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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Marissa Carter Ph.D.
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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
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.
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
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 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 Nugsut RPh,9 Adrienne PS Smith MD,10 Robert J. Snyder11

1Penn North Centers for Advanced Wound Care, West Warren, PA, 2School of Nursing & David Geffen School of Medicine, Div. Geriatrics, University of California, Los Angeles, CA, 3Strategic Solutions, Inc., Cody, WY, 4Program in Physical Therapy, The George Washington University, Washington, DC, 5Clinical Research Foot Care, Endovascular and Vascular Services, Boston University Medical Center, Boston, MA, 6Intellincere, Inc., The Woodlands, TX, 7Div. Vascular Surgery, University of Medicine & Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, 8Wound & Skin Care Consultant, York, PA, 9Alliance of Wound Care Stakeholders, Bethesda, MD, 10Chief Medical Consultant, Day & Zimmerman, Inc., San Antonio TX 78258, 11Wound 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 study.

ABSTRACT

The study of 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 which can confound results. To address this problem, we require a multidisciplinary approach that provides a research agenda for wound care.

METHODS

METHODS: The POWER panel conducted a literature review of wound care research and survey of wound care professionals to identify research gaps. METHODS: The POWER panel conducted a literature review of wound care research and survey of wound care professionals to identify research gaps. The survey (n = 173) included 19 final questions on wound care research critical areas. Participants were invited to participate by email, phone, and social media. Analysis of the survey results was conducted using thematic analysis. FINDINGS: Participants rated each of the 17 statements using a 4-point Likert scale. The 80% agreement threshold was used to determine which statements were considered for revision by the POWER panel directly (n = 173); 2 organizations reduced participation. Participants rated each statement using a 4-point Likert scale, provided comments, and basic demographic and research background.

RESULTS

90% of participants responded “agree” or “strongly agree” to the statement “Wound care research should incorporate a multidisciplinary approach whenever possible.”

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 on FDA-authorized research.

Statement 5: is that most experimental designs focus on a single intervention when distinguishing the experimental from the control group with “usual care.”

Statement 6: 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.

Statement 7: Highly educated populations are under-represented in clinical wound care research practice and should be included where feasible.

Statement 8: The definitions for intervention(s) provided to the comparison group in any clinical study, typically defined as “usual care” or “usual care,” need to be explicit.

Statement 9: An appropriate but comprehensive dataset should be included in the research design to describe the participants.

Statement 10: Study designs should be reviewed.

Statement 11: Quantitative wound care studies should include a run-in period of the initial assessment when it is appropriate.

Statement 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.

Statement 13: Informed or formal wound registries should be developed with real-world data collection.

Statement 14: The definitions for intervention(s) provided to the comparison group in any clinical study, typically defined as “usual care” or “usual care,” need to be explicit.

Statement 15: An appropriate but comprehensive dataset should be included in the research design to describe the participants.

Statement 16: Study designs should be reviewed.

Statement 17: Clinical wound care research should include rates of recurrence where feasible.

Statement 18: Highly educated populations are under-represented in clinical wound care research practice and should be included where feasible.

Statement 19: The definitions for intervention(s) provided to the comparison group in any clinical study, typically defined as “usual care” or “usual care,” need to be explicit.

DISCUSSION POINTS

Table 1: Participant Demographics & Research Background

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<thead>
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Table 2: Final 19 Statements on Wound Care Evidence Based Research (Alliance POWER panel)

| Statement | 1
|-----------|---
| 1 | There is a need for a guidance document in the field of wound care research.
| 2 | Wound care researchers, product developers, manufacturers, policy makers, nurses, clinicians, and consumers should be educated on wound care research guidelines.
| 3 | All human wound care research conducted in the United States should be guided by the principles of Good Clinical Practice (GCP) in accordance with FDA regulations.
| 4 | The study design of research conducted in wound care should include evaluation of cost-effectiveness and/or its economic impact when appropriate.
| 5 | Wound care clinical research should include evaluation of the cost-effectiveness and/or its economic impact 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 study.
| 8 | Phase I wound care research need to reflect both the goals of the intervention and clinical practice.
| 9 | Study designs should be reviewed.
| 10 | Study designs should be adapted to the wound care setting.
| 11 | Quantitative wound care studies should include a run-in period 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 educated 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 comparison group in any clinical study, typically defined as “usual 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 | Study designs should be reviewed.
| 17 | Clinical wound care research should include rates of recurrence where feasible.
| 18 | Informed or formal wound registries should be developed with real-world data collection.
| 19 | Comparative groups, composed of multiple researches working in concert, should be formed in order to facilitate and standardize the research process.
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—but without the same investment in research.
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
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


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 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?

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 outpatients, > 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.

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”

USWR data, 8,611 patients (15,499 wounds) from the U.S. Wound Registry
Exclusion criteria in wound healing RCTs have real world implications

Novitas “LCD” for Bioengineered Skin Substitutes

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/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

Quoted from the Novitas LCD on skin substitutes

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
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
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.
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?
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: Characteristics of Adaptive Designs](image)
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

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.

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

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

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.

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\cite{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

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.
Example of Wound Care Health Economics Research Using USWR Data

**Limitations**
- Simplified rates of healing/mortality
- Small samples for model inputs

**Strengths**
- Comprehensive healthcare provider cost
- Real-world data
- Realistic health states

Cost savings

Increased benefits
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?