WCCC
WOUND CARE COLLABORATIVE COMMUNITY

Driving Innovation in Wound Care Summit

SAWC Spring WHS | WOUNDS

Breaking the Barrier: Discovery and Innovation in Wound Care

Presented by The Wound Care Collaborative Community (WCCC) at SAWC Spring 2024 (Non-Accredited)

SAWC Pre-Conference, Monday, May 13, 2024

Marriott World Center, Orlando, FL

Executive Summary

Session	Speaker(s)		
Keynote Address: Breaking the Barriers to Achieve New Discoveries and Innovation in Wound Care	**Keynote Speaker:** William Li, MD, WCCC Board Member		
Opening Remarks: Disrupting the Barriers to Innovation with Evidence and Collaborations	**Program Chair:** Vickie R. Driver, DPM, MS, WCCC Chair, Board of Directors		
Panel 1: Drilling Down on Disrupting Barriers in WC Innovation—Buy-in and Collaboration	**Panel Chair:** Howard Walthall, JD, WCCC WG Chair	**Panelists:** FDA CDER: Dev Verma, MD (Virtual) FDA CDRH: Yu-Chieh Chiu, PhD WCCC: Alicia Orapollo, MD, WG Chair. WCCC: Bill Ennis, DO	Industry: Emma Wright, PhD, BSc Mölnlycke Industry: Michael Steadman, Urgo Medical Industry: John Harper, PhD, MiMedx Industry: Katie Mowry, PhD, Organogenesis
Panel 2: Alternative Primary and Co-primary Endpoints	**Panel Chair:** Vickie R. Driver, DPM, MS, Chair WCCC Board of Directors; Co-Chair: Alisha Oropallo, MD	**Panelists:** FDA CDRH: Cynthia Chang, PhD FDA CDER: Dev Verma, MD (Virtual) WCCC: Peggy Dotson, RN, BS, Treasurer/Sec	WCCC: Lisa Gould, MD, PhD, Vice-Chair WCCC: Marissa Carter, PhD, WS Chair Industry: Howard Walthall, JD, Progenacare Industry: Cristina Taylor, MSHS PA, Convatec
Panel 3: Generating and Reporting Evidence	**Panel Chairs:** Marissa Carter, PhD, WCCC WS Chair Marjana Tomic-Canic, PhD, WCCC WS Chair	**Panelists:** FDA CDRH: John Azeke, PhD FDA CDER: Dev Verma, MD (Virtual) WCCC: Caroline Fife MD, WS Chair WCCC: Lucian Vlad, MD	WCCC: Shabnam Vaezzadeh, MD, MPA WCCC: Randy Schwartz, WG Co-Chair Industry: Amy Law, MBA, Solventum- 3M Industry: Monique Rennie, PhD, Mölnlycke
Panel 4: Real-World Evidence in FDA and Payer Decision-Making	**Panel Chair:** Joseph Rolley, MSIA, WCCC Work Group Chair	**Panelists**: FDA CDRH: Cynthia Chang, PhD WCCC: Caroline Fife, MD, WS Chair WCCC: Member, Bill Ennis, DO WCCC: William H. Tettelbach, MD	ECRI: Dheerendra Kommala, MD Industry: Matt Pine, Intellicure Industry: Kira Rupprecht, MBA, Reapplix Industry: Beate Hanson, MD, MPH, Convatec
Panel 5: Defining Standard of Care in Wound Care	**Panel Chair:** Maribel Henao, DPM, MSPT, Organogenesis and WCCC Workstream Chair	**Panelists:** FDA CDRH: Cynthia Chang, PhD, WCCC: John Lantis, MD, WG Vice-Chair	Industry: ECRI: Dheerendra Kommala, MD Industry: Industry: Yi Arnold, PhD, MBA, Integra Industry: Tim Jacobson, CFA, Noxy Health
Q&A and Closing Remarks	**Program Chair:** Vickie R Driver, DPM, MS, and Session Chairs		

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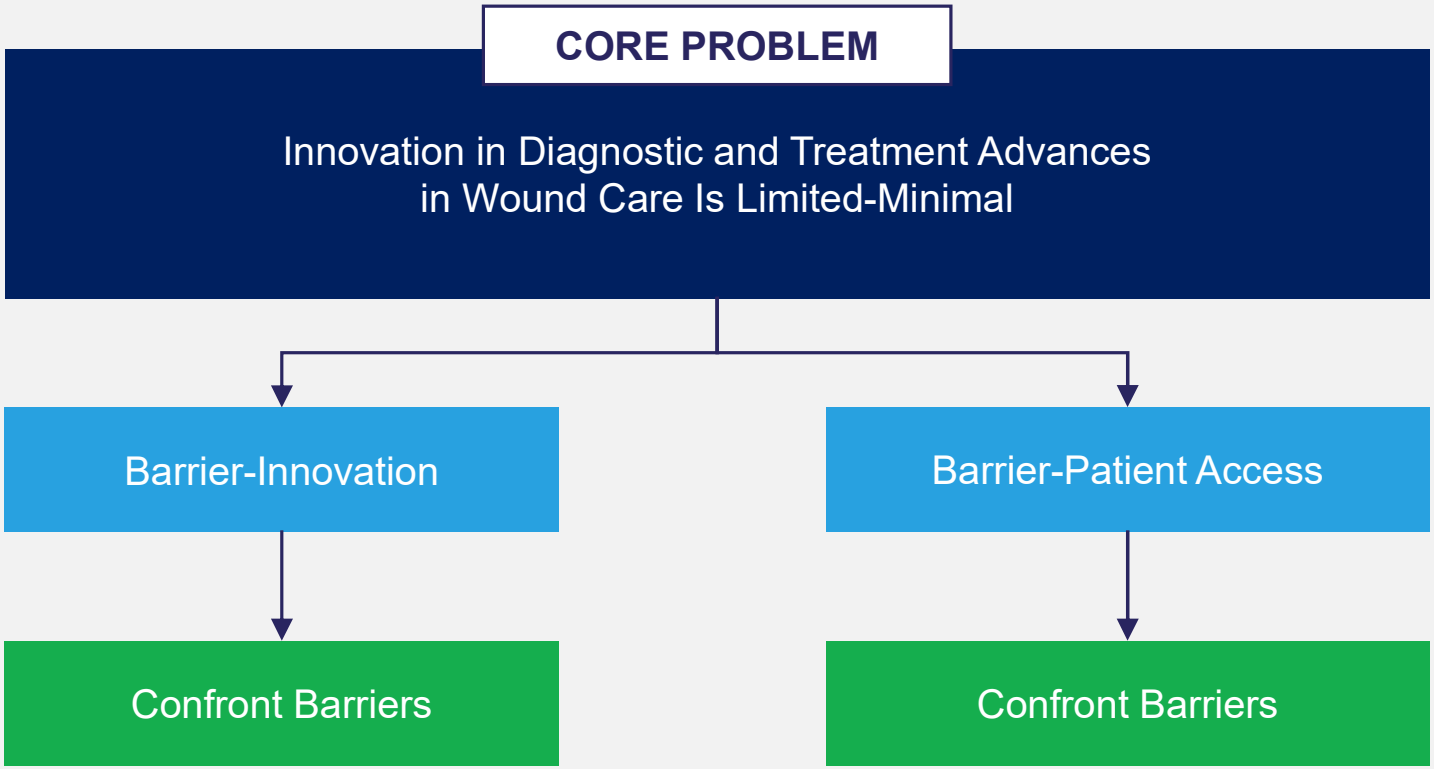
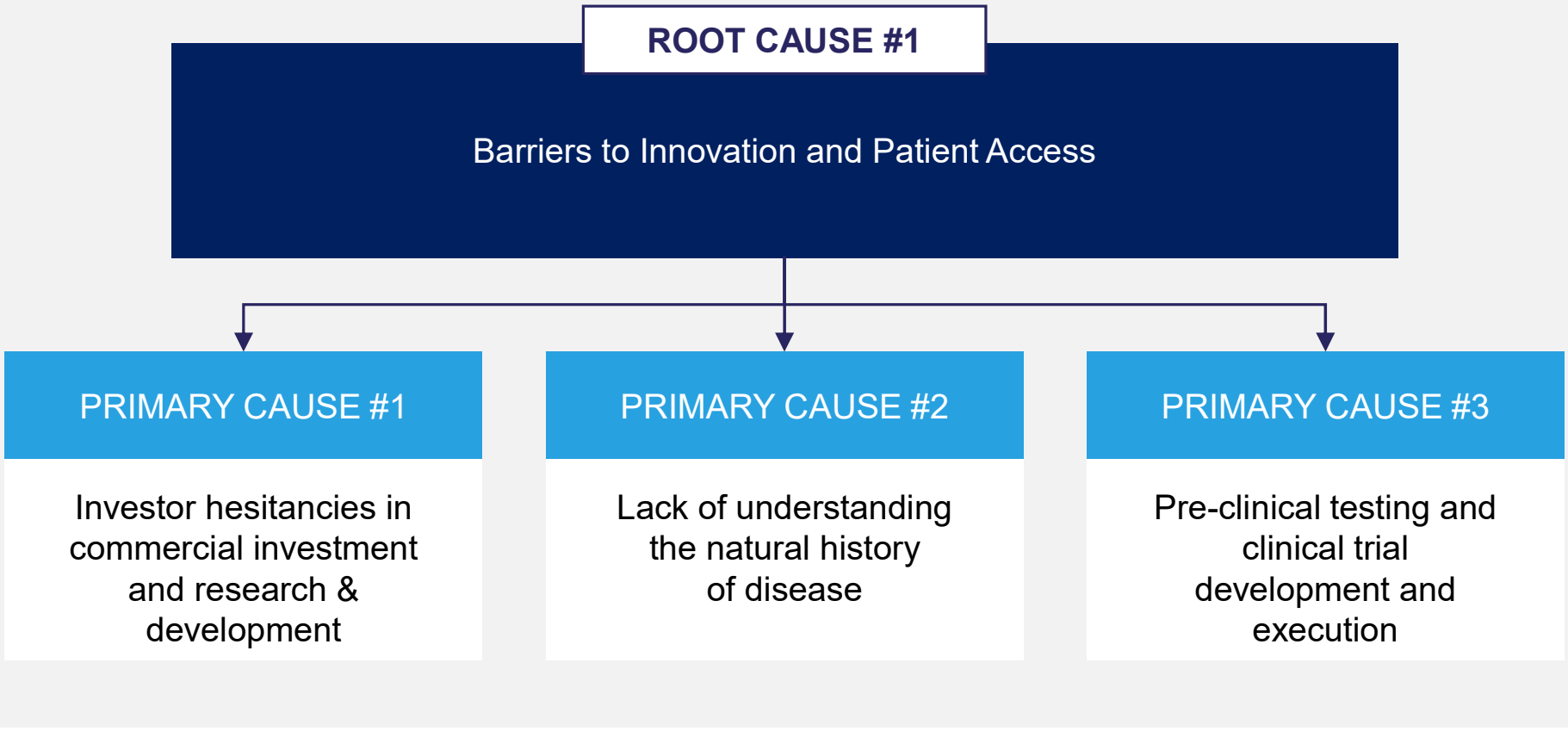

CORE PROBLEM
Innovation in Diagnostic and Treatment Advances in Wound Care Is Limited-Minimal
Barrier-Innovation
Barrier-Patient Access
Confront Barriers
Confront Barriers


ROOT CAUSE #1
Barriers to Innovation and Patient Access
PRIMARY CAUSE #1
Investor hesitancies in commercial investment and research & development
PRIMARY CAUSE #2
Lack of understanding the natural history of disease
PRIMARY CAUSE #3
Pre-clinical testing and clinical trial development and execution

Panel 1:

Drilling Down on Disrupting Barriers in Wound Care Innovation – Buy-in and Collaboration

Panel Chair:

Howard Walthall, JD,
WCCC Chair GAPS WG,
CEO, ProgenaCare

Organization	Name & Title
FDA CDRH	Cynthia Chang, PhD, Director, Division of Infection Control and Plastic Surgery Devices
FDA CDER	Dev Verma, MD, Medical Officer
WCCC	Alisha Oropallo, MD, Chair TWG, Director Dept. Vascular Surgery, Northwell Health
WCCC	Bill Ennis, DO; CMO, Healogics
Mölnlycke	Emma Wright, PhD, CMO, EVP RA&Q
Urgo	Michael Steadman, CEO Urgo NA
MiMedx	John Harper, PhD, CSO, SVP R&D
Organogenesis	Katie Mowry, PhD, VP R&D

WCCC = Wound Care Collaborative Community; WG = working group

Discussion Points

Panel 1

Discussion Topics	Panelist
FDA Perspectives • What barriers has the FDA identified to innovation in wound care? • How can the wound care community and the WCCC best collaborate with the FDA to overcome the barriers identified by the FDA and the WCCC?	CC DV
Clinician and Research Perspectives • How do the barriers to innovation that the WCCC has identified impact patients and patient care? • How should clinicians and researchers leverage the work being done by the WCCC, the FDA, and others to help overcome these barriers?	AO BE
Industry Perspectives • How do the barriers that the WCCC has identified impact innovation projects within your organizations? • How should industry participants leverage the work being done by the WCCC, the FDA and others to help overcome these barriers?	EW MS JH KM
Closing Thoughts • How can the FDA and the WCCC best collaborate to remove or mitigate the identified barriers and accelerate innovation in wound care?	All

FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community

FDA Perspectives

Panel 1

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What barriers has the FDA identified to innovation in wound care?

- Despite the massive public health burden, there's only one approved product for the treatment of a chronic ulcer, which was approved over 25 years ago in 1997.
- No primary specialty cares for these patients.
- Patients often receive poor care from seeing a PCP, or they get bounced around.
- The barriers that the FDA can most impact are related to clinical trial endpoints and design. The tools that measure the endpoints also need to be agreed upon between Sponsors and the FDA.
- One of the challenges in recruiting subjects with chronic ulcers to clinical trials is limited mobility. More decentralized and virtual trials can help but will require improvements in diagnostics and measurement devices to assess endpoints in patients' homes. Again, we need validated, approved tools to measure endpoints.
- Additional endpoints that may be clinically meaningful to patients include improvement in pain, decreased incidence of infection, and improved ambulation.
- The FDA acknowledges that sponsors perceive the cost and time to perform two adequate and well-controlled trials as a barrier to product development. In certain scenarios, Sponsors may be able to perform one adequate and well-controlled trial with appropriate confirmatory evidence (eg, natural history data or real-world data). Sponsors should discuss their development plans with the FDA early in development.
- Updating clinical trial considerations and endpoint selection in clinical trial design are important, but more work needs to be done beyond these two issues alone (eg, the need for increased basic funding for basic science and translational research).

FDA = Food and Drug Administration; PCP = primary care provider

FDA Perspectives (continued)

Panel 1

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What barriers has the FDA identified to innovation in wound care?

- Many incoming products for pre-market review are for products with similar technology, the same indications, or the same claims that have already been cleared and are already marketed.
- Need additional creativity, new technology, and new ideas.
- There are areas of the 2006 Guidance that could provide patient benefits to the overall wound care experience that have yet to be explored by any new products.
- Room for growth in devices to assess risk and inform clinical decision-making, as well as in the diagnostic space.
- There is potential for more innovation utilizing the *de novo* pathway.
- Encourage the development of products that address different aspects of patient care beyond complete wound closure and treatment of the wound.
- Need a broader diversity of products that may address additional endpoints.

How can the wound care community and the WCCC best collaborate with the FDA to overcome the barriers identified by the FDA and the WCCC?

- Keep doing what you're doing. You're the experts, and they're your patients.
- The problem is bigger than just any one institution or any one expertise area alone, so find the gaps and fill them.

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FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community

Clinician and Research Perspectives

How do the barriers to innovation that the WCCC has identified impact patients and patient care?

- All patients are affected when we lack a consensus on how to manage them.
- There are opportunities for the immunosuppressed population that we're starting to see more of in our practices.
- There are additional barriers that we haven't identified, such as social determinants of health, biomarker development, and clinical testing.
- B.E. cited an article[1] demonstrating that the most impactful parameters on the likelihood of wound closure were size, duration, and location of the wound, rather than comorbid conditions.
- Alternative trial design protocols should be considered, as in oncology.[2] These trial designs would require the field to agree on terminology and diagnostics.
- Therapeutics drive therapy in wound care, and diagnostics drive therapy in other fields of medicine. The industry has been hesitant to develop diagnostics in wound care. Even when they are developed, provider adoption, clinical efficiency, and reimbursement act as barriers.
- We should use basket-based trials, which use real-world data initially to generate hypotheses and then lead to RCTs.
- We need to stop letting therapeutics drive the industry and we need more focus on diagnostics. We're applying the most advanced therapies without knowing what is causing a patient's struggle to heal. Is it the cells? Scaffolding? The matrix? Cellular senescence? Bacterial load?

How should clinicians and researchers leverage the work being done by the WCCC, the FDA, and others to help overcome these barriers?

- Clinicians, researchers and industry can help disseminate the work that the WCCC and the FDA are doing to a broader wound care community.
- Dissemination and awareness can help drive a consensus, which will lead towards new innovation for patients and improvement in regulatory guidance development.
- We need agreement as a community on the mission-critical metrics to make sure we are all capturing the same information.

1. Cho SK, et al. Development of a Model to Predict Healing of Chronic Wounds Within 12 Weeks. *Adv Wound Care (New Rochelle).* 2020;9(9):516-524.
2. Ravi R, Kesari HV. Novel Study Designs in Precision Medicine - Basket, Umbrella and Platform Trials. *Curr Rev Clin Exp Pharmacol.* 2022;17(2):114-121.

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FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community

Industry Perspectives

Panel 1

? How do the barriers that the WCCC has identified impact innovation projects within your organizations?

- Investors are investing in the commercial side of a product that is already having success because success is evaluated based on revenue rather than patient outcomes.
- We need to shift focus from products in a box to the precise problem that the patient is experiencing.
- We need some wins to bring investors into the innovation side.
- Innovations can take forms other than products, such as services, digital innovations, and intuitive products.

- We need to help the industry move away from focusing on the profits of products and become more patient-centered.
- We need to drive innovation in education in a profitable way.
- Take the approach that every person *can* heal a wound, but something is keeping these patients from healing their wounds. What is keeping the wound from healing? It's likely a combination of things (oxygenation, microbiome, etc.).

- We may be able to use big data to predict whether a product is going to work or not.
  - Unfortunately, companies are not interested in which patients their products are NOT going to work on.
- Can we define subtypes and collect data through clinical trials and natural history to distinguish responders and non-responders based on the mechanism of action?
  - This should reduce the number of failures.

FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community

Panel 1

Industry Perspectives (continued)

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How should industry participants leverage the work being done by the WCCC, the FDA, and others to help overcome these barriers?

- Could we work toward an industry-wide registry where each patient using a particular product is registered, and we can collect real-world evidence?
- It requires that we all agree and understand how the data will be used, but it could change the game.
- We also need to all commit to embracing and implementing the information coming out of the WCCC. We need to make sure to apply it and publish accordingly.

- Clinical trial design and patient selection are *critical*.
- The challenge is balancing clinical trial populations that are designed to be as reasonably homogenous as possible. Meanwhile, the real-world evidence is thoroughly heterogeneous. How do we marry the two when everyone is using different metrics and endpoints for real-world data?
- We need to design ways to collect adequate data in the real world that can be analyzed without being too time-consuming with a lot of manual data entry.

- We need to move to a fee-for-outcome approach, not a fee-for-service approach so that we are driven and paid by clinical outcomes.
- We can use WCCC to allow us to communicate and engage in a protected environment.
- Understand the underlying disease taking place with the patient, and THEN you understand about restructuring their wound.

FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community

Closing Thoughts

Panel 1

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How can the FDA and the WCCC best collaborate to remove or mitigate the identified barriers and accelerate innovation in wound care?

- We can come to a decision on endpoints, quality measures, metrics, and standard of care (SOC).
  - Industry does not adequately assess the impact of SOC and overestimates the deltas.
  - We should accept that people will do better in a trial than if they are in the wound care center.
- We should use a predictive approach, some real-world data, some honesty, some collaboration, and some ability to predict what the product will realistically do.
- We need to accept that the wound has a life cycle, and we're only addressing the middle point.
- We can develop an analysis to determine or at least predict responders and non-responders to narrow the number of total patients enrolled and give a higher opportunity for success.
- We can follow through and take on leadership roles.
- We can continue in smaller venues.
- We can work to understand the population that our treatments don't work on. Understand the non-responders.
- We shouldn't develop cool products and then *push* them into the market. Instead, we should develop products that address why a wound won't heal and they will be pulled into the marketplace.
- From the FDA: industry emphasizes that trials are expensive. Yes, but so is the cost of caring for these patients. The FDA is committed to approving safe and effective treatments.
- If small, fragmented companies do not have the finances to support development, they might consider combining into larger entities that can. They may also consider working with the WCCC work groups and workstreams.
- Clinical trials could use a basket trial design where a targeted therapy is evaluated across multiple types of diseases (one drug for multiple wound subtypes).
- They could also do umbrella trials where several drugs are evaluated for a single disease in subjects stratified into subgroups. Industry could combine forces to do that. Work to develop a systemic product for a chronic non-healing wound.

WCCC WOUND CARE COLLABORATIVE COMMUNITY

FDA = Food and Drug Administration; SOC = standard of care; WCCC = Wound Care Collaborative Community

Closing Thoughts (continued)

Panel 1

How can the FDA and the WCCC best collaborate to remove or mitigate the identified barriers and accelerate innovation in wound care?

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Industry needs to collaborate and work together on clinical trials. We all have products that are tagged in different aspects of wound healing. So why are we all trying to do very similar studies where our product may be influencing just one or two components of that healing? Why are we working against each other when we could come together, fund the appropriate things, and focus on the patient, the quality of life, and their experience, not just the actual physical clinical outcome?"

FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community

Panel 2:

Alternative Primary and Co-primary Endpoints

Panel Chair:

Vickie R. Driver, DPM, MS

Chair, Board of Directors WCCC

Professor, Washington State University

Organization	Name & Title
FDA CDRH	Cynthia Chang, PhD, Director, Division of Infection Control and Plastic Surgery Devices
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WCCC	Lisa Gould, MD, PhD, Vice-Chair
WCCC	Peggy Dotson, RN, BS, Secretary/Treasurer
WCCC	Marissa Carter, PhD, Workstream Chair
ProgenaCare	Howard Walthall, JD, CEO
ConvaTec	Cristin Taylor, PA-C, DPT Senior Director Medical Affairs

WCCC = Wound Care Collaborative Community

Discussion Points

Panel 2

Discussion Topics	Panelist
1. How will endpoints other than complete wound healing encourage innovation?	**DV CT AO**
2. What is the difference between multiple, co-primary, and co-composite endpoints? What are the expected implications on study size and cost of using co-primary or composite endpoints?	**MC HW**
3. How and when are single versus multiple endpoints needed? What FDA guidance is available to support decision-making in crafting a clinical trial? Include the point that meaningful endpoints are few, especially those that are validated.	**CC DV CT MC**
4. What is the patient's perspective regarding the need for additional primary endpoints?	**LG PD**
Closing: • The WCCC and the FDA need to work closely together utilizing the research completed by the WEF-CEP and the WCCC tools working group to guide the process for broader usage of additional primary endpoints. • The WCCC recommends that the WCCC work with the FDA to draft an updated wound healing guidance document or an amendment to the existing draft guidance.	**VRD DV CC PD LG**

FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community; WEF-CEP = Wound-Care Experts/FDA-Clinical Endpoints Project

Panel 2

How will endpoints other than complete wound healing encourage innovation?

- The goal is to evaluate information on methods and devices to measure new endpoints and engage industry researchers and patient-reported outcome (PRO) developers.
- Looking for tools to support the percent area reduction (PAR) and percent volume reduction (PVR) as primary endpoints.
- We need to measure length and width, but this often overestimates the area of the wound by over 44%.
  - Digital imaging can reduce that variability and record progress over time.
- Complete wound healing is too unrealistic a goal. Looking to adopt something other than complete wound closure but still clinically meaningful to patients.
- The FDA shares that just partial PAR alone is NOT clinically meaningful to patients. Patients want 100% healing.
  - However, the FDA has become more open to a *co-primary* endpoint, in which something like 50% area reduction is combined with something inherently clinically meaningful to patients. PROs like pain improvement, increased ambulation, or decreased incidence of infection could be considered. The co-primary endpoint must be measured accurately and score changes must be predefined and meaningful. Do we aim to reduce pain by two points? Four points? Sponsors need to do this work and to provide the data to show how and why the changes would be meaningful. What is the threshold and why?
- The endpoint needs to match what the product actually does.

FDA = Food and Drug Administration; PAR = percent area reduction; PRO = patient-reported outcome; PVR = percent volume reduction

Panel 2

What is the difference between multiple, co-primary, and co-composite endpoints? What are the expected implications on study size and cost of using co-primary or composite endpoints?

Trials with a co-primary/composite endpoint will be more expensive, require a larger sample size, and will take longer.

You will also have lower success rates for both the treatment and the control groups. Don’t do it unless you must.

You have to pick a co-primary with some motion. It should respond or reflect the wound healing; otherwise, you won’t have a successful trial, no matter how well the wound heals.

How and when are single versus multiple endpoints needed? What FDA guidance is available to support decision-making in crafting a clinical trial? Include the point that meaningful endpoints are few, especially those that are validated.

Panel 2

- Multi-component endpoints are essentially measuring various aspects separately to evaluate the efficacy.
- Multi-component endpoints have unique challenges compared to co-primary endpoints, one of which is difficulty with the interpretation of calculated scores.
- In contrast, co-primary endpoints are distinct outcomes that are given equal importance in evaluating the efficacy versus the multi-component, where you don't need to win on all of them. For a co-primary EP, you have to win on everything. That's usually a high bar to win on multiple components. Generally, two are acceptable. For wound-healing, an example would be 50% area reduction combined with decreased pain or 50% area reduction combined with improved ambulation.
  - Using co-primary endpoints gives a clear and focused assessment of specific outcomes deemed most important for evaluating treatment efficacy and simplifies data analysis.
- Regardless of what endpoint is chosen, they need to be measured in an accurate way with clinical outcome assessments. The development of the clinical outcome assessment for drugs/biologics requires submitting evidence to CDER that the outcome assessment is “fit-for-purpose,” which means the level of validation associated with a tool is sufficient to support its context of use. The Sponsor would need to provide the following key elements of evidence to support that the instrument data can be used in labeling:
  - Intended use: was instrument evaluated in intended population?
  - Well-defined: is the concept(s) well defined?
  - Content validity: does instrument measure concept of interest? [for a patient-reported outcome, this needs to measure a concept of interest to patients].
  - Construct validity: is there quantitative evidence in support of validity?
  - Reliability: Does instrument generate consistent and reproducible results?
  - Ability to detect change: Is instrument sensitive to detect change?
  - Score interpretability: how much change is meaningful? Is score change reflective of meaningful change?

FDA = Food and Drug Administration

How and when are single versus multiple endpoints needed? (continued)

Panel 2

- Regardless of what endpoint you choose for drugs, there always has to be a demonstration of a safety endpoint because we don't want the product to slow the rates of healing.
- The rate of healing must be at least similar to the SOC.
- Consider what phase you are using in your trial because you're going to be interested in different things at different phases of a drug trial.
- We may end up with two or three primary endpoints and we need to be willing to pay the price (biome, biomarkers, inflammation, pH, etc.).
- Complexity is easier to aim for with clinical trial design. It's harder to decide on just one, what is minimally necessary to show? How does that minimally necessary criteria show that you are safe and effective?
- Complex designs are not patient-centric. Designs need to have the patient at the center to show safety and efficacy to them.
- We need the same success criteria to translate from animal models as well.

SOC = standard of care

Panel 2

What is the patient's perspective regarding the need for additional primary endpoints?

- Patients really fear infection. They want to see reduced recurrence of infection and reduced amputation.
- They want an improved quality of life (ability to do things independently, decreased social isolation, and decreased pain).
  - It isn't all about wound-healing. It's about allowing these patients to have a life while they're healing their wounds.
- They also want increased access to care.
- Challenges remain. How do we decrease odor or decrease drainage? How do we develop tools to measure those?
  - Unfortunately, we still lack great tools to measure some of the patient-reported outcomes, but we are making progress (drainage).
- We also need to consider that different endpoints may occur across different timelines. If we want to measure whether ambulation is faster, drainage is reduced, or pain is reduced, that may take much longer than the 12 weeks observed with PAR. It may take 20 weeks or 40 weeks.
- If the drainage drops significantly, or they can suddenly get out of a total contact cast and into a walking boot, that's enormous for a patient but may not be making their mobility completely wonderful.
- We need tools to measure PVR, undermining, and tunneling.
- Can we find some minimal criteria across the board that will validate a tool in use today that's already approved, that's already on the market, and being used to measure wounds? If we can satisfy these criteria, can we adapt or have a modified MDD-type checklist that would help the FDA understand that these tools already on the market do what they say they're going to do? Then they could be valid for current trials for the measurement of PAR in a modified approach.

FDA = Food and Drug Administration; MDD = medical device directive; PAR = percent area reduction; PVR = percent volume reduction

Panel 2

Key Points

We need to create parameters for wound bed prep because so many of our products have been utilized on wound beds that are not well prepared and then they fail.

There’s a real challenge with image-based diagnostics when the SOC does not reproducibly or reliably detect the change in endpoint.

It’s not only about how well the result agrees with the gold standard, but it's also about how accurately the gold standard measures what it’s supposed to.

SOC = standard of care

Closing

Panel 2

The WCCC and the FDA need to work closely together utilizing the research completed by the WEF-CEP and the WCCC tools working group to guide the process for broader usage of additional primary endpoints.

The WCCC recommends that the WCCC work with the FDA to draft an updated wound healing guidance document or an amendment to the existing draft guidance.

Regarding updates to the 2006 Guidance - FDA staff can and do participate to lend their regulatory expertise and to inform the outputs of all the workstreams and the results of the work being done by the WCCC.

- They could not directly work on drafting anything but would continue to lend expertise on the regulatory context and regulatory perspectives to help with the scientific work being done.

In the WCCC, we are the experts in this field on the ground.

The FDA is open to receiving recommendations to the guidance and will do what is in their power to ensure stakeholders have access to helpful information to address common challenges.

The WCCC can send proposed recommendations for inclusion in a guidance for FDA to consider. Only the FDA has the authority to issue FDA guidance documents and ultimately FDA will decide what policies to adopt and how to communicate those policies publicly.

FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community; WEF-CEP = Wound-Care Experts/FDA-Clinical Endpoints Project

Panel 3:

Generating and Reporting Evidence

Panel Chairs:

Marissa Carter, PhD,
WCCC Chair, Clinical Trial Initiative WS

Marjana Tomic-Canic, PhD,
WCCC Chair, Pre-clinical Trial Initiative WS

Organization	Name & Title
FDA CDRH	John Azeke, PhD, Lead Reviewer
FDA CDER	Dev Verma, MD, Medical Officer
WCCC	Caroline Fife, MD, RWE Group Co-Chair and Co-Founder and Chief Medical Officer, Intellicure
WCCC	Lucian Vlad, MD, Clinical Associate Professor, Atrium Health Wound Care and Hyperbaric
WCCC	Shabnam Vaezzadeh, MD, MPA, CEO, Exquisite Biomedical Consulting
WCCC	Randy Schwartz, BA, Board of Directors
Solventum	Amy Law, MBA, VP Health Economics, Outcomes Research and Market Access
Mölnlycke	Monique Rennie, PhD, Global Director Medical Affairs

WCCC = Wound Care Collaborative Community; WG = working group; WS = workstream

Discussion Points

Panel 3

Focus	Questions	Panelists
Barriers (human clinical)	What is the methodology of the process for developing wound care human clinical trial reporting guidelines?	MJC: JA/RS/DV
Acceptance	Assuming that the guidelines can be published, how will industry and clinical trial investigators implement them?	MJC: CF/AL/MR
Buy-in (pre-clinical)	When reporting guidelines in multiple wound journals, what are the challenges to adoption/implementation of standardized reporting among stakeholders?	MTC: JA/LV/RS
Immediate/long-term steps (pre-clinical)	What are the best approaches and concrete steps to implement pre-clinical testing guidelines for reporting?	MTC: SV/AL/MR
Closing Discussion	How can WCCC, industry, and the FDA work more closely together on reporting guidelines and standards for pre-clinical and clinical trial areas? The same groups should help incorporate standards and guidelines into an updated draft of the wound healing guidance document or amendment to such document.	MJC/MTC: DV/RS/AL/CF

FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community

Call to Action Items

Panel 3

- Understand the barriers that prevent standardized reporting of human clinical trials.
- Understand the barriers to implementing guidelines to reporting of pre-clinical animal and human testing.
- Identify specific steps towards the implementation of pre-clinical guidelines among stakeholders (research, industry, FDA).

FDA = Food and Drug Administration

Panel 3

What is the methodology of the process for developing wound care human clinical trial reporting guidelines? Have you ever seen anything missing from clinical trials that you consider to be important? What advice would you give us for developing wound care clinical trial reporting guidelines?

- Sponsors are highly encouraged to utilize the pre-submission process with the FDA to obtain guidance on patient selection, trial design and ensuring the selected patients are representative of the target group. A significant amount of guidance is available that way.

If you're going to develop something like clinical trial reporting guidelines, what's important that we don't normally use or don't care about right now that you think we should be reporting?

- We need to be very specific about what the guidelines will cover. Publications? Poster presentations? Symposia presentations?
- The guidelines need to be realistic, timely, and flexible. Different media beyond journals should be allowed to communicate data.
- Guidelines need to meet the industry's compliance requirements.
- The guidelines should also not be exceedingly burdensome (for example, requiring a 10-year trial).
- It would be very beneficial to include what tools are accepted/approved.
- The guidelines need to be updated more frequently to address some of the upcoming technologies and devices, such as telehealth apps, which may be impacting patient engagement in wound care.

FDA = Food and Drug Administration

Panel 3

Have you ever seen any differences between drug and device clinical trials that you consider important and worth noting? How should we develop wound care clinical reporting guidelines?

- Drugs have a very high evidentiary standard for approval (much higher than devices) because drugs and biologics have the potential to be absorbed into the body and have systemic safety effects.
- The requirement for drug trials is that they are adequate and well-controlled, including the study population being well-defined (minimize bias with blinding, etc.).
- There needs to be a comparison of the drug with an appropriate control to provide a quantitative assessment that the drug is better or at least not worse (ie, a superiority trial or non-inferiority trial). We can use a placebo or placebo plus standard of care for the control.
- SOC should be standardized, especially when using combined data across multiple sites. It's also very important that when several sites are included, all must follow not just SOC but also the method of assessing endpoints and measuring certain things. Clinical site inspections are designed to verify this. One bad apple can throw out the entire program. The number of sites as well as the degree and methods of training should be disclosed.
- We need to address the "age of wound." We need guidelines or standards on how to document the wound upfront.

SOC = standard of care

Panel 3

Assuming that the guidelines can be published, how will industry and clinical trial investigators implement them?

- Don’t make it mandatory. Use terms like ”guidelines” or “flexible.”
- We need to work with the journals to get them on board and emphasize that this is the agreed upon “standard.”
- We need to incentivize the various stakeholders to play nice in the new sandbox and appreciate that each stakeholder will likely have a different incentive.
- Stakeholder engagement will be very key.
- Ongoing communication is critical (publication, publication, publication).
- We need to be able to say, “We did an industry-sponsored trial according to the WCCC guidelines, which is an organization that represents the entire field.”
- We can’t forget about the ultimate stakeholder (the patient) and communicate to them plain-language summaries to help them educate themselves on the therapies and diagnostics that are being used on them.

Panel 3

How can WCCC, industry, and the FDA work more closely together on reporting guidelines and standards for pre-clinical and clinical trial areas? How can standardized reporting help this process on your end?

Pre-clinical data is mostly to support safety, not efficacy. We need to be sure it doesn't harm the process of wound healing.

Pre-clinical testing in animals is informing the clinical trial design regarding the timing, frequency, dosing, toxicity, etc.

That said, sponsors can use one pathway, which requires one adequate and well-controlled trial supported by relevant animal models, as confirmatory evidence of efficacy.

Animal studies need to better represent the target patient population. Design and reporting need to provide a great deal more specific documentation regarding the types of wounds, details of experimental design, assessment methods, and how they could be applicable to the potential patient population.

Then, in clinical trials, a wide array of patient demographics and wound types are needed.

FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community

Panel 3

How can pre-clinical reporting help in the design of clinical trials?

- Pre-clinical testing design should be carefully chosen based on the specific patient population for which it is being developed.
- Pre-clinical reporting documents can help standardize design and comparison of studies.
- It is difficult to translate because animal models lack the complexity of real patients in clinical practice.
- Guidelines for training are industry-driven.
- Wound healing is tightly and spatially regulated across time. Different processes (epithelialization, angiogenesis, matrix deposition, etc.) are happening at different times within different regions of the wound.
- Standardizing the reporting is important but standardizing the actual procedures and work across devices, for example, is more important. All products need to measure the same way.
- Rather than assessing the proof of efficacy for healing a wound throughout the whole wound healing process, pre-clinical studies should assess the temporal and spatial relationship of wound healing, focusing on one of a few different cellular processes. This can yield targeted therapies for a single cellular process that can be combined with others.
- There will be no magic bullet that will heal them all. The complexity of the wound healing process and what we already know about pathophysiology suggest that we should not focus too much on solely trying to get one product to heal the entire wound, rather potential to combining products including repurposing and off-label use.

Panel 3

How can we best approach the implementation of these pre-clinical guidelines? How do we actually get the buy-in? What are the top three steps we need to accomplish in order to integrate this into life?

- For entrepreneurs, it is highly beneficial to know the minimum requirement for pre-clinical and clinical studies at the beginning. These are the groups that fuel innovation for the bigger companies.
- Communication from every angle on every venue, sharing success stories, dissemination, and publication.
- One incentive is to consider AI. If we harmonize the generation of data, all the AI tools will thrive on the data fed into them.
- We should generate alignment internationally because the borders don't exist when it comes to our patients.
- We should contact journals other than the main wound journals, where up-and-coming industries would be more likely to bring data.
- We can't get all of the journals in the world on board with WCCC standards so we need to go a different route.
- We can look at other associations and conferences for their scientific content review submission guidelines.
- If we as a community are committed to using these reporting guidelines in publications and reporting, they will attract attention and will help widen implementation. The proof is "in the pudding."

> *But it really comes down to just communicating on all fronts that we can and leveraging the unique megaphones that we all have."*
>
> **Monique Rennie, PhD**

WCCC WOUND CARE COLLABORATIVE COMMUNITY

WCCC = Wound Care Collaborative Community

Panel 3

How can we track the success of this? What would you recommend as a measurable outcome of implementation?

- Have we made it stick?
- Indicate by when we hope to be where; establish milestones for all to harmonize.
- What number of publications have adhered?
- What has been the adoption of the guidelines or the tools?
- Get collaborators from academia and industry to sign on in alignment and show their support.

So, one-liners from the panel in terms of getting all the things that we want to get done. What are the barriers? What are the hurdles? Do you have any quick answers to that? Pre-clinical or clinical?

- One huge hurdle is convincing physicians and nurses that documentation matters. We don't pay people for the quality of their documentation. "The crappiest documenter wins."
- Using more patient-reported outcomes in reporting. It would help the FDA better gauge the benefit-risk ratio.
- Missing assessments. These are more important than refining the therapeutics and treatments.
- Implementing clinical decision support systems in EMRs.
- Make sure the guidelines don't hinder innovation but rather support and facilitate innovation.
- Standardizing reporting of pre-clinical testing will help with the design of the studies, scientific and peer review of papers, and grant applications, all of which advance the field and support clinical developments.

EMR = electronic medical record; FDA = Food and Drug Administration

Panel 4:

Real-World Evidence in FDA and Payer Decision-Making

Panel Chair:

Joe Rolley, MSIA,

WCCC Chair RWE WG,

Principal, JTR Business Consulting, LLC

Organization	Name & Title
FDA CDRH	Cynthia Chang, PhD, Director, Division of Infection Control and Plastic Surgery Devices
WCCC	Caroline Fife, MD, RWE Group Co-Chair and Co-Founder and Chief Medical Officer, Intellicure
WCCC	William Ennis, DO, Chief Medical Officer, Healogics
WCCC	William Tettelbach, MD, Chief Medical Officer, Restorix Health
ECRI	Dheerendra Kommala, MD, Chief Medical Officer
Intellicure	Matt Pine, President & CEO
Reapplix	Kira Rupprecht, CEO
Convatec	Beate Hanson, MD, MPH, Chief Medical Officer

WCCC = Wound Care Collaborative Community; RWE = real-world evidence; WG = working group

Panel 4

Questions	Panelists
Question 1: Barriers	
• Given the lack of RWE for use in regulatory and payment decision-making for wound technologies, what do you see as barriers to collecting RWD that meets a fit-for-purpose threshold of 'sufficient quality, relevance and reliability' for labeling expansion or coverage determinations? • How will the outputs from WCCC RWE projects improve this situation?	K. Rupprecht B. Hanson M. Pine W. Ennis
Question 2: RCTs vs. RWE	
• The Natural History Project will leverage real-world data to characterize the real-world chronic wound patient versus those commonly studied in RCTs today. We understand why the FDA and payers want to understand efficacy in an environment where there are few confounding variables, but that fact virtually necessitates non-generalizable trials. • Are you concerned about that reality? • Can real-world databases facilitate comparative effectiveness research better than RCTs given that many patients have multiple wounds and wounds of mixed etiology? • How do you foresee the outputs from the Natural History Project impacting your decision-making for DFUs and VLUs and what actions will you take to incorporate the findings of this project into your decision-making?	C. Chang D. Verma D. Kommala W. Ennis W. Tettelbach

WCCC WOUND CARE COLLABORATIVE COMMUNITY

DFU = diabetic foot ulcer; FDA = Food and Drug Administration; RCT = randomized controlled trial; RWD = real-world data; RWE = real-world evidence; WCCC = Wound Care Collaborative Community; VLU = venous leg ulcer

Panel 4

Questions	Panelists
Question 3: FDA RWE Guidance	
The recent proposed guidance for RWE describes a process for real-world studies that is perhaps even more challenging and expensive than RCTs. Further, concerns regarding the use of RWD center on the potential for statistical bias, variabilities in delivering the standard of care, and access to RWD. • Why would a sponsor choose to conduct a real-world study instead of an RCT, which is traditionally more acceptable by both the FDA and payers? • What role can/should the WCCC play in assisting wound researchers navigate the FDA's RWE processes?	C. Chang D. Verma D. Kommala W. Tettelbach C. Fife
Question 4: The Future	
The Medicare Administrative Contractors just released proposed LCDs for skin substitutes. Among the requirements for coverage is high-quality evidence for each product and indication. This will necessitate almost the entire industry conducting studies at the same time over the next months. • What role, if any, do you envision RWE and in particular, AI-driven RWE, being utilized as high-quality evidence to support coverage decisions? • How will the outputs from the RWD Landscaping Project and the Natural History Project help support industry and other study sponsors for skin substitutes or other wound technologies? • How will WCCC's work impact evidence planning and funding of industry's pipeline and portfolio products?	K. Rupprecht B. Hanson W. Ennis W. Tettelbach C. Fife

FDA = Food and Drug Administration; LCD = local coverage determination; RCT = randomized controlled trial; RWD = real-world data; RWE = real-world evidence; WCCC = Wound Care Collaborative Community

Panel 4

? Given the lack of RWE for use in regulatory and payment decision-making for wound technologies, what do you see as barriers to collecting RWD that meets a fit-for-purpose threshold of 'sufficient quality, relevance, and reliability' for labeling expansion or coverage determinations? How will the outputs from WCCC RWE projects improve this situation?

We have no ICD-10 code for a diabetic foot ulcer, but we can use other techniques, such as Boolean logic, to pull lower extremity codes out of the data. Notably, having a code does not necessarily indicate a correct diagnosis. Filters are needed to validate.

We need a solid bridge that leads to patient access.

We need one set of transparent rules that apply to FDA Medicare commercial payers, the assessment companies.

We are all competing for patients, and they are limited by inclusion and exclusion criteria.

We need to agree upon the metrics for the real-world data fields for entry, even down to defining a DFU or a PU on the foot or a diabetic wound to the lower extremity or a venous ulcer on a diabetic person.

We need additional training, especially on diagnoses. Perhaps the WCCC can create a type of certification for those conducting clinical trials for data entry so that the data is consistently reported (something to incentivize).

WCCC WOUND CARE COLLABORATIVE COMMUNITY

DFU = diabetic foot ulcer; FDA = Food and Drug Administration; ICD = International Classification of Diseases; PU = pressure ulcer; RWD = real-world data; RWE = real-world evidence; WCCC = Wound Care Collaborative Community

Panel 4

Given the lack of RWE for use in regulatory and payment decision making for wound technologies, what do you see as barriers to collecting RWD that meets a fit-for-purpose threshold of 'sufficient quality, relevance and reliability' for labeling expansion or coverage determinations? How will the outputs from WCCC RWE projects improve this situation? (continued)

- We have to design studies for success in the *real world* without selectively creating inclusion and exclusion criteria to influence the delta or guarantee success.
- Results from in-hospital, real-world trials do not reflect results in RCTs.
- Both RCTs and RWD have a place, and we need to find that commonality and pursue both.
- We cannot answer all questions in one RCT, so we have to strategically define patient populations.
- The challenge with RWD - garbage in, garbage out.
- The data systems aren't collecting helpful data to provide research-ready data. EHRs are not focused on wound care and don't communicate well with other EHRs. We need to agree on metrics for RWD data entry. Can the WCCC sponsor a certification process for data entry?
- We need infrastructure and requirements on the data collection companies (HIPAA protection, data warehouses, etc.)
- Aim toward 'pay for performance' and make the data available and collectible to get there.
- Manufacturers must bridge the gap between fulfilling an unmet need to gaining patient access.

> '…It really feels like being part of a revolution and it's the real-world evidence revolution.'
> **Beate Hanson, MD, MPH, CMO**

WCCC WOUND CARE COLLABORATIVE COMMUNITY

HIPAA = Health Insurance Portability and Accountability Act; RCT = randomized controlled trial; RWD = real-world data; RWE = real-world evidence; WCCC = Wound Care Collaborative Community; EHRs=electronic health records

Panel 4

?

The Natural History Project will leverage real-world data to characterize the real-world chronic wound patient versus those commonly studied in RCTs today. We understand why the FDA and payers want to understand efficacy in an environment where there are few confounding variables, but that fact virtually necessitates non-generalizable trials.

Are you concerned about that reality? Can real-world databases facilitate comparative effectiveness research better than RCTs given that many patients have multiple wounds and wounds of mixed etiology? How do you foresee the outputs from the Natural History Project impacting your decision-making for DFUs and VLUs and what actions will you take to incorporate the findings of this project into your decision-making?

- RCTs are really designed to show product safety and effectiveness; there are strengths and weaknesses to RCTs.
- The FDA is committed to being able to use fit-for-purpose RWD to generate RWE.
- The outputs of the Natural History Project could be very useful in informing clinical study designs, such as appropriate time points to assess a specific patient subpopulation or situation. They could also help clarify SOC decisions or the control arm.
- Having natural history data can help interpret the study results of an RCT or inform about comorbidities and interventions.
- We should accept that some patients won't be helped by a pill or device. Instead, good SOC and good wraps that are actually covered by insurance may be effective. Some may need to go to the OR. We have a misalignment between what the industry wants to develop and what the real world needs.
- The outputs could be very helpful when using one adequate and well-controlled trial with confirmatory evidence to decrease cost and time of development. You could use the natural history data as real-world evidence or a historical control.
- RWD can validate findings of RCTs and can be used to give preliminary findings that would indicate where RCTs should be conducted.
- However, if RWE should be used to validate otherwise non-generalizable studies, why bother doing non-generalizable RCTs at all?

DFU = diabetic foot ulcer; FDA = Food and Drug Administration; OR = operating room; PU = pressure ulcer; RCT = randomized controlled trial; RWD = real-world data; RWE = real-world evidence; SOC = standard of care; VLU = venous leg ulcer

Panel 4

-continued-

Are you concerned about that reality? Can RW databases facilitate comparative effectiveness research better than RCTs given that many patients have multiple wounds and wounds of mixed etiology? How do you foresee the outputs from the Natural History Project impacting your decision-making for DFUs and VLUs and what actions will you take to incorporate the findings of this project into your decision making?

- A combination factor; both RCTs and real-world date have roles, but the data need to be standardized.
- Can we potentially simultaneously allow for more than one indication if we did an adequate fit-for-purpose filter to help design the clinical trial?
- We have an issue with generalizability in not just the patient population but also the size of the wound and duration of the wound.
- We aren't choosing *either* real-world *or* RCT. We need to augment both together to meet FDA safety and efficacy, patient needs, and access needs.
- Coverage and payment policy decisions don't seem to respect the more generalizable RWE studies even when they do come up. Instead, decisions are made from non-generalizable studies.
- We need data on real-world patient supplements, especially those that impact healing. But we can't just use that data to push a product to market. It should also be given to primary care providers because they are the ones seeing these wounds at the beginning, before a wound clinic is needed. They could benefit from knowing the real-world data from the Natural History Project to make recommendations (take fish oil, etc.) before the wound is much worse in the end.
- A standardized approach to real-world data collection does not necessarily reflect SOC.
- We need to be able to compare data across practice settings (hospital-based, private clinics, post-acute care, etc.).
- We need to make sure we *understand* the data generated and interpret it correctly.
- We need to be honest about healing rates. Some people never heal. If we say 'everybody heals' then it gives the perspective that everyone will be fine and we don't need money for research.

FDA = Food and Drug Administration; RCT = randomized controlled trials; RWE = real-world evidence; SOC = standard of care

Panel 4

?

The Medicare Administrative Contractors just released proposed LCDs for skin substitutes. Among the requirements for coverage is high-quality evidence for each product and indication. This will necessitate almost the entire industry conducting studies at the same time over the next 12–24 months. What role, if any, do you envision RWE and in particular, AI-driven RWE, being utilized as high-quality evidence to support coverage decisions? How will the outputs from the RWD Landscaping Project and the Natural History Project help support industry and other study sponsors for skin substitutes or other wound technologies? How will WCCC's work impact evidence planning and funding of industry's pipeline and portfolio products?

- The pharmaceutical industry gets a lot of funding because everybody's worried about adverse events. We're going to have a challenge in trying to integrate data sets without the kind of funding that pharmaceuticals have.
- Ideally, we could complement a stronger pilot study with a real-world database to confirm on a larger scale. But sometimes larger RCTs will still be necessary because newer products haven't been around long enough to be in the databases.
- Once again, the information in the databases may not be too helpful if the reporting and metric assessments are not standardized.
- With new products, we need to go prospective but catch retrospective. We need payers and regulators to allow for more comprehensive evidence generation with additional combinations.
- One issue is that no coverage is based on RWE. CMS reimbursement decision-makers are not in the wound world.
- We have to aim to show safety for regulatory purposes while giving payers enough to show the effect.
- RWE is important for continuing to feed the publications to show efficacy so that we can retain coverage.
- Perhaps a CED program should collect data on all wound types for a 'grace period' to provide access to data later.
- RWE can be used in several ways: as the primary data set to support an indication expansion, as a control arm, to generate objective performance criteria, as a generalized control, or to augment post-market requirements.
- Ultimately, clinical evidence is clinical evidence. The source could be an RCT or RWE. RWE just gives more flexibility of where it could come from. We get more power from more sources.
- Both RCTs and RWE have a role to play, but we need a level of standardization to analyze data and the spectrum of acceptance.

AI = artificial intelligence; CED = coverage with evidence development; CMS = Centers for Medicare and Medicaid Services; LCD = local coverage determination; RCT = randomized controlled trial; RWD = real-world data; RWE = real-world evidence; WCCC = Wound Care Collaborative Community

Summary of Notes from Dr Driver

Panel 4

Regardless of what we do next, barriers to patients having access to innovative treatments and advanced care must be disrupted.

Our patients should expect no less.

We must engage with international collaborators

Integrating different perspectives, experiences, resources, and expertise beyond US borders could achieve better outcomes.

Our hope is that the WCCC's research efforts will:

- Provide necessary tools for developing new, safe medical technologies for our patients
- Improve the process so patients who need it the most are not left behind.

How do we incorporate a diverse population and not leave patients behind?

Recognize that evidence that is inclusive of all patients is the bridge, and the end of the bridge is improving patients' access.

To make real change in our profession, we all need our feet held to the fire: clinicians, industry, academia.

Change the vocabulary to a more positive tone and work together to make change- understand that this is not a short-term goal.

EMR capture for wound-related cases is dismal. What is the best system to use to help make change?

Perhaps we adopt a process for capturing important data in a way that makes sense and isn't on the back of what we're already doing.

If RWE is captured in a standardized, productive way that can be used measurably and predictably, it can help guide clinical trial decision-making.

The WCCC must help inform CMS. Our work can help influence policy decision-making.

It's time we consider repurposing existing safe drugs with big pharma. We have pulled together our disease state. We know a lot about it, and we have credible data to discuss.

WCCC WOUND CARE COLLABORATIVE COMMUNITY

CMS = Centers for Medicare and Medicaid Services; EMR = electronic medical record; RWE = real-world evidence

Panel 5:

Defining Standard of Care in Wound Care

Organization	Name & Title
FDA CDRH	Cynthia Chang, PhD, Director, Division of Infection Control and Plastic Surgery Devices
WCCC	John Lantis, MD, WG Vice-Chair
Integra	Yi Arnold, PhD, MBA, Head, Global Medical Affairs
ECRI	Dheerendra Kommala, MD, Chief Medical Officer
Noxy	Tim Jacobson, CFA, CEO

Panel Chair:

Maribel Henao, DPM, MSPT,
WCCC Chair SOC WG,
Senior Director, Organogenesis

WCCC = Wound Care Collaborative Community; RWE = real-world evidence; SOC = standard of care; WG = working group

Panel 5

Questions	Panelists
Discussion Point Q1: Barriers	
As discussed in the beginning of the presentation, SOC in clinical trials has been poorly defined and variations to what constitutes SOC have been observed. In addition, SOC has been defined differently in guidelines. • At the completion of this project, when a unified consensus for SOC has been established and published, how would you incorporate the results of this project when reviewing or designing/completing clinical trials in the future?	C. Chang R. Snyder Y. Arnold D. Kommala
Discussion Point Q2: Current Results of SOC Project	
• Looking at the initial results of the SOC project so far, do you foresee any issues with these recommendations as compared to what you are currently designing as SOC in clinical trials?	J. Lantis Y. Arnold T. Jacobson
Discussion Point Q3: Outputs	
There have been discussions to update the FDA Guidance Document, Chronic Cutaneous Ulcer and Burn Wounds–Developing Products for Treatment, that was published in 2006. • What types of outputs do you need to see from our group that would facilitate adoption by the FDA into the Guidance Document? For payers (eg, published practice guidelines, consensus document)?	C. Chang D. Kommala

WCCC WOUND CARE COLLABORATIVE COMMUNITY

FDA = Food and Drug Administration; SOC = standard of care

Panel 5

Questions	Panelists
Discussion Point Q4: Future Phases	
Our project will be divided into phases, with the first phase establishing the fundamentals of SOC. • What levels of detail should be included in the next phase of the project? (eg, Offloading-what type? Frequency of debridement?)	C. Chang R. Snyder Y. Arnold D. Kommala
Discussion Point Q5: Future Phases	
• We are planning on using an eDelphi method to complete consensus on the first phase of this project. Do you agree with this method or are there better alternatives? • Do you anticipate us facing any obstacles using the eDelphi method?	J. Lantis T. Jacobson D. Kommala

SOC = standard of care

Panel 5

? At the completion of this project, when a unified consensus for SOC has been established and published, how would you incorporate the results of this project when reviewing or designing/completing clinical trials in the future?

- It would ensure standardization across study sites and allow comparison among clinical studies across the product landscape.
- The community establishes the SOC rather than the FDA.
- The community really has ‘best clinical practices’ because some high-volume centers can’t or don’t do certain things. We should collaborate and say that only centers that play by the rules should be enrolling patients in trials.
- Small start-ups may know very little about commercializing a product, so a unified consensus for SOC is incredibly important. It would allow these companies to design appropriate trials to commercialize their technology more effectively.
- The SOC is not likely to be a single point. It is more likely a spectrum stratified by various patient populations. This approach would enable clinicians and patients to benefit from the appropriate SOC while allowing the industry to innovate and develop the right products or technologies for each target patient population.
- Can we come to a consensus on the spectrum of SOC acceptability? How do we make sure that it's implemented consistently?

> “Wound care is what we do. Wound healing is what patients do if they can.”
>
> **Lucian Vlad**

FDA = Food and Drug Administration; SOC = standard of care

Looking at the initial results of the SOC project so far, do you foresee any issues with these recommendations as compared to what you are currently designing as SOC in clinical trials?

Panel 5

We need to elevate the SOC to make it closer to best clinical practice because SOC has historically been subjective.

Payers want to see comparison. The comparison really should be my new product versus something that everybody uses. Well, what is that?

It comes down to designing trials. Companies would like to design one trial that they can pay for once and can show superiority but also say to the payer, we're better than something you already pay for.

Having too many endpoints in a trial is difficult. L=o

It may limit some of the high-volume centers.

It will increase the cost of the trials. Theoretically, we could decrease enrollment timeframes to be more realistic. But overall, we should do it right instead of doing it quickly.

SOC is only half of the clinical design question. The other half is the inclusion/exclusion criteria. That comes down to what endpoint the FDA is willing to accept. But industry is then forced to choose patients that they can win with, leading to the same kinds of trials repeated over and over.

We should be able to expand to PROs or pieces of the puzzle like perforation, neogenesis, or angiogenesis that actually help the wound progress along. That is a clinical trial that is more reflective of the population because you're not trying to heal everybody. You're showing a specific effect.

We should actually work backward:
Prophetically update the endpoints, then work backward to determine the guidelines necessary to reach those endpoints

FDA = Food and Drug Administration; PRO = patient-reported outcome; SOC = standard of care

Panel 5

What types of outputs do you need to see from our group that would facilitate adoption by the FDA into the Guidance Document? For payers (eg, published practice guidelines, consensus document)?

First, the WCCC proposes an updated Guidance. The collaborative community is welcome to send recommendations to the FDA for consideration. Second, facilitate general adoption for the broader community, especially with publications. We need published information, consensus guidelines, published and peer-reviewed in some way that can be used for standardizing practice across the board.

FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community

Panel 5

What levels of detail should be included in the next phase of the project (eg, Offloading-what type? Frequency of debridement)?

- That is not up to the FDA. However, it may be wise to focus on areas that lack much consensus, where conflicting recommendations exist, or areas that lack information. Also, look at areas with potential for a big impact on outcomes.
- The SOC needs to be as specific and granular as possible. It should not just be a checklist because different sites may be technically checking off the box but doing so improperly. For example, looser vs tighter lower extremity compression…What is the standard? Or debridement? How much debridement? To what level?
- This should require training/cross-training to bring everyone as close as they can to reach a consistent level of efficiency.
- The SOC can be influenced by payers. Anecdote: practice in NY takes up to 8 weeks for offloading to be paid for. So, offloading within 8 weeks becomes the SOC.
- How do we include supplements in the SOC?
- We also can't let it take several hours to enroll a patient for a trial.
- When considering recruitment time costs, there is tension between being too specific and not specific enough. We also can't be too specific about, for example, exactly which offloading boot to use because it may not work for every patient. Ulcer location and patient compliance are additional factors to consider.
- Pull information from real-world evidence databases and wound registries to determine what is generally agreed upon and then proceed from there.
- Start with CMS-approved quality measures and use reporting to create databases.
- We may also shift into thinking about what is not acceptable because it may be easier to find a consensus. What *is acceptable* may end up as a spectrum.

CMS = Centers for Medicare and Medicaid Services; FDA = Food and Drug Administration; SOC = standard of care

Panel 5

We are planning on using an eDelphi method to complete consensus on the first phase of this project.
Do you agree with this method or are there better alternatives?
Do you anticipate us facing any obstacles using the eDelphi method?

- It is a good method. It would be a powerful document that allows for an important conversation.
- One caution is to not include only experts for input. The committee members should not all share the same perspective. Perhaps we should put it out for public comment after the eDelphi process.
- The downsides to the eDelphi process are that it takes time and multiple iterations. We would also need to define the expert.

Key Points from Dr Driver

- We have had discussions with payers/CMS. There are not many of them, unlike the FDA. They say that we should come together first, tell them what we're going to do, and invite them to our meeting. They say to work on the evidence and bring it to us. So, we just need the evidence. (We also need to look at their own CMS guidance. That's only fair.)
- We are not subservient to the FDA. We are collaborative with the FDA. We are the experts. We are the community. We do the work. They give an opinion.
- We will be going to the Critical Path Innovation Meeting (CPIM) again. This is important to enlighten and educate all three divisions of the FDA.
- We have to publish every single thing that we do.
- Looking at what is *unacceptable* vs what is *acceptable* is an important perspective. Most of the time we are looking at what isn't working more than what is working.
- We need more prescriptive clinical trials. We can't run it like a clinical practice. If we don't follow the rules, we will ultimately get data that we can't utilize. Garbage in, garbage out.

CMS = Centers for Medicare and Medicaid Services; CPIM = Critical Path Innovation Meeting; FDA = Food and Drug Administration

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Driving Innovation
in Wound Care Summit

SAWC Spring
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WOUNDS

Q&A with Program Chair:
Vickie R. Driver, DPM, MS

Q&A Session

Where does a product's ease of use come into play in endpoints? Does the product need an OR or application in a doctor's office? Does the product need monitoring daily, weekly, etc, or require visits to a physician or a wound care nurse? How does success depend on compliance by physician and patient?

- The question speaks to many potential benefits beyond the endpoints that might normally be measured in a clinical study. The CDRH really looks at a benefit-risk calculus with the totality of evidence, including patient perspectives. With that being said, having accurate ways of measuring these benefits is important.
- A new approach is being validated in which patients use simple language to measure themselves rather than numerical measurements (eg, slightly better, much better, was this easier, did this reduce my workload, did this make it easier to do without a nurse?).
- Using the patient perspective may be more 'measurable' and interesting to the FDA in terms of safety and efficacy.
- It incorporates the incremental benefit for the patient moving to healing and back to life.
- The more complex a device or diagnostic is, the more important it is to assess the human factor/ease of use. The user must be part of the algorithm.

CDRH = Center for Devices and Radiological Health; FDA = Food and Drug Administration; OR = operating room

Q&A Session (continued)

To Dev Verma:
Bill mentioned the importance of diagnostics to properly assess and stage patients like what is done in oncology. What would reasonable endpoints be for diagnostic and/or assessments staging for wounds?

- The value of diagnostics is not just in endpoints but also enriching the subject population to those most likely to benefit from the product. It can also be done in subgroups of products. It should be done in a way that the product is still generalizable in terms of endpoints.
- For example, all wounds heal by granulation and epithelialization. Diagnostic devices are being developed to measure wound bed prep, which would presumably measure the degree of granulation. Improvement in granulation could then be used as a clinician-reported outcome. Perhaps that can lead to a primary efficacy endpoint.

To Dr Driver:
What will be the major update on the 2006 Guidance and when will it be available? Any tentative timeline in addition to the regulatory requirements? Will the guidance also take reimbursement mechanisms into consideration?

- WCCC is assembling a committee to develop recommendations to the FDA for modifying the 2006 wound healing guidance document. Our recommendations will be based on evidence gained over the past 18 years. We hope to have our recommendations draft prepared by Q4 of 2024.
- The FDA is supportive of this work and will make the final decision as to whether a new guidance will be issued.
- Don’t wait for an updated guidance to be published. Please continue to develop validated patient-reported and clinician-reported outcomes.

FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community

Q&A Session (continued)

A primary need identified across all these panels is the need to establish consistent metrics to facilitate innovation and quality assessment. What is the path forward for adopting these and bringing them to the FDA, and what happens after to ensure that it has a real impact?

- We have to ensure validation and show the FDA why it matters to the population being studied. We also need to show why we think it may be applicable to the broader population once it is on the market.
- Clinicians, academicians, and industry representatives rely on guidance from the FDA on what to incorporate into a trial (endpoints, diagnostics, etc.).
- The FDA has released several guidance documents that may not have 'chronic cutaneous ulcers' in the title but do apply. There is a guidance on patient-reported outcomes and how to develop content validity or construct validity. There are almost a dozen FDA guidance documents on real-world evidence that are not specific to chronic wounds but still apply. There's also guidance that discusses multi-component endpoints and composite endpoints that came from the statistics team.
  - Patient Reported Outcome (PRO) Guidance*:
    - June 2022: Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments
    - Feb 2022: Patient-Focused Drug Development: Methods to Identify What Is Important to Patients
  - Substantial Evidence of Effectiveness (SEE) With 1 Trial and Confirmatory Evidence*:
    - Sept 2023: Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence
  - Multicomponent/Co-primary endpoints*:
    - Oct 2022: Multiple Endpoints in Clinical Trials
  - Master protocols guidance*:
    - Dec 2023: Master Protocols for Drug and Biological Product Development

FDA = Food and Drug Administration

**This guidance was not mentioned specifically at the summit but is shared here as a direct reference.*

Q&A Session (continued)

Will adding a surrogate endpoint and lowering the bar for clinical trials drive innovation?

- When we add a surrogate component, covariates, or variables, it's harder to statistically reach a conclusion or validation. So, we need to be sure to understand what the product is being used for.
- Most of the endpoints suggested are not surrogate endpoints. That is a different concept. We are actually discussing which endpoints are clinically relevant enough to be an achievement of their own. Shrinking a wound to 90%, with no draining and no smell, would be a great outcome for patients.
- Surrogate endpoints are predictors of another endpoint. These have yet to be determined in wounds.
- Also, we are not talking about lowering the bar for clinical trials. We are talking about defining standards and raising awareness.

To Dr Li:
What are the prospects of gene therapy for wounds?

- Research in pediatric retinal disease has validated a very sophisticated gene delivery system. We should certainly look at the approved biologics and think about what gene we might administer to a wound for a similar pathway.

Q&A Session (continued)

Why is there resistance to creating and recognizing the specialty of wound care in the medical community, when acknowledging the specialty by creating a true certification for dedicated practitioners allows patients to be directed to the right place and specialty and create a solid database for research?

- Most people realize that wound care is dynamic and needs to be very comprehensive and interdisciplinary. The 'resistance' really lies in understanding that education across the board has to be adopted amongst different societies. Universal education could help move that needle forward.
- The biggest challenge in wound care is that it's multispecialty. So many medical disciplines and surgical disciplines encounter wounds, and each has different contributions. These meetings allow each to come out of their silos to work together.

There was a professor, William J. Jeffcoate, who published a recommendation consensus on clinical trial reporting guidelines for DFU back in 2016 in *Lancet*. What would be the major differences that the GAPS group will work on to update in this area?

- We're reinvestigating the literature to determine a minimum data set to ask people to collect. That was still 8 years ago so that doesn't mean we shouldn't do it again.
- Also, there were no guidelines other than the FDA, which is very general and not for wound care specifically.
- A lot of things have also never been discussed like comorbidities, SES data, and caregiving data.

DFU = diabetic foot ulcer; FDA = Food and Drug Administration; SES = socioeconomic status

Q&A Session (continued)

Has WCCC considered the American Society of Testing Materials (ASTM), the American Association of Medical Instrumentation (AAMI), or other consensus standard bodies for guidelines, best practices, or standards of development and publication?

- They don't really publish standards that are directly related to what we're talking about other than dressings. And Sarah Griffiths is leading that work on dressings.
- We could develop international consensus standards, test methods, guidelines, or best practices and use these as an independent way to publish in a consensus manner rather than publishing in just one journal or specific area of medicine.

Will there be regularly scheduled updates to the clinical and pre-clinical reporting guidelines? This can increase the relevance and impact the guidelines.

- Yes, we have a clinical meeting about every six weeks. Howard also runs the GAPS meeting at a higher level.
- In terms of clinical guidelines, we envision this to be a live document with regular updates to the original form.
- All meetings are listed on the website.

Q&A Session (continued)

For a Natural History Project, were any data from the VA utilized? Because I'm not surprised about the autoimmune comorbidity. I often see that at the VA and question whether it will be yet another disease that will be linked to Agent Orange. Eventually we knew amyloidosis was linked.

- We don't have access to any data from the VA.

The challenge is not collecting RWD as much as it is having the carriers look at it and use it in their decision-making. Carriers in CMS, as the leader, must come up with a clear, solid process to submit data and then have it used for coverage decisions.

- Agreement from all.
- In general, a lot of these processes are not clear, especially on the payer side.
- Many of the innovators using real-world evidence are small start-ups. We need examples of companies that have gone through the process and blazed the trail. RWE does have a place and should be utilized more, but we need a pathway.
- Maybe WCCC can help companies that want to generate RWE to work with the agency and blaze that trail.

What communication have you all had with the CMS regarding MACs about accepting real-world evidence and how can we move this needle?

- We need to have dialogue and at two levels: the CMS level and the MAC level.

CMS = Centers for Medicare and Medicaid Services; MAC = Medicare Administrative Contractor; RWD = real-world data; VA = Department of Veterans Affairs; WCCC= Wound Care Collaborative Community

Q&A Session (continued)

The standardization of decision-making for coverage must go across country, not just carrier to carrier. A patient should not have to cross state lines or move their home to get wound care.

- Agreed. The general policy should be consistent nationwide. But your coverage could be dependent on the payer policy, the Medicare Advantage plan with regional responsibilities. It may not look as universal as it normally would be under fee-for-service Medicare.

How feasible is the idea of creating a wound care patient repository where any healthcare organization could submit data available for research by anyone? How challenging is this? Who would manage this effort? Or am I dreaming?

- The challenge is more about how to get people access and an interface for them to use. The data exists. If funded, it could be done today. We just need the money and time. The same is true for WCCC.
- Other industries combine efforts and build registries and data sets, not just for product but for data. This could be a very good solution for us to take. We will just need heavy commitments and investment of not just money but time and effort.
- There aren't many fields or practices that *don't* work together collaboratively to move the field forward.
- We need the work to be done regardless of whether we have different products or similar products.
- The Diabetic Foot Consortium through the NIH is a great example.

NIH = National Institutes of Health; WCCC = Wound Care Collaborative Community

Q&A Session (continued)

What is the FDA policy on encouraging clinical centers to share general data and historical data with AI companies for free? This can generate ways for better defining patient populations for studies and the relevant outcomes.

- This is a great question, and the FDA doesn't currently have an answer. Generally, companies are pretty protective of their information once they've collected it because it's so expensive to do a trial. But neither FDA participant had knowledge of any specific FDA regulation.
- Furthermore, FDA aside, the CMS systems don't talk to each other anyway. The databases are not interchangeable.

To Dr Driver:
How do we navigate those companies or entities that are not compassionate, or empathetic to our call to action?

- The best thing we can do is convene a willing, brilliant, and honest group of individuals who have and understand data to support what an investor might need to know to invest. A plan to organize such a group focusing on this educational initiative is being discussed now at WCCC. The priority is always to keep patients at the center of our work. We aim to focus on the actual needs of our patients based on their pathology and biology, not on how much money a technology will make. The unmet need is huge, and we need investors to develop innovation to help us heal our patients.

"We're looking to expand our islands of excellence into a sea of excellence instead of a sea of mediocrity"

Lisa Gould

CMS = Centers for Medicare and Medicaid Services; FDA = Food and Drug Administration

Q&A Session (continued)

To Kara Couch with the AAWC:
How can we work together to better inform folks that want to invest in our patients?

- We have to set a standard and hold each other accountable to at least the bare minimum standard. Not having a baseline to work from negatively impacts our patients and our ability to train people. We shouldn't let industry run our training. We need to work with the FDA, CMS, WCCC, and continue the alliance with Wound Healing Society (WHS) to establish a standard. Then share that standard with family practice, internal medicine, etc.
- It's a difficult space to raise assets in. Cancer has 150 times the research funding because nobody asks them to cure cancer, like we're required to completely heal a wound. It's a panacea. An evolution in the endpoints, as we've discussed, can foster greater innovation and give investors more confidence that there is a path to approval and a return on their investment.
- We can't play the blame game. We need to focus on solutions. Working meetings like this can result in conversations and summary articles, which will then spur more discussions and creative thinking. We also can't expect a savior to dictate to each faction exactly what they need to do.

"We need to remember why we're in this. We're in it for the patients. We want patients to get better, to get safe and effective treatments. And I think keeping the patients at the center of our decision-making is key."

Dev Verma, MD, Medical Officer (FDA CDER)

AAWC = Association for the Advancement of Wound Care; CMS = Centers for Medicare and Medicaid Services; FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community; WHS = Wound Healing Society

Q&A Session (continued)

How shall we consider the FDA guidance on diversity in clinical trials in the design of real-world evidence?

- It's important to make sure that clinical evidence is generalizable to a broader patient population. This is a benefit of RWE because it allows inclusion of a broader patient population.
- We also need to consider the diversity of challenges for our patients. Ask ourselves if we have products that address all of our patients' challenges.
- Diversity and inclusion in clinical trials is critical. Most trials are enrolling white males and that does not reflect the patient population. We need diversity to represent those in the world who will actually receive the product. Additionally, some ethnicities may have different genotypes. Therefore, we need to make sure it will be effective for them.

"It's not what does the FDA want, it's what does the patient population need?"

Cynthia Chang, PhD, FDA, CDRH

FDA = Food and Drug Administration

Q&A Session (continued)

To Dr Li:
You gave a great talk about where we need to go and resetting the table. Are we getting there? What do you think about today?

- This conversation is an important step in the right direction. It's great to engage everyone in a non-partisan, level playing field to discuss the issues.
- Ultimately, we need to think about the patients' needs and think creatively about how to address that while avoiding the old traps.

To Dev Verma:
How can the FDA work with drug developers to make registration trials more efficient, given the current investment climate for chronic wound companies?

- Investors and developers should be aware that although two adequate and well-controlled trials are usually necessary to demonstrate substantial evidence of effectiveness, in certain circumstances, sponsors may be able to perform one adequate and well-controlled trial with confirmatory evidence. Sponsors should discuss their plan with the FDA early in development.*

What resources are available or could be developed (Golden Bridge) for startups in Biotech to help fund pre-clinical and early phase going beyond theoretical support, meaning "thoughts and prayers" into tangible grants and research funding where qualified?

- Small startups working together can achieve a great deal more. We can advocate for the development of some of those relationships. WCCC is eager to help guide this process.
- Theresa Jones: The NIH funds all stages of research on diabetic foot ulcers that go through peer review. You can consult the website for information on the grant process.

NIH = National Institutes of Health; FDA = Food and Drug Administration

**See Sept 2023 Guidance: "Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence "*

Q&A Session (continued)

Can one of the takeaways of this summit identify good candidates for a standard that can be brought to the FDA and blaze that path? What are the low-hanging fruit that can become the first-action items? What can we tackle first out of the long list?

- Within the WCCC, so much of this work is being done in parallel by a lot of people. The priorities and timelines shift constantly as we learn more and more. We have a new list resulting from today's discussions. We have immediate goals and far-reaching goals. Some goals have been reached and some are 3-5 years out. After making the decisions to tackle a project, we have to draft protocols, get consensus, etc. There are multiple steps along the way. Sometimes we have to backtrack if we realize something isn't working. We can't and won't do everything so we have to pick the things we believe we *can* do.

Even though the FDA is not standardizing standard of care, from regulatory perspectives, do you think it makes sense if an RCT is using saline-moistened gauze as a comparator standard of care and the outcome reaches superiority? What would you think about such a design, given the standard of care mentioned, in what Regranex compared 25 years ago? Does the agency really not have a say in defining standard of care?

- Unfortunately, this is a hypothetical scenario because companies do test their product against the SOC and find that the SOC is better. But we never see that data at the FDA and it isn't published because no one wants to publish negative trial results. In a sense, the SOC doesn't matter.
- The FDA's mission is to ensure safe and effective products are available to patients. The FDA does not regulate the practice of medicine, and therefore does not dictate what SOC should be. Determination of the exact SOC utilized in trials should be based on expertise (eg, consensus guidelines from societies).

FDA = Food and Drug Administration; RCT = randomized controlled trial; SOC = standard of care; WCCC = Wound Care Collaborative Community

Q&A Session (continued)

Will a new standard of care document be a built-in living document that will be reevaluated regularly?

- Yes, it would be something just like updates and guidelines from different societies.
- The WCCC will need to iron out how frequently it can be updated and what commitments can be made. They will do their best.

How can we link a specific standard of care practice with the biological pathways of healing to assess the ones that have the biggest effect on the cellular and molecular pathways of healing? What will give the biggest bang for our buck? What key element should we push our best effort on?

- We don't want to set the bar so high that people must do 10 different things for SOC, if some of them don't really make a difference. Smaller differences just come out in the wash of randomization.
- Unfortunately, we don't know how the SOC affects the cellular/molecular pathway of patients. The NIH is funding important work in diabetics to help us sort some of this out.
- We need diagnostics and standardized, reliable, validated, and paid-for diagnostics. How are we going to get to the physiology of these particular patients?
- We need to be moving toward personalized medicine.

FDA = Food and Drug Administration; RCT = randomized controlled trial; SOC = standard of care; WCCC = Wound Care Collaborative Community; NIH=National Institutes of Health

Summary and Conclusions

The field needs to move beyond "more of the same."

Unmet needs should drive the advances, rather than products or devices.

The field needs to push beyond incremental advancements and reach for quantum leaps instead.

- Follow examples in the fields of ophthalmology, oncology, and weight loss.

Historically, wound care has always meant complete wound closure as a primary endpoint.

- Instead of wound care, we want wound therapy. Instead of wound closure, we want wound repair.
- We need to reassess endpoints, clinical trial design, and performance measures.

We need to transition from approaching wound care from a 'bird's eye view' of the treetops to the level of the soil.

- What is going on under the hood of the car?
  - Science is looking at cellular and molecular processes, cell pathway signal activation, gene expression with angiogenesis, neurogenesis, regenerative activities, production and deposition of collagen, epithelialization, and remodeling.
- New therapeutics are NOT using the science.

We need to move BEYOND the 3Cs: cleaning, covering, and closure.

- Electroceuticals: the delivery of energy to stimulate wound healing.
- Dietary therapies: biomolecular extracts from food sources can stimulate wound healing; food as medicine.
  - Wound healing from the inside out, rather than the top down (topicals).
- Microbiome therapy: evaluating the possibility of beneficial bacteria.