HARNESSING BIG DATA FOR WOUND HEALING RESEARCH: WHICH IS MORE RELEVANT IN THE QUEST FOR EVIDENCE:

REAL WORLD PATIENT CENTERED OUTCOMES OR RANDOMIZED TRIALS?

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May 25, 2016

ALLIANCE OF WOUND CARE STAKEHOLDERS
POWER THROUGH COLLECTIVE ADVOCACY

OVERVIEW

- Marcia Nusgart R.Ph.- Overview of Wound Care Research Issues
- Elise Berliner Ph.D.-The AHRQ Evidence Perspective- The challenge- why we need high levels of evidence and how we get it
- Caroline E. Fife, M.D.- Real World Data- Why RCTs are not the answer in Wound Care
- Marissa Carter Ph.D.-How to use Real World Data for Wound Care Research

ALLIANCE OF WOUND CARE STAKEHOLDERS
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ALLIANCE OF WOUND CARE STAKEHOLDERS

- Who is the Alliance?
  - *A non-profit multidisciplinary trade association of physician specialty societies and clinical associations whose members treat patients with wounds*
  - *Serves as an "umbrella" association for clinical organizations whose members treat patients with wounds*

- Mission of the Alliance:
  - *To promote quality care and access to wound care products and services for people with wounds.*
  - *Focus on compelling issues of commonality to the organizations in the reimbursement, government and public affairs affecting wound care.*

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CLINICAL ASSOCIATION MEMBERS

- American Professional Wound Care Association
- American Venous Forum
- American College of Foot & Ankle Surgeons
- American Podiatric Medical Association
- American Diabetes Association® Interest Group on Foot Care
- Undersea & Hyperbaric Medical Society
- American College of Hyperbaric Medicine
- Society for Vascular Medicine
- Society for Vascular Surgery
- American Association of Nurse Practitioners
- Dermatology Nurses Association
- American College of Wound Healing and Tissue Repair
- Academy of Nutrition and Dietetics
- National Association for Home Care and Hospice
- American College of Phlebology
- Association for the Advancement of Wound Care
- American Physical Therapy Association
- Visiting Nurses Association of America

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FOUNDATIONS OF ALLIANCE WORKPLAN

- Wound Care Quality Measures
- Wound Care Research
- Reimbursement Issues- Coverage, Coding and Payment
  - Submit Comments to Federal Agencies and their Contractors
    - Agency for Healthcare Research and Quality (AHRQ)
    - Centers for Medicare and Medicaid Services (CMS)
    - CMS Contractors-DMEMACs, A/B MACs
  - Serve as resource to CMS coverage, coding and payment staff for education about wound care

ALLIANCE OF WOUND CARE STAKEHOLDERS
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Development And Validation Of Guidelines For Clinical Research In Wound Care

Alliance for Wound Care Stakeholders' Panel On Wound Care Evidence Based Research (Alliance POWER panel), Thomas Serena MD,[1] Barbara M. Bates-Jensen, PhD,[2] Marissa J. Carter PhD MA,[3] Renee Cordrey PT MPH,[4] Vickie Driver MD,[5] Caroline E. Fife MD,[6] Paul Haser MD,[7] Diane Krasner PhD,[8] Marcia Nusgart RPh,[9] Adrianne PS Smith MD,[10] Robert J. Snyder[11]

[1]Penn North Centers for Advanced Wound Care, West Warren, PA, [2]School of Nursing & David Geffen School of Medicine, Div. Geriatrics, University of California, Los Angeles, CA, [3]Strategic Solutions, Inc., Cody, WY, [4]Program in Physical Therapy, The George Washington University, Washington, DC,[5]Clinical Research Foot Care, Endovascular and Vascular Services, Boston University Medical Center, Boston, MA, [6]Intellicure, Inc., The Woodlands, TX, [7]Div. Vascular Surgery, University of Medicine & Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, [8]Wound & Skin Care Consultant, York, PA, [9]Alliance of Wound Care Stakeholders, Bethesda, MD, [10]Chief Medical Consultant, Day & Zimmerman, Inc., San Antonio TX 78258, [11]Wound Healing Center, University Hospital and Medical Center, Tamarac, FL. Funded from an unrestricted educational grant from the Alliance of Wound Care Stakeholders. ***The investigators retained full independence in the conduct of this research.***

ABSTRACT

PURPOSE: To describe development and validation of a guidance document for stakeholders involved in clinical research in wound care. **DESIGN AND PARTICIPANTS:** A multidisciplinary panel of 11 wound care experts (POWER panel) generated a Preliminary Consensus Document consisting of 17 statements. A modified Delphi approach consisting of 2 web-based surveys was used to reach consensus on the statements and involved over 100 multidisciplinary wound experts. **METHODS:** The POWER panel contacted leadership of organizations with interest in wound care to invite their members to participate in the Delphi process. People interested in participating contacted the POWER panel directly. Only 2 organizations refused participation. Participants rated each of the 17 statements using a 4-point Likert scale. The *a priori* criterion for endorsement of a statement was greater than or equal to 90% of participants responding with "agree" or "strongly agree" to the statement. Statements with less than 90% agreement were reviewed and considered for revision by the POWER panel. **RESULTS:** 119 persons responded to the first Delphi survey (response rate 72%) and produced consensus on 5 of the 17 statements. 12 statements were reviewed, revised and sent to participants in the second Delphi survey. All statements were approved with 90% consensus with two Delphi surveys. **CONCLUSIONS:** The 17 statements provide guidance for the developers and users of new or existing products or devices or interventions, such as assessment techniques, care techniques, mobility/exercise, nutrition, treatment "bundles," or prevention regimens that are being used or will be used in the treatment of wounds, whether acute or chronic.

BACKGROUND

- Wound care research has been criticized because of methodological issues:
  - ✓ RCTs can be difficult due to expense, complicated study designs, and endpoint problems.
  - ✓ Controlled studies are necessary to initially determine efficacy, ***BUT*** may not be generalizable to "*real world*" wound care patients because many have multiple comorbidities or come from highly controlled trials.
  - ✓ Populations that are typically excluded from wound research usually receive multiple different treatments from inception to healing and investigators to define a set of principles to provide direction to all stakeholders involved in clinical research in wound care.

OBJECTIVE

- To address the problems in wound care research a multidisciplinary Panel on Wound Care Evidence-based Research (POWER panel)™ group was convened to develop guidelines in the form of principles to provide direction to all stakeholders involved in clinical research in wound care.

METHODS

DESIGN AND PARTICIPANTS:

- 11 wound care experts, the POWER panel, generated a Preliminary Consensus Document of 17 statements.
- 119 multidisciplinary wound care professionals participated in a modified Delphi approach consisting of 2 web-based surveys to reach consensus on the statements

METHODS:

- Leadership of 17 organizations with interest in wound care were contacted to invite their members to participate in the Delphi process. Those interested contacted the POWER panel directly (n=173); 2 organizations refused participation
- Participants rated each statement using a 4-point Likert scale, provided comments, and basic demographic and research background.
- The *a priori* criterion for endorsement of a statement was ≥90% of participants responding "agree" or "strongly agree" to the statement.
- Statements with <90% agreement and those revised by the POWER panel.

STATISICAL ANALYSIS:

- Proportion of panelists endorsing each item was calculated for responses to both questionnaires. Open-ended comments were content analyzed for general themes.

RESULTS

DELPHI ROUND 1

- 119 of 173 initial respondents completed the survey (68% response rate)
- 4 statements were not endorsed (8,9,10,11); did not require revision; 12 revised.
- Comments focused on application of the statements (i.e., use in different situations), objection to specific words or phrases or content (i.e., lack of clarity), or disconnects (i.e., more than one principle embedded in the statement).
  - Revision largely based on use of specific words or contextual use of the statement.

DELPHI ROUND 2

- 80 completed the survey (46% response rate).
- 14 statements rated; only statement 9 was not endorsed; 5 statements needed revision(4,5a,8b,9,11)

RESULTS

Table 1: Participant Demographics & Background

Characteristic	N (%)
Gender	
Male	54 (47.8)
Age (y)	
18-25	2 (1.8)
26-35	7 (6.3)
36-45	22 (19.6)
46-55	46 (41.1)
56-65	29 (25.9)
> 65	6 (5.4)
Location (region)	
New England	11 (9.9)
Mid-Atlantic	18 (16.2)
East North Central	14 (12.6)
West North Central	5 (4.5)
South Atlantic	24 (21.6)
East South Central	4 (3.6)
West South Central	16 (14.4)
Mountain	11 (9.9)
Pacific	8 (7.2)
Primary wound-related work setting	
Wound care clinic	27 (23.9)
Other outpatient setting	8 (7.1)
Home health agency	1 (0.9)
Long term care	6 (5.3)
Hospital	21 (18.6)
Long term acute care/subacute facility	3 (2.7)
Academic	18 (15.9)
Industry/manufacturer	16 (14.2)
Other	13 (11.5)
Role	
Administration/management	9 (7.8)
Educator	9 (7.8)
Licensed practical/vocational nurse	1 (0.9)
Physical therapist	5 (4.3)
Physician	31 (27.0)
Podiatrist	19 (16.5)
Registered nurse	11 (9.6)
Researcher/scientist	17 (14.8)
Other	13 (11.3)
Years involved in wound care research	
≤ 2	6 (5.3)
3-5	16 (14.2)
6-10	18 (15.9)
11-20	32 (28.3)
> 20	26 (23.0)
Not in involved in wound care research	15 (13.3)
Years involved in wound care clinical practice	
≤ 2	2 (1.8)
3-5	6 (5.3)
6-10	19 (16.8)
11-20	44 (38.9)
> 20	29 (25.7)
Not in wound care clinical practice	13 (11.5)

DISCUSSION POINTS

- Statement 4 focused on new products and devices entering the wound care market are derivations of previously marketed products that have known safety and efficacy profiles based upon FDA–evaluated research.
  - The panel suggests, therefore, that initial research could be cohort designs (i.e., observational studies) to fulfill the requirement of efficacy in products or devices that are modifications of existing products or devices; later trials could use more sophisticated designs.
- Statement 5 is that most experimental designs focus on a single intervention when distinguishing the experimental from the control group with "usual care."
  - However, wounds heal via a series of sequential and overlapping phases, and may have multiple contributory factors. Chronic wounds, therefore, often require multiple

Minimum Criteria to be Included in Wound Care Studies

include in any research design:
Age
Gender
Social status (as appropriate; e.g., socioeconomic status, education level, married vs. single, rural vs. urban, lives alone or with others)
Acuity score (if appropriate and available)
Ethnicity/race
Comorbid medical conditions (as appropriate).
ADLs and functional measures
Health habits (e.g., nutritional status, exercise, tobacco, alcohol, and drug abuse)
Additional measures as appropriate.

Wound etiology
Wound duration (prior to assessment/treatment)
Compression (for venous leg ulcers)
Offloading (for pressure and diabetic ulcers)
Debridement (frequency, types of debridement)
Moist wound healing (type of treatment)
Vascular assessment (how accomplished)
Surface area measurement (e.g. length x width, and method of measurement)
Evaluation of tissue depth (how measured; whether measured in size or involvement of tissue)
Location of the wound
Tissue types
Bacteriology as appropriate
Use of validated tools
Research-based standard wound assessment.
Other criteria as appropriate.

Table 2: Final 19 Statements on Wound Research

1. The need for a guidance document in the field of wound care research.
2. Wound care researchers, product developers, manufacturers, policy makers, payers, clinicians, and consumers should be educated on wound care research guidelines.
3. All human wound care research conducted in the United States should follow the principles of Good Clinical Practice (GCP) in accordance with FDA regulations.
4. The study design of research conducted in wound care should be matched to its purpose.
5. Wound care clinical research should include evaluation of simultaneous and/or sequential interventions when appropriate.
6. Wound care research should incorporate a multidisciplinary approach whenever possible.
7. Research design should include parameters that are appropriate for the type of the study.
8. Primary endpoints in wound care research need to reflect both the goals of the intervention and clinical practice.
9. Study design should be reviewed.
10. Study design should be open to amendment.
11. Quantitative wound care studies should include a run-in period as part of the initial assessment when it is appropriate.
12. The rationale for inclusion and exclusion criteria in wound care research should match the goals of the study but the generalizability of the results to wound care populations should also be spelled out.
13. Highly vulnerable populations are under-represented in clinical wound care research practice and should be included where feasible.
14. The definitions for intervention(s) provided to the comparator groups in any clinical study, typically defined as "moist wound care" or "usual care," need to be explicit.
15. An appropriate but comprehensive dataset should be included in the research design to describe the participants.
16. An appropriate but comprehensive dataset should be included in the research design for any study that involves wound evaluation.
17. Clinical wound care research should include rates of recurrence where feasible.
18. National or formal wound registries should be developed with real-world data collection.
19. Cooperative groups, composed of multiple researchers working in concert, should be formed in order to facilitate and optimize wound care research.

CONCLUSIONS

The statements provide guidance for developers and users of new or existing products, devices or interventions, such as assessment techniques, care techniques, mobility/exercise, nutrition, treatment "bundles," or prevention regimens that are being used or will be used in the treatment of wounds.

WHY THE EMPHASIS ON CHRONIC WOUND CARE?

- Chronic wound care includes many different etiologies:
  - Diabetic foot ulcers
  - Venous Stasis ulcers
  - Pressure ulcers
  - Arterial ulcers
- Chronic wound care is a severe economic burden in the U.S.– perhaps 5% of the total Medicare budget
  - VLU- affect 2% of the population in U.S. costing $1.5-3 B dollars annually
  - Diabetic foot Ulcers: ~$13B annually
  - Pressure Ulcers-- $12B annually

Prevalence is approximately 8% of the total U.S. population which is about the same as heart failure –only without the same investment in research

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WHY THE EMPHASIS ON CHRONIC WOUND CARE?(cont.)

- Wound care patients are difficult to study due to:
  - Co-morbidities
  - Guideline suggested interventions but there are many combinations of individual wound characteristics
  - Order and combinations of treatments used are varied

- Many different wound care technologies
  - Pressure ulcers- surgical dressings, support surfaces
  - Venous ulcers- compression bandage systems, compression hosiery, surgical dressings
  - Diabetic foot ulcers- total contact casting, negative pressure wound therapy, cellular and/or tissue based products for wounds, surgical dressings

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The AHRQ Evidence Perspective- The challenge- why we need high levels of evidence and how we get it

Elise Berliner, Ph.D.

Why Randomized Controlled Trials?

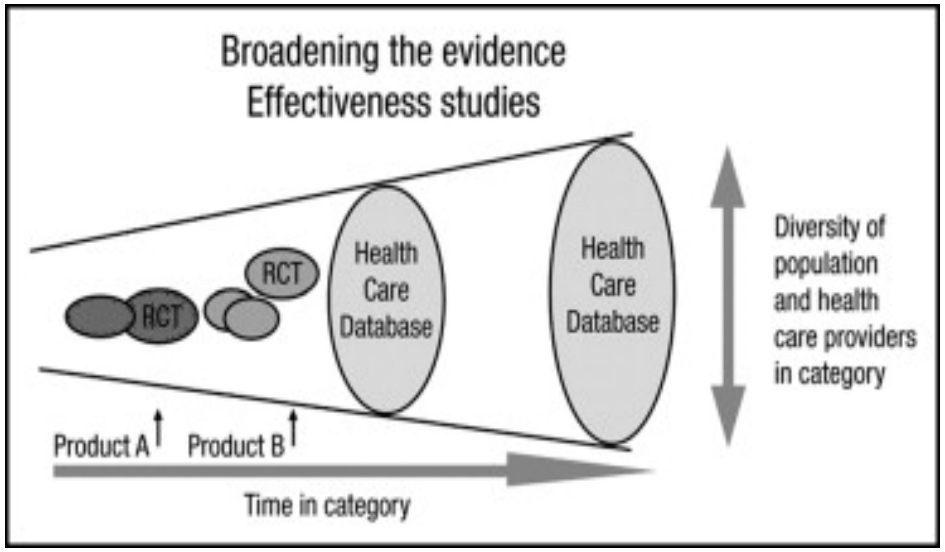
- The observed benefit or harm with the intervention compared to alternatives is due to the intervention itself and NOT to confounding characteristics of the patient, setting, etc.

- Understanding of all potential variables is key

"Randomization properly carried out…relieves the experimenter from the anxiety of considering and estimating the magnitude of the innumerable causes by which his data may be disturbed"

R.A. Fisher 1935

Why Clinical Trials Often Don't Measure Effectiveness



- Difficult to capture real-world complexity in an RCT
  - Multiple simultaneous variables
  - Restrictive patient selection criteria
  - Adherence to protocol in RCT not equivalent to practices in community practice

Figure from: Silverman SL 2009. From Randomized Controlled Trials to Observational Studies. American Journal of Medicine 122 page 114.

Evaluating the Impact of Database Heterogeneity on Observational Study Results

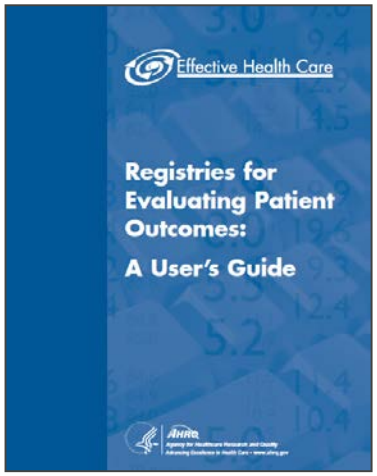
Estimated Relative Risks from the New User Cohort Design

Databases Differed by:

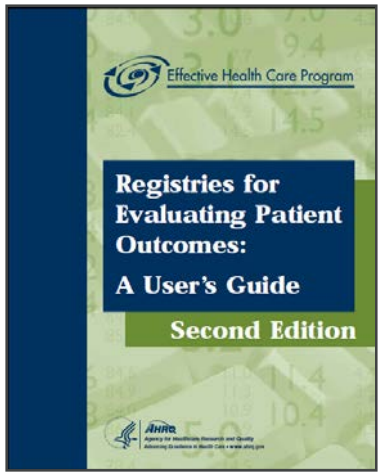
- Covered populations
- Completeness of the data capture
- Patient susceptibility to adverse events
- Accuracy of the recorded information

Madigan et al. (2013) Am J of Epidemiol 178: 645-651

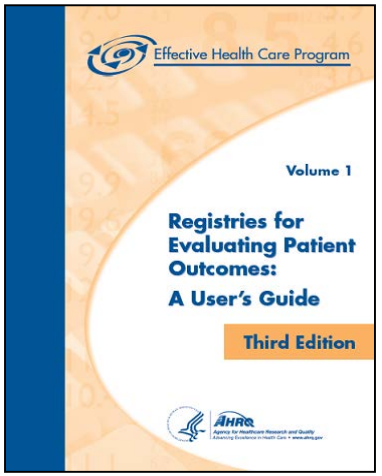
Driving Consistency and Quality in Patient Registries



1st edition, 2007



2nd edition, 2010



3rd edition, 2014

4th edition, 2018

Gliklich RE, Dreyer NA, Leavy M, eds.

Registries for Evaluating Patient Outcomes: A User's Guide

3rd edition. Two volumes. AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014.

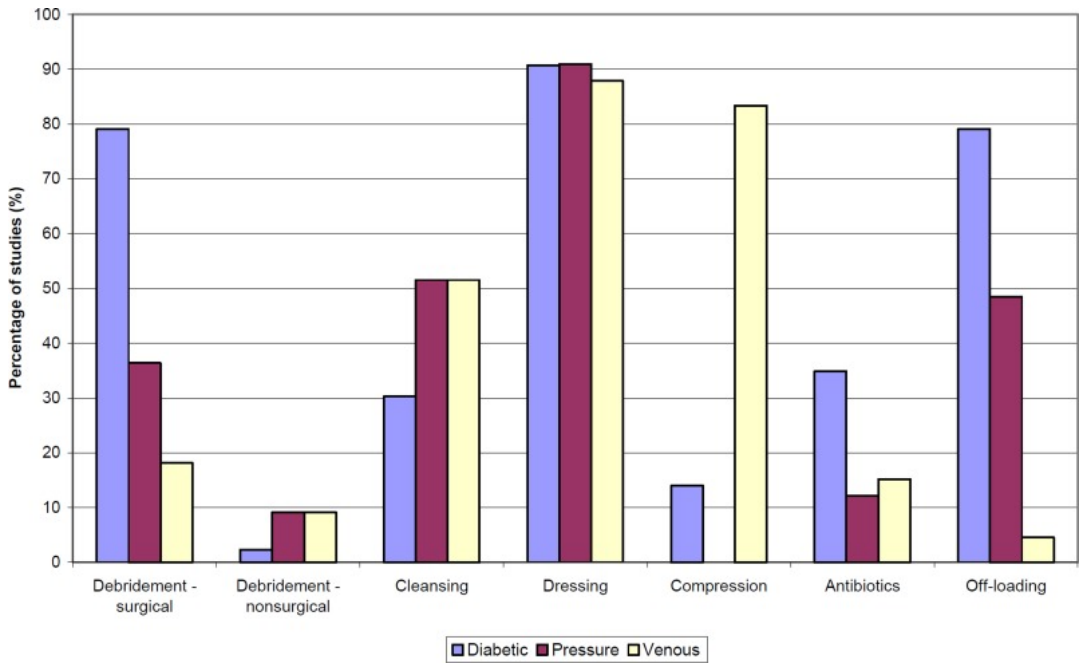
Available online, in e-book format, or in print at: http://www.effectivehealthcare.ahrq.gov/registries-guide-3.cfm

Many Variables in Evaluating Effectiveness

- Patient population
  - Defining wound and patient characteristics that impact effectiveness
- Protocol of use/Provider variables
  - Characterizing variables in provision of the intervention
- Timing of use
  - Impact of complex series of prior, concurrent, and subsequent interventions on outcomes
- Outcome assessment
  - Wound healing, recurrence
  - Blinded assessment needed?

Basic Wound Care Modalities

- Basic modalities of wound care include: cleaning, debridement, dressings
- These modalities are often not done (or reported?) in clinical trials, are they done in clinical practice?



Usual Care in the Management of Chronic Wounds: A Review of the Recent Literature [Internet]. Lau J, Tatsioni A, Balk E, et al. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Mar 8.

Advanced Treatments

- Is benefit attributed to the advanced treatment or variation of application of basic modalities or one or more of the advanced treatments or combination?
  - Advanced support surfaces or bed technologies
  - Advanced surgical dressings
  - Cellular and/or tissue based products for skin wounds
  - Hyperbaric oxygen
  - Negative Pressure Wound Therapy

Question:

- Can we collect detailed and standardized information across patients, settings and treatments to understand which factors lead to improved outcomes?

Real World Data- Why RCTs are not the answer!

Caroline E. Fife M.D.

Exclusion criteria for all wound RCTs 1996 – 2006

- For DFU studies, no ulcers > Wagner Grade II
- Diabetes as a co-morbid condition for any study other than DFU
- Venous stasis except in VSU trials
- Alcohol/drug abuse
- Anticoagulant treatment
- Cellulitis or local wound infection
- Cancer or recent cancer treatment
- Collagen vascular disease/connective tissue disease
- Rheumatoid arthritis/autoimmune disease, any type
- Scleroderma/lupus, any autoimmune disease
- Charcot foot changes in DFU
- Corticosteroid treatment any reason
- Deep venous thrombosis/pulmonary embolus
- Gastrointestinal disease of any kind /any Liver disease/Hepatitis
- Renal impairment/ESRD/Renal dialysis/Renal transplant
- Any organ transplant
- In diabetics, HbA1c > 8-10
- Nutritional impairment/Albumin < 3.0 mg/dl
- Osteomyelitis
- Peripheral arterial disease

These are common to all studies but some have additional ones

RCT Subjects vs. Real Patients with Wounds

- Among 8,611 wound center out-patients, > 50% would have been excluded from 15/17 major RCTs that brought novel products to market (1996- 2006)
  - 88% wound related RCT patients would be excluded at the "first pass"
- 3 of 4 major trials bringing new products to market enrolled patients healthier than the "girl on the street" based on utility scores.

"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.

Typical RCT subjects?

U.S. WOUND REGISTRY

Typical Chronic Wound Patient (n=8,611)

- Ave. age: 60.4 years
- Ave. wound duration at consultation: 189 days (6 months)
- Ave. co-morbid conditions = 6
  - 16% with CAD
  - 10% current smokers
  - 8.4% on prednisone
  - 5% have renal failure or transplant
  - 26% of wounds that were not specifically diabetic foot ulcers were in patients who had diabetes
- 54% of wounds were considered "infected"

Image off the internet

USWR data, 8,611 patients (15,499 wounds) from the U.S. Wound Registry

U.S. WOUND REGISTRY

Exclusion criteria in wound healing RCTs have real world implications

Novitas "LCD" for Bioengineered Skin Substitutes

NOVITAS SOLUTIONS
INNOVATION IN ACTION
A CMS CONTRACTOR • ISO 9001:2008 CERTIFIED

https://www.novitas-solutions.com/policy/jh/l32622-r4.html

LCD L32622 - Bioengineered Skin Substitutes

Print

Contractor Information

Contractor Name:	Contractor Number(s):	Contractor Type:
Novitas Solutions, Inc.	04911, 07101, 07102, 07201, 07202, 07301 [illegible]02, 04111, 04112, 04211, 04212, 04311, 04312, 044[illegible]04412	MAC Part A & B

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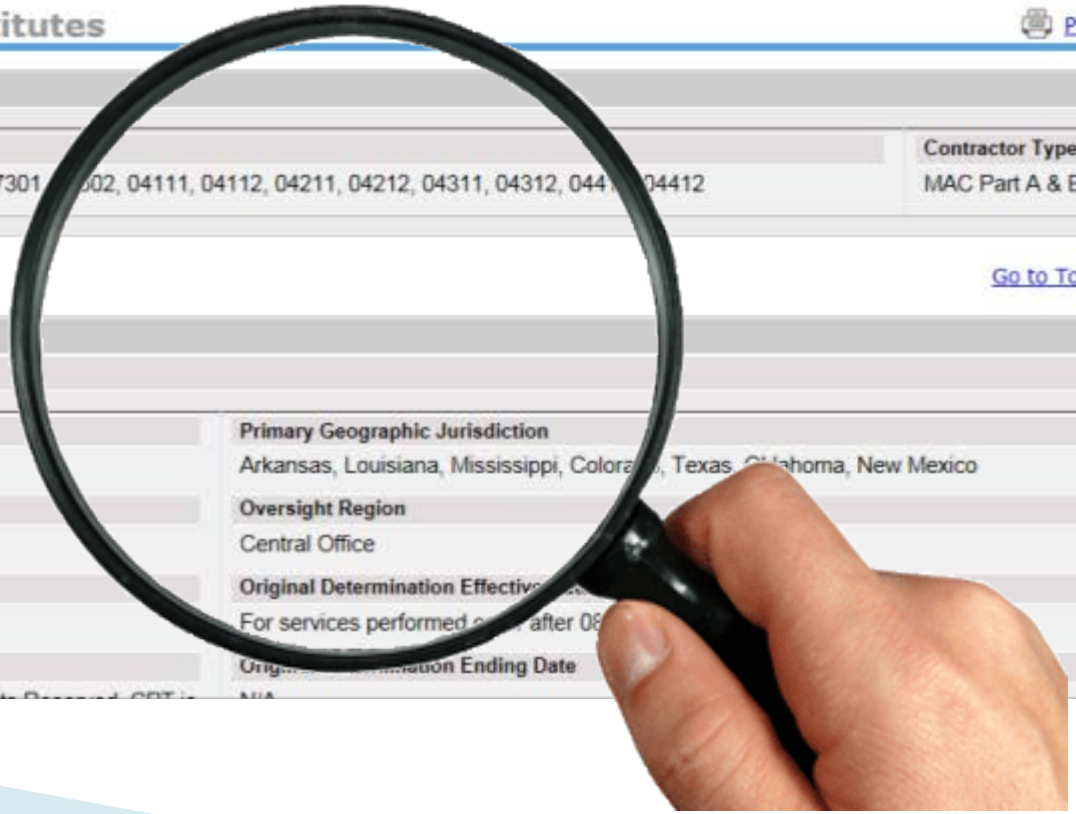
LCD Information

Document Information

LCD ID Number	Primary Geographic Jurisdiction
L32622	Arkansas, Louisiana, Mississippi, Colora[illegible], Texas, Oklahoma, New Mexico
LCD Title	**Oversight Region**
Bioengineered Skin Substitutes	Central Office
Contractor's Determination Number	**Original Determination Effectiv[illegible]**
L32622	For services performed [illegible] after 08
AMA CPT/ADA CDT Copyright Statement	**Ori[illegible]nation Ending Date**
CDT only copyright 2002-2014 American Medical Association. All Rights Reserved. CDT is	N/A



Coverage policy mirrors RCT Exclusion Criteria

- ". . . 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/oxyg
- ". . .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

Quoted from the Novitas LCD on skin substitutes

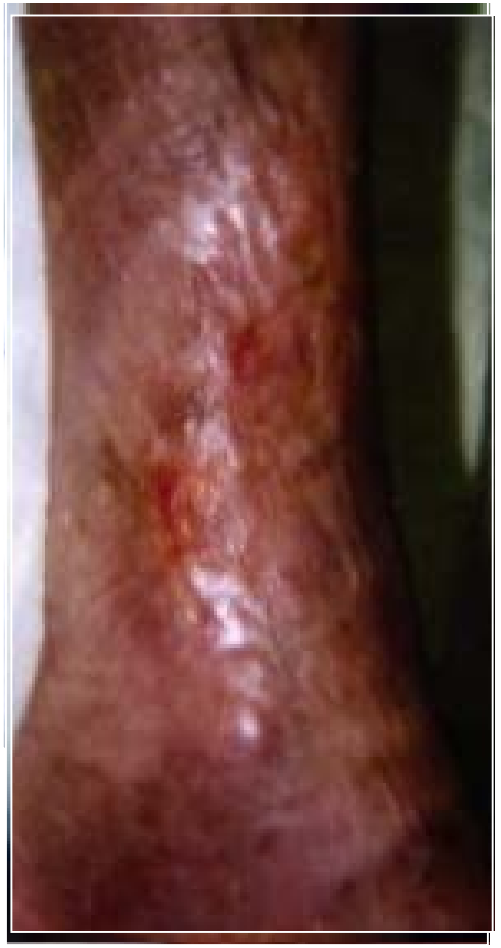
https://www.novitas-solutions.com/policy/jh/l32622-r7.html

Product use exclusions, the identical twin of the RCT exclusions

Meet a Typical Leg ulcer patient

72 y.o. woman with a *5 month* history of leg ulcer from minor trauma—*3 exclusions for a cellular based product*

1. **Rheumatoid arthritis**
2. **On prednisone and methotrexate**
3. **Poorly controlled diabetes**



Healed with a cellular based product that was used inappropriately based on the Novitas Local Coverage Determination (LCD) policy.

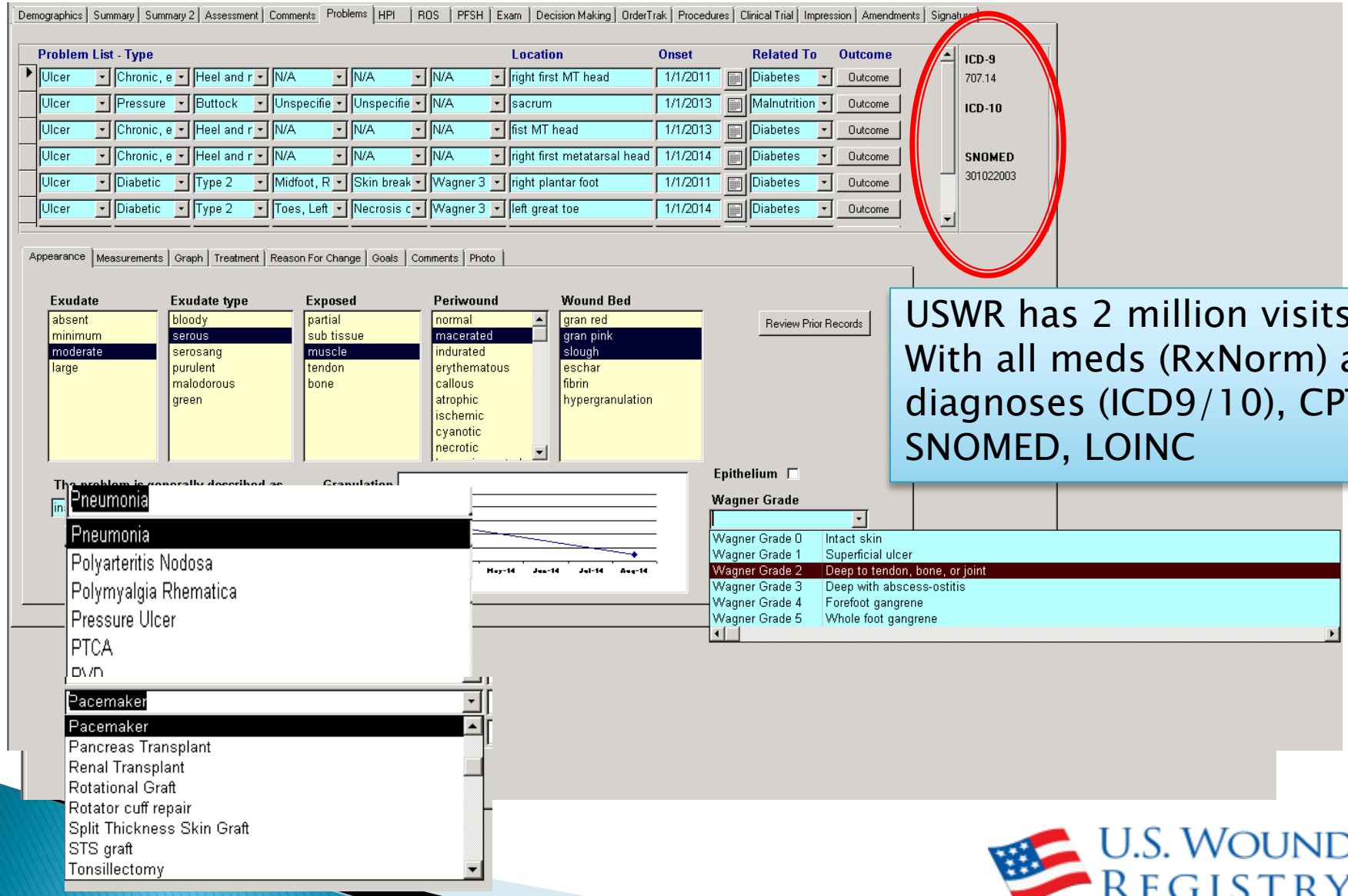
Because of the way these studies are performed, the patients who need these products can't have them.

Real World Trials (e.g. cohort trials enrolling risk stratified sick people) are the way forward

- We MUST HAVE generalizable trials
  - We must know if new products work in usual patients
  - We must have coverage policies that allow products to be used on the patients who need them
- We need data collected in a uniform way
- We need an INCENTIVE for providers to transmit data
  - The US Wound Registry (USWR) is harnessing PQRS and Meaningful Use (MU) mandates to obtain needed

https://www.uswoundregistry.com/specifications.aspx

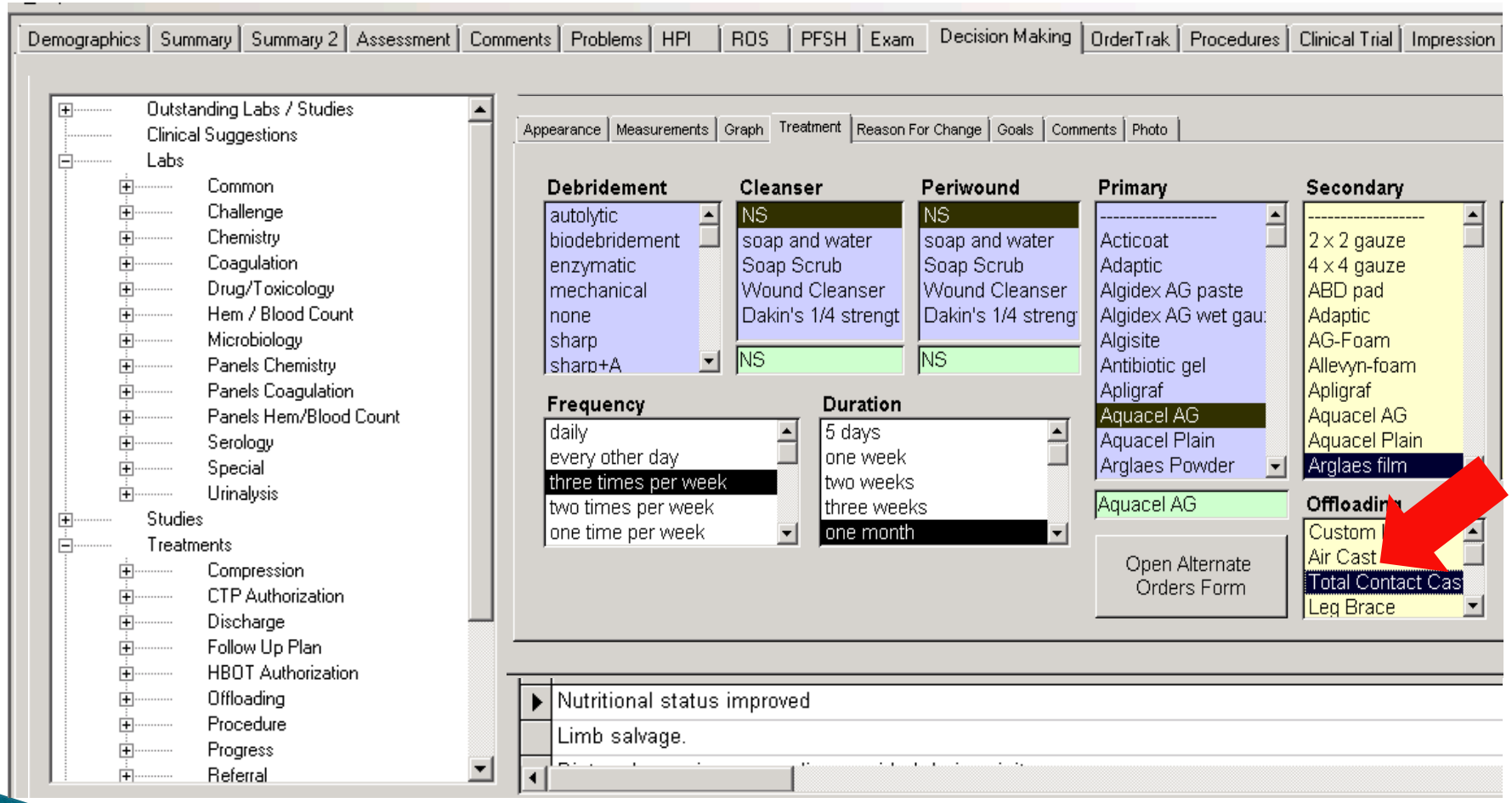
More than 120 Hospital based outpatient wound centers agree to collect data in a structured format and share it for benchmarking and research



USWR has 2 million visits
With all meds (RxNorm) all diagnoses (ICD9/10), CPT, SNOMED, LOINC

U.S. WOUND REGISTRY

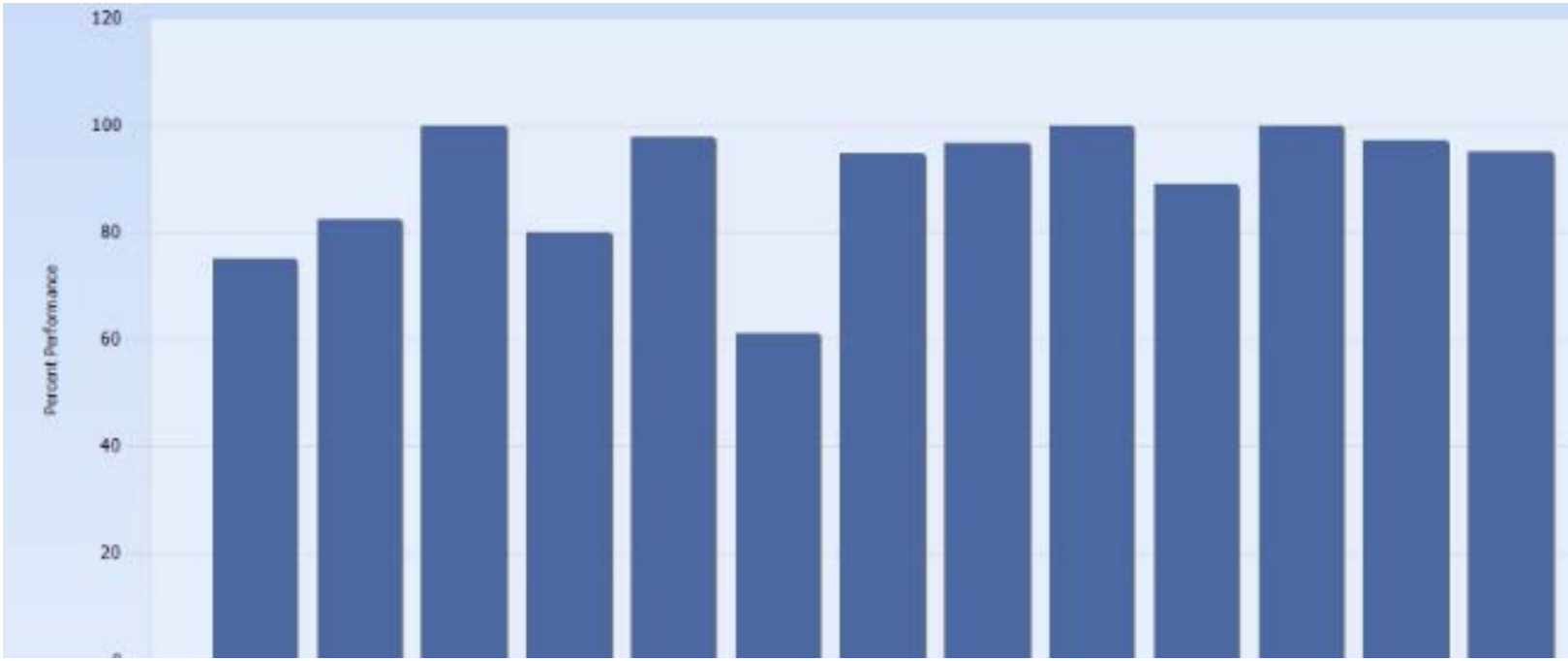
Clinical Decision Support Drives Consistent Evidence Based Care and PQRS Success



Once the clinician documents off-loading on the problem tab, the off-loading clinical suggestion disappears.

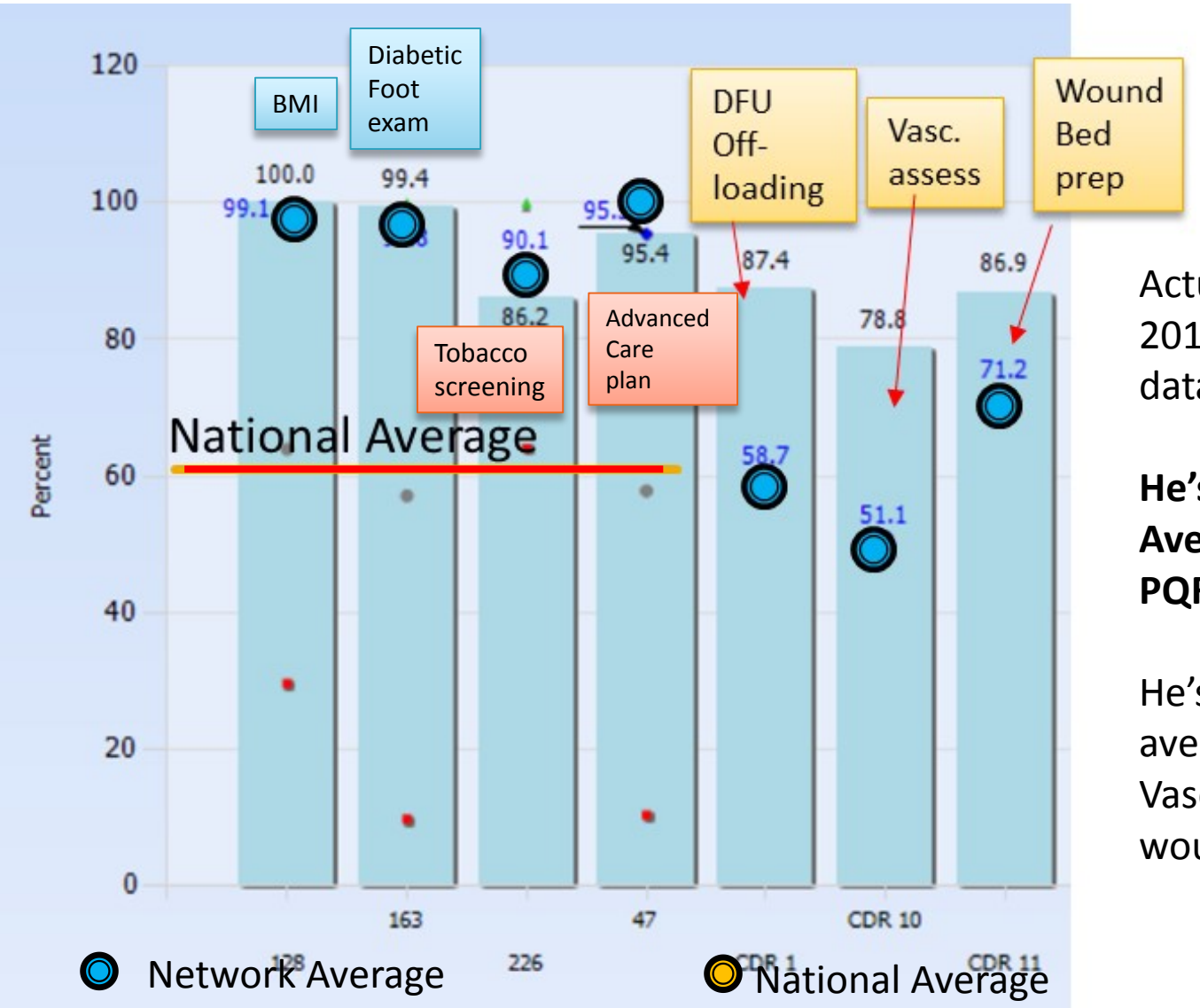
% of diabetic foot ulcer visits with adequate off-loading (by Provider at a large hospital system)

How Consistent Care is Ensured to make real world data more useful



Individual Providers at one institution

Good Care = Value Based Compensation = Reliable Data for Research



Actual data from an MD's 2015 PQRS performance data.

He's above the National Average on all national PQRS measures.

He's above the Network average for DFU off-loading, Vascular assessment and wound bed prep.

Real World Data in wound care harnessing PQRS and MU requirements

- The Wound Healing Index (WHI)– 7 mathematical models that allow risk stratification of the major wound categories (venous, pressure, DFUs, surgical, etc.)
- US Wound Registry (USWR) is a Qualified Clinical Data Registry (QCDR); develops quality measures in wound care
- Clinicians transmit data via eCQMs (for PQRS credit) and Continuity of Care Documents (CCDs) to meet requirements of Objective 10 of Meaningful Use.
- Clinicians obtain benchmarking services
- Data are used for CER
  - **Is it possible to get clear answers from messy real world data?**

1. Development of a wound healing index for patients with chronic wounds. SD Horn, CE Fife, RJ Smout, RS Barrett, B Thomson, WWR, Volume 21, Issue 6, pages 823–832, Nov-Dec 2013.
2. A predictive model for pressure ulcer outcome: the Wound Healing Index. SD Horn, RS Barrett, CE Fife, B Thomson, Adv Skin Wound Care. 2015 Dec;28(12):560-72.
3. A Predictive Model for Diabetic Foot Ulcer Outcome: The Wound Healing Index. Fife Caroline E., Horn Susan D., Smout Randall J., Barrett Ryan S., and Thomson Brett. Advances in Wound Care. November 2015 (open access).

U.S. WOUND REGISTRY

How to Use Real World Data for Wound Care Research

Marissa Carter Ph.D.

Alternatives to "Conventional" RCTs for Generating Inputs for Health Economics

- Pragmatic RCTs
- Cohort designs
- Cohort multiple randomized controlled trial
- Waiting list trial design
- Patient-selected controlled trial
- Retrospective analyses from registries or large healthcare databases

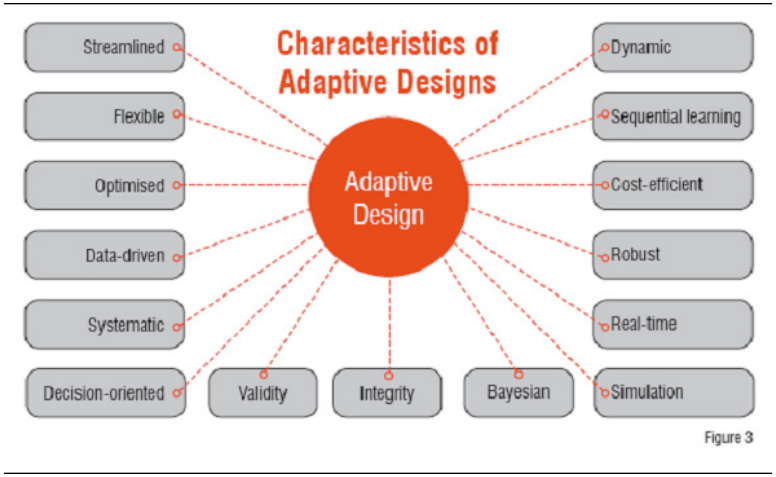
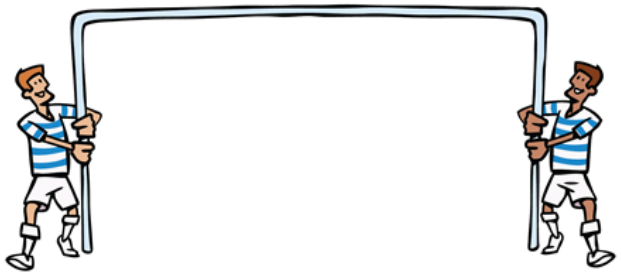


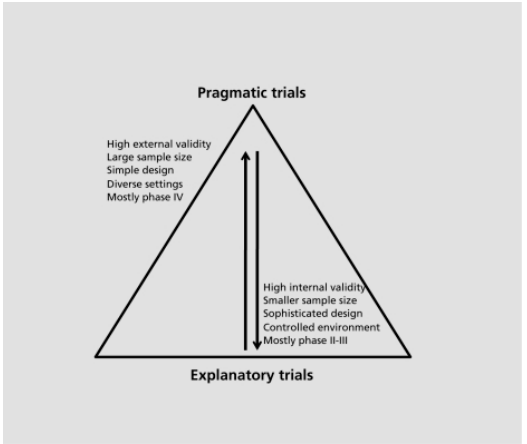
Figure 3

The Pragmatic RCT

- Pragmatic RCTs are designed to more mimic real world life and practice while retaining controlled trial characteristics
- Typically inclusion and exclusion criteria are much wider or looser ("opening the goalposts")
  - Health economic analyses may be more realistic
  - Sample size has to be much larger than usual
  - May be very costly if study period is >12 weeks
  - Doesn't address patient/trial fatigue for control group(s) unless crossover permitted

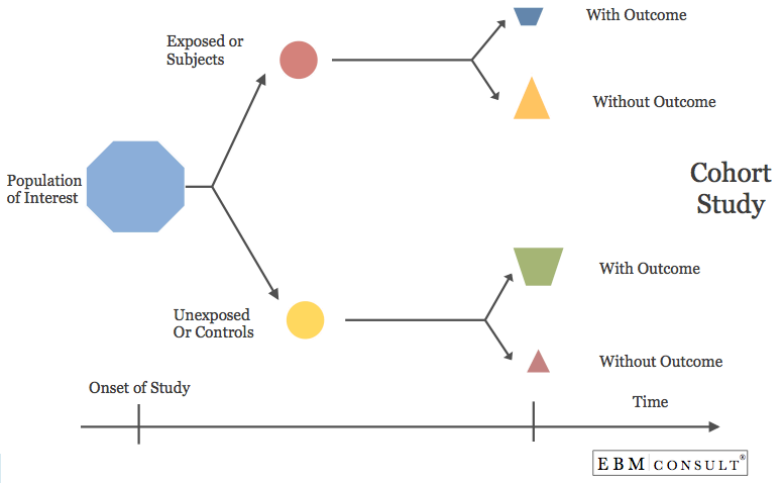
Patsopoulos MA. Dialogues Clin Neurosci 2011;13:217-24.





Classic Cohort Designs

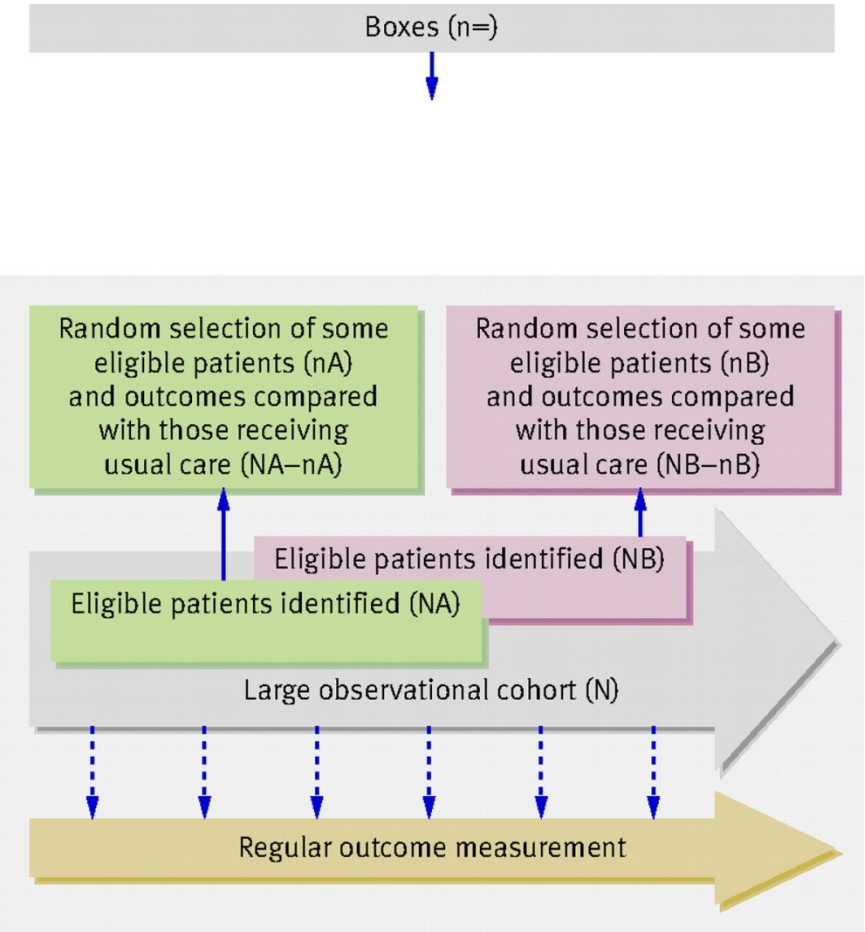
- Can define populations to be observed, as well as treatments
- Much cheaper than RCT
- Can collect cost data concurrently
- Sample size has to be based on reasonable outcome estimates and statistical power
- Much longer study times can be used, **BUT** may start to lose large numbers of patients
- Requires sophisticated statistical analysis



The Cohort Multiple Randomized Controlled Trial

- Large observational cohort of patients with problem is recruited (N)
- Outcomes regularly measured.
- For each RCT identify all eligible patients from cohort (NA).
- Some eligible patients (nA) are randomly selected and offered intervention.
- Outcomes of randomly selected patients (nA) compared with NA.
- Process can be repeated for further RCTs

Relton C, et al. BMJ 2010;340:c1066.



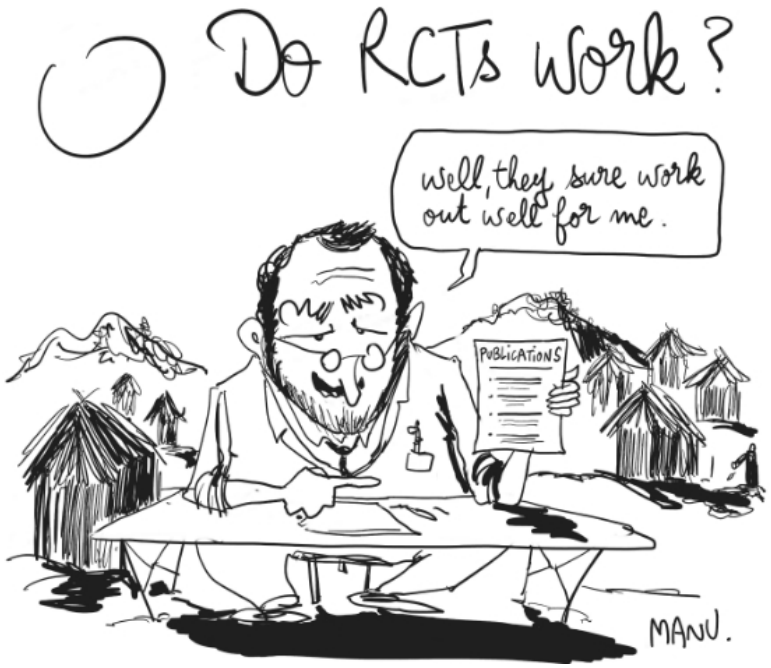
The Waiting List Trial Design

- Randomly assign the same intervention now or later
- Solves problem of losing patients in trial because the feel they are "not getting the good stuff"
- A variant called dynamic wait listing permits random assignment to intervention condition multiple times in a trial (alternative to cluster randomization)
- Could also use a cohort setting in which a case finding determines allocation (e.g., higher risk of amputation)
- Health economic analysis looks at delay; important because in most RCTs the intervention arm(s) has no delay

Brown CH, Wyman PA, Guo J, Peña J. Clin Trials 2006;3:259-71.

The Patient-selected Controlled Trial

- New proposal designed to address enrolment/patient retaining issues
- Patients would either be happy with random allocation (interventions/SOC) or select the arm they most want to be in based on their understanding of risk and with physician input
- Distribution to the study arms objectively measures equipoise.

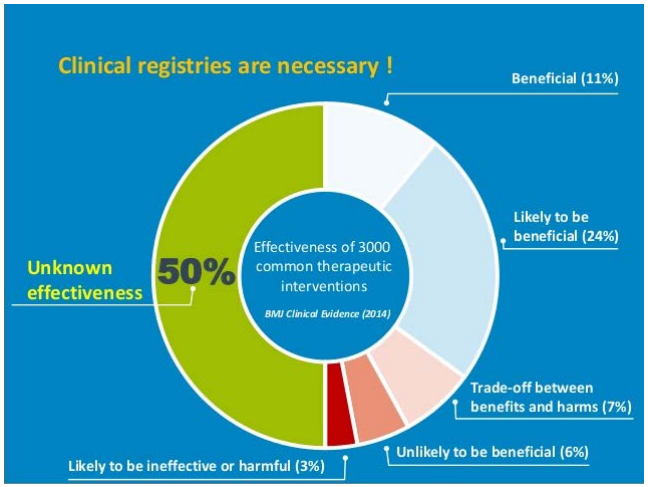


Omel J & Schwartz K. ASCO Post 2014;5(9).

Retrospective Analyses from Registries or Large Healthcare Databases

- Real world data
- Relatively cheap to conduct compared to clinical trial
- Need to define:
  - Intervention/control populations
  - Outcomes and study time period
- Need to adjust outcomes for wound severity and patient comorbidities; **challenging!**
- Missing data may be a big problem

Malmenäs M, Lowton K, Morin I, et al. ISPOR. Available at: https://www.ispor.org/sigs/PR/Analysis-of-Effectiveness-in_patient-registry-data.pdf



Propensity Score Approach

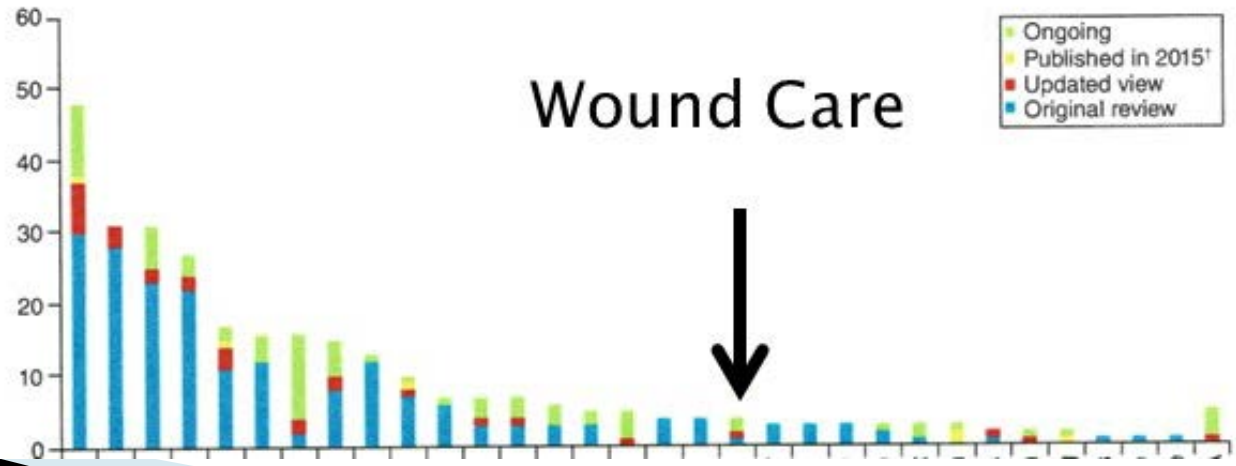
- Propensity scoring uses group membership (treatment, for example) within logistic regression based on entered covariates
- In wound care analyses, can control for variables related to wound severity and patient comorbidities
- Cannot control for what cannot be measured or missing confounders
- Overconditioning/overfitting are potentially serious problems that are often glossed over and can generate considerable bias
- Many matching algorithms possible based on scores
- The overlap issue is paramount
- Other alternatives include discriminant function analysis, regression trees, or neural networks.

Patorno E, Grotta A, Bellocco R, et al. Epidemiol Biostat Pub Health 2013;10:e8940-15.
Clarke KA, Kenkel B, Rueda MR. 2011. Working paper. Available at: www.rochester.edu/college/psc/clarke/

Core Outcome Sets

- Another issue we face is the lack of homogeneity in reported outcomes for wound care studies
  - This is a problem for simple meta-analysis
  - Tunis et al[1] refer to this problem as a lack of agreement regarding core outcome sets (COS)
  - A number of current initiatives are in progress to help, but it may be many years before these come to fruition
  - BUT different wound care objectives **may still require** additional outcomes or different COS

Tunis SR, Clarke M, Gorst SL, et al. J Comp Eff Res 2016;5:193-205.



Lack of Innovation in Wound Care Research

- Why is wound care research lacking innovation in the way studies are conducted, especially post-marketing studies?
  - Lack of money, expertise, and resources
  - Issues with innovative endpoints and trial designs not approved by FDA
  - CMS and other third party payers not always receptive to new designs/endpoints (e.g., argument that complete wound healing not always relevant)
  - Need gold standard methodology for registry research.

NOVEL RESEARCH
SENSE • FACTS • PERSPECTIVE

Example of Wound Care Health Economics Research Using USWR Data

Limitations

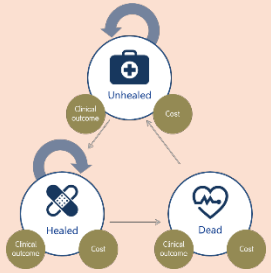
Simplified rates of healing/mortality

Small samples for model inputs

Strength

Comprehensive healthcare provider cost

Real-world data



Realistic health states

+1 ulcer fre

Cost savings

Increased benefits

Conclusions

- Clinical studies have always been used to generate health economic analyses but using conventional RCTs may be problematic
- There are lots of alternatives to conducting conventional RCTs
- All approaches have strengths and limitations
- Choice depends on what you are trying to demonstrate and available finances and resources
- Retrospective analyses of large databases are particularly challenging and require detailed reporting of methodology

Final Thoughts for Discussion

- How will we determine which interventions actually drive better outcomes?
- How do we get the data quality to be high enough?
  - How will we harmonize outcome definitions?
- Which study designs are the best going forward?
- Who should pay for those studies?
  - Can health plans, government agencies or manufacturers collaborate?