# Inconvenient Truths about Chronic Wounds from Real World Data

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# 2019 Analysis of Medicare claims for wound care (complete Medicare dataset)

- Started with the complete list of diagnosis codes seen in ~200 outpatient wound clinics obtained from the US Wound Registry
- 16.4 % of Medicare beneficiaries have a chronic wound
  - 10.5 million people
  - Prevalence up by 3.4% since 2014 (particularly among patients < 65)
- Most expensive and most common:
  - Surgical complications
  - Pressure ulcers
- The "wounds with no name" still represent a staggering percentage – meaning the "chronic ulcer" and the "traumatic wound"
- Cost: Estimates: **$22.5 billion to $67.1 billion**
- Most costs are *outpatient*
  - Costs have shifted from the HOPD to the physician's office and the home

ORIGINAL RESEARCH

Chronic wound prevalence and the associated cost of treatment in Medicare beneficiaries: changes between 2014 and 2019

https://www.tandfonline.com/doi/full/10.1080/13696998.2023.2232256

# RCTs don't study the most common problems

- Diabetic foot ulcers: 0.7%
- Venous Ulcers: 0.9%
- Pressure ulcers: 1.8%

**3.8%**

- Surgical wounds: 3.0%
- Traumatic wounds: 2.8%
- Chronic ulcers: 2.3%

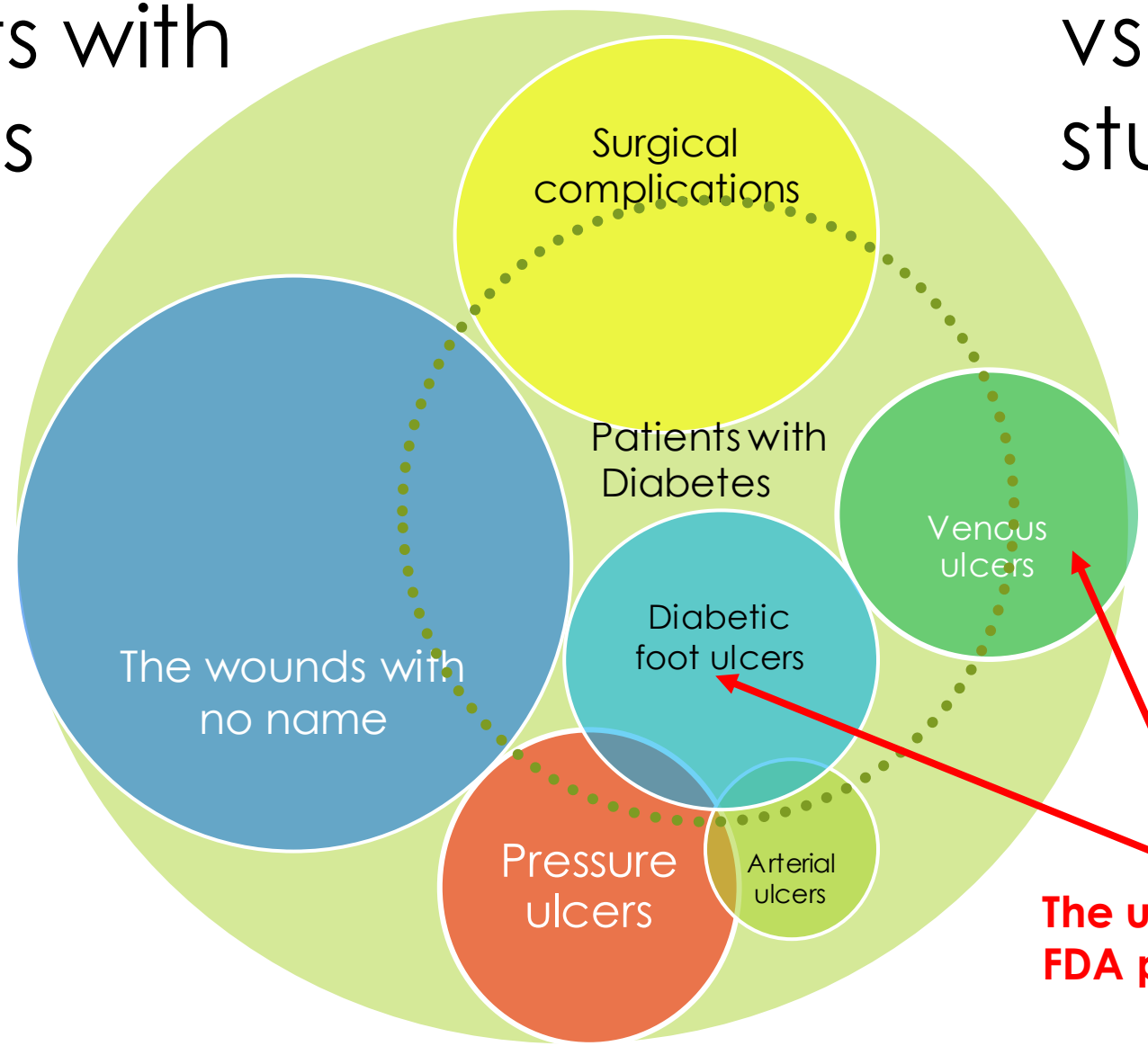
**5.1%**

**The most prevalent wound type are "the wounds with no name" (traumatic wounds that don't heal and chronic ulcers that aren't DFUs, VLUs ore pressure ulcers).**

https://www.valueinhealthjournal.com/article/S1098-3015(17)30329-7/fulltext

# Patients with wounds vs. what we study






"The wounds with no name" are the largest category of chronic wounds/ulcers.

Half of all patients with any ulcer type have diabetes.

There is substantial overlap among wound/ulcer "types".

**The ulcer types involved in FDA prospective clinical trials**

# The design of RCTs has real world implications for Medicare coverage policy

- 1999
- 72 y.o. female
- Rheumatoid arthritis on prednisone and methotrexate
- Non-insulin dependent diabetes– poorly controlled
  - 5-month history of enlarging leg ulcer due to minor trauma

Healed with NPWT and a cellular product.

Why was this Medicare fraud?

# The design of RCTs has real world implications for Medicare coverage policy



## Exclusions in the RCTs

- No ulcers that expose muscle, tendon, bone or joint
- Alcohol/drug abuse
- Anticoagulant treatment
- Cellulitis or local wound infection
- Cancer or recent cancer treatment
- Collagen vascular disease/connective tissue disease
- RA/Scleroderma, Lupus – any autoimmune disease
- Charcot foot changes
- Corticosteroid treatment
- Gastrointestinal disease of any type
- Renal disease of any type
- Any organ transplant
- In diabetics, HbA1c > 8-10
- Nutritional impairment/Albumin < 3.0 mg/dl
- Osteomyelitis
- Peripheral arterial disease

## Requirements in the LCD for a "skin substitute'

- ". . . not involving tendon, muscle, joint capsule, or exhibiting exposed bone or sinus tracts."
- "Elimination of underlying cellulitis, osteomyelitis, or other infection"
- "Appropriate debridement of necrotic tissue
- "Only applied to wounds with adequate circulation/oxygenation"
- ". . .must not be provided to patients with:
  - uncontrolled diabetes
  - vasculitis
  - rheumatoid arthritis or rheumatoid ulcers
  - radiation and/or chemotherapy within one month immediately preceding application
  - ongoing use of high-dose corticosteroids or immunosuppressants

# We don't have the ICD10 codes we need

- Ulcers
  - Pressure *ulcers*
  - Venous
  - Chronic Non-pressure
- Ulcer types without codes
  - ~~Arterial Ulcers~~
    - We can only identify these as "chronic non-pressure ulcers" in patients with atherosclerosis
  - ~~Diabetic foot ulcer~~
    - We can only identify these as "chronic non-pressure ulcers" of the foot in diabetics


*the **International Classification of Diseases 10th Revision** (ICD-10) developed by the World Health Organization (WHO)

# We can't clearly classify most wounds/ulcers: Can you name this ulcer?

*Photo property of C. Fife, MD*

A heel ulceration in a diabetic with peripheral arterial disease would be best diagnosed as a:

A. Pressure Ulcer
B. Diabetic foot ulcer ("Non-pressure Chronic ulcer")
C. Arterial ulcer ("Non-pressure Chronic ulcer")

# Wound Subjects in RCTs vs. Wound Patients in the Real World

- Among 8,611 wound center out-patients, > 50% would have been excluded from 15/17 major RCTs
  - 88% wound related RCT patients excluded at the "first pass"
- 3 of 4 major trials bringing new products to market enrolled patients healthier than the "girl on the street"

"Show girl" trials

- Average patient age:
  - 60.4 (1 - 104) years
- ~2020
  - 24% with CAD
  - <1% current smokers
  - 8.4% on steroids
  - 8% have renal failure or transplant
  - 54% of wounds that were not specifically diabetic foot ulcers were in patients who had diabetes


*"Estimating the Applicability of Wound-care Randomized Controlled Trials to General Wound Care Populations by Estimating the Percentage of Individuals Excluded from a Typical Wound Care Population in Such Trials:" Marissa J. Carter, Caroline E. Fife, David Walker, Brett Thomson, Advances in Skin and Wound Care, 2009, 22: 316-24.*

**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,[b] *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* (%) | Excluded | | | |
| No. of patients with VLUs ≥20 $cm^2$ | | 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.

Serena TE, Fife CE, Eckert KA, Yaakov RA, Carter MJ. A New Approach to Clinical Research: Integrating Clinical Care, Quality Reporting, and Research Using a Wound Care Network-based Learning Healthcare System.
Wound Repair Regen. 25(3): 354-365, 2017.

# Chronic wounds are a SYMPTOM, not a disease

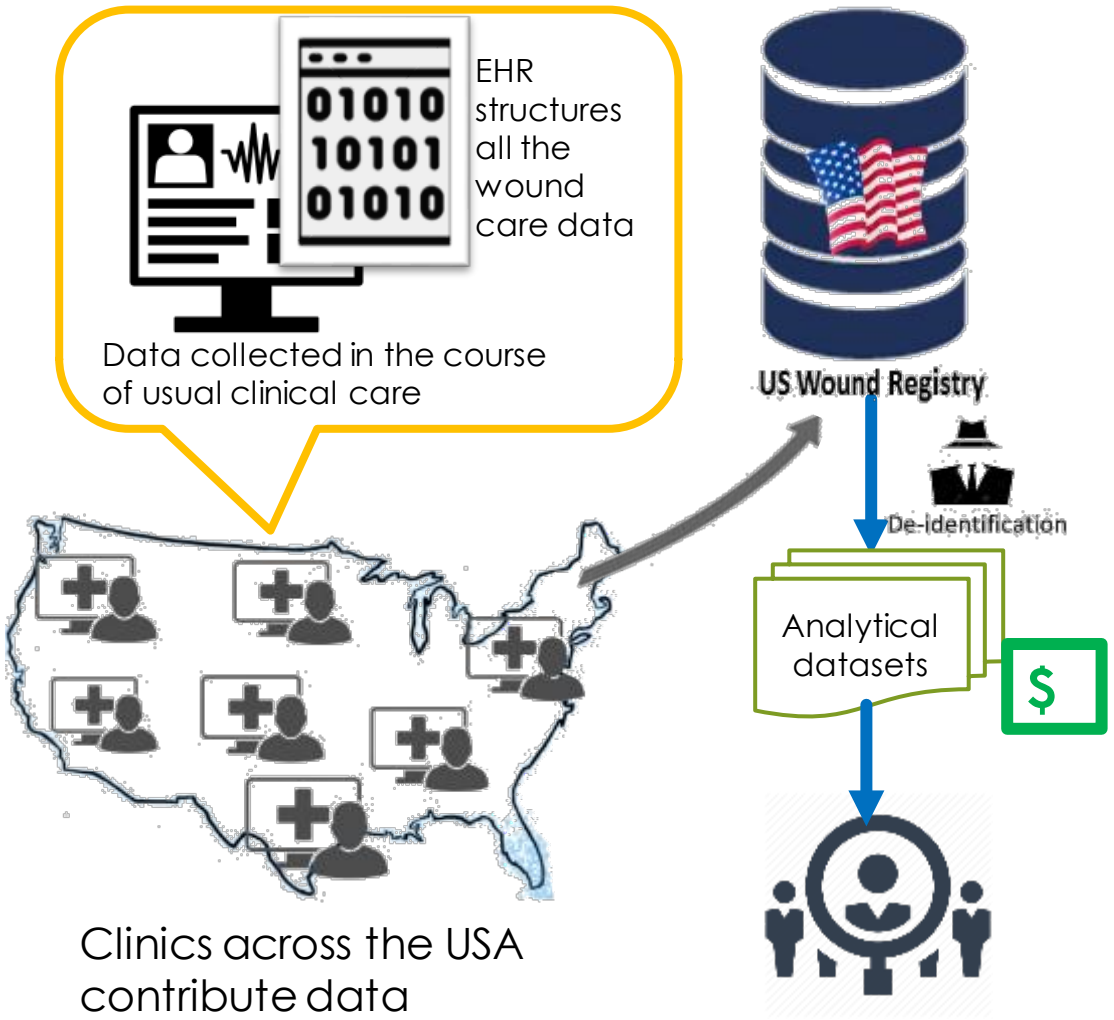
- **The mean number of serious conditions per patient is 8**
  - 59.9% had utility values for comorbidities/conditions, which were worse/lower than their wounds' values.
  - The mean minimum utility value was 0.5
- Nutritional deficits are rampant but underdiagnosed
  - Malnutrition and nutrient deficiencies (both diagnosed and undiagnosed) are rampant
  - 68% of chronic wound patients score at risk or malnourished on the Mini-nutritional assessment
- **The average patient with a non-healing wound takes 12 medications**
  - Many drugs significantly impact healing

Meds taken by a patient with a chronic "venous ulcer"

The Impact of Underlying Conditions on Quality-of-Life Measurement Among Patients with Chronic Wounds, as Measured by Utility Values: A Review with an Additional Study. Adv Wound Care (New Rochelle). 12(12): 680-695, 2023.

# Registries directly from an EHR (e.g., USWR)

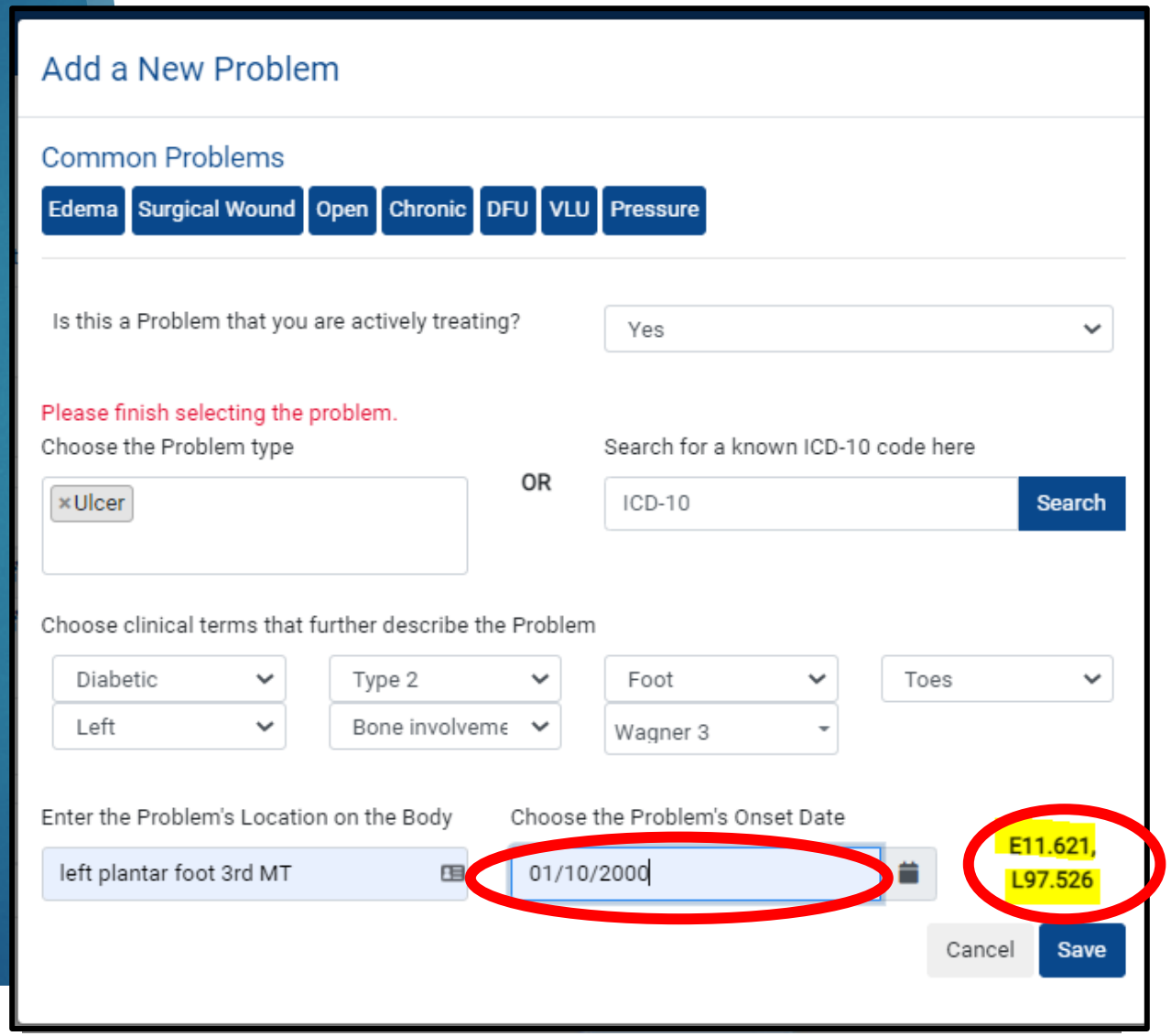





- Clinical data are entered at the point of care in real time
- The electronic medical record (EHR) collects the data in a format for research or "research ready" data
- The entire EHR is structured (all medications, conditions, treatments, etc.)
- There is no secondary data entry by anyone – no extra work
- Patients/wounds are followed until outcome
- Data are aggregated inside the US Wound Registry (USWR) which is a Medicare recognized "Qualified Clinical Data Registry" (QCDR)
- No patient consent is needed
- The entire treatment course of each wound is known
- The Wound Healing Index (WHI) is available to create matched cohorts
- **Data are collected on all products making CER possible.**
- Data continue to accrue due to normal product usage
- All costs are associated with data use and analysis
- **There is no selection bias because data are collected on all patients and all wounds**

To obtain real world data, we first need to know the correct diagnosis.

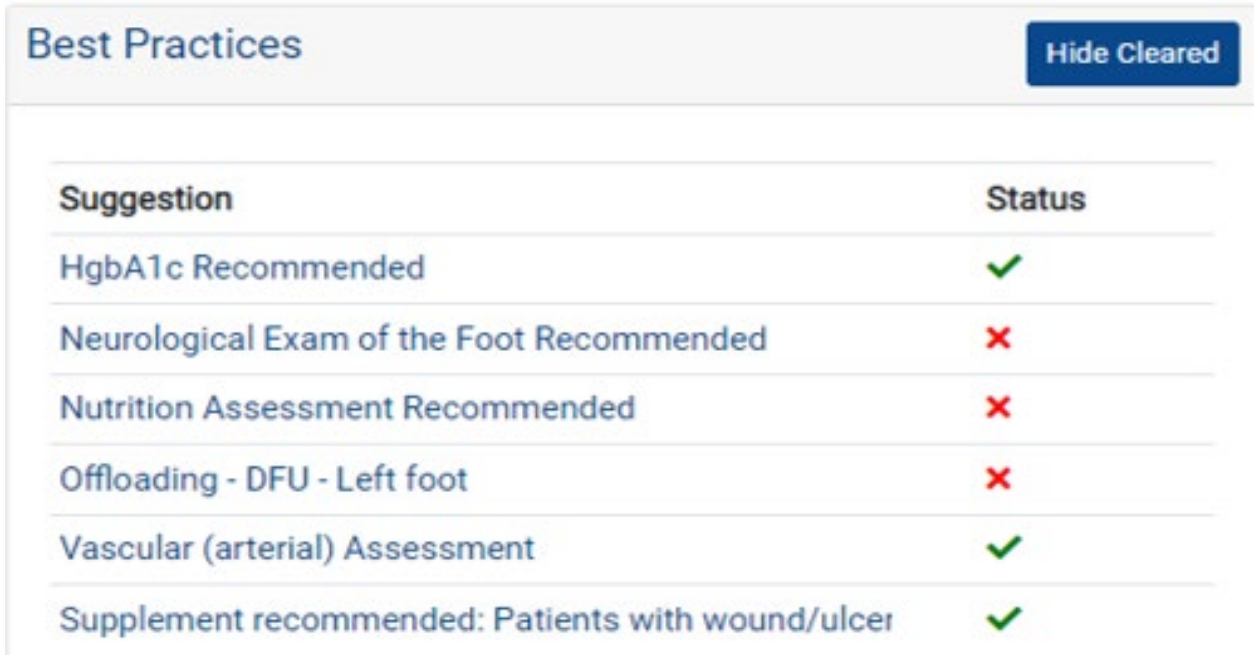
Without specific ICD10-CM codes for DFUs and arterial ulcers, "linked codes" must be created.

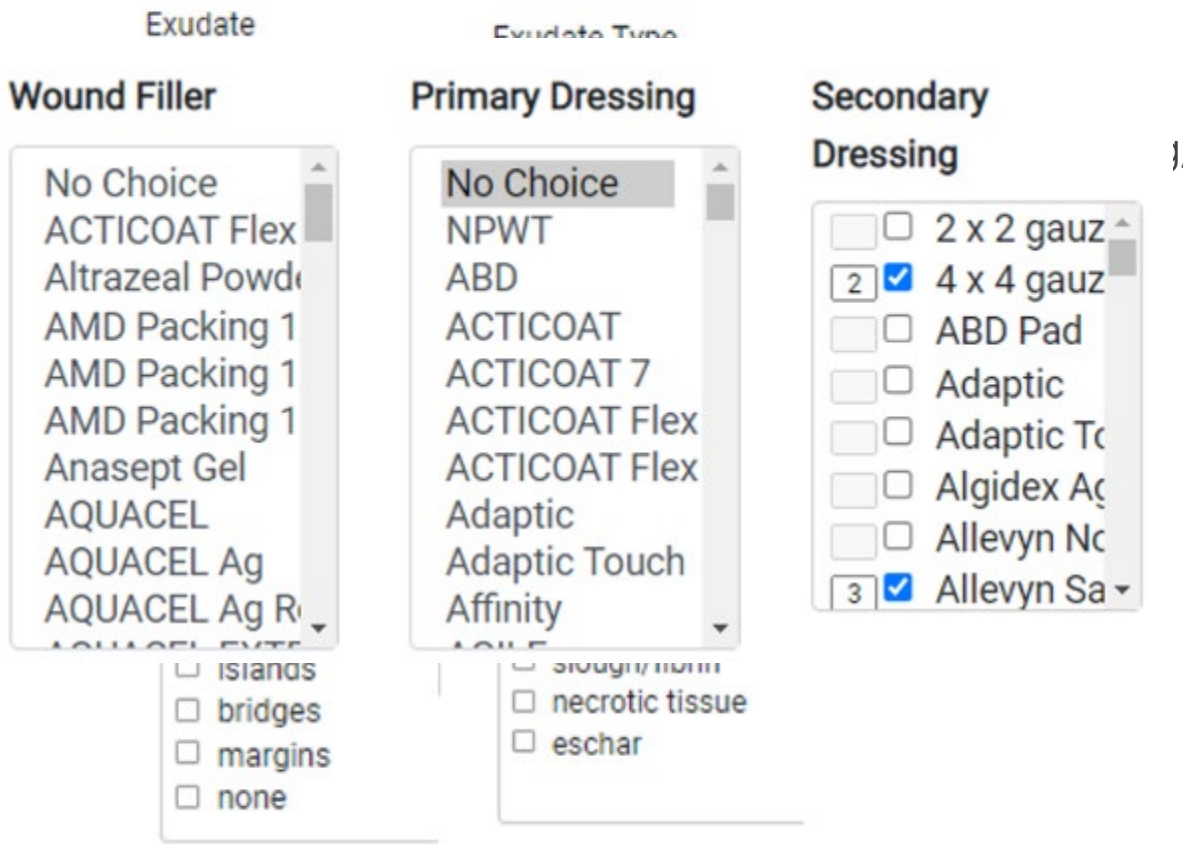



A DFU is identified with a combination of the code for diabetes and a chronic ulcer.

This means that research can be done knowing the clinician identified the problem as a "DFU."

# RWD requires collecting structured observational data and knowing whether SOC was provided



# Real world wound observations

- Exudate Amount – in wound-visits
  - None: 18%
  - Minimum: 28.8%
  - **Moderate: 46%**
  - Large: 7.1%

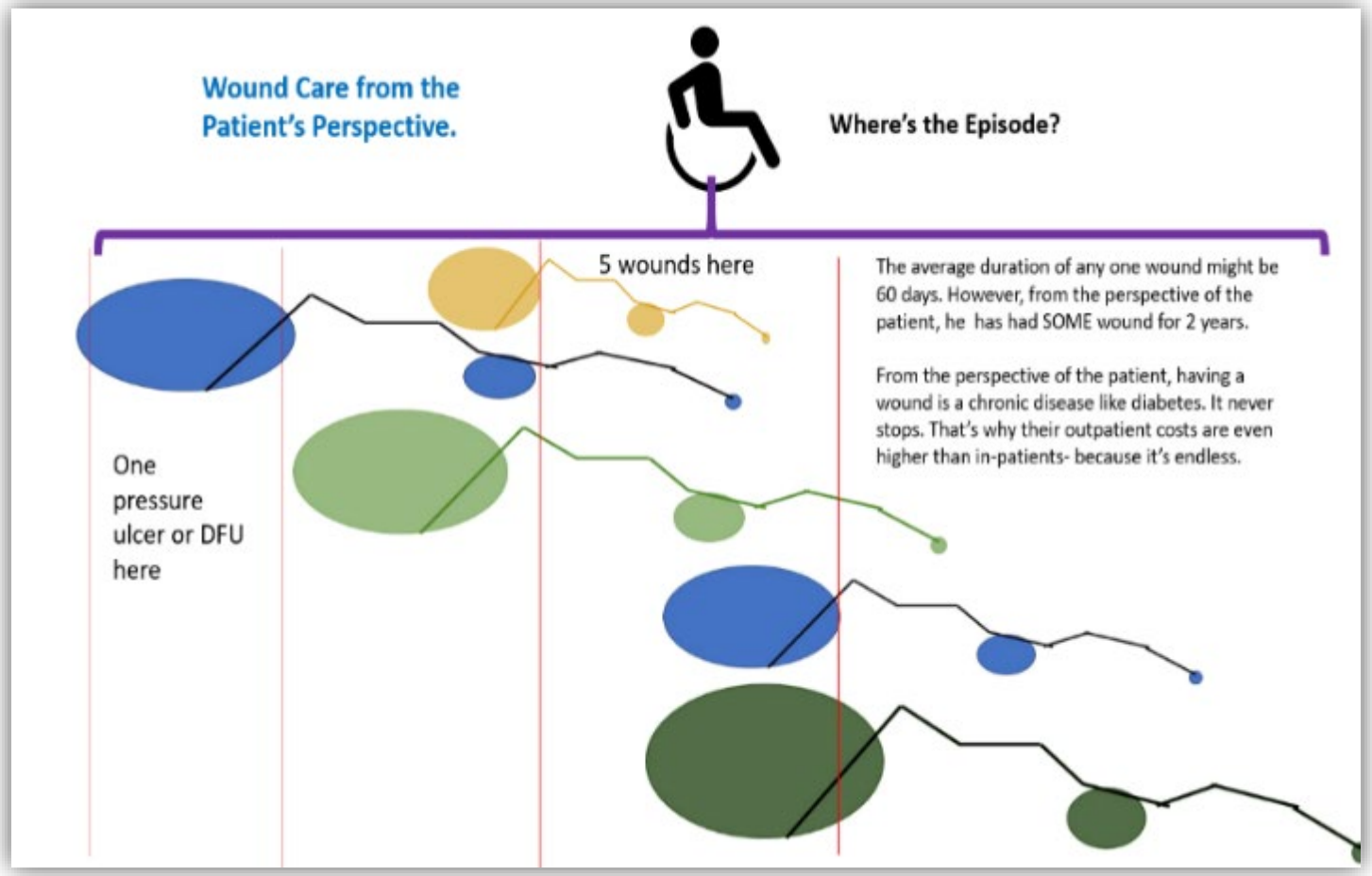
46.8% none to minimum

53.1% moderate to large

- Exudate characteristics:
  - Malodorous: 35%
  - Frankly bloody drainage since the advent of new oral anticoagulants

# We need the perspective of the patient and not the ulcer

- About 40% of patients get a new wound while still in service for the original one
- **Healing likelihood is inversely proportional to the total number of wounds present on the body**
- Wounds are rarely of the same type



# Reported "Healing Rates" are a fantasy

- A systematic analysis of 48 RCTs:
  - 2,620 control subjects; 2,624 wounds
  - Overall healing rate for controls: **40%**

In a systematic survey of wound center websites from all US States, 85% reported a **mean healing rate of 92%,** usually within 4.3 weeks.

**Inflated healing rates may represent the biggest threat to innovation.**

Controls in RCTs

- **PUs: 40.0%** **(2 trials)**
- **VLUs: 42.7%** **(20 trials)**
- **DFUs: 37.9%** **(26 trials)**

USWR at 12 weeks ~35%

- **PUs:** **29.6%**
- **VLUs:** **44.1%**
- **DFUs:** **30.5%**

USWR ~ 48% (no time limit)

- **56.9%**
- **43%**
- **45.1%**

https://www.liebertpub.com/doi/10.1089/wound.2017.0743

# Risk stratification is mandatory (It's the comorbid conditions that determine healing . . . )

- The DFU WHI score has a value of 0-100 and incorporates the following parameters:
  - ❑ Patient age
  - ❑ Patient ambulation score
  - ❑ Patient disposition at end of evaluation visit
  - ❑ Concurrent number of wounds
  - ❑ Patient on dialysis or is post-renal transplant
  - ❑ Patient has PVD
  - ➢ Wound area
  - ➢ Wound age
  - ➢ Wagner grade
  - ➢ DFU infection/bioburden status

**Patient Parameters**

**Wound Parameters**

Fife CE, Horn SD, Smout RJ, et al. Adv Wound Care 2016.

Development of a wound healing index for patients with chronic wounds

Susan D. Horn, PhD[1]; Caroline E. Fife, MD[2]; Randall J. Smout, MS[1]; Ryan S. Barrett, BS[1]; Brett Thomson, BS[2]

ABSTRACT

Development of a Wound Healing Index for Patients with Chronic Wounds. Wound Rep Reg. 21; 823-832, 2013.

A Predictive Model for Diabetic Foot Ulcer Outcome: The Wound Healing Index. Adv Wound Care. 5(7): 279-287, 2016.

# The WHI suggests that most subjects enrolled in CTP RCTs would get well on their own


2018 Unpublished data from USWR. Courtesy of Marissa Carter, PhD.

# USWR Data on the use of CTPs

- Date range: 2/1/2021 – 1/23/2024 (~33 months or 2.75 years)
- Clinics/practices/SNFs: 484 (majority HOPD)
- Practitioners: 879
- Patients: 116,926 patients *3.6 wounds/patient*
- Wounds/ulcers: 418,770 wounds
  - There were only ~2 concomitant wounds per patient on the date of CTP application
- CTP treated wounds: 5,544 (1.3% of all wounds/ulcers)
- CTP brands: 115 (analysis was brand agnostic)

# Inconvenient truths about Real-world CTP applications regardless of wound type

- Tissue type exposed on the date of application
  - **Sub Q: 53%** (compared to 34% of all wounds)
  - **Muscle: 7.1%** (2.1% overall)
  - **Tendon: 5.2%** (0.8% overall)
  - **Bone: 10.4%** (2% overall)
  - Others (unknown, epithelium, fascia, intact skin, adipose)
- Green/malodorous drainage
  - 3.1% (vs. 1.7% overall)

22.7% of applications (in which the procedure is properly documented) are over deep structures

# Inconvenient truths about Real-world CTP applications regardless of wound type

- Non-viable tissue
  - Not recorded: 10.7%
  - None: 3% (vs.7.5% overall)
  - 0 – 25%: 8.9% (vs. 7.1% overall)
  - 25-50%: 12.6% (vs. 7.4% overall)
  - **Over 50%: 64.7%** (vs. 25% overall)

77.3% of CTP applications (in which the procedure is properly documented) are in wounds with ≥ 25% necrotic tissue.

# CTP use by wound type

| Wound/Ulcer type | Overall % | CTP Rx % of that ulcer type |
|---|---|---|
| Chronic ulcer | 51,508 (12.3) | 1,070 (19.3) |

Overall, there are far more chronic ulcers than DFUs, but DFUs represent the wound type most commonly treated with CTPs, followed by VLUs (due to payer coverage).

# Ugly truths about Real World CTP use

- Wound Type (it's not DFUs and VLUs)
  - **We most need treatments for the "nameless wounds/ulcers"**
- Wound severity
  - **They are routinely applied over deep structures**
- Wound bed prep:
  - **They are routinely used over wounds with non-viable or necrotic tissue**
- Quality of Care:
  - **DFU off-loading on application visit: 44.4%** (2,987/6,724)
  - **VLU compression on application visit: 66.3%** (2,878/4,342)
  - (I am not presenting data on lack of arterial screening, lack of nutritional screening or other ways that LCDs are breached)

# Ugly truths about Real World CTP use

- **Patients have more than one wound at a time**
  - Overall: Median 2 (1-13; SD 1.4)
- **Each wound is bigger than most of the available products affordable in the HOPD**
  - Overall max *per wound*: Median **9.4 cm2**
  - At application: Median **3.7 cm2**

# Regardless of contributing factors, all wounds heal via an identical process

*Photos property of C. Fife, MD*

Ulcerated hematomas, dehisced surgical wounds, pressure ulcers, and neuropathic DFUs all heal the same way – granulation and then epithelialization.

# Diabetes does not a "diabetic ulcer" make

- Many patients with VLUs and pressure ulcers have diabetes.

*Photos property of C. Fife, MD Do not reproduce without permission*

Both these patients have diabetes. That does not make these *diabetic ulcers.*

# All of these diverse problems *are* "DFUs" – Most in the real world are Wagner 3 – not Wagner 1!




*Photos property of C. Fife, MD Do not reproduce without permission*

# Venous reflux does not a VLU make




All 3 of these were **originally coded as venous leg ulcers** because the patients have venous reflux.

**Between 25% and 50% of problems called "VLUs" in the real world are NOT venous ulcers.**

# We ignore a lot of VLUs in research

## >30 % of ulcers classified as venous can't be measured as discrete lesions

By the way, these are all of the same patient over a 2-year period.

# These acute *wounds/blisters* from edema will be coded as VLUs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Blisters are due to profound edema, usually acute on chronic heart failure, with or without sleep apnea. **They will be coded as "venous leg ulcers" so that needed compression bandaging is covered by payers.**

# All non-healing traumatic *wounds* are really *chronic ulcers*

A traumatic wound that has not healed in 30 days is supposed to be re-coded as a "chronic ulcer" but often continues to be called/coded as a traumatic wound.

# The future of innovation depends on risk stratification and honest outcomes reporting

This practitioner heals 70% of the ulcers that had a 25-50% chance of healing.

In this case, a 70% healing rate is a HUGE success.

The target for advanced therapeutics are not the wounds that are *expected to heal or those that can't be healed,* but the wounds that can be healed with intervention.