WCCC
WOUND CARE
COLLABORATIVE
COMMUNITY

Member Meeting

April 18, 2023
5:00 PM ET

THANK YOU WCCC VOLUNTEER MEMBERS

Welcome and Agenda

I. Welcome
II. Guest Speaker Introduction
III. Presentation: Reporting of Clinical Trials by Dr. Marissa Carter
IV. Q&A/Discussion
V. Work Group Updates
VI. Other Business
VII. Adjourn

Upcoming Member Meeting Schedule
5pm ET/4pm CT/3pm PT
July 25, 2023
October 24, 2023

Reporting of Clinical Trials

Marissa J. Carter, PhD, MA, MAPWCA

Chair, Clinical Trial Committee, GAPS Work Group

WCCC

www.woundcarecc.org

Background

- Wound care journals do not insist on authors using guidelines for the reporting of clinical trials despite their existence for decades
- Frequently, important pieces of clinical studies are missing
- There are also issues in the lack of general reporting for patient- and wound-related variables
- This makes understanding of clinical studies and related health economic studies problematic
- In addition to guidelines, we need for our wound care community a "minimum core dataset"

Guidelines (Equator Network)

- **CONSORT**: randomized trials
- **STROBE**: Observational studies (epidem
- **PRISMA**: Systematic reviews
- **SPIRIT**: Study protocols
- **STARD**: diagnostic/prognostic studies
- **CARE**: case reports
- **AGREE**: clinical practice guidelines
- **SRSQ**: qualitative research
- **ARRIVE**: animal pre-clinical studies
- **CHEERS**: economic evaluations

Extension of Guidelines

STROBE (5 examples of 19 extensions)

1. Reporting and Guidelines in Propensity Score Analysis: A Systematic Review of Cancer and Cancer Surgical Studies
2. The REportingof studies Conducted using Observational Routinely-collected health Data (RECORD)Statement
3. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE)
4. CONSISEstatement on the reporting of Seroepidemiologic Studies for influenza (ROSES-Istatement): an extension of the STROBEstatement
5. STROBE-AMS: recommendations to optimise reporting of epidemiological studies on antimicrobial resistance and informing improvement in antimicrobial stewardship

- 561 guidelines on EQUATOR but **nothing** about wounds

When Guidelines Are Not Mandatory

- When journals don't insist on mandatory guidelines, crucial pieces of studies are likely to be missing:
  - Patient flowcharts
  - Detailed standard of care
  - Statistical power calculations or analytical techniques
  - Key populations
  - Demographics.
- This is because the level of effective peer review has to be much higher (most peer reviews are biased even if reviewers are experienced)
- As a result, many studies get downgraded during the systematic review process
- This is a disservice to authors, sponsors, and the community
- (Crucially flawed studies should **NOT** be published.)

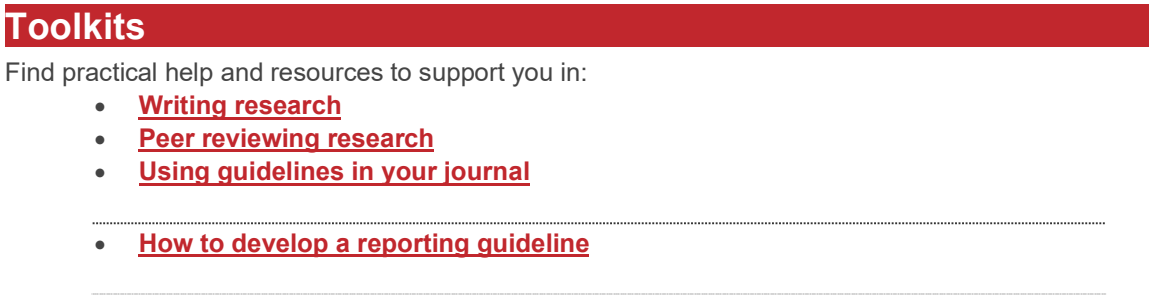
Walking Through CONSORT…

- Brolmann et al do a nice job of walking prospective sponsors and clinicians taking part in RCTs on how to do a better job in conducting and reporting
- Authors point out that CONSORT is only a framework; the actual content of what you report matters a lot
- Authors also lay out how to write a good manuscript for the trial.

Brolmann FE, Eskes AM, Sumpio BE, et al. Wound Repair Regen 2013;21:641-647.

How Do we Encourage the Use of Guidelines?

- Contact wound care journal editors
- Editors should involve their editorial boards
- WCCC provides detailed rationale
- JAMA Dermatology has an excellent template for how it should be done in their author guidelines
- HMP Communications is our “test” case.



Toolkits

Find practical help and resources to support you in:

- Writing research
- Peer reviewing research
- Using guidelines in your journal

- How to develop a reporting guideline

Study of External Validity of VLU RCTs (I)

- Systematic review of 144 RCTs involv
- Focus on generalizability of RCTs, inc status, ethnicity, and recording and r and comorbidities.

[1]Gethin G, Ivory JD, Connel

Wound Repair Regen 2019;2

Wound Repair and Regeneration

SYSTEMATIC REVIEW

External validity of randomized controlled trials of interventions in venous leg ulceration: A systematic review

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The work is attributable to The School of Nursing & Midwifery, College of Medicine, Nursing & Health Sciences, The National University of Ireland, Galway, Ireland.

ABSTRACT

We set out to evaluate quality of reporting of data related to external validity from randomized controlled trials (RCTs) assessing treatment interventions for active venous leg ulcers. Using a systematic review study design, we identified 144 full-text RCTs of treatment interventions, where the wound was assessed and published in English from 1998 to 2018. We found that the median study sample size was 75.5. Weighted mean wound size was 13.22 cm^2 and weighted mean wound duration was 22.20 months. Forty-six (32%) reported numbers screened for eligibility and 27 (19%) reported the number who declined to participate; 19 (13%) reported on patient ethnicity; 60 (42%) reported comorbidities; and 5 (4%) reported current medication use. When reported, 60/102 (59%) excluded patients with an ankle-brachial pressure index <0.8; 68/135 (50%) were conducted in Europe, 6/135 (4%) in Asia, and 74/104 (71%) were conducted in outpatient facilities; 3 (2%) reported socioeconomic factors and 88 (61%) reported on adverse events. We concluded that there is inadequate reporting of data related to external validity in reports of RCTs assessing venous leg ulcers treatment interventions. Significant variability exists in the ankle-brachial pressure index cutoff point for inclusion or exclusion, making generalizability difficult to assess.

INTRODUCTION

Venous leg ulcers (VLUs) are a chronic, debilitating condition and represent 7.5–13% of all wounds in patients[1,2] and up to 90% of ulcers in the lower leg.[3,4] They affect up to 1.5% of the adult population[5] with both prevalence and incidence doubling in those over 65 years.[4] Annual estimated costs to health-care systems of £266million[6] have been reported in the United Kingdom (UK). The protracted course of healing and propensity for recurrence affects patients in psychological, psychosocial, and financial domains. Efficacy of interventions to improve VLU healing outcomes is best determined through the randomized controlled trial (RCT).

The RCT is the "gold standard" for assessment of the efficacy of interventions and should be reported using the CONSORT (Consolidated Standards of Reporting Trials) statement framework.[7] Ideally, health professionals are guided by RCT evidence to optimize patient outcomes. Evidence from RCTs is used by clinicians to guide clinical decisions and by payers and policy makers to support recommendations for the adoption of new therapies in clinical practice. Although high-quality RCTs are conducted within rigorous and controlled conditions, this may impact on and compromise the external validity (generalizability) of findings to specific patient groups. It is argued that researchers, funding agencies, ethics committees, medical journals, the pharmaceutical industry, and their governmental regulators all neglect proper consideration of external validity.[8]

Despite their rigorous design, the applicability of results of RCTs to individual patients has been debated[9,10] and it is estimated that 30–95% of people do not meet the inclusion criteria for many intervention trials that are related to their condition/disease.[11–13] It is argued that in judging external validity, an understanding of how patients were referred, investigated, and diagnosed (i.e. their pathway to recruitment); as well as how they were subsequently selected and excluded is often much more informative than a list of baseline characteristics.[14] The proportion of eligible participants who refuse to enter a clinical trial is relevant for the generalizability of the trial, as it may indicate preferences for, or acceptability of an intervention. Similar considerations may apply to clinician preferences.[7]

The use of stringent selection criteria in RCTs ensures a homogeneous patient sample, optimizes internal validity of the study by reducing variance, and removing potential confounding, so increasing the likelihood of finding a true association between treatment exposure and outcomes.[9] A comprehensive description of the eligibility criteria used to

RCT Randomized controlled trial
VLU Venous leg ulcer

Study of External Validity of VLU RCTs (II)

- 32% Reported numbers of patients screened for eligibility
- 13% Reported patient ethnicity
- 42% Reported comorbidities
- 4% Reported current medication use.
- 2% reported socioeconomic factors
- When reported, 59% excluded patients with an ABPI <0.8
- 61% reported on adverse events
- 50% reported BMI
- Nonreporting of major comorbidities and current medications is a concern for estimating external validity.
- Significant variability exists in ABPI cutoff point for inclusion or exclusion, making generalizability difficult to assess.
- **There is inadequate reporting of data related to external validity in reports of RCTs**

How Do We Tackle This Problem?

- Bear one thing in mind: the more information we collect the **more expensive and time-consuming** the study becomes in terms of work
- Frame the concept in terms of the **MINIMUM** information we need to collect on patient- and wound-related parameters
- Other: e.g., caregivers or support network; insurance, urban or rural location, etc.
- We need a rationale for **EACH** piece of information
- We need to define the information structure
- We need to support data collection with results from the literature
- This would be a WCCC project with the results published in a wound care journal with much further dissemination via multimedia and presentations

Example: Patient Demographics

Method: Prospective: select from medical history taken during screening period; retrospective: extract from medical records

Age

Sex (assigned sex at birth?) or gender?; transsexuals (1.6 million in USA) not being enrolled in clinical trials

Race-ethnicity

Education level

Income level

Support system? Recent research suggests this is an important predictor of poor health

Rural versus urban (access to healthcare)

Others

Example: Patient comorbidities

Report a key number of comorbidities relevant to wound healing? Which ones?

Here are the big 5: diabetes; chronic kidney disease; chronic heart failure; COPD; afib

Should we select comorbidities based on how they affect wound healing? Interfere with treatments? More general?

Provide numbers and percentages by treatment group(s)

Use in more sophisticated statistical analysis? Data- or hypothesis-driven or specified a priori as in a statistical analysis plan?

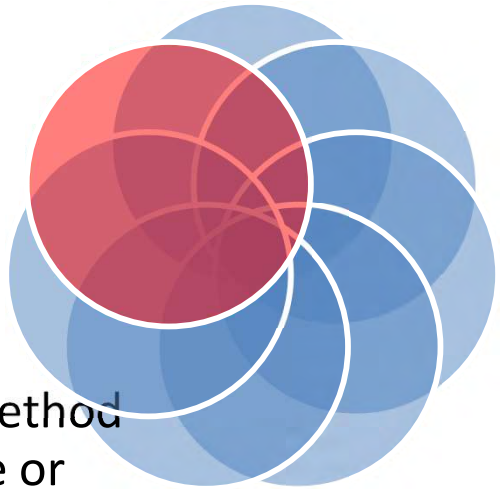
Is it enough to say that patients have a comorbidity or should we attempt to provide more information (severity, grade, etc.) Particularly important for disease underlying the wound type(s) under study; diabetes (duration, type, for example)

Example: Wound-related Variables

Area (mean (SD); median (IQR); range

Other descriptors, such as quantity and type of exudation

Wound age (definition; mean [SD]; median [IQR]; range



Neuropathy (DFUs); extent?

Wound types (if not a study of one wound type)

Ischemia (method to include or exclude; units; mean [SD], median [IQR], range if included

Severity

Example: Standard of Care

- Reviewers complain that in clinical trials standard of care is frequently not well defined
- Define offloading in detail (if appropriate)
- Define compression levels (if appropriate)
- Define dressing types and change frequencies and who is doing the dressing changes
- Debridement: type(s) and frequency; where is the wound being debrided?
- Infection management: detailed diagnostic algorithm(s); strategy for treatment(s); including antimicrobials, antibiotics; etc.
- Arterial status (LE; degree of ischemia; methods); revascularization strategies
- Other?

Questions?

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Tools Work Group

- 2023 Objectives:
  - Complete a review of the provided data from manufactures on their devices [evidence, testing, publications, clinical uses]
  - Establish similarities & potential quantification of testing per technology types
  - Work through the potential Pfizer/ DiME collaboration to review their evaluation of imaging devices
  - Compare data sources, develop a working list of requirements for validation of measurement devices for PAR/PVR
  - Incorporate 1 or more patient endpoints w/ PAR/PVR & tools to measure to validate for use in FDA trials
  - Prepare publication of findings as a guidance for future devices

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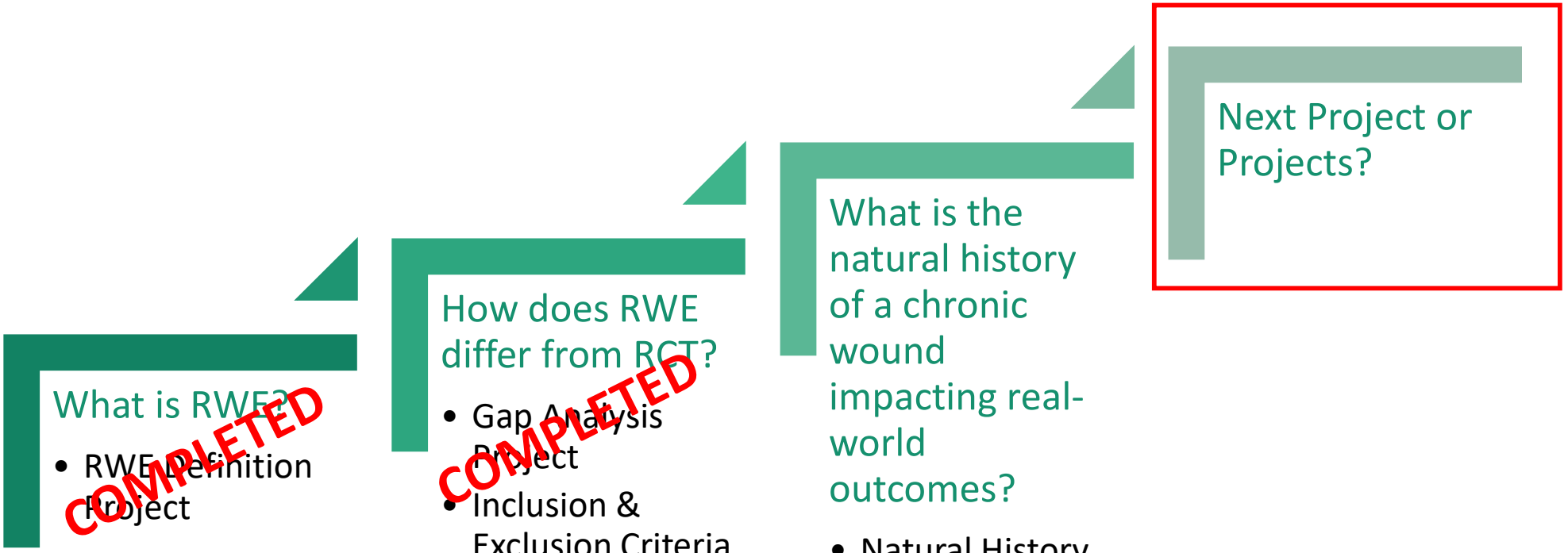
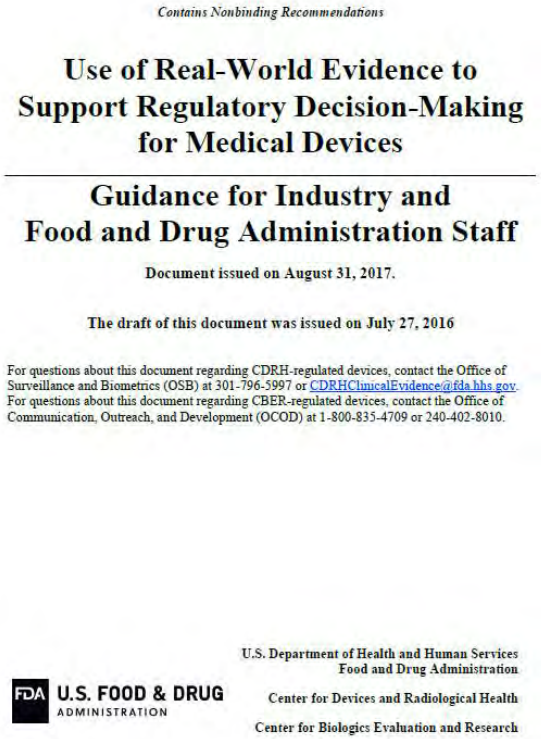
RWE Group Update to WCCC Board of Directors March 2023

WHICH PROJECTS TO CONTINUE OUR JOURNEY?



Our RWE Projects Should be Framed Around FDA RWE Guidance Documents



Contains Nonbinding Recommendations

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

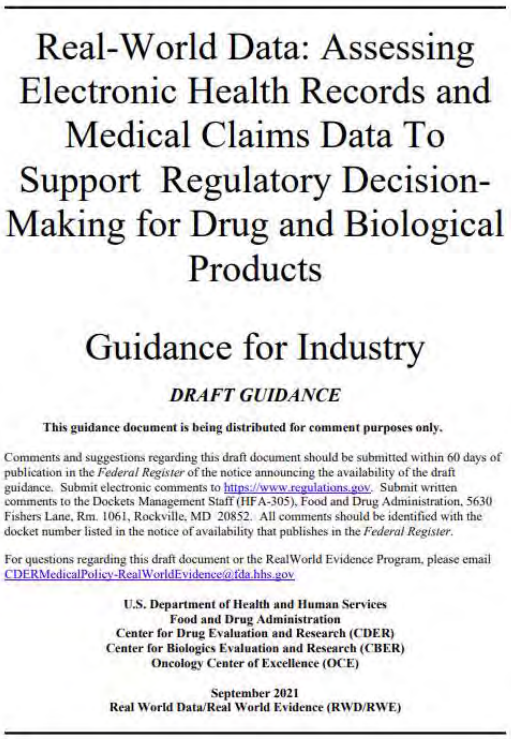
Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or CDRHClinicalEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research



Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document or the RealWorld Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2021
Real World Data/Real World Evidence (RWD/RWE)

Documents provide guidance on:

- ✓ Whether RWD are 'fit for use'
- ✓ Whether a trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question
- ✓ Whether a study conduct meets FDA regulatory requirements (e.g., for study monitoring and data collection)

FDA: Regulatory Context in Which RWE May be Used

Which of these regulatory decisions based on RWD are of highest priority?

1. Generating hypotheses to be tested in a prospective clinical study
2. As a historical control, a prior in a Bayesian trial, or as one source of data in a hierarchical model or a hybrid data synthesis
3. As a concurrent control group or as a mechanism for collecting data related to a clinical study to support device approval or clearance in a setting where a registry or some other systematic data collection mechanism exists
4. As evidence to identify, demonstrate, or support the clinical validity of a biomarker
5. As evidence to support approval or granting of an Humanitarian Device Exemption, Premarket Approval Application (PMA), or De Novo request
6. As support for a petition for reclassification of a medical device under section 513(e) or (f)(3) of the FD&C Act
7. As evidence for expanding the labeling of a device to include additional indications for use or to update the labeling to include new information on safety and effectiveness
8. For public health surveillance efforts. Through ongoing surveillance, signals are at times identified that suggest there may be a safety issue with a medical device. RWE may be used to refine these signals for purposes of informing appropriate corrective actions and communication
9. To conduct post-approval studies that are imposed as a condition of device approval or to potentially preclude the need for post market surveillance studies ordered under section 522 of the FD&C Act

Sub-Group Recommendations for Projects 2023+

What do real world patients look like?

- Natural History Project

What is the true standard of care today?

- Usual Best Care Project

Which patients benefit from immediate access to advanced care?

- Conservative Treatment Period Challenge Project

What specific RWD/RWE meets FDA thresholds for regulatory decisions?

- Fit for Purpose Project

Usual Best Care Project

- Replace ill-defined "standard of care" with consensus “Usual Best Care"
- Develop specifically defined Usual Best Care for diabetic, venous, arterial, pressure, and mixed etiology ulcers including:
  - Minimal required diagnostic tests
  - Specifications of standard (non advanced) interventions and technologies
  - Wound progression metrics (biomarker-based?)
  - Definition of non progression

Conservative Treatment Period Challenge Project

- Challenge the “30 day conservative treatment followed by 12 -16 weeks of advanced car” paradigm.
- Create a decision algorithm that identifies chronic wound patients that:
  - Are likely to heal with "usual best care"
  - Are likely to never heal
  - Are likely to benefit with immediate access to advanced treatments

Fit for Purpose Project

- Expand the use of RWD/RWE in regulatory decision making
- Gain agreement on:
  - The type of RWD that would be "fit for purpose" and meet the threshold of "sufficient quality, relevance and reliability"
  - The type of RWE to demonstrate safety and effectiveness for labeling expansion decisions, among others.
- Create a toolkit for study sponsors for:
  - Creating RCTs with pragmatic features that allow for generalizability of results
  - Qualifying existing real-world databases and designing new RW studies and registries that meet FDA's quality, relevance and reliability thresholds

GROUP RATINGS SO FAR

Natural History Project Update

- Overall project cost estimate of $250k requires us to segment the project into prioritized deliverables over the next 12 – 36 months
  - We may lose some efficiencies, but gain a hedge if early findings do not provide meaningful results
- Exploring potential databases and vendors
  - NetHealth
  - USWR
  - NESTcc
  - Medicare claims databases?
- Bridge-to-Data (Database profiling service)
  - Obtaining a quote within next 2 weeks to conduct database vendor search
  - Expect cost to be between $12k and $20k
  - Once we have a refined, prioritized vendor list, submission of Requests for Information will follow
- Natural History Project plan will be segmented and restructured based on available evidence and sources
  - Requests for Quotation to be issued to select data vendors including USWR and NetHealth

Our Goal

Leverage existing RWD to deepen our understanding of the complexities of patients with chronic wound and how to determine which interventions achieve best outcomes for each type of patient and wound.

Work Group Updates

- Gaps
- Tools
- Real World Evidence (RWE)

Other Business

- WCCC/DiME/Pfizer Partnership
- 2023 WCCC Driving Change in Wound Care Summit at SAWC Fall
- Patient Engagement with WCCC
- 2022 Executive Summary Available for Download at www.woundcarecc.org/executivesummary

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