information bias, systematic error from secondary data entry, interpretative/ analytical bias	Internally audit and ensure accurate and compliant medical billing	Calculation of facility service levels for medical billing at outpatient wound centers	Time and wound size were not found to be surrogates for actual work performed, whereas a near normal distribution of results was found with a new acuity-based scoring system.	The acuity-based scoring system ensures complete documentation and data completeness, because any item that is scored as having been performed must have corresponding documentation in the EHR. Today, there are more than 200 items related to work elements tracked by the EHR that determine the facility level of service; their completion rates	H

		reveal how completely the facility was able to document.	
Determining true physician work for the purposes of billing using the internal audit function	Physicians were found to provide higher levels of care than the levels of services provided by facilities.	A major incentive to participate in the USWR is the internal, real time EHR auditing that is performed to calculate the appropriate level of service and accurately capture physician work (which may be incomplete when using a paper-based system), thereby ensuring compliant and accurate billing.	L
Extraction of real world billing data from 3 hospital-based outpatient wound centers and their practitioners in them to establish their relative contribution to a potential physician hospital organization.	Based on 6,762 patient (887 initial consultations and 5,875 follow-up visits) and Medicare-allowable reimbursement rates, mean physician revenues represented approximately 25% of total revenue vs 75% provided by procedures.	The use of the purpose built EHR that is designed to capture billing data serves as motivation for complete documentation, because the EHR is linked to revenue.	O
Use of benchmarking data to facilitate management of a wound center	Data extracted from EHRs of 100 wound centers in 32 states found that patient volume, operational efficiency, revenue cycle management, and regulatory compliance drive a wound center's management performance.	The implementation of the Stage 2 MU-certified EHR, which supports quality reporting and facilitates the selection of correct diagnosis codes, along with a business plan to adopt value-based, revenue can optimize wound center management.	Q
Fair analysis of the physician work of hyperbaric chamber supervision for reimbursement purposes	• Among 11,240 patients undergoing HBOT at 87 USWR facilities, their mean number of comorbidities and medications was 10 and 12, respectively. • The mean number of HBOT treatments supervised per physician per day was 3.7 at monoplace facilities and 5.4 at multiplace facilities. • Patients undergoing HBOT generally suffer from multiple, serious comorbidities, require multiple medications, and therefore need the	Transmission of structured EHR data created a rich data repository that allows for rapid analysis and resulted in a fair modification to the reimbursement rate of HBOT chamber supervision (of $112.06).	21

	care of a properly trained physician.

ADL = activities of daily living; CER = comparative effectiveness research; CPG = clinical practice guidelines; DFU = diabetic foot ulcer; EHR = electronic health record; HBOT = hyperbaric oxygen therapy NPWT = negative pressure wound therapy; PU = pressure ulcer; QOL = quality of life; RCT= randomized controlled trial; REF = reference; TCC: total contact casting; USWR = US Wound Registry; VLU = venous leg ulcer; WHI = Wound Healing Index.

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