U.S. FOOD AND DRUG ADMINISTRATION

Wound Healing Workshop

Virtual Workshop Via Zoom

Day 2

Friday, April 29, 2022

9:00 a.m. to 3:25 p.m.

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C O N T E N T S

C O N T E N T S (continued)

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P R O C E E D I N G S

(9:00 a.m.)

FDA Introductory Comments – Felisa Lewis

DR. LEWIS: Good morning, and welcome to day 2 o of the FDA Wound Healing Workshop. I am Dr. Felisa Lewis. I am the moderator for the a.m. session, for the first one.

Yesterday, as a review, you heard a lot about the challenges and complexities of wound healing, and thank you to all of the speakers, panelists, and especially the patients who participated in the Patient Voice session. That was extremely valuable to hear that perspective of someone who is actually dealing with chronic wounds that are not healing.

This morning, and today, we are going to now turn to some of the work that is being done in this field of wound healing to try to help get to solutions that do lead to better outcomes, and this morning, we have a very exciting panel of a number of different speakers.

Today in our morning session we have these

particular objectives. We are going to look at the current areas of research in wound healing and explore how that research in wound healing can be applied to innovative product development.

As a review, the common understanding of normal wound healing is that it does go through four distinct phases: hemostasis, coagulation, the inflammatory phase, the proliferative phase, and then the matrix and remodeling and scar formation. Generally, this would be a fairly orderly process that would occur over the course of one month, but when we talk about the difference between acute and chronic wounds, this is a very complex and coordinated series of phases that includes, on the left-hand side, in the normal wound, hemotaxis, collagenesis, collagen degradation, and collagen remodeling.

In addition, there are a number of other processes such as angiogenesis, epithelialization, and the production of new cells and cytokines and so forth that are vital to developing a normal and healthy wound healing milieu.

The chronic wound, on the right-hand side, as you can see, can deviate from this process, and at this point when it gets into that deviation, it is hard to bring it back to becoming a normal healthy wound healing environment. When these deviated processes are perpetuated, this can lead to an imbalance of abnormal processes that overwhelm and supersede the productive and healthy wound healing process.

Much of the research in wound healing has focused on correcting the deviant processes and optimizing the environment to allow wounds to heal. On the left side in the orange box are some examples of the approaches and the techniques used to address the symptoms of the wounds to optimize wound healing, however, this clearly hasn't been enough.

In this session, you are going to hear from several speakers and panelists who are, in essence, peeling back the onion to delve even deeper into the pathophysiology of wound healing to develop some exciting new approaches and targets for wounds

healing, and I think this portends well for the progress that we can make in trying to get these chronic wounds to heal in an orderly manner.

So today, we have three speakers, and then our panelists, some additional experts. First you're going to hear from Dr. Ira Herman, who is the senior director of biological engineering for precision healing and also the professor and director emeritus for the Center for Innovations in Wound Healing at Tufts University.

Dr. Kirsner you heard from yesterday speaking about the challenges in clinical trials. Today he will be speaking about the wound microbiome.

Dr. Geoffrey Gurtner, who is the chair of the Department of Surgery and also professor of biomedical engineering at the University of Arizona, he is going to be speaking about mechanical transduction and barriers to innovative product development.

Then on our panel, we have Dr. Gerecht, who will be speaking about engineered bioscaffolds; and

Dr. Jones, Teresa Jones, who is the program director for diabetes complications at the National Institute of Diabetes and Digestive and Kidney Diseases at the NIH; Dr. Marjana Tomic-Canic, who will be speaking on translational research, she is the William H. Eaglstein Chair in wound healing and also the vice chair of research and professor of dermatology, and the director of the Wound Healing and Regenerative Medicine Research Program in the Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery at the University of Miami Miller School of Medicine; and then finally, Dr. Chandan Sen, who is the Distinguished Professor and J. Stanley Battersby Chair of Surgery at Indiana University, whose expertise is in biomarkers and translational research.

So we'll go ahead and kick it off with Dr. Herman.

Welcome, Dr Herman.

Presentation – Ira Herman

DR. HERMAN: Thanks so much, and good morning everybody. As Dr. Lewis mentioned, we had

a terrific day yesterday hearing not just from practitioners and from folks at the FDA, but also from patients and their harrowing stories. Of course, Dr. Marcus yesterday mentioned in her opening remarks about how we're experiencing this remarkable and scouring health burden, not just nationally, but globally.

I thought it be worthwhile just to remind everyone that on the backside of a pandemic, the viral pandemic that we've been experiencing in the past few years, the silent pandemic of non-healing wounds, as we heard from our patients, is absolutely real.

When you look at the incidence, the number of cases -- this is from 2015, then our paper that we published in 2016 -- you can see that there's almost equivalence between the number of cases for cancers from chronic wounds. So this is a real problem, locally and globally, as I mentioned, but not just a silent pandemic, but a real pandemic.

We in precision healing are trying to understand exactly how we might be able to

understand what a wound might be experiencing in real time and at the point of care. It's often been said that you can't know where you're going. unless you know where you've come from.

We spoke about yesterday, and we know for a fact, that there have been almost no medicines that have been developed over the past 20 years that are focused on healing wounds, and that there are products that are able to perhaps intervene in what might not be completely optimized ways.

We want to be able to understand, and barcode as best we might, where a given wound might be, and to develop companion diagnostics that are not only able to understand where a wound is, but where a wound is going. That will enable practitioners at the point of care, regardless of whether it's an expert in care like Lisa Gould, Caroline Fife, or Rob Kirsner, or Geoff Gurtner, but that in fact we may even see, with this kind of technology and product development, that the patient will become a practitioner. And that's our hope, that experience and expertise will give rise

or give way to diagnostics that are accurate, that are precise, that are personal, and that we can actually rely on that are predictors.

Today in my few minutes, I've been charged with talking about a construct that Rob Kirsner and I, Jeff Davidson, Paul Bornstein, and Greg Schulz brought to the forum in the context of how to describe what's ongoing in a wound and what might be the dynamic and reciprocal signaling pathways that control wound dynamics, and dictate to what extent to give a wound that's in a non-healing state, entrapped in a chronically inflamed state, and position the wound in order for it to heal.

In our discussion yesterday, we talked a little bit about what's wrong and what's broken in wound care and why this space is fragmented, and not just from an education perspective. As Caroline Fife so smartly said, medical students are not really trained, and there are no specialties that actually focus on wound care in particular, or the remodeling, or the pathophysiology that takes place during healing. And we talked about why this

space is fragmented even on the technology side, and we covered how few trends and formative medicines have been developed.

I put this up as an opportunity to make everybody sit and think about, if you were to try and heal this conundrum, as I call it, where would you start, and what might be the first principles that you begin with, and why might you start there?

If you had a technology toolkit -- the proverbial what if -- if you could do this, what would you want in your toolkit, what would it look like and how might you use it, or whom might be using it? What might be the best practices or protocols that would be embedded in it and how might you be able to ensure across the care continuum, whether being a payer, or a practitioner, or a patient, and how might you make sure that everyone has a value-added position in the equation?

This was actually showed a little bit by Sally Lewis in her introductory comments, and this really represents the scar contradistinction

between wounds that are unable to heal and wounds that don't. In the context of dynamic reciprocity and in the conversation that takes place, regardless of tissue compartment, we're not necessarily just talking about what might be the biochemical signals, or the molecules, or the cells, but in fact there are physical chemical interactions, physical controllers, whether it might be pH or mechanical straining.

You'll hear from Geoff Gurtner later in this session on matrix remodels in response to injury, and that the remodeling process itself, the action of the proteases that contribute to the remodeling, give rise to bioactive fragments in the matrix that then go on and signal themselves within the epithelial compartment to stimulate the migration and proliferation of the epithelial cells that enables the reparative process.

Regardless of whether we're talking about let's say the remodeling of the vasculature in the deep dermis, or the remodeling of the bricks and mortar let's say of the dermal compartment, all of

this is actually ongoing as the microenvironment controls the responses to injury.

We spoke yesterday and had discussion a little bit about how the microenvironment controls the healing dynamics, and so too is the case of non-healing wounds, where it's not just about the commensal microbes that contribute to the healing process let's say in the healing wounds, but in fact the biofilm-associated microbes and the other opportunistic pathogens that Rob Kirsner will talk about following my few minutes here with you.

So whether diabetes gives rise to a matrix that's glycated or contributes to the reactive oxygen species, we'll hear a little bit from Chandan Sen how macrophages that have inflammatory cascades can be converted so that macrophages that are contributing to the inflammatory response are actually signaled to give rise to a healing response by their production of things like TGF-beta and interleukin-10.

The cytokines skewing that we know, which exists in the microenvironment of the wound bed,

again, a dynamic and reciprocal signaling pathway, or set of pathways, that contribute to the non-healing stage and impede migration or proliferation in the epithelial compartment; or the excessive overburdening of the proteases that contribute to the destruction of growth factors survival signaling entities and receptors that might be necessary in to complete the circuit to do the healing.

As we know, all of these cells that contribute to the healing process, which are not indigenous to the wound bed proper within the dermis or the epithelial compartments, these come from the circulation and are delivered by homing and binding and unbinding across the epithelial cells that enable the extravasation of these cells to do their work in the connective tissue compartment of the wound bed; so, too, these are dynamic and reciprocal processes.

I've dubbed this a conundrum, that metalloproteinases destroy the growth factors or the microbes contribute to an elevated inflammatory

status and impede what might be the vascularization that's so essential for healing.

It was Mina Bissell who actually brought to biology this term of "dynamic reciprocity," and Rick Schultz and I, together with Rob Kirsner as I mentioned, and Jeff Davidson, and Paul Bornstein, we thought that this construct would be valuable in the context of wound healing because, indeed, the microenvironment does control the cellular and molecular responses and dictates whether or to what extent the given wound is able to heal.

Regardless of stage of healing or compartment of healing, whether within the dermal or epidermal compartment, dynamic and reciprocal signaling refers to this ongoing interaction that takes place between the indigenous and immigrant cells and their local microenvironment.

Again, I think that I'm expanding this construct not just to be, how should I say, exemplified by the signals that take place that are molecular or chemical, but also the physical signaling that is so important, whether it be

simple pH of the local microenvironment that I'll share with you in a minute -- the activity of a given protease population that can actually go on and destroy matrix or actually promote healing by slightly tweaking the basement membrane upon which epithelial cells need to crawl and proliferate in order to heal wounds and go to closure.

Again, this was referred to and alluded to. We all know this; that regardless of whether we're talking about the phases of healing that stop the bleeding or promote the inflammatory response -- and some good, not others, maybe not so good -- during the reparative and remodeling processes, regardless of wound state across the entire continuum of healing, dynamic and reciprocal signaling is important in order to regulate the extent of healing.

Here we can see, as I've laid out, whether it be during the stopping of the bleeding or during the inflammatory cascade, proliferative or remodeling steps, you can see the binding of platelets and their association with matrix or, as

I said, the differentiation/extravasation of myeloid progenitor cells that come from the bone marrow that can actually then find their way out of the vasculature into the connective tissue locally in the wound microenvironment; for example, this is the case as monocytes differentiate to macrophages, and then convert as inflammatory reparative, macrophages; then again, fibroblasts making a signal from the matrix environment that they find themselves, and endothelial cells on a basement membrane just like epithelial cells, needing to talk with the local microenvironment in order to do the work that they have to do in order to heal the words.

I think that this is an overlooked component of this dynamic and reciprocal signaling pathway; that is the role that pH plays in not only protecting the skin, integral to shielding from the environment any microbial peptides that are present on the skin intact, and the acidic microenvironment of the intact skin. We all appreciate that, indeed, when skin is injured, alkalinity and

contribution from the plasma itself raises locally the ph. In fact, there have been limited clinical studies that indicate, indeed, stark control of the pH in the wound microenvironment is essential for optimizing what might be healing dynamics.

I think, as we alluded to yesterday, the DARPA program is developing smart dressings, wherein, for example, in Tim Sia's [ph] lab, they're using microbots to try and locally activate pH control by sensing and actuating, using smart dressings. I think that this will be an important opportunity for us going forward.

We also know that non-invasive imaging techniques have shown us and help us to guide debridements where biofilm-associated microbes are impeding healing by stimulating the innate and adaptive immune responses that contribute to the excessive inflammation in the wound bed. We know that these microbes are actually quite pH sensitive, and that in a basic environment of the non-healing wound, it's going to foster microbial pathogenesis by stimulating proliferation in the

cells.

We also know that pH is key to macromolecular assembly, and especially collagen cross-linking the production of the basement membrane stimulation of the vascular response by creating basement membrane macromolecules, as well as building the matrix, the bricks and mortar of the matrix, in the dermal compartment. We also know that, indeed, pH controls the activity of the metalloproteinases that destroy matrix and keep wounds in a non-healing chronically inflamed state. Some of the pH optima for the bad proteases is more alkaline than the beneficial proteases.

So again, this dynamic and reciprocal signaling -- regardless of whether we're talking about pH or oxygen control of cross-linking of collagen and collagen signaling fibroblasts, or epithelial cells, or endothelial cells in the matrix remodeling -- we know that, indeed, fibroblast signaling; the matrix that they make; the proteases that they assemble and activate; and whether, again, the myeloid progenitors coming from

the bloodstream into the connective tissue; again, the homing, the binding, the unbinding; the activity that these cells express, are all regulated by this dynamic and reciprocal signaling.

Then of course, the endothelial cells and angiogenic activation being what it is, we know again that the endothelial cell cues for migration and proliferation come by this interaction that takes place between the cells in the microenvironment that exists in the wound bed.

I'm just going to give you a few examples before I finish and wrap up and give the podium to Rob Kirsner and Geoff Gurtner. You can see, for example, in the context of fibronectin interactions with cells, fibronectin is a multidomain-containing molecule, as Richard Clark early on showed, that could contribute to fibroblasts and other cell signaling.

We know, for example, that one or another of these domains interacts with cell surfaces in ways that regulates attachment and spreading. We also know, for example, as this example shows us, in

response to injury, the interaction of the cells with the extracellular matrix components and the domains that are contained within, dictate whether or to what extent a given population -- in this particular case, fiberblasts -- can spread and respond to injury.

We know, for example -- again, as another example for dynamic and reciprocal signaling -- that the integrins, which are embedded in the plasma membrane, they come together as dimers, are members of a multigene family that recombine and contribute significantly to how cells adhere, how cells migrate, and how cells proliferate.

Especially in the context of the epithelium, we know, for example, that remodeling extracellular matrix by proteases of the advancing front, these cells are producing nicks in the matrix in ways that expose the domains that alter the binding, that promote the migration, and that stimulate the proliferation at the rear as these cells are re-epithelializing and closing wounds.

It is this conversation that takes place

across the continuum of healing, that regardless of whether we're talking about the epithelial cells and the integrins that they express, or the fibronectins, or other matrix molecules, or what might be the pH of the local microenvironment and how it controls protease activity, we know -- for example, as we spoke about yesterday, as Rick Schultz and we have shown over the years -- that there are perhaps several log orders difference in the activity and abundance of proteases that keep concern about whether it's arising from vascular insufficiency of diabetes.

Here too is another example of dynamic modulation and reciprocity where, for example, FGF on its own -- fibroblasts growth factor on its own -- is not able to really signal efficiently, and that by binding to heparan sulfate proteoglycan in the extracellular matrix, dimerization of the receptor population takes place.

So in closing, I just want to say thank you again to the organizers for a terrific meeting, and also to remind everyone that it is the local

microenvironment, and we are absolutely in desperate need of smart diagnostics, companion diagnostics that not only are able to characterize what a wound is doing currently, but also be predictive in a way that will teach us what the healing trajectory might be and how we might pair the optimized treatments so that wound care across the continuum is not only precise, but it's personal. And again, I want to thank everyone for their attention.

Presentation – Robert Kirsner

DR. KIRSNER: Hi. I'm Robert Kirsner, chair and Harvey Blank Professor of the Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, and I'm going to briefly talk about the wound microbiome in wound healing.

Now, oftentimes this mechanism of chronicity in chronic wounds has been proposed that bacteria causes inflammation and proteases that leads to decreased growth factors and unresponsive cells. The idea is that if somehow you could eradicate bacteria, you can lead to a healed wound.

Unfortunately, only limited data demonstrated that complete healing is seen with this paradigm, while there is some data for reduction in wound size with this paradigm.

In clinical practice, infection is typically based on clinical features; that is a combination of bioburden, bacterial virulence, and host defense leads the microbes to go from contamination, through colonization, critical colonization, local infection, and spreading and systemic infection, where at some point the amount of virulence and diminished host defenses leads to bacteria, causing inhibition of wound healing.

Classically, 10^5 bacteria has been suggested as a threshold for wound infection. The problem is that we do not routinely quantitate bacteria in clinical practice, and also the question is whether or not it's the bacteria or the environment that is really causing the problem. Furthermore, this data that was a secondary analysis of a clinical trial found that while greater than 10^5 inhibited healing, even lower levels such as 10^4 to 10^5, inhibited

healing or slowed healing to a degree greater than less than 10^4.

But let's get back to this idea of chicken or the egg. I want to highlight the keratinocyte growth factor trial for venous leg ulcers that took biopsies at baseline and did quantitative cultures. You had to have less than 10^6 bacteria to enter into the study, so there was actually two pathways to getting less than 10^6 bacteria.

The first was that on the first tissue culture, it met criteria, and the second was that the first culture was elevated, but then you could reduce the number of bacteria by any mechanism possible, and then re-culture and have less than 10^5. Interestingly, it was healing differences based on how patients enrolled in the study. If they enrolled with the first culture, 29 out of 42 patients healed at 40 percent, while if they enrolled needing a second culture, that is the first culture at more than 10^6 and then it was subsequently lowered, only 9.3 percent of patients healed.

So you can see that it's possible that the environment of a non-healing wound actually may lead to elevated bacterial counts, and reducing bacterial counts may not be a method to improve healing.

Now, the bacteria that I've just referred to is free floating or planktonic bacteria, but over the past 15 or 20 years in wound healing, how bacteria grow has also become important, specifically related to the formation of biofilm.

Here's an early paper that hypothesized why chronic wounds will not heal, a novel hypothesis. And many people have observed that biofilms are present in a majority of chronic wounds, while they're present in only a minority of acute wounds, suggesting that biofilms may be causal to the non-healing phenotype of a chronic wound.

There's also been suggestion that if you address biofilms as part of wound care, that you'll get better outcomes. This is a typical study that was carried out of 190 patients with chronic limb ischemia, many with diabetes and osteomyelitis.

All of these patients had biofilm-based wound care, and there were great results.

Many of these very hard-to-heal patients healed, but problematic in this study, and many studies like this, is that biofilms were never confirmed prior to institution of the biofilm-based wound care or shown to be eradicated after biofilm-based wound care. So while the concept of giving biofilm-based wound exists, it is certainly less than proven.

There are also novel ways to diagnose bacteria. The standard way that is done in practice is through culture, but more recently, DNA techniques have been utilized. If you use culture as the gold standard, DNA or molecular techniques pick up a significant percentage of the same bacteria that is identified with culture, but if you flip the script and look at molecular diagnostic techniques or DNA sequencing as the gold standard, cultures on the other hand only pick up a small minority of the actual bacteria that are present by DNA sequencing.

Now, if all of these bacteria are present, the question is, what do you do with all those bacteria and how does that help a wound healer? We still don't know that, but what we do know is that temporal stability -- that is maintaining the same type of bacteria in a wound -- is actually associated with poor healing; that is, changing microbiome is associated with improved outcomes. Here's a very nice study that looked at the microbiome over time, and showed that patients who had a changing microbiome were more likely to heal than those people that had a stable microbiome.

We also looked at the microbiome, but in a slightly different way. We looked at three different areas of the wound. We looked at the wound bed, the wound edge, and then healthy skin adjacent to the wound edge. What we found, perhaps not surprisingly, was that many of the bacteria that are found in the wound bed are also found in the wound edge and healthy skin as well. So what we concluded was that bacteria colonize wounds from the wound edge.

Now, this idea is very important because recent data has emerged that oftentimes chronic wounds have bacteria, not on them, but in the cells adjacent to the chronic wounds. Here's an example of diabetic foot ulcer skin, the keratinocytes harboring intracellular Staph aureus compared to control foot skin. The reason for this harboring of intracellular bacteria is one of the key mechanisms in eradicating intracellular bacteria, a mechanism focusing around protein perforin-2 is suppressed in chronic wounds, so normal patients have perforin-2 active. It kills intracellular bacteria, but chronic wounds have a depression of perforin-2, and intracellular bacteria is allowed to proliferate and then re-infect or re-contaminate the adjacent wound.

Now, why are diabetic foot ulcers, as an example, deficient in perforin-2? Well, it seems that the gamma delta T cells are the major resident cells expressing perforin-2, and gamma delta T cells are important in tumor surveillance, and inflammation, and in healing of acute wounds, but

they are depleted in diabetic foot ulcers, leading to this deficiency in perforin-2.

The latest idea is that perforin-2 deficiency leads to intracellular accumulation of Staph aureus around this skin, which activates the AIM2 or inflammasome pathway that actually is associated with non-healing. This pathway leads to a type of inflammatory cell death called pair [indiscernible] apoptosis [ph], which is elevated in diabetic foot ulcers, and then cause it through caspase-1 to release interleukin-1 beta and create an inflammation, although at very low levels that can't even be seen clinically, and this circular pathway continues in diabetic foot ulcers.

In this very brief talk, what I try to highlight is the wound microbiome is very complex, especially as it relates to healing. We know about planktonic bacteria, we know about biofilms, and now we're learning about how bacteria evade detection within the surrounding skin of patients with chronic wounds.

Perhaps these ideas related to bacteria may

lend insight into the pathogenesis of wound healing and novel targets for therapeutic intervention, and for the purposes of the FDA, trial design. Thank you very much for your attention.

Presentation – Geoffrey Gurtner

DR. GURTNER: Hi. This is Geoff Gurtner, and I am currently the professor of surgery and chair of surgery at the University of Arizona, but previously I was at Stanford for the past 15 years. My career really has been devoted to trying to develop small-molecule drugs for chronic wounds and burns, and the reason is that I am a surgeon who takes care of these patients.

The extremes of wound healing really have no current real treatments that are effective. On the left is a chronic wound in a young diabetic patient that was about to get a 10-hour operation with about 3 weeks in the hospital required, and on the right is the late sequelae of a facial burn.

As we discussed yesterday, wound healing is the largest medical vertical without a single small-molecule drug approved, and because it costs

so much, if we had an effective drug therapy, unlike other areas of pharma development, this is an area where we might actually save the system billions of dollars.

No successful drug approval has occurred in wound healing for the past 25 years. The last drug that was approved was PDGF in 1997, and no small molecule has ever been approved, and a small molecule is different from a growth factor like PDGF because it's essentially a chemical. This chart just shows this graphically, that the likelihood of approval when you get from phase 1 to having an approved drug is zero percent in wound healing, and the overall FDA average is about 10 percent.

Pharma companies have been interested, but this space doesn't fit well in the pharma playbook. Unlike other medical conditions, skin injury has real procedural components like debridement and offloading that are very challenging to standardize. I'm also the chairman of the NIDDK Foot Consortium, and we deal with these challenges

in the context of biomarkers every week.

Diabetes has been the focus for pharma, but I as a clinical trialist, as well as a surgeon, can tell you, diabetes is by far the most challenging area to do wound healing trials. The final piece is pharma generally doesn't like to work on formulation or user experience until very late in the game when they know the active works. And when you have something on the surface of human bodies where the patient can manipulate it, it's different than a drug that's injected or ingested, so there are lots of challenges in producing clinical trials that are reproducible.

Because there are no drugs and there is really no pharma presence in wound healing, this space has been dominated by medical device companies. Most medical device companies bring their products either through a human tissue pathway or through a 510(k) pathway, which is, I think we would all agree, somewhat lighter in terms of regulation than a drug pathway.

I think many of the products are certainly

safe. How effective they are is debatable, but they generate billions and billions of dollars for these publicly-traded companies, so there's not a lot of incentive for medical device companies to innovate in developing transformational therapeutics.

I have been for the past 15 years in Silicon Valley. I've started several companies that have been successful. I have generated returns for my investors in the 5 to 10X range, and some of my best friends are venture capitalists or senior pharma executives. The bottom line is, it's not that pharma and venture capitalists don't like wound healing; it's that they like other things better.

So oncology is a much easier place to get a financial return because you don't have to cure cancer; you maybe only have to prolong life expectancy or disease-free remission for a couple weeks, and you then can get a drug where you can charge hundreds of thousands of dollars for a course of therapy. So from a purely financial

perspective, that's a more attractive opportunity than going into something like wound healing.

I think many of us in this space -- and I've been at these meetings for 20 years since I started my career -- keep hoping for the cavalry to come and somehow solve this problem for us. I think we have to disabuse ourselves of that notion. I don't think the cavalry is coming, so I think it's important that the people on this call and the people in this community realize that we have to solve this problem on our own. So we're going to have to do it without somebody coming in and waving a magic wand and making it all better, and the reason we have to do it is because our patients need it.

So With that as kind of background and kind of a very brief overview of the challenges of drug development in wound healing, I'm going to touch on in the next 10 minutes the small molecules that we are developing, one for chronic wounds such as diabetic foot ulcers, sickle-cell ulcers, and one for burns and hypertrophic scarring.

As Caroline Fife said yesterday, when you have wounds that are going to heal, they are almost always characterized by this granulation tissue formation, which is really little loops of capillaries, and you get increased vascularization of the wound bed, and then the keratinocytes migrate over it.

As a clinician who has seen thousands of patients in a wound healing center, you know when a wound isn't going to heal. It has very scant granulation tissue, and it stalls. So most of the things that we see, although they may come from different diseases, the final common pathway is that there's not enough granulation tissue to support keratinocyte migration.

We've been looking at this, again, for 15 years, trying to understand how different disease states compare; new blood vessel formation. We've looked at aging. We've looked at diabetes. We've looked at a variety of diseases.

This is one paper we published 12 years ago on diabetes. These are identical mice genetically.

One is made diabetic, and the observation is if you make an injury in the skin -- so this is a peninsula of skin that we've raised -- in the diabetic mouse genetically identical, all that tissue dies, and in the wild-type mouse, all that tissue lives. If you look at various markers of vascularization, oxygenation, or capillary density, they're profoundly different.

There are many, many things that lead to vascular growth and development -- VEGF, Ang1, a variety of different growth factors -- and as Marjana said, it's a multifactorial thing when we have a wound diathesis or a wound that doesn't heal. So what we did was go upstream of all these growth factors and go to the transcription factor, which is HIF-1 alpha. The discovery of HIF-1 alpha, Gregg Semenza, Bill Kaelin, and Peter Radcliffe won the Nobel Prize in 2019, and it's a master transcription factor that turns on all of those growth factors that lead to new blood vessel formation, as well as changes from aerobic to anaerobic metabolism, and basically allows cells

and tissues to survive tissue ischemia.

What we have found, and this is all published data, was that diabetes directly blocks the activity of HIF-1 alpha primarily by blocking its ability to assemble into the transcriptome, which then leads to an inability to turn on all those proteins and growth factors that lead to new blood vessel formation such as VEGF, SDF1, and all the other hypoxia response genes. This was published about a decade ago, so when you don't have the ability to turn on the gene transcription, you don't get protein production.

Knowing that, we spent about eight years looking for a molecule that could actually reverse that, and obviously the sine qua non of a successful molecule is it has to stabilize or upregulate this transcription factor. We thought it would be important for it to be a small molecule that could potentially go through the skin. Again, given the challenges in this space, novel chemical entities are much more challenging from an FDA regulatory perspective, so we thought if we could

find a repurposed or FDA-approved molecule, that would be the best, and this is just a list of some of the many, many molecules we looked at.

What we finally found was an old drug, deferoxamine, which is used for hemochromatosis, and what we found was that this deferoxamine actually could block this poisoning of this transcription factor by diabetes through two mechanisms. One is by scavenging free radicals through Fenton chemistry, and then also by decreasing the amounts of the enzymes that dissolve HIF-1 alpha, and what that led to was an upregulation of all those genes that lead to new blood vessel formation.

So what we found was if we used this drug intraperitoneally, we actually instead of that genetically identical mouse with diabetes having all that tissue die, it now all lives because you're overcoming what's causing the diabetes to poison this transcription factor and prevent new blood vessel formation.

We have been focusing on small molecules as

the way to do this, and there are other ways you certainly could do this because we think, ultimately, to take care of wounds, you have to treat not just the wound, but the surrounding skin; the concept of treat the donut, not the hole.

A lot of times we throw these growth factors into this proteolytic milieu and hope for the best, and I think there are unique challenges in the wound environment and in wound trials, and small molecules, because they're chemicals, they're more resistant to proteases and many of the extreme conditions in the wound.

I think when you're thinking about the developing world and being able to scale this across healthcare systems that don't have the same reimbursement and the same cost structure as the United States, small molecules are relatively inexpensive to produce, so we could potentially get this into more disadvantaged situations.

Finally, we wanted to potentially have a molecule that could prevent wounds, and small molecules, really, are about the only thing that

can penetrate transdermally without significant technology innovation.

This is kind of our evolution of this, and what we wanted to do is create a polymer that looked like a bandage that could deliver this DFO, not only into the wound but through the skin, and this again was published about five years ago. This on the upper-right here is the actual product. It's a drug-release polymer that releases DFO. That DFO either gets into the wound or through the skin, upregulates HIF-1 alpha, and increases vascular density. And since we know where wounds occur, and diabetes, and pressure ulcers, we can put this sort of polymer on those areas, and essentially have therapeutic angiogenesis for areas at risk of wound formation.

Again, this was all published in PNAS five years ago, showing that this actually works both in preventing ulceration but also increasing the strength of the healed skin in the context of recidivism for diabetic wound healing, but having improved material properties of the skin that might

theoretically have some impact on secondary diabetic foot ulcer formation.

As we learned yesterday, and I think we'll learn further today, again, all that work was in diabetes. There are real challenges in conducting a diabetic wound trial. On the right is the graveyard of companies that have failed. So as a clinical trialist, there are things that are hard to standardize in a diabetic wound one trial, and what that means is then you have to do a gigantic trial, hundreds and hundreds of patients. And gigantic trials cost hundreds of millions of dollars. And to be honest, if we're doing this ourselves, we don't have hundreds of millions of dollars to spend.

So we decided to look at other potential places where this approach and this product might work. Although many of you in this audience probably don't think this is a simpler indication, sickle-cell ulcers actually are considered incurable by most wound healing specialists because there's really nothing we can offer, but they're

not generally anesthetic. They don't require offloading. They tend to be centered in key centers.

So we decided to go after sickle-cell ulcers using an orphan drug program, and that gives us the ability to lessen our costs, get a shorter time to approval, get extensions of our patent life, and also have preferential pricing and reimbursement. This is a relatively small subset of the wound space. This is one of Caroline's wounds with no name. And importantly, deferoxamine is already used in these patients systemically for iron toxicity and iron overload.

We needed first to show that this actually worked in these patients, and this is, again, published data where we took a humanized sickle cell model and showed we could accelerate wound healing in these patients using this transdermal polymer.

So we've pivoted development to the sickle-cell ulcers. We have an open IND that was awarded and opened in April of 2019. We have

received orphan drug designation from the Office of ODD. We've had an audit of our manufacturing facility in California, and we were planning to start a clinical trial in 48 patients, 2 to 1 placebo, to control in the summer of 2020. And as many of you may remember, this was a time when we actually had a pandemic occur.

So COVID 19 really derailed this program. We had an outpatient clinical trial in the U.S. south, primarily an African American population, which with a well-founded distrust of the healthcare system, a high level of vaccine hesitancy. This trial continues, but we've had a very, very slow rate of enrollment across our four centers.

Because we have had these presentations at various settings, we've had many patients reach out to us to use this in the context of expanded access. Of course I'm not allowed to take care of these patients, but this is a patient of one of my colleagues at Stanford who has a similar disease to sickle cell anemia, which is called beta

thalassemia.

This patient has had an ulcer for three years. This is anecdotal, and I fully admit that, but it's an interesting case study. The patient has received HBO, Apligraf, and all the advanced technologies. Again, in the expanded access context, we've had this patient, and the patient is now healed after 16 weeks. She's been an internal crossover control because during Thanksgiving she didn't want to come in and stopped using the polymer, and the wound got bigger. This was the end of our initial expanded access period, and we petitioned the FDA and got approval for another 6 weeks, during which time the patient healed. This just shows the patient. I think you can see this works by decreasing the iron. You can see the hemosiderosis, which has almost completely resolved.

We had heard a lot from the patients, which I think are the ultimate beneficiaries of all this. This is just a quote I'll let you read yourself. I think this was a patient that really had lost hope,

and I was really remarkably happy that this worked, and the wound remains healed.

In the final few minutes -- that's kind of our work in underhealing chronic wounds -- we also take care of burns. I'm the director of a burn center here in Arizona. This is the sequelae. I have a pan facial burn that I took care of at Mass General when I was an intern, and you can see are horrible results. There's nothing I can do surgically as a plastic surgeon to fix this.

One of my mentors at the Boston Shriners Hospital is Matt Donelan, who made the offhand comment that "scars form where there's tension," and that led me to work in this area for about 20 years, trying to understand, how is it that tension forms scars and fibrosis? As a surgeon, we all know that's true. These are Langer's lines, and surgeons are taught to orient our incisions parallel, not perpendicular, to these lines because they're lines of minimal skin tension.

The simple experiment, again published, is where we took a mouse obviously genetically

identical and changed the levels of mechanical force, and got about a 10-fold difference in the amount of fibrosis; so not stretching of the scar, which people talk about, but an active biological process where you have more scar deposition.

We've kind of developed a device, and this device is approved. It's essentially a shrinking bandage. This shrinking bandage creates a mechanically privileged environment, and that has now gone through clinical trials. It went through a 510(k) clearance process and has gone through multiple randomized-controlled trials, all of which were statistically and clinically significant. The market has spoken. It has about a 93 percent approval rating.

Unfortunately, this device, although it's very good for scars and incisions, isn't going to help the patient that we started this journey on, which this is the same patient 6 months earlier when he was in the emergency room, and after 6 months of having famous Harvard professors take care of him, obviously a dismal result.

So to fix that, we need to come up with a biomolecular approach, so we have looked at hypertrophic scars to try to find, again, bottlenecks, because this is a multifactorial process, there are multiple genes involved, and what we want to find are the things that control those genes.

The one that we have found through ingenuity pathway analysis, which is a bioinformatic program, is focal adhesion kinase. It's the first messenger in mechanotransduction on the inside of the cell membrane and leads to a collagen deposition and inflammation. So we've gone on, and pharma fortunately was working on focal adhesion kinase, not for scars and fibrosis, but for cancer because it's involved in cancer. There have not been any approvals of these drugs, but we were able to out-license one from Verastem, and we're in the process of working with the FDA to open an IND.

Again, most burns are taken care of with hydrogels, so we wanted a sustained-release hydrogel that would release this agent. As we

spoke about yesterday, pigskin is the best model of human skin, so we did a pig model of deep partial-thickness burn injury -- this is the last few slides -- and what we found was at early time points, we actually saw an acceleration of healing and that the wounds -- and these are deep partial-thickness injuries -- healed faster, and that's at one month.

The really exciting thing -- and it is important to accelerate wound healing, but most burn wounds will heal because they're in healthy patients -- was that we actually saw a skin regeneration at the 6-month time period, where we actually saw hair, skin appendage, and regrowth. And if you look at this using very various bioinformatics software programs, this skin that has regenerated actually looks very much like unwounded skin with basket-weave architecture.

So we're currently working with the FDA. We had a very collaborative pre-IND meeting in May, and we're continuing to perform the tests that were required. We have an orphan application in

process. We anticipate submitting our IND in Q4, and we have a clinical trial site with one of my colleagues, Ben Levi, at Parkland Burn Center in Dallas.

So with that, I'll conclude. Again, as someone who practices in this field, we don't need more silver dressings or amniotic membranes, which probably have been used for thousands of years. What we really need are things that are going to change the biology, and I think small-molecule drugs for chronic wounds and burns are potentially transformational for patients. And with that, I will close and hand it back over to the moderator.

Panel Discussion

DR. LEWIS: Thank you very much to all of our speakers for their insightful presentations. We have 30 minutes for our panel, and I hope that this discussion will be just as thoughtful as those presentations and help further probe into ways that we can overcome the obstacles of conducting wound healing clinical trials.

Just as a reminder, the public attendees can

submit comments and questions to the Q&A box, and we'll address them as time permits, and we hope to summarize the answers to the questions that we cannot address today in the panel through a post-meeting summary document.

On our panel, as a reminder, we have our speakers, Dr. Herman, Dr. Kirsner, and Dr. Gurtner, and then joining us on our panel, we have Dr. Jones, Dr. Gerecht, Dr. Tomic-Canic, and Dr. Sen.

For our first question, I'm going to direct it toward Dr. Gerecht and Dr. Tomic-Canic.

As translational researchers, what challenges have you encountered in helping translate the work that you do to developing products for use in humans?

DR. GERECHT: Maybe I can get started.

I think what we heard, especially in the last couple presentations, is basic science is still lacking. Our understanding of the healing and the reoccurring of the wounds is lacking, and we really need to work on understanding the biology

of the healing to be able to develop more targeted therapeutics.

I think Dr. Herman mentioned the DARPA program, and the DARPA program is focusing on soldiers, which is a population that is relatively healthy and younger, and of course it's different from the population of non-healing wounds. Also, understanding the regenerative processes and signaling in the different populations I think would help.

From my own experience in wound dressing, there are some requirements of the FDA. For our case specifically, it was the bench testing that Dr. Guan from the FDA presented yesterday that just don't align with newer technologies with advanced materials. It's problematic, and it would have been better if we knew it early on, but as in academia, we are not always aware of all of that.

One thing that was surprising for me -- and I'm a bioengineer, so I'm not that close to the clinics -- is it's kind of a wild west in terms of how physicians treat wounds. The clinical

approaches vary, and as we develop these protocols, you go to one place, and they treat wounds like that, and the other is different. I think developing the protocols of the treatment, along with the products, would be really helpful.

I'll tell it Marjana comment.

DR. TOMIC-CANIC: Sure. I think we could go a half hour just discussing this question because there are layers of hurdles when you are doing translational science because you're kind of placed between a rock and a hard place.

As a scientist, whether you are applying to funding agencies or sending a manuscript, when you study humans, that you cannot manipulate very easily, you are basically labeled as descriptive scientists; so you take something, and then you analyze it, and you're describing it.

A scientific approach typically challenges anything you discover, and you need to prove it by manipulating it, which you are forced to go back to the animal models. And that's where the major translational component gets even more challenging

because we don't have a good model that is very representative of the human condition, whichever wound we are talking about, simply because we are humans, and these are different species, however close or mechanistically they might get, like pigs, for example.

That kind of challenge has not been sold or resolved, so you need to go study humans, and then reapply that into animal models to prove that whatever you discovered in patients actually can be manipulated. That's one of the major challenges that we have encountered.

The other part is when you are a scientist in academia, the translational aspect on pushing that forward -- I think Geoff just gave us a great example of how this can be successful but, you know, the infrastructure in every place is not the same. So the ideas, and protection of these ideas and discoveries, are always challenged by the timelines. We are pushed to publish, we are pushed to get grants, we are pushed to actually publicly depose our inventions and discoveries. On the

other hand, in order to protect that, you can't do that for a significant period of time.

I think this translational aspect of pushing it out of your discovery and getting it through the processes to actually be able to develop further, I think is a significant challenge in translation, other than obviously going back to the models, and I'll stop here.

DR. LEWIS: Thank you, both of you, for your insights. It does certainly sound that we still do have some work in getting the research into actual processes that will lead to actual products.

Dr. Gurtner, and actually Dr. Herman, both of you do research and are really intimately involved all the way to product development. Would you concur with their observations, and do you have any additional thoughts?

DR. GURTNER: I personally think that the best model for humans is humans, so I think not being able to get into the clinic is, I think, a real impediment to progress being made. If you look at other spaces, they have terrible animal

models, like idiopathic pulmonary fibrosis, the bleomycin lung model is a terrible model, yet drugs are developed, and there actually are approved drugs.

I think searching for the perfect model to kind of figure it all out I think, in my opinion, it's kind of a road to nowhere. I think letting us, in a safe way, get into the clinic, I think that's where real advances are always made, is when you finally get things into the clinic; and that's where the rubber meets the road; and that's where you have the biggest impact. The sooner you can get there in a safe and ethical way, I think the better.

DR. HERMAN: Yes, I agree with that. Again, I think it's important for us to appreciate that while wounds may look the same, they may be in fact different. And not only are they different holistically, but different heterogeneically speaking. In other words, what's happening on one side of the wound or in one region of the wound, it's not necessarily good or bad.

For us, I think it's important to appreciate that we need to really have an understanding of what the wound is doing currently in order for us to really pair what might be treatments that are going to be optimally designed for healing dynamics. I think that it's not necessarily that we don't have the appropriate medicines but, in fact, maybe we're not doing the right thing, at the right time, for the right reason.

Again, I think having an understanding of -- take a car, for example, and your car isn't running. Is it because it doesn't have gas, or because there's a fuel line block, or is a distributor broken? So all the things that I just mentioned give rise to the car not going down the road, which is the same symptom.

The same is the case in a wound that's not healing. Why is it not healing? Is it because of microbial burden or is it because the protease levels are to the moon? So how might we pair what might be treatments based on the advanced diagnostics that we're trying to develop? I think

that that's a key point here that I just want to re-emphasize.

DR. LEWIS: Dr. Kirsner, you have some thoughts as well?

DR. KIRSNER: Yes. I just wanted to dovetail on something that was mentioned by Dr. Gurtner, and that is the idea that the human model is the best model for human disease.

As an example, when this new paradigm of perforin-2 deficiency and perforin-2 killing intracellular bacteria was being developed, most of the work was done in animal models, and it wasn't until the translation to humans in wound healing was it then accepted by a major journal and considered as a paradigm-shifting idea.

I think while models are good, the human model is the best model, and as Geoff pointed out, this is true not only for wound healing, but across all of medicine.

DR. LEWIS: Yes, and I think that's a theme that we heard yesterday, particularly in the Patient Voice, that, really, for each patient,

there are different circumstances and there are unique characteristics.

To segue into our next question, I think one of the themes, too, that we heard is why there are some commonalities, perhaps there are opportunities to tailor treatments to unique individual circumstances based on things like pH, for example. But one of the other areas where research is really happening in a space is in the use of biomarkers.

I'd like to call on Dr. Sen and Dr. Jones. First of all, can you explain what research you're doing as far as biomarkers, and perhaps define what you mean by biomarkers and how they might be utilized to help develop innovative products for patients with non-healing chronic wounds?

Dr. Sen, would you like to start?

DR. SEN: Is it for me, Dr. Sen, or Dr. Jones?

DR. JONES: For you, yes.

DR. LEWIS: You can go ahead, sir.

DR. SEN: We heard during the Ira Herman talk about the importance of having essentially a

sneak preview. He mentioned that as a predictor in viewing the healing factory. The biomarker does exactly that. If we consider the wound, it has two essential and fundamentally related components. One is that it's a structural defect. You have a structural defect; that's why we call it a wound, but it's also a functional defect.

If we draw from the studies that are currently going on in the Diabetic Foot Consortium, we have one study that essentially looks at not only filling of the hole, the donut hole that was said, which is the structural component, but also the restoration of the function of the skin, which is the barrier function of the skin.

Now, the background of the study, just to give an example, was the observation in pilot studies on chronic wound patients done by our group and the group of Dr. Geoff Gurtner, and observed that about a third of all wounds that closed essentially closed without the restoration of barrier function.

Today the definition of wound closure is

where the gap is covered by skin, and there is no discharge, and it stays that way for 2 weeks. That's the current definition. It does not account for the functional aspect of the closure or the restoration of barrier function.

Now, what this pilot study observed, which has now led to a full-blown study that is currently happening at the Diabetic Foot Consortium, is that if the wound closed, only structurally but not functionally, that wound is more likely to recur. We know that wound recurrence is a major problem and is a major cost burden in healthcare.

So in this particular case, the TEWL study, or the transepidermal water loss study, is looking at those cases where the wound is closing as currently and taken to be the marker of closure, which is covering of the wound and no discharge for 2 weeks. And in those cases where this is happening without the restoration of barrier function, we are then looking at the wound records. And in this case, according to the pilot study data that we have seen, wound transepidermal water loss

measurement at the site of the wound is a predictor of, or a biomarker of wound recurrence. This is one example of a biomarker that's currently being studied.

There's also another biomarker that has been studied, which is a molecular biomarker run by Dr. Marjana Tomic-Canic and team, and that's looking at a particular gene that you measure the wound edge, which is a predictor of healing or non-healing. If you have a sneak preview into whether the wound is about to heal or not about the heal, one would have an objective foundation to move to plan B, if you will, and to move to a more aggressive form and save that limb from amputation before it goes too far down a negative path.

Dr. Jones?

DR. JONES: Yes. Thanks. That was a great introduction. I just want to thank the organizers. It's been really a fantastic workshop. I've learned a lot.

I'm a program director at NIDDK and the project scientist for the Diabetic Foot Consortium,

which was started in September of 2018, with the main goal to develop biomarkers for diabetic foot ulcers, and that was the feedback we've heard from experts in the field, many who are attending this workshop and you've heard from.

That was the key missing link in clinical research for diabetic foot ulcers. You can appreciate it from the talks that these biomarkers act as a window into the wound. I'll just give the FDA definition for a biomarker. It's a defined characteristic that's measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions, and can be molecular, histologic, radiographic, or physiologic characteristics. These are all types of biomarkers.

So as you said, we're working to develop biomarkers that can predict healing, can predict recurrence, and that could diagnose infection. And we hope that this will be a good resource for the community because as part of this, we're collecting

wound fluid, wound tissue, blood, serum, and images and longitudinal data on patients who are suffering from diabetic foot ulcers, and collecting it in a standardized manner.

I guess it's so important, as you've heard, that these biomarkers can really act as a bridge from all the advances we're seeing in technology and discovery of different pathways, and really apply that to the wounds. As we heard yesterday, it's very disheartening for patients to have these wounds, and have them be open without any objective measured, besides visually looking at them, that they might be responding to a certain therapy.

So there are other reasons to study biomarkers such as refining clinical trial entry and better diagnostics, but I think a main one is to really be able to understand what's going on with a certain treatment for a patient. Thank you.

DR. LEWIS: Thank you, Dr. Jones. I think that certainly highlights the fact that we do want to optimize -- trying to stratify patients, if you will, by predicting, if you will -- who will

respond, as you said, and that will help with hopefully getting good results and good outcomes in clinical trials, and getting products approved.

Dr. Herman, you had some thoughts?

DR. HERMAN: It's a great discussion, and I think having an understanding of where a wound is and where it might go is exactly what we're after.

I think that we appreciate that, in time and space, the wound is not stagnant. So having an understanding of what might be one or another biomarker, whatever that might mean, at a given time may not necessarily be helpful for a practitioner aimed at trying to hasten healing or get a desired outcome and closure.

So I think it's really important for us to appreciate that we need a comprehensive toolkit. I shared early on in my talk, brief as it was, the need for a toolkit that's comprehensive in a way that can characterize not just the molecules, but perhaps what might be some of the physical and chemical cohorts that are controlling wound dynamics.

We know, for example, how important pH is, and Geoff commented about how tensegrity is, introduced by Don Ingber, and we've shown, for example, micromechanical strain of endothelium can convert an endothelial population from a quiescent population to one that's actively angiogenic.

So I think it's not just about the molecules, and I think it's not just about a given biomarker, but it needs to be done dynamically over time so that we can see moment to moment, in real time, at the point of care, what's happening in the wound in order for a practitioner like Rob Kirsner or Geoff Gurtner to know what exactly to do for that particular patient so that they are not patients that are not getting the appropriate care, regardless of where they might be in the United States or the world.

DR. LEWIS: I think that's an excellent point.

Dr. Tomic-Canic, you have some thoughts?

DR. TOMIC-CANIC: I just want to say, although I agree with everything that's being said,

and I think that there is a need for maybe even a longitudinal way of kind of dynamically testing the evolution of what is going on with wounds, I think that also there is a value and very high clinical utility, if you want, of being able to predict who is going to heal up front.

If you can predict who is going to heal with standard of care, you can actually direct more advanced therapies to patients who will not, and you will also have tools that can actually select them when you are going into clinical trials, which I think is also useful.

As a part of Consortium, Dr. Sen mentioned we are also looking at open wounds, collecting the tissue biopsies from the wound healing edge as a debridement tissue, which is typically discarded. That is an extremely valuable source of information that we are using to look at proteins, and develop tissue biomarkers that can be utilized routinely in a clinical simple routine pathology test that can actually predict who is going to heal in 12 weeks and who is not. So developing that type of

biomarker, again, it's utilization in a clinical space that we're hoping to develop.

In addition to that, I would mention also that Consortium is working on systemic biomarkers because, again -- we talked about this a little bit yesterday -- there is a systemic presence. We talked about this, whether this is a disease or this is a symptom.

There is a systemic presence of molecules that basically reflect the presence of the wound on a patient. And again, whether we are looking at blood or urine, or other samples that can be obtained from patients, I think, again, that's a source of information that can be utilized to develop a different set of biomarkers, again, predicting the clinical outcomes, and I think that's what Consortium is looking at.

DR. LEWIS: Thank you, Dr. Tomic-Canic.

Dr. Kirsner?

DR. KIRSNER: Yes. One thing I wanted to mention is because wound healing is a relatively low-tech specialty, I think that many approaches

are going to be valuable. It's not as if we have one unmet need; we have multiple unmet needs. So a lot of the approaches you're hearing are not whether there's a need for a single best one, but all of these approaches, if they come to fruition, will benefit the patients, and also benefit a variety of aspects of clinical trials.

I'm actually quite excited about the opportunity for these approaches to be handled, whether they're a single point or longitudinally over the care of a patient.

DR. LEWIS: Thank you, Dr. Kirsner. This is an excellent discussion.

Dr. Sen, you also have some comments.

DR. SEN: Yes, I think to step back a little bit, and given the nature of the community we have today, it's very important to emphasize the point I think briefly addressed by Dr. Gurtner, that although the final goal is to close that wound, that cannot be the only goal as we test different therapeutics.

As we talked about this, the reason I bring

that up in the context of biomarkers is when final wound closure is the goal, then, pretty much, all the biomarkers seek to predict final wound closure; but when we all agree that final wound closure cannot be the only goal, as we develop different types of therapeutics, we will then lay out some intermediary goals. And for those intermediary goals, there could be biomarkers that predict those intermediary goals.

That is something that is ahead of us that we need to address when we all agree that complete wound closure cannot be the only goal as we approve drugs and devices at the FDA.

DR. LEWIS: Thank you all for your comments on that question. We just have about five minutes left in our panel, so this is a question I'd like to address to all of the panelists.

From a pathophysiology and product development perspective, in your opinion, what are the greatest barriers to innovative product development for non-healing chronic wounds?

Dr. Gurtner, why don't we start with you?

DR. GURTNER: Yes. I think, for me, the greatest barrier -- and hopefully this workshop will help -- is just, I think, a lack of understanding by some of the stakeholders about how serious and disabling, and even life-threatening, many of these conditions are.

Having dealt with different branches of the agency, I think there needs to be maybe more of an equipoise about risk and benefit to try to take care of these patients because, again, no small molecules -- I've dealt with other branches, and clearly the cancer branch is much more aggressive. Cancer is a disease that everyone understands kills people and is very dramatic, but these diseases are also non-trivial; and I guess, for me, having an evolution in our ability to kind of get things into the clinic, and not just things that come through a 369 human tissue exemption because we have hundreds of those, and it's kind of like practicing medieval medicine right now as a clinician.

So I think we really need to get real therapeutics and drugs into this space, and for me,

being able to work with the agency to figure out how to get things into patients -- real things that will transform the disease progression -- is for the big challenge.

DR. LEWIS: Yes, I think that's an excellent point.

Dr. Herman?

DR. HERMAN: Yes, that's a good point, Geoff.

I think that Rob Kirsner alluded to this yesterday, that NIH, and FDA, and I think the Diabetic Foot Consortium are good examples of bringing different agencies, people with different backgrounds, and experience, and expertise, to the problem. Education, in general, I think is deficient across the public's awareness for how significant global health challenges actually represent.

Again, I want to hammer down on the point that I was making earlier in my talk, for this particular meeting, that it's not just about products for therapeutics; it's about products for

diagnosis as well. Being able to actually know, to get a QR code for a wound over a space and time, is going to be pivotal, I believe, in getting patients to the endgame or patient healing, which will be good for everyone involved, not just the payers or the practitioners, but for the patients especially.

DR. LEWIS: I think you make an excellent point, Dr. Herman, that, really, everything from education, to the researchers, and the clinicians, and everything up until insurance companies and being able to gain reimbursement for therapies and procedures related to wound healing, it's going to take, really, a concerted and coordinated effort to really make progress in chronic non-healing wounds.

Any last thoughts? We have a minute.

DR. KIRSNER: I'd just like to make a quick thought. First, I want to congratulate the FDA for having this meeting.

Patients are being treated, and they're being treated with products that don't have the high level of evidence that the FDA typically requires for approval. Because of that, the

patients are not getting the safe and effective therapies that they deserve. So I think taking a hard look at trying to modify endpoints and to get patients a higher level of evidence and safety of products is critical, and I think that making the outcomes more attainable will raise the level of patient care throughout our community.

I think this is a great step in doing this, but I think this is a serious problem with serious outcomes for patients, and better therapies, even if they're not necessarily perfect, are going to be better than what we currently have.

DR. TOMIC-CANIC: Just to add to that, I think the combination -- we talked about that approach to treatment is going to be combinatorial. So if you have more products that actually meet the level and criteria of efficacy, even for different endpoints that are not necessarily full closure, you will increase the level and the tools that can be combined. I think that this is really the key element, that the more products you have, then you can actually apply them and target them in a more

precise way to actually help the wound heal. That's one of the issues.

The other one I would raise again and re-emphasize is understanding, really, the pathophysiology of patients. Again, the research needs to be supported in a much more meaningful and orchestrated way to actually get to the bottom of understanding this disease, because we still are at the very surface of it.

DR. LEWIS: Thank you very much to all of our speakers and panelists. I think this has been an excellent and enlightening session, and I think for anybody who is involved in the space of chronic non-healing wounds, you give us a lot of optimism. We have a lot of people who are not only invested in doing the research, but also in eventually getting those products to approval and marketing.

With this, we are now going to move into a 10-minute break, and we'll look forward to coming back at 10:40. Thank you very much.

(Whereupon, at 10:31 a.m., a recess was taken.)

FDA Introductory Comments – Joy Mejia

DR. MEJIA: Good morning. I'm Joy Mejia, medical officer in the Division of Dermatology and Dentistry, and I'm happy to introduce this session of the workshop, as its aim is to identify potential ways that the agency and other stakeholders can interact to overcome the challenges we've been discussing, challenges specific to the implementation and execution of clinical trials.

Following the speaker's presentations, I will be moderating the panel discussion. Public attendees may submit comments and questions to the Q&A box, and we will address them as time permits. students. We hope to summarize answers to questions we cannot address in today's panel through a post-meeting summary document.

The speakers and panelists that we will hear from in this session have done a tremendous amount of work to identify challenges to executing clinical trials, encourage innovative drug and product development, and address how trials for

non-healing chronic wounds can be better designed; so during this session, we will elaborate on the roadblocks to implementation of clinical trials for non-healing chronic wounds, and explore how to design clinical trials that may be informed by real-world data and employ risk stratification.

Before we hear from our speakers and learn about approaches that might help to address clinical trial challenges, I want to highlight some of the key challenges that were discussed yesterday.

Major issues with chronic wound trials is the recruitment and enrollment of subjects. Criteria excluding chronic wound patients with multiple comorbidities slows enrollment. Variability due to comorbidities of complex patients, along with the variations of the wounded cell, dictates relatively stringent exclusion criteria, leading to slow recruitment and a study population not representative of the general wound population. Our speakers will discuss how non-reporting of major comorbidities, as well as

difficulty of controlling for the effect of comorbid disease on healing impedes generalizable trials.

Also, as Dr. Kirsner described yesterday, depending on market climate, industry sponsors may adjust their eligibility criteria -- in other words, broaden their inclusion criteria -- as opposed to study a more discreet patient population.

Another challenge is overestimating subject enrollment, which leads to poor site selection and overuse of protocol changes to speed enrollment. Protocol changes then often result in a different population being studied and differences in delivery of standard care. The time and cost to conduct chronic wound trials is often underestimated, causing long trial duration and early subject discontinuation.

The availability of the general chronic wound population can be unpredictable and often leads to trials that take much more time than originally anticipated. These patients especially

have difficulty adhering to strict treatment regimens and schedules due to their comorbidities, and can potentially be without active study treatment for a relatively lengthy duration of time.

Drs. Gould, Carter, and Fife will be speaking about some of these major hurdles in the setting of comparative effectiveness trials; applicability of wound care randomized clinical trials to the general wound care population; as well as patient registries, real-world data, and real-world evidence.

Dr. Lisa Gould has been practicing plastic and reconstructive surgery with an emphasis on difficult wound problems since 1999. Dr. Marissa Carter is a biostatistician-epidemiologist, spending a great deal of time designing, monitoring, and analyzing clinical studies in the fields of wound care and quality of life. Dr. Caroline Fife is a professor of geriatrics at Baylor College of Medicine in Houston and the chief medical officer of Intellicure, LLC, a health

information technology company. She's also the executive director of the U.S. Wound Registry, a non-profit organization recognized by CMS as a qualified clinical data registry.

The panel for this session is comprised of subject matter experts from the FDA, clinical practice in the industry who are here to also offer their expertise in this space. Dr. John Concato is an internist and epidemiologist who serves as the associate director for real-world evidence analytics in the Office of Medical Policy in the Center for Drug Evaluation and Research;

Dr. Jaideep Banerjee leads the medical science liaison's team for advanced wound management and global political strategy for biologics at Smith & Nephew;

Dr. Matthew Cooper is chief medical officer for the Medical Solutions Division and director of global safety at 3M Healthcare Business Group;

Dr. Thomas Serena is founder and medical director of Serena Group, a family of wound, hyperbaric, and research companies, and his areas

of interests are in decentralized trials, amputation prevention, and infection diagnostics;

Mr. Nico O'Kuinghttons is vice president of commercial U.S. head of decentralized clinical trials for Huma; and Mr. Joseph Rolley is a principal for JTR Business Consulting and has been actively involved in industry and professional associations, including AdvaMed, where he co-led the establishment of the wound healing and tissue regeneration sector.

With this well-versed group, this session will hopefully identify opportunities to address the challenges of designing and conducting trials for non-healing chronic wounds and encourage paths forward. To begin the discussion, I'd like to introduce the session's first speaker, Dr. Lisa Gould.

Presentation – Lisa Gould

DR. GOULD: Thank you, Maryjoy.

I have been asked to talk about wound closure in clinical trials and then dovetail that with comparative effectiveness research. It may

surprise you to know that we actually don't have a definition of wound closure. It's primarily based on clinical observation. There is the FDA definition, which was just discussed in the last session, and I'm going to discuss a recent RCT for diabetic foot ulcers that utilized a rigorous definition, and we've tried to differentiate between wound closure and wound healing, and then draw that into the impact on comparative effectiveness research.

If you look at the scalp wound, the question is whether it's healed. On the left, that was described as not healed as there was scant drainage on the dressing, and on the right, it was described as healed. It looks very similar, but if you look closely, there's a shine over the wound, it had no drainage, and that was a thin layer of epithelium, and therefore that wound was deemed healed.

This is a diabetic foot ulcer, and the question is, is it closed or is it healed? On the left, that was described as closed by the practitioner, but there is a layer of callous

that's actually obscuring what's going on underneath, and the patient returned 2 months later with purulence under what appears to be a blistered area with that callous now lifted up.

This is a sacral pressure ulcer originally described as not healed. Comparing the left to the right, they look quite similar, but on the right it's described as healed because there was no drainage on the dressing, even though there's still a small scab.

In this leg wound, initially it was not closed, and then it had a small skin graft, and 8 days later it was described as closed, and you can see the difference between the two.

The FDA Guidance for Industry of 2006 described what would be considered complete closure. Now, there are other endpoints, but new therapies for patients are approved only if they support complete healing, or facilitate surgical wound closure, or improve cosmesis and function of healing. Most of our chronic wound patients aren't concerned about cosmesis, but Dr. Gurtner did show

some issues where cosmesis is certainly a big problem.

But complete closure is really one of the most theoretically objective and clinically meaningful endpoints, and the FDA definition is skin re-epithelialization without drainage or dressing requirements -- and the way I read it -- confirmed at 2 consecutive study visits 2 weeks apart. In my reading, that's a month; that's 2 visits. But most people interpret it as it's closed, and then we'll see them 2 weeks later, and if it's still closed, that's healed.

This is a histologic example of open versus closed, and on the top you can see the open wound. The black markers show the original size of the wound, and then the white markers show the edge of the epithelium, and in the histology below that, you can see a nice stable epithelium, designating a closed wound.

These are also closed wounds with the histology quite different. On the top, you can see that the wound actually does appear closed. It has

an epithelium that goes all the way across but it's not adherent to the underlying tissue, and on the bottom is similar to that scalp wound, where you can see where the epithelium stopped. Then there's a non-cornified epithelium, and the moisture barrier has not been re-established, which Dr. Sen talked about with the transepidermal water loss, and this probably would have high transepidermal water loss.

We created a conceptual diagram in this paper about wound closure versus wound healing so that people can see, with kind of a cartoon image, what we're thinking, where a closed and actually healed wound has the full thickness epithelialization across that wound bed, and that should be stable. It may not be as good as what Dr. Gurtner described with some improvement in the scarring, but it should be stable for most of our chronic wound patients, and that would be a more rigorous definition, but again, right now that's a visual definition.

In a recent clinical trial, we intended to

set the bar high and implement this process into a clinical trial. Again, it might surprise you to know that in a review of a large number of randomized- controlled trials, including over 7,000 wounds, only 7.8 percent of those followed the FDA definition of wound closure, 40.6 percent reported that the wounds were healed by epithelialization, and 28 percent actually didn't even define healing.

We felt it was important to try to standardize what is called wound healing closure in clinical trials. In that, we had four points. One would be 100 percent epithelialized; two, surrounding tissue is normal in color, and that should say without callous or macerations; and then three is complete absence of exudates, no drainage; and four is no clinical signs of infection in and around the former wound site.

Then using blinded adjudicators, if the wound was deemed healed in the clinical trial, photographs were sent to three blinded adjudicators who then opined whether they agreed. If they did not agree, they sent it back to the trialist to go

back and continue the trial for another week or two.

We were concerned that this rigorous definition would delay our outcomes, and then this trial would look very strange to everyone because of the delay in healing, but it did give us really strong confidence in the outcome. And indeed, if you look at the results with the number healed with the topical product, it was similar to what we see in other trials, where in the control, about 40 percent of the patients healed, and then in the product application, 74 percent healed in 54 days, with mean time of healing to 54 days. So it wasn't out of the realm of what we usually see, and we had very good confidence that those wounds were actually closed.

That then brings us to comparative effectiveness and what goes on with wound healing. With comparative effectiveness, we're trying to compare two different products to see what's working as opposed to randomized-controlled trials, where we want to just show efficacy usually of one

thing and find out does it work. So the key aspects are direct comparison patients in a typical day-to-day clinical care with the aim of tailoring decisions to the needs of individual patients.

Most of these are done through systematic reviews of the literature or review of large established databases. Very few are done with prospective registries or cohort studies in a prospective fashion.

I just put together a chart so we can look at the differences between an RCT and comparative effectiveness. RCTs are looking at efficacy; CER is looking at effectiveness. Does the product work with an RCT? It's a highly controlled environment with a homogeneous population, whereas CER is product applicability with a comparator looking at clinical reality in a diverse range of patients.

In RCT, there's going to be a randomized application of the product. In comparator effectiveness, it's the clinical judgment or preferences determining the use, so there could be quite a bit of bias there. In RCT, the outcome

should be predefined. In comparative effectiveness, the outcome is by the clinician. RCT demands rigorous documentation because that's all pre-populated, and that's part of the trial, whereas comparative effectiveness is dependent on clinical charting, particularly when it's done retrospectively.

I pulled what I could find in terms of examples of comparative effectiveness in wound care. One of the very early ones was the SNAP versus negative pressure, versus, quote/unquote, "modern dressings" in diabetic foot ulcers. This was done in 2011, and it was a literature review. The only thing that really was recorded was the closure at 16 weeks, and it showed non-inferiority of SNAP versus negative pressure wound therapy, but obviously the, quote/unquote, "modern dressings" were inferior in this particular sample.

If we look, the rest of these are actually supported by one company. They had a mousetrap and kept catching the mice. So it was really done with a similar pattern across the board, and you can see

there are some with diabetic foot ulcers and some with venous leg ulcers, and a fairly large number of patients but not even between the two groups.

What I thought was striking was the wound closure. If you're using the same product, you might expect that the wound closure rate would be similar, but you can see there's quite a bit of variability. If you look at the human fibroblast-derived dermal substitute and the median time to healing, in one study it was 12, but in another it was 20. I find that that's interesting, and it may be one of the problems of comparative effectiveness research and not actually having a known endpoint or a definition of wound closure.

There are only two that I could find that are prospective comparative effectiveness research in wound care. There may be others, but these were what I found recently. One looked at all wound types, which kind of gets to the question of is a wound a disease or is the disease causing a wound?

I looked at wound closure at 12 weeks with a fairly unrealistic outcome for this particular

product, then the other one compared across three different things, looking at standard of care with even groups, but a very small study, again, looking at wound closure with a completely unrealistic outcome of 95 percent wound closure at 6 weeks. But it was prospective and it was comparative, so we have to give them credit for trying to do that.

These are the references for all of those comparative effectiveness trials. But again, I think one of the problems is that we don't have a definition of when those patients were deemed closed because they're not done with that in mind.

I know in my clinic, the nurses ask me if I want to close out a wound, and if I'm not planning on seeing the patient back because it's so small that they can just manage it themselves, I may call it closed, which is what would then be documented in the clinical record, and that's what gets assimilated when people are going back into the charts.

So what is the value of comparative effectiveness research? Well, obviously, we know

that randomized trials are the gold standard for comparing treatment efficacy, but the population-based registry data can be very helpful, particularly if it's either difficult or impossible to perform randomized studies. That's an example from some of the cancer studies, where it would be unethical to randomize, and it may be valuable for our field as well.

It could be less costly to perform, although prospective comparative effectiveness with very, very large samples is going to have a cost. It should include a wider range of patients that would usually be excluded from RCTs. And I think that by looking at these, it can help inform future randomized-controlled trials that would expand our inclusion so that our patients are better represented.

Obviously, there are some problems. It depends on the EMR. There is missing data. Safety data are not documented. There's a selection bias. We really don't know why these patients got this product. It may have been the practitioner's

preference for a particular product and they use it over and over. We don't know that, and we don't have a definition of when those patients are healed or discharged. They may be discharged prior to complete healing.

Then I looked at could we actually do prospective comparative effectiveness trials, and if so, who would fund it? Because it's hard to get a company to go head to head against another company, we'd need both of them to fund it; or if they're going to compare their own products, do they really want to see one of them fail? And I think that that is problematic

We also have a need for caution. There are examples in the literature when comparative effectiveness research actually contradicted randomized-controlled trials. One example is comparing breast brachytherapy to whole breast radiation, where there were very, very strong clinical trials favoring whole breast radiation, and now there's comparative effectiveness research that shows that partial breast radiation is better,

and better accepted by patients for early breast cancer.

Then in the prostate cancer field, comparing a SEER-Medicare analysis of men with prostate cancer, the addition of androgen deprivation to radiation therapy increased the mortality, and that directly contradicts for high-level randomized-controlled trials.

So what do we do with that information, and where do we go with that if that were to happen in wound care? Which I would suspect it will contradict the randomized-controlled trials. We'll either get a wash and we won't see a result, or we'll see something that's very different to our highly selected randomized-controlled trials.

With that, let's look at the next slide, and I think that's it. I just want to say that there's been growing support of comparative effectiveness by the NIH and by PCORI. Now PCORI, It has to have a patient-centered outcome, but that's something that we're trying to incorporate into all of our clinical trials.

So I think that even though we have a paucity of comparative effectiveness research right now, it will grow, but it has to be done right in order to gain good understanding of the meaning and make these trials truly be able to be compared across the board; not just within one trial, but with each other. So I'll stop there.

(Pause.)

DR. GOULD: I probably talked too fast, and Maryjoy is elsewhere.

DR. MEJIA: No, we're waiting on the next slides to be projected for Dr. Carter.

Presentation – Marissa Carter

DR. CARTER: Good morning, everybody, and thank you, Dr. Mejia, for letting me speak.

I'm going to talk about applicability of wound care randomized-controlled trials to general populations of wound care. Some background on this, when we're making a comparison, you are talking about a relatively tiny population from a controlled trial -- patient parameters, wound care parameters -- and you're going to compare it to a

vast wound care population, maybe the same kind of wound and so on and so forth. That process in which we look at all the different outcomes and all the different things that happened in the trial is known as external validation, although sometimes in the literature, you'll see this referred to as generalizability.

If you were to compute, looking at inclusion and exclusion criteria, the two situations here, what you could do mathematically is say, what is the percentage of people in the trial in terms of eligibility versus in the general population? In this particular example, the red circle defines the general wound care population and that pretty small beige circle defines the specific trial, and that's typically the case, exactly as I've shown it. There aren't a huge number of people in the trial that really relate to the general wound care population. You've got much more severe wounds and very different parameters.

Quite a long time ago, Dr. Fife and I decided to explore that previous slide a little bit

more, for the first time. We looked at 17 randomized-controlled trials for indications of diabetic foot ulcers and venous foot ulcers, in which interventions -- and we call them high tech, but they were mostly drugs, devices, and biologics, and so forth, and what we were trying to figure out is the eligibility in the general population in those specific trials.

If we looked at the 17 trials, 15 of those would have excluded 50 percent or more with those kinds of indications of wounds. What was interesting is if we removed some of the less clinically important criteria, we still ended up with 14 out of 17 percent will be excluded, somewhere between a quarter and a half. That was our first really serious benchmark.

Other people have tackled this kind of issue of generalizability or external validity. This particular study was a systematic review of just under 150 randomized-controlled trials involving venous leg ulcers, and what was interesting about it is those trials were published over a spread of

20 years, from '98 to 2018. These authors -- and they come from Europe -- focused primarily on the generalizability, but they were looking at things like socioeconomic status, ethnicity, other patient parameters, recording and reporting of medications, and comorbidities, and some of the things they found were kind of shocking.

Let's start by looking at screening rates. Only a third actually reported them, which means that two thirds did not report any kind of screening data. We don't even know how many people were actually eligible for the trial. Surprisingly, 13 percent only reported patient ethnicity; 42 percent reported comorbidities, but these were very selective and they were certainly nowhere near comprehensive; and shockingly, small numbers reported things like current medication use -- we know lots of medicines affect wounds healing -- and socioeconomic factors. That's a huge issue. Lots of patients don't have access to good wound care, but don't know anything about who they are.

Even when we look at something like major, or I would say macroischemia, which we can define by ABPI, it's less than 0.8; still, only 40 percent didn't even bother to look at that. A shocking 40 percent didn't even report on any adverse events. You know, that's a primary thing, right? We want to know if something is safe. Fifty percent only reported BMI.

The bottom line with all of these kinds of things -- and I totally agree with the authors of this publication -- is there's a totally inadequate reporting of data regarding external validity. In other words, we don't even know in these trials that are published who these patients truly are, what their problems are, what their wounds are like, and so on and so forth. That's our first big point.

Second, there are a lot of other things about these trials in the general wound care population that matter; standard of care. Standard of care actually varies quite a lot between randomized-controlled trials, and you think in a

tightly controlled trial, you wouldn't see that. We tried to minimize that by training sites to certain levels of care and so on like that, but you can see -- and I've looked at dozens of dozens of trials in my life -- there is a huge difference between the way someone does debridement and the way someone actually does offloading of a wound, from clinic to clinic, or trial site to trial site.

In controlled trials, we tend to do things on a regular basis. We see patients every week or every two weeks. Is that realistic? No. In fact, even weekly debridement, which is quite common in a lot of randomized-controlled trials done in this country, just doesn't happen in the real world that way. You might see it one week, and then three weeks later, there's debridement done, and maybe two weeks later another, and they could be quite different than normal sharp debridement.

So seeing patients and doing things to them on a regular basis is not something that happens in the real world like it does in a randomized-controlled trial, and that's probably even less so

given the last two years we've gone through in the pandemic.

Finally, I would say in the real world, the more complex the wounds in others, the more serious it is, the more severe it is, and so on like that, the harder it is, actually, to define standard of care because we know typically as wound care practitioners what standard of care is for a fairly simple wound like wound care management; moist wounds; debridement; offloading where appropriate; compression for VLUs; and so on like that.

But when you have a real severe wound, there are a lot of surgeries and a lot of other things you have to do, and pretty soon you have a hard time defining what SOC is. And that SOC, or standard of care, itself is frequently poorly documented, and I've seen a lot of documentation from RCTs where it's poorly documented, so we need to do a lot better.

Wound severity classification, we are all familiar with these legacy systems, DFUs, and we talk about UT systems, University of Texas, or

Wagner. Dr. Armstrong and Dr. Conte several years ago attempted to create a much more comprehensive and much more logical way of looking at wounds called WIFI. It was a brilliant series and pieces of work. It's not widely adopted.

Look at pressure injuries. As Dr. Fife pointed out yesterday, ICD-10, we still call those pressure ulcers. But this is a work in progress. We look at the last 20 years of trying to define these things; it's all over the map. Why is that? Because we keep discovering different mechanisms of injury. There are at least three, and there are probably more.

There are lots of wound types that have this so-called mixed etiology. For example, you have a venous leg ulcer; it's not a true venous leg ulcer. It's got an arterial component. It's got an inflammatory component. It's vasculitic. The wonderful example that Dr. Fife made yesterday of the heel wounds -- pressure, diabetes -- and what other things are going on in terms of the mechanisms of injury?

We exclude all of those kind of things in controlled trials. What about the nameless wounds? Some 40 to 50 percent of all the chronic wounds we encounter in the real world, all of those are missing in action. We never do trials on them, so we don't know anything about them. We don't even know how to treat them irregard to all the different products out there that are covered in maybe the three big different kinds of wounds. So we end up with this horrible disconnect between randomized-controlled trials and nice intervention patterns of frequencies compared to the real world.

Here are some implications of this. What tends to happen is when the new drug, device, or biologic gets approved, those inclusion and exclusion criteria that we used in the protocol, in the publication, those kind of exact things are what defines whether a patient gets it or not, and then we're talking about coverage.

What happens a lot of the time is chronic wounds that really don't need advanced therapeutics end up getting these things, and if the standard of

care was good -- and in a lot of facilities it is -- we're actually increasing the cost of the system. You want to know why wound care cost so much? There's something right at it [indiscernible]. But the camaraderie [indiscernible] of facts is there may be a lot of advanced treatments out there that actually could treat more severe wounds or patients with more severe comorbidities, but we just don't know if it's going to work because nobody's done any trials with those kind of patients and wounds.

Finally, what's been pointed out in this, and posing them over and over again is chronic wounds are a symptom of the underlying disease. If we don't care or try to control the underlying disease, all bets are off.

So summing up some final thoughts about this external validity issue, it's a huge problem; it's not getting better. Our own work has showed that, in surface, in last 20-25 years. We have a long way to go. One of the things we could do is improve reporting patient comorbidities, drugs, and

things like that.

What is it going to take for sponsors to attempt to do that? We know it's a question of money. If you actually have to collect a lot more data on patients and wounds during the trial, it's going to cost you a bunch of money, so that's one component. But maybe it's what is the need for this? Well, we can define what goes on in a randomized-controlled trial. We can actually do a better comparison with general wound care populations. We need to figure out how to better do that.

Another problem is the types of chronic wounds. It's like if we insist on -- and I understand the FDA's perspective on this. Believe me, every etiology gets a single wound. If it's a single trial and it ends up with dozens of different kinds of trials for one product just to get coverage and just to get approval, what could we do to simplify that? Is there some particular things that we could condense, certain etiological approaches, certain kinds of mechanisms to make

that simpler, so that when patients benefit, we do fewer trials?

Lastly, in summing up this whole thing, this whole applicability issue really has to do with pragmatic trials, on the left-hand side, not many inclusion/exclusion criteria and very big gates, to very, very tightly controlled randomized-controlled trials on the right-hand side. We need to find this balance. We need to have a much longer, better conversation between sponsors and researchers and agencies in order to find that right balance.

I'm going to stop there, and thank you for listening, and if you have any questions, leave them for the panel discussion.

DR. MEJIA: Dr. Fife, will you be sharing your screen?

DR. FIFE: Yes, I'll share my screen, please.

DR. MEJIA: Okay.

Presentation – Caroline Fife

DR. FIFE: Thank you for letting me talk

about patient registries and real-world evidence. It's a great segue thanks to Dr. Carter.

Why I got interested in this happened in about 1999 with this 72-year-old woman who had rheumatoid arthritis, was on prednisone and methotrexate, and had poorly controlled diabetes. I managed to get her leg healed with the first cellular skin substitute product that came on the market, which I had been one of the principal investigators. I was so proud. I felt things had really begun to change because I'd already been here almost a decade, until I found out that I had committed Medicare fraud.

As Dr. Carter alluded to, just to put a face on this, I had performed this clinical trial. The exclusion criteria for the trial had been diabetes as a comorbid condition unless you're in a DFU, rheumatoid arthritis and steroid use, which I refer to as Thing 1, my Medicare regional administrator had decided to create coverage policy that mirrored these exclusion criteria so that I couldn't use the skin substitute in a patient with uncontrolled

diabetes, vasculitis, rheumatoid, arthritis, and steroids. It was as far back as 1999 that I realized that this is how coverage policy was going to go, and I didn't find that to be acceptable.

Dr. Carter's already alluded to the study that we did in 2009 looking at 8,600 wound care patients, and determining that what we really had done up to then was only what I would call show-girl trials; that 3 out of 4 trials that brought products to market enrolled patients that were healthier than the girl on the street, whereas our patients looked like this.

The interesting thing is that in 2009, we had about 16 percent of patients with coronary artery disease; 10 percent were still current smokers; and about 8 percent on steroids; 5 percent with renal failure transplant; and about 26 percent of patients who were being treated for some wound type other than a diabetic foot ulcer had concomitant diabetes.

Well, in 2020, we now have about 24 percent of patients with coronary artery disease, and very

few of them are still current smokers; still about the same percentage on steroids; now 8 percent have renal failure or a transplant; and half of them have diabetes, even if they're not being seen for a diabetic foot ulcer. And I would say that we have data to suggest our patients are getting sicker along this time frame.

It's very funny that Dr. Carter and I put the same slide in our presentation. I'm a simple girl. I've worked with Dr. Carter for many years, and I'm humbled by her mathematical acumen. I'm just a family practice doc. I don't know what you call this; it's just wrong. It is a moral problem -- if it's not a statistical one -- that we only look at a tiny fraction of these real-world patients, and then I'm held responsible for whether they can or can't realistically get a product.

So the only way to understand the rest of this data set, or the rest of the world, is with real patient registries, and they are fraught with various types of bias: selection bias, documentation bias, recall bias, channeling bias,

all the things Dr. Carter already brought up, and things Dr. Gould brought up about defining the outcome, defining things like ischemia, controlling for usual and customary care, and that's even before we talk about patient consent and IRB.

Back in the beginning, I said I'll take the AHRQ document on, creating registries with the overarching theme here that we're talking about and using information we collected in the usual conduct of care in hopes of using it and repurposing it for research.

When I started this, the AHRQ book was in a second edition; now it's in its fourth. In the first page, they explain the fact that registries use observational study methods to evaluate specified outcomes, diseases, or conditions, and then it spends the rest of the 400 pages talking about the ways to control bias.

Historically, one of our challenges is that lots of things are called registries. It's like the word "love." I love my car. I love my dog. They're not all the same thing. Historically we

said, let's take structured data fields to answer very specific research questions, get an IRB, get patient consent, and deidentify the data. The problem with that is that you have a huge problem with selection bias.

Now we have the opportunity for a big data approach, and they're very successful big data projects going on right now that don't really suffer from such a problem with selection bias because the potential data set is so big and has such a broad sweep. But the challenge then becomes defining a data model when you're not specifically able to design your structured fields in order to answer a specific question, so you have to define a data model. And so much in wound care is not easily defined by structured models as they exist now, like ICD-10, and RxNorm, and the other structures that we're commonly familiar with.

As CMS began its journey to the quality payment program, they developed entities that existed for the purpose of reporting quality data to CMS on behalf of physicians. We've been through

many iterations, the most recent one of which is the qualified clinical data registry, which was created in 2014, and we had data registries going back to 2008; that's when we got into this.

CMS has said while we want to get clinical data on quality from physicians, the real purpose of these qualified data registries is to understand the natural history of disease, the cost or clinical effectiveness to monitor safety, and to measure quality. So what we're really doing is leveraging CMS reporting requirements and/or documentation that's required for billing in order to abstract some data for clinical research.

Now, the advantage here is that you don't have selection bias. You get all the patients, all the wounds, but only from the centers that participate. There's no patient deidentification. These are identified patients. That's the way it works for CMS qualified clinical data registries. There's no patient consent. We know who they are. The purpose is safety and effectiveness, but we do use IRB on the backend.

QCR and specifically the U.S. Wound Registry is what I understand, and that's what I'm going to talk about, but I don't want to imply that this is the right answer or the only answer. I just wanted to explain, in a very specific way, how we've tried to tackle some of the problems that have already been identified this morning and yesterday. It all depends on how well the data are structured. What we really did was create a very detailed structure of an electronic health record, and then the content of the entire EHR is transmitted to the registry at night.

In order to do that, the first thing we had to do is to try to figure out what kind of wounds we were talking about. Yesterday, I discussed the way the ICD-10 system works; that boo-boos are divided into wounds that are usually surgical and traumatic and ulcers that are usually relevant to your underlying disease, and there is no code for a diabetic foot ulcer or an arterial ulcer.

So we structured a way that clinicians could make a series of clinically relevant decisions in

order to get to a code that we help them identify. Rather than just using a grab-bag, that is a lookup tool, we asked them, "Is this a wound or an ulcer? If it's an ulcer, what kind is it: arterial; chronic; with no name; a pressure ulcer; a diabetic; or a venous ulcer?" If they say, for example, that it's a diabetic ulcer, they identify the diagnosis of the diabetes, then they go through the coding required for a chronic ulcer code. But we also insert a Wagner grade in there, which is not directly relevant to any ICD-10 system, and it's not necessarily the best method, but it relates a lot to coverage policy, which is why we kept it. Then we create artificially a conjunction of codes that then say this is a diabetic foot ulcer, and we do the same for arterial ulcers.

We have an advantage in wound care, that lots of things we do really are structured. Anybody who's listening on this call could take the back of a napkin and structure the observations we generally make for wounds: the size; the depth; the drainage; characteristics; what type of tissue

is exposed; and the various treatments, which we even collect by brands.

Outcomes are somewhat standardized in that healing or closure, amputation, death, we can identify those. I could talk a little bit later about the issue of healing, which is challenging, and I won't say we have an answer, but I have an explanation.

The problem we have, even with these outcomes, is that they're not necessarily what you think they are. A good outcome could be a partial foot amputation with preservation of ambulatory status, and a bad outcome could be a wound that gets 50 percent smaller, but a year from now still isn't healed. So it's not as simple as, say, this is what happened because there are connections to what is anticipated the impact will be clinically.

Now, the other challenge we had, which has been alluded to by Dr. Carter, is the challenge of risk stratification, but in order to submit data to CMS from a QCDR, you have to have an outcome measure, and you have to risk stratify it so that

physicians caring for the sickest patients don't appear to have worse outcomes than their peers.

We had to create a risk stratification for wounds. We did that with Susan Horn, and we couldn't continue to do what has been done, and continues to be done at many wounds centers, which is to say that they have more than a 90 percent healing rate. The only way that you can achieve that in the real world is to simply sweep under the carpet any wounds that don't heal, and say that they were in palliative care.

So in order to report data to CMS, it has to be everybody. You can't cherry-pick. So we developed a suite of seven models that comprise both wound and patient factors so that we can report the healing rate in comparison to the likelihood of healing, and those end up being a series of 7 to 10 questions for each of the wound models. Even if you're not using this EHR, we can provide the questions, and we do have a clinical trialist, for example, that will go through these questions for the data model, and then we can

provide a predicted healing index for patients that they're enrolling in a clinical trial.

Dr. Carter has also alluded to this, and this is her analysis of our data. When we looked at, using the Wound Healing Index, the simple question of -- I said, "Let's make a Venn diagram of the patients who get cellular products in randomized trials and how they compare to the real world." The Venn diagram we came up with had circles that do not intersect. This is an estimated wound healing index in venous ulcers that were enrolled in clinical trials versus venous ulcers who got skin substitutes in the real world.

The sad impact of this little diagram is that these subjects were enrolling, or at least we had enrolled by 2018, in these trials patients or wounds you could predict were going to heal anyway, as opposed to the patients who really get them, who you would predict are not going to heal anyway. So as has been alluded to, in the real world, we are treating worse wounds than we enroll in our RCTs.

Now, that's an opportunity and a problem

because we have had data utilized for comparative effectiveness studies by manufacturers, and you haven't seen it published because the healing rate for their products looks so much worse than their RCTs. Even when they heal wounds predicted to fail, there's a fear on the part of manufacturers to be the first one to brag about a 50 percent healing rate when, in fact, 70 percent of those wounds would have been predicted to fail.

Somehow we have to have a reset on the expectations so that manufacturers aren't afraid to talk about this. But the other challenge is it gets harder to show that your product, product A, is substantially different than product B by the time you get to very sick patients.

The next thing we had to tackle was controlling variations in care. Just as Dr. Carter alluded to, that's a big challenge, and one of the only ways that we felt we could tackle it was to develop quality measures that would be approved by CMS.

In 2014, the U.S. Wound Registry

collaborated with the Alliance of Wound Care Stakeholders to develop a suite of relevant quality measures for wounds, and we leveraged the documentation that's required for billing or other purposes in order to make these count, but we also give clinicians real-time feedback on measure performance inside the EHR, which they can completely ignore.

What we found is that clinicians who pay attention to these checks and X's will actually have a risk stratified healing rate that's better than their peers. The ones that are paying attention to diabetic foot ulcer offloading, VLU compression, and arterial screening do better than the ones who don't; although the criticism often is, "Well, aren't you just measuring their documentation?" And the answer is, "Apparently not," because we're also reminding them every year the patient needs a new arterial screen, and perhaps you forgot to do arterial assessment in this patient. That seems, in my opinion, to be the key difference that we see.

These are the measures that CMS has approved for 2022 that are relevant to wound care. We did have one that was wound-related quality of life. It failed miserably because it was too burdensome for physicians to report, and also because the wound-related quality of life turned out to have no correlation whatsoever with the outcome of the wound.

I can talk about that more later, but by the time you have a patient that has 10 comorbid conditions, the wound, while it causes a lot of suffering, may or may not be the driver for their quality of life.

The three quality measures we focus on the most are adequate offloading, non-invasive arterial assessment of any lower extremity wound or ulcer, and adequate compression. When I talk about things like adequate compression, there is a list of products at the backend of this that are evidence-based for adequate compression and ACE wrap, leg elevation, or TG Grip [ph] do not work. You have to use a product that has evidence behind

it, so it does get very much into the weeds about what we say was done as a good job, and we know the performance rate for any clinician when we're looking at their data.

What happens is we have clinicians who make documentation at the point of care. It's not done later. It's not done by another party. It's done by the nurse and the doc. We then take this data from all this interest that participated in the U.S., and every night, it's transmitted to the registry.

We do quality measure performance. We can report back to the physicians on their quality performance, and then on the back end, we can deidentify the data set for market research, comparative effectiveness, or other types of learning, and we can report quality data to CMS for monetary purposes if the clinicians wish to do that. In fact, very few clinicians do because they have no financial incentive under the quality payment program to participate. Really, their institutions are supporting things like BMI and

smoking cessation. They have zero incentive to report the difficult measures that we've created. It's primarily valuable for research.

Just to get a little more detail behind the disconnect that Dr. Carter was alluding to, with Dr. Serena, we looked at a series of six clinics that he was managing that were also performing clinical trials. And just to put a face on this, when we compared the real patients enrolled in a diabetic foot ulcer trial, or subjects enrolled, versus the real patients they were seeing, 12 percent of the real patients had renal failure, all of which were excluded from the clinical trial. There were 4.3 DFUs per patient in the real world; only one is ever included in the trial. Forty-three percent of them had Wagner grade 3, which is a limb-threatening ulcer, whereas a clinical trialist invariably report Wagner 1's and easy Wagner 2's.

The initial diabetic foot ulcer surface area was 3 times larger than those in the RCTs, and we could look at the estimated Wound Healing Index and

predict that the ones enrolled in the RCT were probably going to heal regardless of what treatment they got, and the ones in the real world were not. This is true both for the diabetic ulcer patients, as well as the venous ulcer patients. That is the world in which we live.

What we have tried to do with the registry -- again, I'm not saying this is the answer; I'm just telling you the tools that we've tried to use to handle some of these areas of bias -- is we try to handle patient selection bias by making sure that we take the data from all the patients, and all the centers, and all the wounds they have.

We have structured an EHR specifically to collect this data, which also handles billing, which is the incentive for getting the data correct. We have structured the comorbid conditions, and we use a structure that's available like ICD-10. We know their comorbid conditions. We know their drugs and all their meds. We don't have all their labs.

The data are entered at the point of care by the clinicians. There's no post hoc vetting of these outcomes for marketing purposes. The completeness is driven by the linkage to billing. We have both patient-level, problem-level, and problem visit-level data. We can stratify the major wound categories by Wound Healing Index.

We try to control the standard of care by performance of quality measures that CMS has approved that were developed by industry and by all of us. We have an IRB on the backend to monitor the deidentification, and we have data from 2014 to the present, with more than 2 million visits, the majority of which have photographs.

Our major weakness is that the only people who can participate are those who have this purpose-built EHR. We now have both the Cerner app and an Epic app available. That has been our goal from the beginning, is to find a way to get real-world data that's usable.

We published a paper on standards for creating registries from electronic health data

specifically for wound care that have been entirely ignored, including by journals that publish papers. We've created a white paper, which I would refer to only as a good start. The wound healing collaborative community has taken it on as a task and effort to further develop the standards for creating registry data from EHRs, and I'll stop there.

I see you, Tom. Hey.

DR. SERENA: Yes, I'm just on a bit early, Caroline, and just listening.

DR. FIFE: That's ok. I was reaching the end of my time.

DR. MEJIA: The agenda calls for just a five-minute break, so we'll reconvene at 11:40 for a panel discussion.

(Whereupon, at 11:36 a.m., a recess was taken.)

Panel Discussion

DR. MEJIA: I just wanted to thank our speakers for their very thoughtful presentations, and I hope the panel discussion will be just as

stimulating. Just as a reminder, public attendees may submit comments and questions to the Q&A box, and we will address them as time permits. Again, we hope to summarize answers to questions that we can't address in today's panel through a post-meeting summary document.

The first question is one that I'll direct to the whole group, but I'll have Dr. Fife start us off.

What are specific examples of how real-world data paired with risk stratification are being used to inform the design of prospective wound healing interventional trials?

DR. FIFE Yes. I'm excited to report there are some innovative thinking manufacturers that have done two or three interesting things. The first one is they've asked us to tell them what the likely loss of recruitment will be based on a list of exclusion criteria. So even though they may have to use certain exclusion criteria, they want to go into it knowing we're going to lose 10 percent of people because of renal failure;

we're going to lose X percent because they're on steroids. That's a really useful tool.

We can also give them a sense of what the real-world enrollment rate will be. If they tell us what the characteristics of the wound are, we can tell them approximately how many are going to present to the average center in a given time frame.

The other thing that is most gratifying to me are the manufacturers that are brave enough to tackle more serious wounds. They have asked the logical question of what would the expected healing rate be of Wagner 3 ulcers with bone exposed? No one else has studied those, and we don't really talk about them in that way.

We know very little about natural history, so it's exciting to be able to say this is what you can expect, here's your benchmark, and this is how many people are going to get amputated and how many are going to get hospitalized [inaudible – audio gap], and I think that is powerful for them.

The other way the Wound Healing Index has

been used is to help provide a real-world cohort for a clinical trial or for postmarketing studies. If they want to have a sense of how their product is comparing once it gets out in the real world, we'll provide a real-world cohort for comparison.

DR. MEJIA: Do we have anyone else to give witness as to what they've seen as far as real-world data with risk stratification?

DR. SERENA: This is Tom Serena. We've used Caroline's data to tell us what the control group's [inaudible - feedback] -- U.S. registry data forever, since it was published, to tell sponsors and others who are planning trials, what is your expected standard-of-care rate when there was [indiscernible] a real standard-of-care rate.

I would agree with Caroline as well, that we've seen, probably in the last two or three years, that a sponsor's far more interested in doing trials on sicker patients. We just completed a trial on patients with pressure ulcers more than a year in duration who had all failed negative pressure. We'd love to see more of those.

Unfortunately, there haven't been enough of those. But those kinds of trials are very important to the patients that we see every day at the clinic.

DR. FIFE: Yes. Speaking of negative pressure, we did a study at the request of the FDA to look at reading a negative pressure in patients on anticoagulants. Because all of the patients on anticoagulants were excluded from the clinical trials, no one knew what the risk was going to be. So it was exciting to be able to offer safety data like that, so I think that's powerful stuff.

DR. CARTER: Yes.

Yes. I've used Dr. Fife's and other people's data for a lot of things. For example, I spend a lot of time with sponsors back and forth at the FDA; for example, stratification, we were worry about extreme cases in wound sizes --

DR. FIFE: Yes.

DR. CARTER: -- exposure level, and things like that.

So we'll often look at the data and try all kinds of different things, and that guides us, like

they might tweak the exclusion criteria, and we might decide base stratification levels on those kind of things. So I would say they use it more and more.

DR. FIFE: One of the things that we don't have a lot of insight into, since most wound trials look at surface area because depth is hard to measure -- but that's fine if you use a shallow wound. If you start to enroll deeper wounds, it's a fascinating question of what drives the closure rate. Is it the depth or the surface area? Because you have to fix the depth first. So those are the kinds of questions people ask us because they need to have a sense of what's going to happen in 12 to 16 weeks.

I think the other thing we can provide is a reality check, that a 12-week trial, if you want to use bad wounds/sick people, you're going to have to have awful tiny wounds if you've only got 12 weeks and a sick person.

DR. GOULD: I think as we go forward, the real-world data can help us, but we have to

understand, really, what its limitations are. In that paper where we looked at the wound closure and wound healing, in the real-world evidence that we looked at, there were 901,000 wounds, and no study. used the FDA definition of wound closure, and 89 percent didn't even define their assessment method.

So as we go forward, we need some structure to what the real-world evidence is, and really put some goalposts in there to make it valuable, because we want to use it.

DR. FIFE: That may be one of the purposes of the photographs because we do have photographs almost every time, so we can use those. And we've done that before, where we weren't really sure about the closure rate. I've gone and looked at the photographs of the patients to figure out whether they healed or not, based on visualization.

If you use a follow-up at a certain time frame, wound centers, by definition, aren't supposed to keep seeing people who are healed, so it makes it harder for us to do long term.

DR. GOULD: Yes. How do you get to the problem of the diagnosis? I'm in clinic, and it's a square peg in a round hole. So I have the 86 year old who banged her leg on the dishwasher door, but her real problem is that she has venous insufficiency and also some arterial insufficiency. But it gets classified as a traumatic wound, and I don't usually reclassify those because that was the etiology, although I know some people do because then they can put their product on it.

DR. FIFE: Yes, it's more likely that it's coded to coverage, so our bigger challenge is taking all the venous ulcers and figuring out the 50 percent of them that are venous. That is about the reality, half of things coded as venous, or venous, and we know that from photo analysis, as well as from asking things like can you see bone or tendon? Because you shouldn't do that in a venous ulcer.

DR. CARTER: In fact, one of the biggest problems when you analyze huge, big data sets in real world is when you look at the wound type and

other kinds of things, you know there are problems with what Dr. Fife has just said. How do you clean it up? Do you really want to clean it up? And those are some of the issues that you deal with analysis.

Real-world evidence is incredibly a messy business

DR. FIFE: If I could have a plea for this meeting, it's that we would develop standard criteria for a wound. My big problem I get from wound centers is you have pyoderma that's had venous ablation. We could create criteria to say this is a venous versus an arterial ulcer, and we don't have a publication like that.

DR. CONCATO: Hi. This is John Concato. If I could interject, this is a fascinating discussion, and there's so much to unpack regarding what's been said in the excellent presentations and in the last few minutes. But as an internist and epidemiologist who doesn't work specifically in this area but who does work on, quote/unquote, "real-world evidence," I find both good news and

bad news in the discussion so far.

I think the bad news is that the challenges are considerable, as we've heard. The good news is the remarkable similarities across different clinical disciplines, which means we can all benefit from lessons learned. And the main point, big-picture comment, that I'd like to just toss out, and we don't have to discuss it too much, is the multiple related concepts that have come up so far of validity and generalizability, regulatory approval, practice of medicine and coverage, and last but not least, randomized trials and comparative effectiveness, or randomized trials and real-world evidence, which is why I interjected at this time.

I just want to say we should recognize that each of these concepts are a continuum, not an either/or situation. It's really not randomized trials versus comparative effectiveness, or randomized trials versus real-world evidence. And again, we may or may not wish to get into further discussion, but I think, overall, my starting point

is we need better data, we need better tools to generate such data, and we need to be clear about what specific research question is being addressed with each particular study protocol.

I don't know that anyone who presented would disagree. I think I've aligned with what we heard, and likewise everyone on the panel. But just as a big picture, it's not as if real-world data or real-world evidence are -- when the dust settles, we've had these type of data sources before. We've had these type of epidemiologic study designs before, including randomized trials, and what's changed is the availability of big data.

My last point is I'm encouraged. I'm old enough to remember when oncology trials and cardiovascular trials were criticized for not being generalizable enough. What would oncologists at the Department of Veterans Affairs do when the New England Journal of Medicine published a paper on patients younger than 65 with no comorbidity, and when they go on to wards [indiscernible], it's hard to find a patient like that in the VA, and yet we

figured it out.

So I'll pause here. Thank you for giving me a little bit of time, Joy, but I just wanted to sort of calibrate the big picture as we get into the weeds, as we should and as you all are in the trenches doing this important work. But hopefully, these comments, again, will help to frame the landscape. Thank you.

DR. MEJIA: Thank you. I want to have --

DR. CARTER: I think Dr. Concato makes a great point because he's right; it's a continuum. My left-hand slide here is the wild west, and on the right hand, the really, really serious controlled group. But we can move this goalpost like this, and the question is, how risky is that, and when do you want to do it?

DR. MEJIA: Thank you, Dr. Carter.

Mr. Rolley, I see that you want to --

MR. ROLLEY: Yes. I'm going to maybe throw a little different perspective on here. We have in the past utilized registry data to study informed decision making, and in some cases, clinical

trials. If you have a new product that's relatively new on the marketplace, a lot of times the databases don't have any information on your product. So we've actually had to utilize claims databases, and we've used CMS.

We've also utilized Premier and other private claims databases, which are relative big data. They're huge databases. They don't have specificity oftentimes in them in terms of the coding that's available, so what we've learned is that you have to have a researcher that really understands wound care and can piece together the puzzle and all the different puts and takes as you're looking at the data.

But we have used them fairly successfully in informing clinical study design and giving, frankly, even broader insights on the overall marketplace and understanding the patient. Things like resource utilization, comorbidities, length of stay, those types of things you can piece together out of these claims databases as well. So I'm just throwing that out as another option.

DR. FIFE: And why can't we have an ICD-10 code for diabetics but also in arterial ulcer? Why is that impossible when they're four code sets for venous? Why can't we have that? Whose job is that?

DR. GOULD: AMA.

DR. SERENA: That is the AMA.

I'd like to just say one thing that dovetails into what everyone's been saying and what Marissa just said a minute ago, and that is we do see more recent clinical trials beginning to marry closer to real-world data. I have to admit and I could say it was a great idea of ours, but I'd be lying.

It's really Medicare in these postmarket trials saying, "You're not treating our patients. Great trial; not our patients." So we've taken Medicare's criteria in our postmarket trials and incorporated them into our trial; so the 4-week period, half the patients have to be over 65, and you look at the results, and they're very different.

I think this sort of idea is going to do what Marissa said, bring the wild wild west and the very rigid trials where it's not our patients into harmonization. That's something I think is well worth the effort.

DR. FIFE: I don't remember who said it, but whoever the speaker was who said cancer patients die, before it became more difficult to look at Social Security numbers, we were asked to do a trial looking at how many patients who were treated for severe pressure ulcers were still alive in a year -- and it's harder to use the Social Security numbers now than it was then -- 15 percent of patients were dead within a year after their last visit to a wound center for a bad pressure ulcer. Like, wow! That's a year; 15 percent are dead. It seems like that's a message that is important, but we're not talking about it.

DR. CONCATO: Caroline, that's a general problem. Patients with advanced heart failure and advanced COPD, as we know, often have survival rates as dismal as many cancers. It's another

continuum; it's a spectrum [indiscernible].

DR. FIFE: Yes, and 25 percent of our patients have heart failure. So they don't live very long, and wounds are kind of the harbinger of their death.

DR. MEJIA: Great. Thanks for that discussion.

Dr. Gould, did you want to comment further?

(Dr. Gould gestures no.)

DR. MEJIA: Okay. Alright.

I'm going to shift things a little bit. The next question is a multipart one that deals with digital health tools. With the increased use of digital tools, like mobile health platforms, specifically wearable devices, how is or how can patient-generated data be used to inform clinical trials?

I'm going to open the floor up to anyone? I know doctor Serena and Nico O'Kuinghttons, you're experts in this field.

MR. O'KUINGHTTONS: I think that's a great question, and I'd love to hear the comments of

Dr. Serena, who's been at the forefront of using technologies and really understanding what's applicable from a novelty, but also from a practicality. I think he has great lessons to share.

DR. SERENA: Well, thank you, Nico.

I'm just the guy conducting the trials. We have to have the people that make the technology and make it easy to use, and that's something that his group has done very, very well. That was the key. When it was 25 pages, and you had to go through three screens to get in, your patients just simply weren't doing it.

So this ease of technology has really been a big plus, somewhat pushed by the pandemic, but in a very positive way. We went first to completely decentralized trials, in the sense they were decentralized from a sponsor perspective, in which we just completed two DFU trials, and not a single person on the team was at any site. It was all done completely virtually. That went to now we're doing trials where the only person in the nursing

home is the nurse, and everything's done digitally.

Our next set of trials, which we've started, the entire trial's conducted in the patient's home. We have a number of these trials. I think that's where it's going, and we're really hoping that this technology will continue to improve. I'm sure it will; they're always working on it. It's pretty exciting. You learn a lot more.

One of the fascinating things about in-home trials is patients heal better. I don't know why that surprised me; it shouldn't. You always think you've got to come to the clinic and you'll heal better, but that's not true. They actually do better in the home, at least initially. I don't have enough data to really say that with confidence, but the initial observation from our team was, "Wow. They seem to be healing better when we treat them at home."

The other thing is we have access to patients I didn't even know existed. I really was shocked this past week. We were getting ready to do a trial, and the nurses were showing me the

pictures of the patients that were being seen in the home, and I said, "I've never seen those patients. Who are these people? I haven't seen them."

So I think the other huge advantage to decentralized trials is going to be the fact that we can really access patients that we're not doing, that aren't ever seen in clinical trials, when we're conducting in the clinics or hospitals.

DR. COOPER: I wonder if I might add a comment that's complementary to what Dr. Serena just shared. In our experience, which is a growing experience with remote monitoring of negative pressure wound therapy in out-of-hospital at-home patients, we found that the proactive approach really enhances compliance. It allows us to shorten the time of problematic application of the devices. The results with healing are far accelerated, and the total cost of care is down because patients are compliant with the care. So there are a couple of different factors to think about as we try to include those patients for

study, comparative results, historic results, et cetera.

DR. FIFE: The key is we have to have something that you know matters. That's a challenge because we've got a lot of technology out there, and we don't know whether it matters, as has happened. That's what we found with the quality of life. We had a tablet. The patients could answer the quality-of-life questions. It was transmitted to the registry. It didn't matter because the questions turned out not to be relevant to what happened to them.

DR. CARTER: I think Dr. Serena makes a great point. It's like he says -- and I understand this is just an observation at this point -- that people do better with devices and stuff at home. I think that's totally right. It's like they're not going to a foreign environment. They're in a happy, caring environment, for the large part. Even if they're in a nursing home, they're not being forced to go somewhere else.

So I see in trial work, especially over the

next 10-20 years, the introduction of patient-centric technology, this is stuff that whatever environment patients are in, it's going to get transmitted. It's going to be a totally decentralized trial. And the kind of data that's going to be transmitted is going to be even more advanced than the kind of stuff we get today. I'd love to see that.

DR. FIFE: We will have arrived when we do patient-centered trials. Since the patients always have more than one wound, and we always look at one wound, I'll know we've arrived when we're looking at the patient.

DR. CONCATO: Well that, Dr. Fife, is something that could be addressed as a stand-alone issue, or discussed at least as a stand-alone issue. But again, I just want to make sure, in case there's lack of full awareness, that the FDA is very active in these areas.

For example, in December of 2021, there was a guidance published on digital health technologies and the emphasis on verification, validation, and

usability. It's our, quote/unquote, "current thinking," but it should help stakeholders and sponsors understand how we're going to move forward. And again, it's reassuring. We usually bring up examples of what we're wearing on our wrist, and are our steps accurate, and how could they be used in, say, a Parkinson's study. Here, it's a different clinical context, but there should be lessons learned.

Likewise, to Dr. Serena's point, I agree entirely. While digital health technologies and decentralized trials are, if I could say, highly correlated -- and not to invoke statistics here -- they're not one in the same.

Yes, with COVID, we were very involved with making sure that trials of non-COVID therapies could be continued during the pandemic, and that largely rested within the regulations, actually, and finding ways to get the job done. And that accelerated what had been trend already, but there was a lot of hesitancy.

We wished the pandemic didn't happen, and it

was not a silver lining, but it did force us to figure out ways to push this along. So hopefully we'll, again, take advantage of the experiences we've had and put it to good use, in this case for wound healing therapies.

DR. GOULD: I think what's really good is that other industries have taken this on and there's huge competition. These are not wound healers; these are IT people that look from the outside in and say, "What are these wound healers doing? Why are you only measuring a wound as a rectangle?" They're not rectangles.

Some of that has come along and moved fast. We're still stuck on being able to actually measure the whole wound, though, and that's going to be a big challenge, is measuring depth, measuring undermining, measuring tunneling, and then being able to do that in the home, which it will come, because there's so much competition. But I think that that's going to be something that we need to do, and need to tackle, and then make it easy for the patients and their caregivers to be able to do

it and transmit it. Most of my 85-year-old patients who have wounds that are not accessible by them don't have caregivers that are going to be able to do it as well right now, but it will come.

MR. O'KUINGHTTONS: One of the biggest takeaways that I see across other therapeutic areas -- and I think we've remained focused for a good reason on the wound -- is the patient journey, and meeting the patients where they are.

Dr. Serena mentioned something about these different care settings, where you may find patients where they wouldn't necessarily be seen in a wound care center or travel to a wound care center, and really finding those patient-centric solutions that are addressing the patient at home or addressing the patient in a certain state.

I think that's really important, and those are the lessons learned that I'm seeing from other therapeutic areas. Our helping address some of the barriers that we may or may not see here is the inclusion of other underserved populations that don't necessarily have access to those clinics or

those facilities. This is an ability to really remove the geographic areas and be able to achieve and address the populations that we don't necessarily see. I know we focus on chronic or comorbidities and also the age, but also the underserved population that we see in many regions that are affected by some of these pandemics, it's really important.

That's the hope that I see. Regardless of payment, and regulatory, and how things are going to be reimbursed on the long run, it's really addressing and bringing technologies that are meeting the patient there as opposed to the patient meeting the provider where the provider is.

DR. MEJIA: Thank you for your comments.

DR. SERENA: One last comment is that Nico and I were in a meeting. I don't know if it was sponsored by FDA. I can't remember if it was sponsored by FDA. It was in 2019. We were having lunch, and all the important discussions happen over lunch. One of the FDA individuals asked me if I was doing decentralized trials yet, and I said,

"Well, I was worried about FDA." And he said, "We're ahead of you on this. We're looking at decentralized trials. Why aren't you doing them?" And it was at that moment that I kind of looked over at Nico and said, "Alright. Let's go." That was really the beginning, and I'm not just saying that because it's an FDA call. That's true. That's a true story.

The last point I want to make on this is that Caroline mentioned patient-centered outcomes and endpoints, and I think that's really important. It's funny how in the home the endpoints are slightly different, and maybe it's just because I'm not good at picking up these in the clinic.

Odor and drainage are far more important to patients in the home setting than they are in the clinic setting. I mean, they don't care if they pour exudate all over my floor in the clinic, but at home it's totally different, and this is the feedback we get from our nurses. "Boy, if I could just get control of the exudate."

We'll have almost a hundred nurse

practitioners going to the home by the end of this year, and the calls are, "I can't get this healed." We certainly get those, but a lot of it is, "Mrs. Jones, really, we've got to get the odor controlled," because she's in her home, and we've got to get the drainage controlled. We change the dressing, and the daughter can change the dressing.

I just wanted to throw that out, too, because that was another eye-opening experience as far as what patients want when they're in the different settings.

DR. MEJIA: Great. Thank you. Wonderful insight.

For the next question, I think we can start with Dr. Carter, but others are also encouraged to provide their thoughts. In addition to informing future randomized-controlled trials that expand inclusion for better patient representation, what are some other ways that comparative effectiveness research can inform clinical trial design, other than better patient representation?

DR. CARTER: What I actually say is what do

you really want to do with your, quote/unquote, "randomized-controlled trial?" A lot of times I have discussions with sponsors and some like that, and they have this -- I wouldn't say blanket, but they certainly have this very fixed idea, and part of the problem I would say goes back to regulatory issues of 501(k).

A vast majority of trials in wound care were done that way, so in a sense -- and it goes back to something that was said yesterday in the workshop, and that is, the quality of those studies is way less than the ones that are actually approved in terms of FDA, whether it's PMA or something else.

Part of it is understanding what real-world evidence can do for you in terms of designing a trial and designing a population, and once you start to explore that, you start to get a sense of maybe actually including more patients isn't quite so risky. It's like if you never had access to that data, you've got this terrible barrier and fear of, "Oh, my God. If I start treating serious patients, if I start treating serious wounds, my

product's going to fail, and it's going to be a disaster, and the whole company is going to shut down." But if you start to explore real-world evidence and data, maybe that isn't so true, and you start to get a sense of, "Well, actually, we could do a little better."

DR. FIFE: Lisa, your hand is up.

DR. GOULD: Yes. I was going to say --

DR. MEJIA: Dr. Gould, and then Dr. Banerjee.

DR. GOULD: Yes. We heard yesterday that it is very important to the patients that their wound is closed, but I think that the real-world evidence can help us understand what happens along the way. I think we really need to get away from the concept that one product heals a wound. That's not how we do wound care. That's not how wounds heal.

So we can use the real-world evidence to help us understand at what point does a wound stall when something has been used 6 weeks, 8 weeks, 12 weeks, and then when should it be changed, and then also looking at some of the intermediary

endpoints.

So we have to have a goal of, yes, we want to close wounds, but we have to have a goal that gets us to a certain point, and then know that we should switch things up to get to that final healing. I think if we looked really closely at real-world evidence, we could figure out how to make it talk to us.

DR. FIFE: There's a lot of sensitivity around access to care, and having done RCTs, it can be very difficult. We enroll almost no non-English-speaking patients because it's so hard to do consent, then there's a lot of discomfort on the part of minority groups, so they're underrepresented.

As a result, their outcomes are different, in the real world anyway, and we don't really know what that means. So I think we can use real-world trials to understand what targets we might want to have, to have a representative population, but maybe also to get a sense of whether our products work the way we think they do, in everybody.

DR. MEJIA: Dr. Banerjee?

DR. BANERJEE: Yes. Thank you. I wanted to follow up on what Dr. Gould just said, and also Dr. Carter. If I can go back to the real-world evidence discussion, something that we didn't talk about is trying to understand how many applications should be done for a lot of these products, which are weekly applications or multiple applications, and we're having that conversation.

Medicare is trying to figure out that there is a lot of overuse and abuse of a lot of these products. How do we determine that this product should be used 3 times or 4 times, or is it not enough? Do you waste money if you're restricted to 2 or 3 applications or should we use it for more?

Real-world evidence can really give us some indication that some of these products need to be applied for multiple weeks for at least a certain amount of time to then, even if you stop it, the wound will still close on its own. So that's, I think, a good place where real-world evidence can really work together with RCTs to help in good

clinical decisions.

Another, from the industry perspective, is in comparative effective research. I think there is resistance in industry doing it just because of the risk of what happens if my product doesn't do well as compared to my competitor.

I think two comments here are, one, if there are opportunities for industry to work with academia, the problem is industry trying to sponsor a product like this because of this space [indiscernible] if there are other brand opportunities, say from WHS or SAWC [ph], where there is an incentive for academia to go and take some of these technologies and do a comparison on their own, as opposed to depending on industry to sponsor a product like this.

The other comment I have to make is, if you look at RCTs, especially in the wound care space, the big problem of why we cannot use RCTs to make a decision of whether this product is better than that is because of such a difference in the standard-of-care arm, and not only the

standard-of-care arm, but also the demographics of some of the patients that each clinic would treat.

I think each RCT should be reporting not only just wound closure rates, because that can be misleading, but they should do what AHRQ has started doing, either the hazard ratio or risk ratio. When you're doing an intervention, you're normalizing to standard of care the same RCT. If you do that, then I think that can give you an idea of whether one kind of intervention is better than another kind of intervention. But if you don't do that, just looking at RCT data and just looking at closure rates may be misleading for some of these complicated wound types.

DR. FIFE: I just want to say one thing about abuse, and that is when you look at claims, it conflates all the wounds. So what we see from real-world data is that there really isn't a problem with a realization. The patient has 3 or 4 wounds. Each individual one is being treated appropriately, but you don't see that when you do the clinical analysis because you think it's put on

15 times for one wound. That's not how it works. So I think that's another insight that we get from the real-world data that's problematic when you look at claims.

DR. SERENA: You bring up another really good point, and that is that early clinical trials did follow the oncology model with very stringent run-in periods. We stole that idea from oncology, and now we have these 4-week run-in periods that cause a tremendous number of screen failures, but it's a price you pay to get a more heterogeneous group, and a sicker group. You can have a much higher index acuity score, as Dr. Fife was talking about earlier, because the patients that get through that screening period really need the product.

They're just getting ready to publish now the main reason people screen fail in trials with 4-week run-in periods, and you'd be surprised, or you wouldn't be surprised; they heal too quickly. Even at that standard of care for 4 months, when you put them in a trial and really control the

standard of care rigorously, they heal.

DR. FIFE: Yes, this is a big plea for quality metrics because --

DR. SERENA: Yes, exactly.

DR. FIFE: -- that's what we saw with quality metrics. In the decade we've been pushing quality measures, arterial screening rates have increased dramatically, and it's changed the wound rates, and it' so basic. But we have a lot of fancy technology and then we don't do nutritional assessments. If we just implemented quality metrics, it would make a difference.

DR. MEJIA: Mr. Rolley, do you have your hand up?

MR. ROLLEY: Yes. Thanks for that.

Great discussion. I agree with all the points being made here, and just to maybe add a bit on the real-world evidence side, I'm a firm believer in the value of that.

My comment would be that the study sponsors, though, to get people to sponsor real-world evidence studies, the audience for that has to be

receptive as well. We've got FDA on the phone. I think we probably have CMS as well. But the commercial payer is another one out there that is not on board with real-world evidence.

Medical device companies are not that well funded. They're not pharma companies. You can only do so many of these studies with products with short life cycles before you have to move on to something else. So we have to have all the audience at the table here, and agreeing that this can supplement. And I would think in the payer world, they should be receptive to real-world evidence because that's the world they pay for products in, so why not understand how these products are actually being used and what kind of results they're getting?

I just point that out, that to get that to actually be adopted by study sponsors, we're going to need to get all the stakeholders and the recipients of that data to be on board.

DR. CARTER: I think what Joe said is terribly important, but I think we need to look at

a wider context. Why is it we don't do huge amounts of this in wound care? I think it's because a lot of people, including some of the stakeholders that Joe just talked, don't really trust it.

That means we have not done a good job with stating what the golden rules should be, what the standards are, implementing them, and then making sure everybody agrees these are the standards that we want to have in wound care, and if you want to publish it, you've got to meet these standards.

I think, good God, one of the things I see all the time when I peer review trials is only 20 years ago we had consult criteria for RCTs. None of the major wound care journals and studies insist that we have to have these for each peer-reviewed paper that comes through the door. Why not? This is not rocket science. It's not hard. We don't take care of the standards that many organizations within wound care actually put out and spend a lot of time and money on. It's like we just ignore them. How can we fix that?

DR. FIFE: Back to something Dr. Banerjee said, is when we do comparative effectiveness studies, published or not, the manufacturers are often angry because their product wasn't applied every week. Well, no one asked what were the criteria the clinician used to decide to put it on. We don't put things on weekly just because that's why the clinical trial is done. There is a thought process that goes into it, and no one ever says, "Hey. Was it because it stopped getting smaller?" There are things we could measure to answer that question.

That gets to the issue of this 12-week episode of care, which Medicare payers are wanting to put on us if a real patient is in service for 7 months. Could we use some real-world data to get some reality check on the distance between these applications, and why it is what it is, and how many months it really takes to get all the wounds healed?

DR. MEJIA: Dr. Banerjee?

DR. BANERJEE: Also, I just wanted to follow

up on what Dr. Rolley just now said. I think it's just sad that a lot of these tougher wounds, which are not part of any of these RCTs, are not covered because no one has done a study on those. From the industry perspective, people might be scared in doing a trial for these tougher wounds -- I mean, complex wounds, exposed structures -- and the only way of getting data, to Dr. Carter's point, and doing it properly, for Medicare to believe it, is real-world evidence. It's very difficult.

If you get good data from real-world evidence, maybe the next step is to plan an RCT, but to plan an RCT, what would be the endpoints? What would be the length of trial? What should be the number of applications for this trial? I think it's critical that we look at this real-world evidence first to make sure that we don't waste money and time, and the RCT is properly designed. So I think it really complements each other.

DR. MEJIA: Great. Thank you so much.

We've got about a couple minutes left. I see Dr. Gould wants to weigh in, and then,

Dr. Concato, I wanted to see if you had a final comment as well.

DR. GOULD: I just wanted to point out the incredible data that Dr. Gurtner showed, where he was giving this drug, and when the patient took a hiatus off for Thanksgiving, you saw the wound got worse, and then there was another hiatus as they switched over to -- I can't remember if it was a crossover or what.

I've never seen a clinical trial designed that way. Our clinical trials are designed to give something weekly, whether it needs it or not. Our hyperbaric treatment is daily, and that doesn't make sense physiologically. But nobody's ever done the stop, and look, and see is this product actually working when I take a hiatus or can it go on to heal based on that?

Again, that's something where perhaps some real-world evidence could be used or a totally novel clinical trial design to show us the product's truly working.

DR. CONCATO: Thanks, Joy. If you're giving

me an opportunity, I'll say some closing thoughts, and so much to talk about here and an excellent discussion. I will just say that sometimes real-world evidence is used to just mean results of descriptive analyses, and that's certainly not the regulatory definition.

So with that caveat, my main answer is that the attention to fundamental methodologic principles is critical. We take it for granted that we know what we're doing is. How good a study is, is a combination of multiple decisions along the way.

I would like to leave this session with the thought that the increasing use of new technologies, decentralized trials, and registry-based studies, which we didn't have a lot of time to talk about, are not mutually exclusive. And by the way, you could use a registry to bind patients for a trial, you could use a registry to do a study, et cetera, but mainly what we should look for are opportunities where an appropriate study design analyzes fit-for-use data, and I'm

quoting from our 2018 real-world evidence framework. If you're interested, I'll send it after this session.

That third leg of that stool is that studies have to be conducted properly to meet FDA regulatory requirements. And even if the successful examples aren't immediately transportable to another context within wound care, or from, or to other disciplines, important lessons we'll learn, and we'll be in a much better place -- while I would like to say months, but more realistically -- in the years to come.

So thank you very much for inviting me. I hope this was helpful. I certainly have benefitted a lot, so thanks to all my fellow panelists and the presents.

DR. MEJIA: Great. I agree. I think this has been a very, very insightful session for this workshop, and we're actually, I think, headed to better things.

It's lunch break, so we'll be back at 1:05, and I appreciate, again, everyone's insightful

thoughts and input. Thank you.

(Whereupon, at 12:21, a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:05 p.m.)

FDA Introductory Comments – Dev Verma

DR. VERMA: Alright. Welcome back, everyone. Our next afternoon session will focus on assessing clinical benefit in non-healing chronic wounds. Our objectives for this session are outlined here. We hope to recognize the importance of clinical outcome assessments that are context relevant for patients with non-healing chronic wounds and identify the process of how to develop fit-for—purpose COAs.

In the subsequent talks and panel, we'll be hearing from the following people. Dr. Julia Ju is a reviewer in the Division of Clinical Outcome Assessment at FDA, whose expertise lies in the areas of qualitative and quantitative research methods, patient preference study design, and patient-reported outcomes.

Dr. Vickie Driver is the chair of the Wound Care Collaborative Community; system-wide medical director of the Wound Care and Hyperbaric Centers

at INOVA Health Care; a member of the Wound Healing Society Board of Directors; professor at UVA School of Medicine; and past president for the Association of the Advancement of Wound Care.

Dr. Anne Klassen is a professor in the Faculty of Health Sciences at McMaster University. Her areas of research have focused on development and validation of PRO measures for pediatric and adult conditions, and she's the co-developer of the Q-Portfolio Patient-Reporting Outcome Measures that are used worldwide and have gone through the FDA MDDT qualification program.

Dr. Andrea Pusic is the chief of Plastic and Reconstructive Surgery at Brigham and Women's Hospital, professor of surgery at Harvard Medical School, and director of the Patient-Reported Outcomes Value and Experience Center at Brigham Health. She's a leader in the area of PRO and a co-developer of the WOUND-Q.

Dr. Selena Daniels is a team leader in DCOA at FDA and leads a team of expert analysts who provide consultation and advice on COA endpoint

development and validation, including considerations for clinical trial design, conduct analysis, interpretation and reporting for regulatory determinations. Prior to joining FDA in 2015, Dr. Daniels worked in the Health Economic and Outcomes Research Group at Allergan.

Dr. Kathy Fritsch is as statistical reviewer in CDER and reviews a wide variety of drug product applications in the Division of Dermatology and Dentistry. She has a particular interest in study design, drug product labeling, multiplicity, and subgroup analysis, and she's contributed to several statistical and dermatology guidance documents.

Dr. Daniels will be moderating the panel, posing questions to the panelists, and we will start with Dr. Ju's talk.

Presentation – Julia Ju

DR. JU: Good afternoon. My name is Julia Ju. I'm a reviewer in the Division of Clinical Outcome Assessment, Office of New Drugs, CDER. Today I'm going to talk about the regulatory approach for development of clinical outcome

assessments, in general. I will also share some considerations in wound healing assessments.

Patients are experts in their disease. With this recognition, FDA's Patient-Focused Drug Development Initiative, PFDD, began in the early 2000s to incorporate the patients in the development of clinical trial endpoints for medical products. The goal is to use a systematic approach to capture patient experience and perspectives here in a way that can inform regulatory decision making and can be described in labeling accurately and informative to healthcare decision making.

These definitions are provided for your reference, as we use these terms often. The purpose of a clinical outcome assessment, COA, is to understand the clinical benefit or clinical outcome of a treatment or intervention, for example, how a patient feels -- [inaudible – audio lost].

MR. TETLOW: One moment while I get the video queued back up, please.

DR. JU: -- functions, or survives ways of

treatment.

There are several types of COAs. The commonly known patient-reported outcome, PRO, is based on a report that comes directly from patients without a measurement or interpretation of their response by anyone else. A clinician-reported outcome involves a clinical judgment or interpretation of the observable signs, behaviors, or other manifestations of a patient's disease or condition. An observer-reported outcome is usually considered for patients who cannot self-report reliably; for example, infants or individuals who are cognitively impaired. A parent or caregiver can report observable signs or behaviors related to a patient's condition.

A performance outcome assessment involves a standard test that the patients complete independently. The patient's performance is usually assessed by a trained individual. Digital health technology tools may be used to complement the traditional COA approaches that I mentioned above to inform the overall benefit-risk framework

for a medical product.

One example of a digital tool would be a wearable to capture a patient's daily activities in a real-world setting to derive clinical outcomes assessment data such as walking speed; distance; fall episodes; sleep duration or disruptions; or seizure episodes.

This road map describes at a high level the necessary steps to develop a COA. It starts with understanding the disease or condition and the patient population. The next step involves conceptualizing clinical benefit, identifying important and relevant concepts that reflect a clinical benefit. After that, you may either select an existing COA measure, modify it, or develop a new COA measure to rate [indiscernible] a specific drug development program.

As you have heard during this workshop, there are many challenges for COAs in wound healing trials. We haven't reviewed a lot of COAs specific to wound healing. We hope this workshop provides some useful information to assist in the

development of fit-for-purpose COAs for future wound healing clinical trials.

Due to the heterogeneity of the patient population, wound type and intended intervention effect is very challenging to develop a COA that can be used across wound healing trials. Another challenge is that wound healing may be affected by many external factors. For example, depending on the origin or location of the wound, the patient's physical activities, diet, comorbidities, or living environment may affect the wound healing.

Pain is a core concept in wound healing assessment, however, the presentation of pain differs in wound subtypes. Wound pain can arise from tissue damage or from dysfunction of the nervous system, or both, which is often the case in chronic wounds.

Additionally, wound pain has many causes, often interlinked, that may be related to the wound itself, wound infections, the interventions such as dressing removal and the debridement, or other local pathologies such as edema. All those add to

the challenges in pain assessment in wound healing trials.

We also acknowledge some other concepts that are clinically relevant and important to patients such as odor and itching, however, those concepts are difficult to measure. Regarding odor, multiple COA types may be warranted for adequate assessment, which may include the patient-reported, observer-reported, and possibly clinician-reported outcome assessments. These COAs would likely need to take into account whether odor is evident with wound dressing intact or removed and the proximity to the patients; for example, odor within 6 feet of the patient.

For this and other challenging concepts, it would be helpful to discuss measurement and strategy with the agency. We are not aware of any validated scales for odor assessment. Such assessment would need to be fit for purpose and demonstrate meaningful and interpretable changes.

If a particular sponsor is considering developing such skills, they could obtain

regulatory advice through their IND or consider going through the Drug Development Tool, DDT, COA Qualification Program.

Regarding the itching assessment, clinical benefit may be difficult to observe and interpret, as itching can be a result of a number of factors such as skin dryness, sweating, and the wound healing itself. Additionally, untreated wounds sometimes may also be the cost of itch. Therefore, it may be difficult to determine whether worsening of itching means that wound is healing or worsening.

While we recognize itching as a clinically relevant concept, you may wish to consider relegating this assessment in the endpoint hierarchy, as this concept may potentially be unsupportive of the primary endpoint unless the investigational product is expected to reduce itching.

It is critical to specify a defined clinically relevant and important concept that can be used to detect treatment effect. A regulatory

concept is the aspect of an individual's clinical, biological, physical, and functional state or experience that the assessment is intended to capture or reflect.

Concepts can be identified through qualitative studies such as patient interviews, clinician interviews, or literature reviews. Once the targeted concepts are specified, you may select or develop a fit-for-purpose COA and a prioritized COA of related endpoints that can be used to support labeling.

This graph shows the key elements we review to evaluate whether a COA measure is fit for purpose. The sponsor needs to submit evidence supporting these key elements to demonstrate that the COA data can be included in labeling. We will review the intended use of the instrument to evaluate whether the concept used is appropriate; whether the content or concepts are well defined in the instrument; whether there's adequate qualitative and quantitative evidence to support the content validity and other measurement

properties such as construct validity, reliability, and ability to detect change. Lastly, we will evaluate the score interpretability to determine the threshold of a clinically meaningful way the patient changed scores [indiscernible].

As it was mentioned earlier, pain reduction is important to wound patients, however, pain assessment can be challenging. Here are some considerations for pain assessment. The development of pain assessment should incorporate the patient's input so that it will measure the patient's pain experience fully.

As we heard yesterday afternoon, there was quite variability in how pain was described and originated. Description about the type of pain to be measured should be provided in the question stem. Include a diagram showing the region of pain and the location of the wounds if possible.

Another consideration for pain assessment is that the recall period and assessment frequency should be selected based on the target pain type and how pain presents in the targeted population.

The target of pain for assessment could be background pain that is felt at rest instead of pain during mobilization or coughing, procedural pain during dressing changes, or operative pain during debridement. Lastly, it is important to capture analgesic use and other rescue medication use at a baseline and during the trial to help interpret pain assessment data. Those could confirm the treatment effect on pain reduction.

In addition to pain assessment, there might be some other concepts to explore measuring in wound healing trials such as physical functioning, mobility, debridement, and the dressing change burden, however, this should be guided by patient input. Some of these concepts may be more appropriately assessed by a clinician.

In summary, incorporation of COAs in clinical trials and the interpretation of COA data require multidisciplinary collaboration. Input from patients, clinicians, and other stakeholders are important for COA measurement, development, and the study endpoint selection.

The sponsor should provide evidence demonstrating the COA measure is fit for purpose; that is well-defined, reliable, and interpretable in the proposed context [indiscernible] of use. We encourage sponsors to engage FDA early and often about the COA measurement and strategy.

This is my last slide providing some links that may be useful to you. Thank you.

Presentation – Vickie Driver

DR. DRIVER: Good afternoon. This is Vickie Driver. I'm very happy to be here today. I'm here today representing the Wound Care Collaborative Community, otherwise known as WCCC, as well as the INOVA Health Care in Northern Virginia and the University of Virginia School of Medicine.

We're going to jump right in. Let's start with this. First of all, fortunately, this collaborative community is an outgrowth of years of successfully working with the FDA and the wound care community on defining meaningful and patient-centered endpoints, otherwise known as the WEF-CEP initiative. The initial work was intended

to fill an important gap by researching the evidence to support the utilization of additional clinical endpoints, especially to be considered in clinical research trials.

Following this extensive research, that I'm going to be discussing, and three publications, and a very wide-based outreach program, the FDA asked us to consider developing a wound care collaborative community, and this was done in just 16 months ago, actually, after developing a charter of the tools program that was actually developed by the FDA.

We're going to stay on this slide for a moment because it's very important to understand the volume of the robust collaboration and research that has been conducted to get this far. It's taken us eight years, and this has been in incorporation with the Wound Healing Society and the Association for the Advancement of Wound Care.

But going back to 2015, we first decided on a priority gap, the need for more than one primary endpoint that could be utilized in clinical trials

besides complete closure, particularly as it relates to efficacy, although this was brought to our attention in a very big way by the pivotal paper written by Drs. Kirsner and Eaglstein. We engaged then with the FDA to define the issue, develop a strategy, and collaborate on the method that would actually be acceptable to the FDA to put forth additional primary endpoints for consideration.

We launched the WEF-CEP, which is, for the wound care experts, an FDA clinical endpoints project, and we started with 28 endpoints. These endpoints were akin to us from previous relationships in projects with the FDA and also found in our own literature.

A multidisciplinary group of wound experts really undertook an initiative in collaboration with the FDA to identify and content validate supporting FDA criteria for qualifying wound endpoints, which are important and relevant to clinical practice and patient-centered outcomes as primary outcomes in clinical trials.

Now, as part of this initiative, our research study, a robust research study, was conducted involving 628 multidisciplinary wound clinicians and researchers from four different groups. In 2016 and 2017, from the analysis of this survey, we confirmed 22 content-validated wound care endpoints by an independent biostatistician that were relevant in supporting clinical practice and relevant to or making a difference in patients' lives. Now, the survey not only incorporated 629 clinicians, but it was from 13 specialties and represented nine different settings of care.

Then you see in the middle of your slide, we end up with 15 endpoints. Well, how did we get here? Well, we then organized six research teams of volunteers across the U.S. in groups by specialty as it related to the endpoints requirement research. For example, if we were looking at amputation prevention, we would incorporate in this group vascular, podiatric, orthopedic surgeons, as well as physical therapists

who really understood this endpoint and how to evaluate the evidence.

From that, we trained these members on the FDA criteria for evidence review and the FDA qualification process, which is very specific, and conducted the systematic reviews. We summarized the clinical evidence based on the FDA criteria for qualifying primary endpoints in clinical trials. We reviewed 550 wound studies, over half a million subjects, and we of course moved into the development and understanding of 15 primary endpoints that had robust content validity of 0.85 or greater.

We shared these preliminary data with the FDA, multiple intervals in person, by telephone conference over these years. And of the top 15 outcomes, which were important to clinicians, which were designated as important for them or their patients, only time to heal was recognized at the time as an important primary outcome required to support efficacy, or safety, in phase 2 or phase 3 studies conducted for FDA clearance.

Then in 2018 and 2020, we conducted a patient survey via an IRB process that yielded 451 responses from patients in 26 states, and it showed us that patients primarily agreed with clinician survey, and this was also published in the Wound Repair and Regeneration.

The opinion survey from people with wounds addressed an important but understudied issue, the gap between clinicians, healthcare, insurance companies, government agencies, and really helping us understand the patient's perspective specifically regarding clinically meaningful and scientifically achievable additional primary endpoints for wound care. The survey for patients was adapted from the clinician survey with adjustment for health literacy, and there's a pilot tested, in fact, to understand that we could actually achieve this goal.

Now, I'm happy to say that we then presented these data, the final six endpoints, to the FDA -- you can see on your right -- and the FDA did state that they were open to discussing each

endpoint with the sponsor, understanding that each endpoint needs to be validated with specific measurement tools that has validation data behind it.

Here are the endpoints mentioned, 15 to your left of your side, and these were based on the data from the survey. Probably to no surprise to anyone, on this slide you can see time to heal is number one, but then if you move to the right, you can see the six new primary endpoints that we recommended. WEF-CEP at that time recommended to the FDA to be considered for conducting randomized clinical trials specifically for efficacy and safety; percent area reduction; reduction in pain; and reduction in infection.

Important of course was increased physical function and ambulation. Quality of life was significantly important to patients in our study. In fact, much of the data from these studies was really focusing on their interest in improving their quality of life.

We also suggested new secondary endpoints.

You can see in the bottom right, reduction in occurrence, percent volume reduction, and bioburden, but we didn't feel at this time that these endpoints had validated tools to measure these endpoints unless they were considered potential secondary endpoints.

At the invitation of the FDA, WCCC was formed. A collaborative community is a continuing forum in which private-and-public-sector members, including the FDA, work together on challenges to really achieve common objectives and outcomes that benefit patients, for real; "for reals," as they say. The FDA collaborative community is part of an FDA strategic priority for 2020, and they have reached their goal.

Developing a collaborative community and such an important initiative, we knew we had to develop a porch [indiscernible], a very sound structure in order to make a difference and to stay in business and get our work done long term. So we went about developing a 501(c)(3), a board of directors, steering committee, and working groups.

And most of all we said to ourselves, "We must identify strategy, process, timelines, and resources for success, stay focus and understand that we are here for patients' needs." They come first. That's what this is all about, and keeping egos off the table, which is, of course, not easy to do in a large community.

This is actually all of the collaborative communities that I'm aware of, and some are large and some are small. We fit sort of the middle. The FDA has done some real solid by actually hosting a meeting where we could all talk together, understanding opportunities, and also some black holes in developing collaborative communities, a very useful process.

Our strategic process is to collectively harness the expertise to identify and close gaps that impede timely access to innovation. That's really what we're trying to do. We will be inclusive to parties who actually see different aspects of a problem and can constructively explore differences. This is critical to us. We intend to

find the gaps and work to close them to improve not just the quality of research, but the quality-of-care standards and new innovations for our patients. Of course we've developed mission vision goals. This is not to teach you all that, but the goal here -- the big goal, the mission -- is to encourage innovation in our field.

Of course the structure is critical. This is just to show you that we're serious about it. We've outlined who does what and what responsibilities will exist as we develop this community.

The board of directors is a very prominent group of doers who have worked towards scientific innovation their entire career. And of course, if any of you out there are looking for work, we would love you to join the WCCC at any level you see of interest here.

You might notice that on the slide in the bottom left is Dana Davis. We do have a patient member at the very pinnacle aspect of this collaboration. Dana Davis has been a patient and

spoke yesterday, and is an important member of the board of directors, as is everyone else. But we want patients' voices to be heard throughout this collaborative community.

We represent many, and what that means is we represent associations; payers; researchers; industry, and all levels, government; the FDA; NIH; CMS; clinicians; foundations; and strategic advisors. These are some of them who represent us today, or at least as many as we could get on this slide before I gave this presentation. But you can see that we are really gathering some very good solid mass here.

Just to point out again, we intend to give people credit as they work with us because they are taking on a significant burden in being part of these processes. This is our steering committee, and you can see it represents research, clinicians, associations, and all the people, industry, including government.

Working groups, and what we've done differently with our work groups is we have three

co-chairs. You can see this represents clinical research, industry, and government, and all of these work groups. We believe it's important to have equal voices and represent many.

Well, when we began this, we thought we were going to have short and long-term goals, but what we've realized is what we really have is long and longer term goals. But we're up for it because, remember yesterday when Dr. Verma discussed the root-cause analysis that was conducted, and that these are the barriers to product development for non-healing chronic wounds? Well, many of these that have been identified, in large part, are what the WCCC is focusing on, looking at natural history of different wounds; alternative endpoints to complete wound closure; standardizing clinical trials; looking at optimal and standardized and preclinical animal models;, et cetera.

This is our real-world evidence work group chaired by Dr. Marissa Carter, and we have two projects that have already begun. One is led by Joe Rolley, the other one by Dr. Fife, looking at

the natural history of patients with wounds, and also developing a method to overcome bias in real-world evidence. Now, these work groups are intense, and there are large working groups. Some are broken into smaller working groups already, but very intensely moving forward.

Our next working group is the Tools Work Group chaired by Dr. Alvarez, and this is critically important because we are very much involved in developing plans along with the Medical Device Development Tool and Drug Development Tools group through the FDA to help all understand how to validate tools, specifically to be used with these newly recommended clinical endpoints that I mentioned moments ago.

The next group is chaired by Dr. Tom Serena. Now, in order to really know what's holding us back, we must know the real challenges in developing new diagnostics and treatments. That's what this work group is all about. We've already started three projects, number one led by Marjana Tomic-Canic, of course, looking at standards for

preclinical models, and also the second and third in progress, designing and working through clinical trial design standards and also addressing standards in dressings, which is critically important.

Bottom line is we believe with our motives aligned, we will speak with one voice. The goal here is to accelerate the development of scientifically based solutions and surely move towards access to the medical innovation that will improve our patients' lives and everyday activity. We believe that, ultimately, the Wound Care Collaborative Community will continue the improvement of overall public health.

Of course, you have to mention Eleanor Roosevelt when you're talking about doing something, changing hearts and minds, and making change by changing our attitudes. We can do this. The wound care community I think has felt defeated. It's time to stare down what we have not been able to overcome, and work together to develop strength to really make it happen.

I just want to close by saying we want to give special thanks to folks that have been working with us over the years, specifically Dr. Cynthia Chang, and now Dr. Dev Verma, and also now Dr. James Rollins, all very important to us. And we want to thank all those who have helped along the way over the years and over the past few months trying to get the WCCC up and running.

Lastly, I want to thank Dr. Carter who introduced the collaborative community to us and helped us understand how to develop it. We also are very pleased that we have leaders that matter. Dr. Gould, Peggy Dotson, and myself have been at the forefront of this initially, but we have many people. Most people on this call that are clinicians, researchers, and industry are involved with the Wound Care Collaborative Community, and we are very grateful to you. Thank you very much for your time today.

Presentation – Anne Klassen

DR. KLASSEN: Good afternoon, everyone. My name is Anne Klassen. I'm a professor at McMaster

University in Canada, and I'm presenting on behalf of myself and Andrea Pusic, who is a plastic surgeon at Brigham and Women's Hospital in Boston. We are very honored to be invited to the FDA to speak about the WOUND-Q, which is a new patient-reported outcome measure that we co-developed for chronic wounds. Here are our disclosure statements.

The WOUND-Q fits within something called the Q-Portfolio, which is a series of patient-reported outcome measures that our team has developed over the year. These are mainly for plastic and reconstructive surgery patients, both pediatric patients -- for example, the CLEFT-Q -- as well as adults. We started with the BREAST-Q, which we published in 2009, and then went on to develop the FACE-Q and the BODY-Q, and some of these other instruments that you see here.

Two of our PROMs, both the BREAST-Q and FACE-Q aesthetics, have been qualified as part of the MDDT qualification process, and we're very grateful for that. We're hoping that eventually

the WOUND-Q also will be qualified.

Just in terms of background, most clinical outcome assessment tools that are used in wound research are objective outcome measures. The inclusion of carefully designed PROMs, though, that measure how people function and feel really does provide an important perspective.

Currently, there are PROMs available for wounds that have been developed, but most of them are for a single wound type for a specific part of the body. Many of them lack content validity because patients weren't involved in qualitative research to develop the content, and some of them lacked robust psychometric properties for measuring clinical change.

Our goal was really to develop and validate a PROM that could be used with all types of chronic wounds in any anatomic location, with strong content validity and calibrated to measure clinical change. We have published our protocol paper. This came out in BMJ Open in 2020. In that paper, we describe our methodological approach, which is

mixed methods, multiphase, and iterative.

Phase 1 is a qualitative phase, and that's really figuring out what is it that we should measure. Phase 2, then, is quantitative, and it's really figuring out which questions are the most effective for each of the scales that we've developed, and how does the instrument work psychometrically. In the next couple of minutes, I'll just go through some of the key findings for these two phases, starting with phase 1.

This is our qualitative phase. We spent a lot of time here. We had an interview guide with topics that we wanted to explore, and then we did 60 in-depth patient interviews. Some of these interviews lasted up to 2 hours. We tried to recruit a maximum variation sample in terms of age and gender, four different countries, wound type, and how long somebody had had their wound.

This is just one example. This is a woman aged 59. She had multiple venous ulcers on her leg for 20 years, so we had our transcripts, and this is how we coded. We did line-by-line coding.

This participant said, "As a result, I stayed home for a year; well, because if I smelled the wound, others would, too." And the interviewer said, "Did it bother you much, that smell?" "Yes, it bothered me a lot. It was really irritating and, yes, actually it gives you an inferiority complex."

So this was coded, and you can see that there were multiple themes for social and psychological impact of the wound. We did this for all 60 of our interviews, and at the end of the process, we had close to 3,000 codes from the 60 transcripts, and we were able to look at our major themes and subthemes in terms of wound type to see what is common and what can we develop that would work for different types of wounds.

Our analysis led to the development of our conceptual framework, and the WOUND-Q framework has four major domains of wound characteristics, so assessment, drainage, smell; and health-related quality of life, and four scales here; and these are process measures, so experience of care, so how

they're treated by different members of the healthcare team and information provision; and then the wound treatment scales are dressing and suction device.

From our publication, we have a data saturation table. We've included that in our publication, and I'm just showing you a portion of it here from the wound characteristics domain. These are the minor themes that we had, and we were able to look and see -- here's across the different patients 1 to 60 -- how many people mentioned each of these different themes. Then this level of detail here was used to form scales.

Here's our wound characteristics domain, and these are three really important scales. The wound assessment ask people how concerned they are about their wound in the past week, and it asks about different characteristics of the wound, such as holes, or swelling, or pain, or how deep and the size of the wound.

The drainage scale and the smell scale both ask how bothered have you been in the past week,

and then different characteristics of the drainage or different characteristics here, the smell coming from their wound.

Once we had our draft scales, we brought them into cognitive interviews. We used a lot of the same participants who took part in our qualitative phase. We find that they're able to then really give great feedback. We did these in rounds, so round one involved 15 participants who gave us feedback on the scales, and we made changes. We showed the scales to experts, made more changes, and then did a second round of cognitive interviews, and finalized the draft. That draft was then given to our translators.

Here's just a quote from one of our cognitive interview participants. This man said, "There were a couple of times where I actually felt a little emotional because the questions really hits the nail on the head. You seem to get it. Sometimes people that are in your life don't get it, so when you read a question that really hits home, it's nice someone actually gets it."

That's what you want to hear. This really showed that the WOUND-Q for this participant resonated with them and had relevant content.

The translators in Danish and Dutch followed the ISPOR guidelines here for translation to make sure that it was done rigorously, and in that they interviewed 38 participants; so these are cognitive interviews. They had input from 12 experts. Then we ended up -- based on their findings, we dropped six items from the WOUND-Q prior to going into our field test; so those were items that didn't translate well.

To summarize phase 1, there were 118 patient interviews altogether and input from 38 clinical experts, and this helped us to ensure that the WOUND-Q has high content validity.

In phase 2, we did our psychometric evaluation. We recruited for our field test study. We recruited patients who were 18 years and older with wounds that had lasted at least 3 months. The method of recruitment did vary slightly. In one country in Denmark, they emailed everyone from a

wound care clinic the link to the survey. The other three countries used inpatient and outpatient prospective recruitment with tablets or paper booklets, then we used Rasch measurement theory analysis to determine the psychometric performance of the items in the scales.

Our sample included 881 participants. Some of them filled out the WOUND-Q more than once, and you can see here country, gender, age, and BMI status. Here you can see the type of wound or cause, and I think we did a good job at recruiting a very heterogeneous sample. The most common wound type was diabetic foot ulcer. Here's how it varied by location, so wounds that were all over the body, age of the wound, and then the wound size.

There are lots of psychometric results, and if you're interested, you can check out our publication. I'll just maybe highlight here the Cronbach alpha. As you can see, they were all very high, the scale's evidence reliability. In terms of construct validity, I'll just show two slides here.

We asked everyone did your chronic wound smell in the last week, and they could answer from no smell to very strong smell. These are our four quality-of-life scales, so higher scores are better, and you can see that it was the lowest score, really, was in those that had the very strong smelling wounds. "Did you have any drainage from your wounds in the last week?" Those that said yes reported, again, there were health-related quality of life on all four scales.

These results are all published in the International Wound Journal. Since we've published it last year in 2021, we've had 35 licensed users from 11 countries get a copy of the WOUND-Q. Twenty-five said they were going to use in research studies, and the total sample size across these studies is about 3,000 participants, so we're really looking forward to seeing some papers coming out over the next few years, and then 28 were used in patient care.

I'll just show you one example of the uptake of the WOUND-Q in patient care. This is in New

South Wales. They're implementing a state-wide chronic wound management initiative with a purpose-built IT platform for PROM data collection and use. They wanted to see the WOUND-Q. They were trying to choose which PROMs to use, and they had a stakeholder group with patients and caregivers, and those people looked at the wounds and gave feedback.

Here's feedback that we got from one caregiver. She brought it home and had her husband fill it out. She said, "It focuses thinking. Something changed. It generated a phenomenal conversation between myself and my husband around his experience of his wound to mine. We had one of the nicest conversations we've had in 40 years he's had a wound." This again, just evidence that it resonates, and it's asking about things that matter to patients.

Just to summarize and the key points, the WOUND-Q was developed to measure outcomes of all types of chronic wounds in any anatomic location. The scales measure wound characteristics,

health-related quality of life, and experience of care and treatment from the patient's perspective. Our multi-method iterative approach, with extensive patient and provider input, was used to ensure that the scales have high content validity. Rasch measurement theory was used to ensure that each scale has interval level measurement properties and strong ability to measure clinical change.

Finally, WOUND-Q scales are each independently functioning, so you can pick and choose, and just use the ones that are most appropriate. It can be used in research, clinical care, and quality improvement. Thank you very much for your attention, and I've put our website here.

Panel Discussion

DR. DANIELS: Good afternoon. My name is Selena Daniels. I'm a team leader in the Division of Clinical Outcome Assessment here at FDA and CDER. I'm excited to be moderating this panel discussion as we discuss as we can integrate the patient's voice into non-healing chronic wound clinical trials by the way of clinical outcome

assessments or COAs

We heard from my colleague, Dr. Ju, that COAs are used to assess clinical benefit, or in other words how a patient feels, or functions, or survives, and I do have some questions for the panelists, and if time permits, we'll take questions from our public attendees. If we're unable to get to those questions, don't worry; we'll address them in a post-meeting summary document.

So with that, let's get started. The panelists can now turn their cameras on if they haven't done so already. As a reminder, our panelists our Dr. Vickie Driver; Dr. Andrea Pusic; Dr. Anne Klassen; Dr. Julia Ju; and Dr. Kathleen Fritsch.

First, I want to thank all of you, all the presenters actually, for their thoughtful and very informative presentations. I appreciated the insight from the various perspectives. There are a lot of important and interesting information shared.

My first question is for Dr. Driver. In your presentation, you described the Wound Care Collaborative Community's journey to define meaningful and patient-centric endpoints. This of course involved patient engagement. And as Dr. Ju highlighted in her presentation, one of the most important steps in developing a COA measurement strategy is to specify and define concepts that are relevant and important to patients, and that are likely to demonstrate meaningful and interpretable changes in clinical trials.

Based on the research that your group has done, can you share with us what symptoms and/or impacts of the wounds have resonated as the most important to the patient experience for non-healing chronic wounds?

DR. DRIVER: Yes. It's a great question, Selena. Thank you.

Basically, within the patient survey, there is a fair amount of text and ranking, which emphasized the patient's concern, specifically odor, drainage, physical function, and isolation.

The patient really shared that they fear infection; they fear reoccurrence. Complete closure is certainly important and their goal, but they know not achievable in most clinical trials, as they learned about that. So those are the most important features.

DR. DANIELS: Thank you for that.

I know we heard from some of our patients yesterday, from our workshop yesterday, that pain seems to be a core symptom. Did that resonate as well from your research?

DR. DRIVER: Yes, absolutely. Pain was critically important, and the quality of life was critical; getting back to work; being able to spend time with their children; go out to dinner; sleep in a regular bed without a huge boot on her foot; and being able to go without weeping wounds. I mean, these things really affect patients' lives every single day. The odor was critical.

Patients talk a great deal about they not only wanted a treatment that worked, but they wanted a treatment that would take them through the

phases. They know it's necessary to get their wounds healed. And it wasn't just let's close it; let's have a comprehensive treatment plan that gets them back to their life.

DR. DANIELS: Got it.

Dr. Pusic or Dr. Klassen, based on your qualitative work that you completed for the development of WOUND-Q, are these symptoms and impacts consistent to what you've heard from talking to patients, and are there any additional concepts that are of importance to patients with non-healing chronic wounds that you'd like to mention?

DR. PUSIC: Thanks, Selena. I can lead off on that a little bit. Everything that Vickie is saying resonates so much because it's a hundred percent what we heard in all these interviews. Pain is certainly very important because it's so much the quality of life, and that's where we really focus.

The WOUND-Q is really about measuring the severity, the impact, on quality of life. That's

really kind of it. Our scales get at things like quality of life, which are things like social isolation; the psychological; the impact on sleep, as you said; social; and just the ability to have a life.

The social isolation that is caused by chronic wounds is just tremendous, and then smell plays into that. Our scales do measure smell separately, but it's the impact on quality of life that the smell has, that drainage has, so it one hundred percent resonates.

DR. DANIELS: Dr. Klassen, did you want to add anything else?

DR. KLASSEN: With developing the WOUND-Q internationally, and interviewing patients in four different countries, and hearing the same kinds of stories come out about the same kind of quality-of-life impact is something that was really great for developing this tool, and to be able to develop something that would work internationally.

Yesterday, the patients' stories completely resonated with the kinds of stories -- and we

talked to 60 patients, which is a huge amount of qualitative research. But yes, what they were saying yesterday just totally resonates with what we heard in the interviews.

DR. DANIELS: Thank you. I'm glad, Dr. Pusic, that you mentioned the specific aspects of the quality of life that's being affected by patients because health-related quality of life is a multidimensional concept, and sometimes can be so broad. So I'm glad you drilled down on those specific components that were affected by the patients.

Not to leave out my regulatory colleagues, Dr. Ju or Dr. Fritsch, from the regulatory perspective, what symptoms and/or impacts, if any, have you seen measured in this therapeutic space, and is it consistent with what we've heard from our panelists?

DR. JU: This is Julia, and if I may start. From the limited applications that we've seen, the 10 [indiscernible] COA measures for wound healing, the most common type we've seen are pain and itch,

but we definitely hear from this workshop, and from the patients, and also from all the panel members, we hear that pain is definitely the core concept to measure.

We also hear that ambulation is really important to patients, particularly if they have wounds on their feet or legs, and the physical functioning is important; that people want to be able to live a normal life. Again, the odor is important to patients from a personal level and a social, psychological perspective. It's important.

We definitely think that what matters most and bothers most to patients is different across different wound types. So we really appreciate the continued input from patients, from clinicians, and from the whole wound care community to inform us what are the most important concepts to patients. Of course, wound type, I think that will help us hugely in terms of regulatory decision making. Thank you. I'm going to stop here.

DR. DANIELS: Thank you.

Dr. Fritsch, I don't know if you wanted to

add anything or not.

DR. FRITSCH: Yes. One thing I find useful is being able to move back and forth from the broader concepts of social or psychological impacts, but being able to move back to sort of the specific.

Is it, I can't move, I can't get up, I smell bad? Because when we do the clinical trials, we often need those specific things measured in order to be able to detect an event. We can't really measure very well, am I more able to have a social life, but we may be able to measure has the odor reduced; can I get out of bed; can I do those things; do I change my dressings less frequently? Those can be detected and allow us to detect efficacy for the particular medical products. So it's important to have both levels and recognize that we need to look at it both ways.

DR. DANIELS: You bring up some excellent points, tying it back to the underlying treatment effect as well.

I don't know -- I'm sorry. Go ahead.

DR. DRIVER: One thing I just wanted to add -- and this was discussed quite a bit yesterday, which is we may have the treatment options for patients. For example, I believe Dr. Fife mentioned where there's a patient with a diabetic neuropathy and there's a patient with a neuropathy of unknown etiology, or maybe it's B12,, et cetera, the patient with the diabetic neuropathy might be able to get the advanced product if they have the right insurance, but the person will never get it approved if they don't have diabetes along with it.

So it is very frustrating for patients to understand that treatments are available, but they have such very small indications, or narrow indications, so either they get too sick or they're not sick enough, and they don't get coverage, and they can't be included on these advanced treatments. That is very frustrating.

DR. DANIELS: Yes, that's good to hear. I thank you for that.

I don't know if anyone else wanted to add

anything related to this topic. If not, we can move on to the next question, and it's to Dr. Pusic or Dr. Klassen.

For symptom assessments, we often see instruments where the symptoms are rated based on their severity or frequency, and based on the portion that the WOUND-Q presented here today in your presentation, the items seem to be related to the attribute of concern and bother. In other words, the questions were asking how much, how concerned, or how bothered are you with that particular wound characteristic.

Does the WOUND-Q include items that assess the severity or frequency of the wound characteristics, and if not, what's the rationale for focusing on the attribute of concern and bother?

DR. PUSIC: I'll take that again, Selena. I'll start it, and then Anne can comment.

It does indeed get at severity but, again, we're looking at the severity of the impact on health-related quality of life. Really, that's

what we're about, is the quality-of-life piece. What we heard over and over again from patients is when they talk about severity of the impact on quality of life, words like "bothered by," "concerned," "worried," and "scared," actually, those kinds of -- so bothered by really resonated with patients as a way to explain the severity of the impact on health-related quality of life, and that's really why that is.

Also, the wound assessment scale, where we've used the word "concern" is because we also anticipate that being really clinically useful. A patient is able to self-monitor their wound and know that there is something that I'm concerned about that would then trigger the clinical team to perhaps intervene. That's the rationale behind that, but it really is about severity of the impact on health-related quality of life. The other four scales that we didn't show you, it's that impact issue and severity of the impact.

DR. DANIELS: Dr. Klassen, I don't know if you wanted to add anything additional.

DR. KLASSEN: I don't have anything else to add there.

DR. DANIELS: Okay. To follow up, you may not have thought about this yet, but how do you envision the use of this instrument to support study endpoints; for example, as a stand-alone instrument or in conjunction with other clinical outcome assessments?

DR. PUSIC: I would say definitely in conjunction. We developed the WOUND-Q with a very specific purpose, which again is to get at the health-related quality of life and also aspects of physical function, ambulation, and those aspects. We anticipate to use it also with clinician-reported outcomes.

I think also to make the point, as a condition-specific measure, the scales are independently functioning, so it really is a pick-and-choose menu. It's been used in a study, and we wouldn't recommend you use all the WOUND-Q scales. We recommend that you think about the hypothesis, think about the impact of the treatment

that is being evaluated, and then pick the appropriate scales to measure that. So that's really how I think we would anticipate it being used.

DR. DANIELS: Cool. I'm hearing a multi-PROM approach.

DR. PUSIC: Multi-PROM, exactly, but it would be complementary. This is about trying to put patient voice into the assessment, so that complementary piece of patient voice in wound assessment.

DR. DANIELS: And I'm glad to hear that you are saying that it's complementary because symptom bother is an important clinical concept, or impact bother is an important clinical concept that's important to patients, and it's just one aspect of symptom burden.

There are some challenges sometimes when you measure symptom bother because it can vary by the function of the disease stage and individual tolerance. For example, patients may report being bothered by a symptom, but the symptom itself may

not be bad, severe; or alternatively, a patient can report being maybe tolerable to that symptom and report less bother. So I think having those additional -- sorry, did you want --

DR. PUSIC: No, you go ahead.

DR. DANIELS: So I think having those additional assessments like assessing symptom intensity or frequency can be useful to give us a complete picture of the patient's symptom experience.

DR. PUSIC: That's really well said, Selena. It brings a really nice example. What we're really interested in are the things that bother patients most. A wound might be deep, but that's not what's getting at the patient. On the other hand, if the wound has a lot of drainage, it's the impact on quality of life.

So some symptoms that we as clinicians might focus on are some of the things we can measure, even just the size of the wound. We measure those things. Again, it's important, but what we were trying to really get at are the things that bother

the patient, and those aspects of symptoms that have the biggest impact on their quality of life, which sometimes, as you kind of alluded to, might not seem like the most severe from our perspective and the way we would measure it, but actually, those are the things that lead to, say, social isolation, decrease ambulation, and all the other things that go along with it.

DR. DANIELS: No, those are great points.

I don't know if any of our other panelists want to add anything else to this topic. I'll give you the space to do so if you would like.

DR. KLASSEN: I was just going to add, though, and say that when you're developing a patient-reported outcome measure, it's always that at some point you have to make some decisions. Are you going to measure severity, or are you going to measure frequency, or are you going to measure impact? There are different ways that things are expressed, and at some point you don't necessarily want to have three different versions of, say, pain. If you want to have a pain scale, you're

going to measure frequency, severity, and impact.

So it is tricky trying to look at the qualitative and really understand how are the patients expressing these concepts and how are we going to measure them. Anyway, I just wanted to add that.

DR. DANIELS: No, thank you. Thank you for that.

DR. DRIVER: I'd like to add that Dana Davis was profound yesterday in her discussion of the fact that she felt guilty. She doesn't have pain. She's been in the hospital -- I'm not going to mention how many times, but more than probably all of us on this panel will be in our lifetime. She carries a pack -- she'll tell you -- of dressings in her backpack every single day. Now, she looks like all of us, but her life is hell, but she doesn't have pain.

So how do we measure quality of life for all patients? This is critically important. It cannot just be by the pain in their wound because many patients of ours just don't have that. They have

other problems. They have many other problems.

When we talk about clinical experience -- and this is something Dr. Gould mentioned to me. When we look at clinical experience for patients, unless we start delivering free hot meals, clinical experience is not going to be widely positive always with patients. Why? Because it's a pain in their ass to come in so often. It's hard on them, to take them out of their life; get transportation; take time off from work; and spend 45 minutes to an hour with us. And it's difficult to hear that it's getting incrementally better, but this is what patients have to go through.

DR. DANIELS: Thank you for that insight, and it's definitely things that we should consider when developing these clinical trials, so thank you.

My next question is actually for you, Dr. Driver. You presented a list of 15 endpoints that resulted from your research. How do those proposed endpoints align with the endpoint you

obtain from patients?

DR. DRIVER: Yes. That's a good question. Actually, all the top endpoints were aligned and derived from the patient surveys. The patient rankings of endpoints were very similar to the clinician and researcher surveys.

DR. DANIELS: Well, it's good to see that there was alignment, and it's refreshing.

DR. DRIVER: And we didn't know just how great it would be, but, I mean, it was very closely matched, and that says, thank goodness, because obviously in this field, to stay in this field and to practice seriously, you have to be very connected to your patients.

We see them more than most of their family sees them, so if you don't really know what's going to change their life and what matters to them, that would just be critically scary to us. So we were pleased. Yes, clinicians are aligned with patients.

DR. DANIELS: On a similar note, Dr. Ju, the endpoints that Dr. Driver presented, they were

endpoints based on science and symptoms, including pain, odor, and depression, as well as impacts such as social isolation.

Can you elaborate as to why there is an interest by regulators to focus on more proximal and symptom-oriented endpoints?

DR. JU: Sure. As we mentioned, FDA pays a lot of attention to the patient voice and patient input, so understanding what is most important to the patient is critical to the development or selection of the COAs and the COA-related endpoints to ensure that the trial adequately collects meaningful patient experience data.

We recommend the sponsor factor in the relevance and the importance of the concept to the target population and whether those concepts are core disease related -- for example, signs and symptoms -- or a disease-related impact, and how they actually fit in, and how they actually inform the clinical benefit.

If the sponsors really tried to factor in all those considerations, I think that will help

them to really develop the endpoint hierarchy. We definitely want to focus on the endpoints, based on disease-specific measures that are assessing the proximal rather than distal symptoms because these measures tend to be more sensitive, which will detect treatment effect.

On the other hand, if the endpoints are based on measures of distal symptoms, those endpoints may not be sensitive enough to move throughout the treatment period because of the other external factors.

DR. DANIELS: Got it. But they could potentially still be measured for exploratory purposes just to still captured that patient experience, correct?

DR. JU: Yes.

DR. DANIELS: Got it.

Dr. Fritsch, what are some of the statistical challenges that you have observed or considered with COA endpoints in non-healing chronic wound studies?

DR. FRITSCH: Yes. I think a lot of it is,

once we get a lot of these concepts that we want to have and measure, and we think they're important, first of all, we have to make sure we match from our patient population to what the medical product can do. Depending on what the product will do, you need to match that up with the concepts that you think can actually be changed within the concept of a clinical trial.

There are a lot of nitty-gritties, exactly how are we going to score these things; how are we going to combine scores from multiple items? And if we do need to combine scores from multiple items to capture the more broader experience that the patient is experiencing, how can we explain that, and interpret that, and understand exactly what is going on with those patients? Because we want to be able to translate this into labeling that makes sense so that we know what to expect when we use these products.

So there are a lot of little details that go on to make sure that we can convert these to scores, or classifications, or whatever, that

people can actually interpret and know what to expect. So we always find that's important.

A couple other things that are important, particularly when we're giving patients a lot of these surveys, is do they know how to answer all the questions, and what do they do if they find a question that doesn't seem to apply to them? We can get a lot of missing data if they're not quite sure. Should I leave this blank? I don't really have that symptom. Should I say it doesn't bother me?

All of those types of things can really, in the end, impact the ability of a scale to do a good job, so we always have to be careful, and we keep that in mind so they have a good idea of how they should answer or when they should leave it blank so that we don't have to guess later what they meant when they leave things blank. So those are some issues that come up when we try and analyze things statistically.

DR. DANIELS: Thank you, Dr. Fritsch.

I don't know if we have any responses from

some of our panelists with regards to what we've heard so far on this topic.

DR. DRIVER: Well, one thing I wanted to mention is a 12-week [indiscernible] clinical trial to measure these outcomes that affect activities of daily living, I wonder if they're really long enough. If you think about it, let's take some of the patients we've heard from yesterday, their life was terrible before. Many of these patients heal a wound to get another one, or they heal a wound, but it takes them a month or two to get back to their life.

So how do you incorporate those data into a randomized clinical trial? You have to have a much longer follow-up period than what we've been able to establish in our RCTS. They're typically only 12 weeks, and we know that in critical ischemia and looking at other diseases, musculoskeletal, et cetera, we have to look at these patients for a long period of time to really gather the data that shows, yes, these patients have been able to go back to their lives, and these changes have

occurred.

DR. DANIELS: Those are excellent points.

I know we're going towards the end of our time, but I do want to ask the question to Dr. Driver, Dr. Pusic, and Dr. Klassen, and either of you can answer or you can elaborate on each other's responses.

Based on your discussions with patients via patient interviews or surveys, what do patients perceive to be a clinically meaningful benefit in non-chronic wound healing? This can be related to wound closure or the symptoms and/or impacts that we've been discussing. I don't know who wants to start us off, but feel free.

DR. PUSIC: I can start us off. I'll just say quickly, I think what our work has shown is a clinically meaningful endpoint is quality of life as expressed by various domains in terms of -- and I would summarize it, though, of getting one's life back in terms of being able to interact and do the things that we do, normally, socially, psychologically, sleep, and all the things of those

core domains, psychological and physical function. I think, as has been articulated, I wouldn't pull one thing out. I think it's a multifactorial approach to looking at things that matter most to patients.

DR. DRIVER: Well, what we found from our survey of almost 500 patients in this randomized clinical trial was six things in particular -- 15 things that matter, but six in particular. Percent area reduction really mattered to them because they understood that this was going to take them to a much better life; reduction in infection; reduction of antibiotics; staying out of the hospital; no surgeries; obviously pain-reduced analgesia care; increased physical function and ambulation, meaning they could go back to what they were doing before. It could be work.

Our patients' average age is mid-50s. Now, these patients, we treat them for a long time, so if you start seeing them in their 50s with a wound, they're likely to live to, what, 85? So we have to find better ways of understanding quality-of-life

measures, but also understanding how to design better clinical trials that can understand when treatments are actually effective, and the importance of probably cost-effectiveness there plays some role.

DR. DANIELS: Thank you for that.

A follow-up question to Dr. Pusic and Dr. Klassen. Unlike complete healing, which is an observable sign to providers and caregivers, clinical and meaningful changes on the WOUND-Q are only known to the patients, and this is for all PRO measures, therefore, patient perspective is more important than ever.

Are there plans to determine what constitutes a clinically meaningful within-patient score change in the WOUND-Q domain scores?

DR. PUSIC: There definitely are. As we've done with our other measures, we've worked on and then published MIDs [ph]. I will just add, though, I think that it's going to take time, and I think the heterogeneity of wounds in terms of locations adds to the complexity of it. That is something

that our group has experience with, and we've done it before, but this is going to be a little more challenging just because of the heterogeneity of conditions and people, and you wouldn't want to get that wrong. It's important that we don't paint things with one brush for simplicity sake when we can't actually be that simple about it.

DR. DRIVER: Andrea, I think that's a critical point because looking at a patient with a venous stasis ulcer who has a few other comorbidities, comparing this to a patient who might have MS, and diabetes, and critical limb ischemia, and also having a wound, you cannot compare these quality-of-life measures. How do we develop these to fit the patient? I think that's really a brilliant, very important point.

DR. DANIELS: Yes, most definitely.

I don't know if anyone has any final thoughts. We are at the time.

(No response.)

DR. DANIELS: If there are no final thoughts, I do want to thank all the presenters and

panelists today for a very fruitful discussion, and I think we've learned a lot. We've heard a lot, and a lot to digest as far as for our regulatory purposes. I hope that some of the information discussed can help inform a COA measurement strategy for sponsors in this therapeutic space to adequately reflect how a patient feels and functions.

So with that, thank you.

DR. VERMA: Thank you all for the excellent discussion. We're actually going to take a slightly shorter break, and we'll reconvene in around 3 minutes at 2:25, where I'll give brief intro comments for our final session of the day, CMS and industry panel. Thank you.

(Whereupon, at 2:22 p.m., a recess was taken.)

FDA Introductory Comments – Dev Verma

DR. VERMA: Alright. Welcome back, everyone. For the sake of time, I'm just going to start a little bit earlier.

Our next and final session will focus on a

CMS and industry perspective. Though FDA doesn't take costs or reimbursement into our consideration in our determination of safety and effectiveness, it is obviously a very important consideration for investors, sponsors, and external stakeholders, and bringing products to market, or even thinking about innovation. Therefore, we wanted to address it briefly in this workshop.

Our objectives for this session are outlined here. We hope to discuss current acceptable evidence for coverage decisions that CMS takes into consideration and identify industry suggestions for improved processes.

We'll be hearing from Dr. James Rollins, who is one of the medical officers in the coverage analysis group in the Center for Clinical Standards and Quality at CMS. He's worked at CMS for 15 years, where he's been involved with coverage decisions, including those related to the management of chronic wounds. While at CMS, he's also director of the Division of Items and Devices.

We'll be hearing from Marcia Nusgart, the

founder and executive director of the Alliance of Wound Care stakeholders, a non-profit, multidisciplinary association for physician specialty societies and clinical organizations, whose members treat patients with chronic wounds. She has submitted wound care quality measures to CMS and tackles issues related to coverage, coding, and payment for wound care procedures and products.

We also welcome again Dr. Caroline Fife. We'll be hearing from Dr. Rochelle Fink, who's a senior health scientist specialist at FDA, and serves as a liaison between FDA and CMS. She works on joint CMS-FDA efforts to accelerate the regulatory and coverage decision-making processes. Dr. Fink is involved in the FDA-CMS Parallel Review Program and CDRH's Pre-Submission Program.

We're also fortunate to welcome again Mr. Joseph Rolley, principal for JTR Business Consulting; and we also have Mark Olmstead, senior director of Market Access and Reimbursement at Smith & Nephew; Amy Law, who leads 3M's Medical Solutions Division, Global Health Economics

Outcomes Research, and Market Access Function; and John Ferros, who is vice president of regulatory affairs at Organogenesis.

Dr. Fink will moderate the panel, and we'll start with Dr. Rollins' talk.

Presentation – James Rollins

DR. ROLLINS: My name is Jim Rollins, and I'm one of the medical officers in the coverage analysis group. I have no financial conflicts of interest.

These are two vehicles by which CMS announces what items and services it will cover. A determination or decision can be an NCD, which is a national coverage determination, which is determined by the secretary, or an LCD, which is a local coverage determination, which is made by the local Medicare administrative contractor or a MAC. But whatever decision is made, NCDs trump LCDs.

What prompts an NCD? An NCD can be internally generated because of the publication of a new important study, major concerns about inappropriate use, or a new technological

advancement with a potential major clinical impact. An NCD also can be externally requested; for example, when a current national non-coverage policy is in place and when there is substantial variation amongst LCDs. Also, external requests can be initiated by patients, advocacy groups, providers, specialty societies, vendors, but they must follow the instructions as stated in the Federal Register.

At the beginning of the NCD process, there is usually an informal discussion between the requester and CMS. This is followed by the submission of the formal request, a benefit category determination, and this is done because if the item does not fall within one of the benefit category groups, it cannot be covered.

There is a review of the evidence by CMS, which is known as an internal technology review. There also may be an external technology review in the form of a technology assessment, which is done by an evidence practice center or done by a MEDCAC committee.

The proposed determination is posted, followed by the final determination, which is posted. In order for CMS to get public input, there are two comment periods, one at the time the formal request is posted, and the second when the proposed determination is posted.

This is a cartoon of the NCD process, and it usually takes a total of 9 months. Depending on whether or not an external review is performed, it may last as long as a year.

I briefly mentioned MEDCACs. CMS often convenes MEDCAC committees on controversial topics. MEDCACs vote only on the quality of the evidence and not on the coverage determination. Not all MEDCAC findings result in an NCD. MACs use information from MEDCAC meetings to make LCDs.

In the past, a decision or determination has resulted in one of three actions: coverage, non-coverage, or left to a back [indiscernible] discretion. Innovators of new products felt that the denial of their new product stifled innovation. Some of these new products were promising, but the

studies had low numbers of Medicare-age participants; thus unable to generalize these findings to the Medicare population.

This led to a paradigm shift, the creation of coverage with evidence development, also known as CED, which began in 2005. In the CED paradigm, an item or service is only reasonable and necessary when it is provided within a research setting where there are added safety, patient protections, as well as monitoring and clinical expertise. CED research studies range from randomized clinical trials to registries.

In CED, Medicare covers items and services on the condition that they are furnished in the context of an approved clinical trial or the collection of additional clinical data. Coverage with evidence development allows for positive coverage when the evidence is insufficient for a more favorable decision.

These two slides represent a cartoon of the coverage process under coverage with evidence development. As noted in the slide, some outcomes

are more relevant to CMS than others. Improved function and participation is an outcome of interest that is important to CMS, and that's important because we'll talk about that in a minute.

Now we will take a look at the use of CED and how it has been incorporated in policy decision making. In 2003, CMS posted the NCD 190.0 Autologous Blood-Derived Products for Chronic Non-Healing Wounds. At the time, CMS felt that the evidence was insufficient and found it not to be reasonable and necessary.

Based on additional input from the wound care community, a reconsideration of the NCD was performed in 2012. The decision was to cover autologous platelet-rich plasma, or PRP, for patients with chronic non-healing diabetic pressure and/or venous wounds if they participated in a CED study. The CED question that CMS wanted to know was, does the use of PRP result in complete wound healing; ability to return to previous function and resumption of normal activities; or reduction in

wound size or healing trajectory, which results in the patient's ability to return to previous function and resumption of normal activities?

CMS received and approved a number of protocols. Some of these approved protocols resulted in peer-reviewed published studies. CMS also reviewed other studies in the medical literature. They looked at guidelines. We consulted with medical and professional societies and had a technology assessment performed by one of our evidence practice centers.

In 2021, based on the published CED studies and other information, CMS was able to alter its position. In their new policy, CMS would nationally cover PRP for non-healing diabetic wounds and allow MACs' discretion to cover all other chronic non-healing wounds.

In summary, through the CED process, CMS was able to change its non-coverage position of PRP to national coverage of PRP for non-healing diabetic wounds, and allow the MACs to make discretionary PRP coverage of all other chronic non-healing

wounds. Thank you. That's it.

Presentation – Marcia Nusgart

MS. NUSGART: Good afternoon. This is Marcia Nusgart. I'm the executive director of the Alliance of Wound Care Stakeholders, and with me is Dr. Caroline Fife. You heard from her both yesterday and today, but actually the hat she's wearing today is as being the co-chair for the Alliance of Wound Care Stakeholders.

The Alliance is the united voice of the wound care community. We advocate on public policy issues that might create barriers to patient access to treatments or care. There are different areas we actually focus on: coding, coverage, and payment for wound care products and services; quality measures; and wound care research, and we serve as a resource both to the Food and Drug Administration and the Centers for Medicare and Medicaid Services on issues related to wound care. We are a multidisciplinary trade association, and our members are physician specialty societies, clinical and non-clinical associations, patient

organizations, and business entities.

Here's a list of the various clinical associations, and we talked yesterday about multidisciplinary. Well, I think this shows a wonderful representation of all the different clinical associations whose members treat patients with chronic wounds, and we're very proud to say that there are our members who help us.

So you heard today and yesterday about some wonderful conversations, and we invite you to Solution-Build, the payers at the Alliance's Wound Care Evidence Summit, where we invite you to connect and collaborate with public and private payers such as Humana, United Healthcare, Aetna, Blue Cross and Blue Shield, as well as CMS.

Those of you who've ever tried to be able to talk to commercial payers about the type of evidence and how they make their clinical decision making, you'll find them to be speakers at our conference. You'll be able to hear what they have to say because they, along with federal agencies and evidence analysis experts and researchers,

medical specialty societies, wound care clinics, and manufactures, we're all going to be able to get together to have a small meeting to talk about how much and what type of clinical evidence do regulators and payers need to give a positive coverage approval and decision for wound care products and services. So we invite you to attend. It's going to be a fabulous conference and synergistic to this wonderful FDA workshop.

By the way, Dr. Verma, congratulations. You've knocked it out of the ballpark over the past few days, you and your FDA staff. So I want to congratulate you on a fabulous meeting today. And you'll see Dr. Verma and some other FDA staff at our meeting also.

In terms of this FDA healing workshop, we did submit preliminary comments on the issues that the FDA did request, which did include a PowerPoint presentation when we met with the FDA in 2015 to talk about some of the issues regarding the 2006 guidance document. And when I looked at some of these issues, it was amazing to me that some of

those issues are still relevant today.

One of those issues that I just wanted to mention is our concerns with the current FDA terminology for product classifications, because currently 510(k) and PMA biological CTP, or cellular and/or tissue-based products, for skin wound products have been placed in these FDA product classifications, indicating that they are wound dressings.

This terminology used for these product categories is outdated and really can't represent the true nature of these products, because the unattended consequences is that payers have been confused with FDA labeling of CTPs as wound dressings, so the payers thus believe that they're topically applied protective covers, and paid them as part of an office visit or an E&M service.

So our recommendation for FDA is to update the classification for CTPs to match the current terminology, to differentiate it from wound dressings.

Our paper today, it was so interesting the

way that we came up with this, because we were actually writing comments to CMS and Dr. Samuel Nussbaum, who helped us with this article, had said to me, "Marcia, well, do you actually know how much Medicare is actually paying for chronic or non-healing wounds?" And I'm like, "No, I really don't know; so let me go research it," and I couldn't find any really relevant type papers on it at that point in time, many years ago. And the reason for that being is because the research had focused on hospital long-term care settings instead of recognizing that so much wound care had been in the outpatient area.

So we crafted this article, and I'm so pleased to say that it has been quoted many times. I think even yesterday some people quoted the statistics from here, on this particular paper. We are going to be updating it this year to use the 2019 and 2020 Medicare data, so stay tuned for that.

I'd like to turn it over to my colleague, Dr. Caroline Fife, that will talk through the

methodology and a number of different issues related to this fabulous paper, and it can be found in 2018 Value in Health, as well as on our website, and you can see also the link below.

Presentation – Caroline Fife

DR. FIFE: Thanks, Marcia.

What we did that was different in this analysis is that rather than going into it assuming that all wound care is represented by venous pressure and diabetic ulcers, we said, "No, wait a second. Let's find out what people go to wound centers for."

So we actually looked at 130 hospital-based outpatient wound centers and got the complete set of ICD-9, at the time, codes that were the reasons people showed up in wound centers. Then we threw that against the Medicare claims data set, and that's when we began to see surprising things, which is all of these nameless ulcers that we talked about yesterday: traumatic wounds; surgical infections; and infections of every type of ulcer.

One of the huge results was the

understanding that the majority of the cost is on the outpatient side. That was a surprise to everybody except the people involved in the paper. But the other thing that surprised even us was if you look inside that green circle, which are the diabetic ulcers, venous ulcers, and pressure ulcers, which we've had people say, "That's 90 percent of what we see." Okay. It isn't.

The yellow arrows there demonstrate the nameless chronic ulcers, the various types of skin disorders, traumatic wounds that never heal, and surgical complications; that, in fact, in terms of prevalence, the DS [ph] surgical wound is perhaps the most common wound experienced by Medicare beneficiaries.

I don't think anybody really understood that, but by the time you layer infections of all of these things on top of that, then we're looking at an enormous number of problems that people are going to seek help for in the outpatient setting, primarily that are not venous, diabetic, and pressure.

When we then started to look at cost, we looked at the cost and if the principal diagnosis was a specific wound type. But then you can look at the cost if it's a secondary diagnosis because there were other reasons that the patient may have been hospitalized. Then if you multiply that by the prevalence rate, you begin to see what the real approximated costs are for some of these conditions.

So because of its prevalence, pressure ulcers represent a big portion, but look at that surgical wound; 24 billion is our estimation. Where is the research and innovation on those? Then if you look at the nameless wounds, the chronic ulcers and the traumatic wounds that never close, we've got nearly $10 billion in those. So it is very worrisome to us that the investment that is in technology is missing at such an enormous cost in other wound types.

The other thing that we realize as we begin looking at these claims is that we can see claims on ulcers that lasted for a year. Now, one of the

things that was brought up in the panel is that when you look at claims, the claims conflate all of the wounds into the same diagnosis, so you can't tell looking at claims that the patient may have 3 venous ulcers or 3 diabetic foot ulcers. But when you look at registry data, and you see the experience of the patient, then there may be times they have 5 wounds, times they have one wound, times they have 3 wounds. But they're getting wounds in crops, and 30 percent of the time they're getting a new wound while they're in service for the wound they've already got.

So it's not just that a wound comes back, which had a lot of discussion, but they get new ones in other places maybe of the same type, maybe of a different type, and they have more than one. That's also contributing to the cost, even though all of our research is wound focused, not patient focused.

We looked at this trying to get a little bit more understanding of the longitudinality of it, and a decade ago, Marissa Carter and I looked at

five years of data, 5,000 patients-ish, 7000 wounds, and in about 100,000 visits; and not surprisingly, we could identify patients who continued to be seen year, on year, on year after, and the cost of those individual cases continued to escalate as each year went by.

That's not surprising, but what is often surprising is the fact that so many patients will be seen for years. That's one of the reasons that the cost accumulates on the outpatient side, because they have wounds for a long time, and they may get new ones by the time that we finish the one that we were starting them for.

So we looked at 5,200 patients who had an estimated cost of $29 million, and we estimated that if you just looked at the prevalence rates of the wound types that we saw, we could see 25 billion on the outpatient side alone. And we estimated that a decade before we did the study that Marcia was alluding to at the beginning, so we were really spot-on in our estimation of what the national expenditure would be, just looking at a

small slice of patients.

Non-healing wounds are more expensive than the ones that do well; that's not surprising to anyone. But the other thing that shocked people was that the healing rates that we were seeing using registry data were not as good as those in our RCTs, or those as good as marketing would suggest, so we needed to look a little bit more closely at healing rates to understand this cost.

We then went and looked at the controls for RCTs, and if you look only at the controls -- this was discussed a little bit yesterday -- you're seeing healing rates less than 50 percent in the controls of RCTs, where you've already said most of the patients enrolled in those RCTs are relatively healthy.

When you look at similar time frames, like 12 weeks at the U.S. Wound Registry, the healing rates are much worse than they are in the controls of an RCT. Remember, we've got sicker patients in the registry. We've talked about that a lot. But even when you give an infinite period of

time -- that is don't put any limitations on the length of time to look for healing in the registry; let them play out as long as needed -- we still see that healing time frames are 33, 36, and 48 weeks, which tells you something about the duration of clinical trials when they're limited to 12 weeks; that part of the problem may be that there's just not enough time for those wounds to heal. But even when you give it as much time as it takes, we still only have about a 50 percent healing rate if you look at all-comers.

To personalize it a little bit, this is a man that I've continued to see. He's 80 years old. He's got severe bilateral, lower extremity lymphedema with venous insufficiency. He has CHF. He has COPD on oxygen. He has renal insufficiency. Every time he gets edematous and we increase his diuretic dose, his kidneys get in trouble. He has underlying diabetes. He gets hospitalized every month for volume overload, and often for wound infections and colonization. What keeps happening with him is that as he gets acute on chronic heart

failure, his legs just split open, and there's no amount of compression we can put him in that will control that.

This is not an unusual case. I didn't just pick the worst possible patient. This is just to give you insight into the challenges that we have with these folks.

In fact, when we looked at the CMS data on the prevalence of diseases in 500-ish physicians who were working full-time in wound centers, you look at the CMS data on their populations, and about 60 percent of those patients that are seen in hospital-based outpatient clinics have chronic kidney disease. More than half have diabetes. Half of them have heart failure. Half of them have ischemic heart disease, and lots of them have atrial fibrillation, which means they're also chronically anticoagulated.

Interestingly, those aren't the six of the most expensive conditions that Medicare is concerned about; those are the ones who have wounds. So I think the fact is the contribution of

chronic wounds to the cost of these underlying diseases has really not been understood.

Wound care is expensive because it's bigger than DFUs, VLUs, and pressure ulcers. Chronic wounds are symptoms of expensive underlying medical conditions. Real-world healing rates are 50 percent or less. When wounds do heal, it takes more than 36 weeks to heal them. The average patient has at least two of them, and they keep coming back or they get new ones.

Sadly, the basic interventions that work well are often neglected, in part due to challenges with coverage policy. Nutritional supplements aren't reimbursed at all, and other types of things we know that are basic interventions are reimbursed poorly for the amount of effort it takes to do them, like total contact casting. Then we have all of these expensive therapies; that we never really look at the real-world effectiveness or the cost effectiveness.

All those things contribute to the fact that we end up with a challenging environment where we

don't understand why cost ratchets up, but it has to do with the complexity of the patient, and that many of those are downstream implications from coverage policy. Dr. Rollins described the process of creating coverage policy that keeps Marcia and me, and all the other folks in the Alliance, very busy making responses to proposed coverage policy.

We'll just make one last pitch to ask you all to join us at the evidence summit, which will be an in-person meeting in Washington, and thanks again for having this meeting. It's been tremendously successful. I have watched every minute of it, and I thank you for the opportunity to listen, as well as speak.

DR. VERMA: Great. Thank you all for those great presentations. We will now start the panel led by Dr. Rochelle Fink.

Panel Discussion

DR. FINK: Thank you very, very much for inviting me to moderate this panel today. It is a really, really exciting subject. I had a few questions for the panelists. Some are more for the

industry and the associations, and then some we're going to point directly to Dr. Rollins from CMS.

But first I'm going to put industry and other stakeholders, non-governmental stakeholders, on the spot. Some of that stems from -- and I appreciate the Alliance of Wound Care Stakeholders filed a comment in the Federal Register notice today. So I read it, and that's where some of these questions stem from.

The first question that I have is there's been some back-and-forth; should the payers just look at real-world evidence, and I know the payers have asked to see clinical endpoints, and it seems like some of the difficulty is sort of coming to a place where both sides are happy.

My question for industry and stakeholders is, what clinical endpoints do you think CMS should look at when determining coverage? Also along with that, what type of a prospective clinical trial design, apart from real-world evidence, do you think would assist CMS in making a coverage decision? So endpoints, and what type of a

clinical trial do you think would be appropriate?

MS. LAW: I'll just start with the endpoints question, and I want to thank everybody for, really, a fabulous conference.

On the endpoints, obviously complete wound closure or complete wound healing -- we have all commented on it -- it doesn't necessarily make sense. I think we heard Dr. Gould say, really, wound treatment is often multiple products at once, and you want to step down as quickly as you can.

We've been leaning a bit more towards percent area reduction, which I believe was on Dr. Driver's list. We're still struggling with the question that was brought up earlier around volume and how to really accurately measure that. So the percent volume reduction, although we love that endpoint, really we are not quite there yet with the technology.

DR. FIFE: Can I jump in and say that I also think we ought to be mindful of what the device is designed to do? Pressure doesn't allow a wound to epithelialize. I don't have a dog in this fight;

I'm just as a clinician saying, you stop it in order to get the skin to grow. Its purpose is to fill in the hole.

So it's always been frustrating to me when you want to look at the impact of something that causes vascularity but maybe actually stops epithelialization; that the endpoint is epithelialization. Can we just have endpoints that are relevant to what the device is supposed to accomplish?

MS. NUSGART: I did not pay her to say that, but thank you very much.

DR. FIFE: You can send me a check later.

MS. NUSGART: Because we always mention something such as negative pressure wound therapy, which may have not been created to be able to have complete wound closure, as well as so many other medical devices. But there are other things that --

DR. FIFE: There are others.

MS. NUSGART: -- that do phenomenally well and that patients really do appreciate, so it's

something to be able to keep in mind.

MR. ROLLEY: I would agree with --

DR. FINK: So you have mentioned --

MR. ROLLEY: I'm sorry.

DR. FINK: Well, so far I think we have things that patients would appreciate, although it would be interesting to dive into that a little bit more. We have "not complete wound closure," and I guess the question is, how much of a wound closure? "It has to be designed for the purpose." Yes, that is true.

Also, nobody's touched on yet what type of a prospective clinical study do you think could be done?

MR. ROLLEY: My comments on a retrospective, it's a bit difficult because your products aren't on the market yet to really have data to go back through. Prospectively, I think if anything came out of the last couple of days, it is the complexities of these wounds. And with all the underlying conditions, the comorbidities, the wounds that Dr. Fife just showed, those are really

difficult -- as Amy was saying -- to have total wound closure as your only endpoint. You have to look at other endpoints besides that, the trajectory of healing.

Some of the things we talked about earlier today in terms of some of the patient-reported benefits, pain is particularly one. There are other endpoints you have, and a pressure ulcer patient, for example, is terminal. The chances of you ever healing somebody like that is slim to none. So would they be in your study? Well, maybe not necessarily. But pressure ulcer patients in particular pose a real difficulty because of the state that they may be in, in terms of end of life, so we have to be open-minded about that.

I think, though, again, from CMS' perspective, most of the devices and most of the products on the market are 510(k). So when we talk about clinical evidence, we're really talking about PMA products that really have to require the data, the studies to be done, because these products are 510(k), and they're going into generic HCPC codes.

Oftentimes, they're policies that aren't really issued. They're not SCDs; they're all LCDs, for the most part.

So from a company perspective, the risk of doing the study sometimes is higher, and if I don't have to do it, I'm not going to do it. But --

DR. FIFE: I also just wanted to say -- and I'm sorry. I didn't mean to cut you off, Joe. But there are some things that matter in terms of cost like rehospitalization rates, also free days. Those are things that that I think really do matter, and they certainly track a cost. Even though most of our costs are outpatient hospitalization, it's an expensive thing we'd like to avoid for many reasons.

But I think we say that CMS doesn't look at cost in determining coverage policy, but nobody believes that CMS doesn't look at cost in creating LCDs or NCDs. We feel it because they read like things that are designed to control utilization, maybe abuse, although we never know exactly what the data behind it are. So maybe it's time for us

to talk about cost in a more open way, as a way to measure whether something's working.

I used to feel uncomfortable with the idea that cost was a surrogate for whether something worked, but I have reconsidered that position. If stuff really works, it ought to decrease the cost of health Care.

DR. FINK: Thank you very much. That's very interesting. I can see if Dr. Rollins wants to speak more on the coverage side, that might be difficult since CMS does not have statutory authority to do that.

I also appreciated, Mr. Rolley, that that was an interesting statement that you had, where basically FDA, 510(k), you're looking at substantially equivalent, where CMS has different statutory authority; again, you're looking at reasonable and necessary for the Medicare beneficiary population, which means that you have two agencies that might be looking at different things.

Alright. Number two, my second question, is

when companies produce products, what endpoints and what type of clinical studies, if any, are companies doing in order to decide what to release to the market?

MR. OLMSTEAD: Rochelle, I'll take that. Mark Olmstead with Smith & Nephew.

Really, when you look at industry, it depends upon what product or solution that we're looking at. So dependent upon the outcomes necessary, it might be an RCT or it might even be real-world evidence like we were talking about earlier today. It all depends upon what are the outcomes that we're looking for and what can we provide that would actually have the best outcomes that we can actually show in regards to the healing of the wound or the change of the wound in size or depth.

So that's an area that definitely Smith & Nephew works very closely with many stakeholders to try to do the right evidence for the right types of solutions, and it's all dependent upon those solutions; so many different things that we

actually utilize for our evidence, including real-world evidence and registries.

DR. FINK: No, I appreciate that. And just to keep putting you on the spot, the clinical evidence that you generate, whatever it is, do you end up publishing it, or putting it in peer-reviewed journals so that others can see it, or is that more kept within the company?

MR. OLMSTEAD: Yes. So it all depends upon what it is that you're actually trying to show as an endpoint. Sometimes there isn't enough patients to actually produce an outcome, so that you don't have that evidence to be published. But oftentimes it will be, and then you decide which journal you might put it in, as an example, or what publication, or even what entity you might share it with.

So it's all just really important to determine what is it that you're trying to solve for, and then do you have the number of patient lives and the right specific types of patients that you're trying to solve for in your outcomes, and

whether or not that is something that is even publishable. So it's sometimes also dependent upon the agency that you're sending in the information to.

MS. LAW: I would just like to comment on the prospective registry idea. We are just getting into that area, so that's fairly new. Historically, it's always been RCT, but I think some of the comments that we heard from Dr. Fife and others yesterday, to the extent that CMS/Medicare could standardize some of the out-of-hospital documentation, whether it's incentivizing, might be an option that Dr. Fife had for the quality measures.

To the extent we can have more consistent data or a risk stratification score that we could use, such as WHI that would have individuals put in age of wound at the beginning of treatment, that type of data could really help us build more powerful evidence. And it might make it a little easier and less expensive in the registry, in the prospective registry, because obviously there's so

much data we want to capture, but helping with those shortcuts might be a way to make that a little bit less cumbersome for industry.

DR. FINK: Thank you. I appreciate it.

Dr. Rollins, do you have anything to add to the discussion?

DR. ROLLINS: Yes. Actually, I had myself on mute.

I agree. The CED, coverage with evidence development, I think was an excellent tool that can be used, and has been used, to get additional information to help to prove that a particular technology is reasonable and necessary for the Medicare population.

Prior to the initiation of CEDs, I think that new companies with new products, when they approached CMS, there was probably a 50/50 approval rate and denial rate. But with CEDs, the number of outright denials have plummeted because, now, even though they did not meet the standard definition of reasonable and necessary, the information was promising, and that allowed for more research to

take place.

Now in terms of the protocols, the protocols that were submitted to CMS were developed by the vendors, as well as the researchers. We worked with vendors who had the protocols and gave them specific information in terms of what we considered important in terms of reasonable and necessary from the patient's perspective; not necessarily from the researcher's perspective, but from the patient's perspective. And the endpoints that we looked at were complete wound healing, as well as reduction in wound size, wound trajectory. But we also coupled it with improved quality of life, resumption of normal activities.

I think that the 15 endpoints that Dr. Driver mentioned earlier today, I think those are excellent endpoints to look at. Had they been incorporated in the protocols that we reviewed and approved, I think that would make the study much more meaningful. We did approve, as I said, a national coverage for non-healing diabetic wounds, but as I said, perhaps if some of those other 15

endpoints were included in protocols, we possibly could have nationally covered non-healing venous as well as pressure wounds. We did not, but we left that up to contractor discretion. But as I said, with other endpoints, that definitely would have helped to tip CMS into perhaps national coverage of those other two, besides the ones for diabetes.

DR. FINK: Thank you. That's very helpful.

Dr. Rollins, I have a follow-up question for you, and that is real-world evidence. There's been a lot of discussion about real-world evidence, and there might be the thought that the information submitted to CMS is only real-world evidence.

Do you believe that all real-world evidence could justify a policy decision, and if not, what along with real-world evidence would be helpful?

DR. ROLLINS: Well, there was a lot of discussion this morning about real-world evidence, and as one of the speakers said, there's pros and cons.

I look at real-world data and I look at real-world evidence, and I think that it's sort of

like in business, they use the term, "I'm drowning in data, but I'm starving, looking for information," especially useful information. And hopefully, over time, real-world data will transition into real-world evidence.

Currently, CMS, we do use real-world evidence in the sense that we have two cardiac NCDs. One uses registry data, the second one uses administrative data. So CMS is open to the idea of using real-world evidence, but as I said, over time, hopefully real-world data will evolve into real-world evidence, which we can use to help us in terms of our coverage policies for other topics.

I'm currently not aware of any NCD that specifically addresses wounds or wound healing in terms of using real-world evidence in making a decision.

DR. FINK: This is interesting, and I have to say, one of the things is I was happy to moderate this panel, as before COVID, I did a talk once, and one of the things I really enjoyed about it -- there were a number of podiatrists

there -- is that nobody was afraid to say what was on their mind. So it was actually a whole lot of fun, and I thought it was super helpful.

So that's why I'm hoping we can have the same spirit here. And let's hear; what does everybody think of what Dr. Rollins just said?

DR. FIFE: I am accused all the time of not being able to keep from speaking my mind. The one comment I'd make about coverage with evidence, which was an exciting opportunity, is that it was challenging because you had to run it like a clinical trial and bill it like you'd bill anything else. It's not an easy thing from the standpoint of the clinician. It hurts. The fact that you have now created a system that requires both things for research and for clinical use is very difficult, but it's exciting to think that there's a window.

The other thing that I think is important is I focused for years on trying to leverage stuff that clinicians have to do to things you need to know. So whenever you tie something to payments or

you tie something to quality, assuming they have to report it, you can end up with data that you might be able to rely on.

The cardiologists have been successful, in part, because they have really expensive devices. They get paid well enough that they can be really focused on their registry. It's a little tougher in wound care, where it's very hard to do a registry for something you get $4 dollars for, so I think that disconnect is problematic. But it is exciting to think that there's a new opportunity. I do think we need to make it easier.

MS. LAW: It's really exciting. The CED, it is incredibly hard. There are other things that Medicare has in place, like consolidated billing that make it difficult for us to do registries around some of these lower levels, but still important products that are used for patients in home health, as well as in the wound care clinic, because the incentives are not always aligned to have the study performed. So that's just one thing.

I am curious if CMS will use real-world data. I think one of its biggest values could also be in reconsiderations for LCDs. We've been understandably wary to reconsider some of the LCDs, but I think the real-world evidence to see how things are actually being used could help us improve some of our policies.

I think one of the things is, as a manufacturer, we're reluctant to do multiple clinical studies on different wound types. That's just so expensive. We talked about the duration. Our last RCT for negative pressure took us 8 and a half years, and that was on one wound type, so we really can't be thinking about multiple wound types. So knowing that there is a way to get LCDs or NCDs revisited using real-world evidence would be incredibly valuable, for the patients, I believe.

MR. FERROS: Rochelle, if I can comment, too, my background is mostly dealing with FDA, FDA policy and such, and I actually applaud FDA for, I think, taking the lead on real-world evidence.

You've published quite a few, a number of guidance documents to help industry in the use of real-world data, and thus real-world evidence.

I think what's important is for all government agencies and all of us to be advocates of real-world evidence. It's powerful. It's powerful data; it's powerful information. I know that the gold standard has been for many years -- just traditionally, the gold standard has been RCT, and that's fine.

We all understand the power of that. But real-world evidence is also powerful. It shouldn't be looked at as inferior, but I think it should be looked at as different. It has certain advantages to it, and the advantages of real-world evidence are things like generalizability and the fact that we've probably got a much wider geography, and the fact that you have typically long-term types of studies relative to the shorter-term RCTs. All these are positives that shouldn't be discounted.

So I applaud a FDA, and I think we should probably all be on that same boat of looking at

real-world evidence and seeing how it can be used.

(Crosstalk.)

DR. FINK: And I appreciate that statement --

DR. FIFE: And there are ways that payers can incentivize us --

DR. FINK: Caroline, I'm going to cut you off.

If I can just say, though -- and this is just from my novice personal thought -- we're sort of on two ends. How can there be both real-world evidence and clinical data that could work for the Wound Healing Association, or the wound healing companies, I should say?

DR. ROLLINS: If I can make a quick comment, as I said, we use an evidence-based medicine approach when we write our policies. Basically, at the top of the hierarchy of evidence, we use meta-analysis, as well as systematic reviews of randomized clinical trials. At the very bottom of that spectrum you've got single case reports.

It would be interesting if through that

continuum of different types of research design, there could be some type of correlation between any of those components and this real-world evidence. And it's possible that maybe real-world evidence could be equivalent to some type of cohort study in terms of the evidence development, or perhaps it could be at an equivalent level of crossover study, or something like that.

So even though the policies are currently driven using evidence-based medicine, it's possible that in the future, as I said, with the use of real-world evidence, it can supplement what we currently have. Whether or not it would act as a substitute, I don't know, but as I say, currently our focus is using evidence-based medicine.

MR. ROLLEY: From my perspective, I would agree that I'm not sure the RCT is going to go away, especially for approval, but I can see where real-world evidence would be useful as an adjunct to build the body of knowledge, the body of evidence; perhaps to expand indications beyond what your current labeling is.

I think it might have been said earlier that a lot of times you're getting approval for just diabetic foot ulcers, and then will have to do an entire new study just for a venous leg ulcer or for a pressure ulcer. As we've heard, and Dr. Fife will say, these are artificial categories to begin with. So leveraging real-world evidence to say, look, if it's working well in the original RCT with a DFU, and we've got good results and other indications, why not expand the indication? I don't see it replacing RCT anytime soon.

DR. FIFE: And let's not forget safety. That's a great opportunity for real-world data. Safety is so important, and we forget about it.

The other thing I was going to say is there are ways that payers can incentivize better data collection. Right now, you can do a good job with data or a bad job with data; you get paid the same, but it doesn't have to be that way.

DR. FINK: That's actually, if I can say, a very good point.

I have another question, though. I know we

keep going to RCTs, and we keep saying whenever we talk about clinical trials, it seems there's been discussion of RCTs. But I was wondering, is there any sort of clinical trial that isn't an RCT? Because I have to say through my experience at Medicare, we sat around in a room, and I'd say, "Yes, RCT is the gold standard, but it's not practical," and at least in my personal opinion it seems that Medicare understands that.

So what would be practical, do you think?

DR. FIFE: I'll dive into something. We designed a trial that wasn't carried out. The sponsor decided against it. But the trial was to have the patients consent for the active agent, and then on the back end we used the Wound Healing Index to create matched cohorts. And then the prospective arm, only the patients getting the treatment had to be consented; you didn't have to consent patients who weren't going to get treatment, who were just going to get standard of care, and then we could make sure that we had enough patients that were matched as a cohort.

I really think that that kind of operational design has a lot of potential, and we have the ability to do it right now if we just have the courage to step forward in that direction.

MR. OLMSTEAD: I believe there might be an opportunity to work with CMMI for a public-private partnership to kind of think about some of these different things that we're talking about today, and yesterday. It's just an opportunity to say we've done it a certain way before, but we know during COVID, we've come together in a completely different way, and have been able to solve a lot of big problems together.

So I'm just wondering if it's an opportunity for us to consider maybe looking at a different payment model that might come out of CMMI, where industry and government together could work on something that would make sense for the right patient and the right specific area that we're looking for in a clinical evidence, and a health economic evidence as well.

DR. FIFE: That could include quality

measures.

DR. FINK: Dr. Rollins, what do you think of that? I know you're in CCSQ, not CMMI, but what are your thoughts on that?

DR. ROLLINS: I think that's a good idea, specifically because a CMMI would set up specifically for that purpose, looking at different types of payment models for different types of situations. Now, I know for a fact that CMMI has been successful in putting in those types of activities. So as I said, I think it's something worth pursuing.

MS. LAW: I love that idea because as manufacturers, we are sometimes disincentivized to come up with products that require fewer treatments because we know they're going to fit into a code. We know what the payment is. We can't invest in it, although we know it would help the patient from going into the wound clinic each week.

So there are a lot of barriers where I think CMMI -- I was very excited when it first launched -- was really just the opportunity to look

at a total cost to treat and a longer duration, and really allow more flexibility, and as I said before, multiple treatment modalities, not just one, in sort of a safe environment to really look -- we have many hypotheses that we don't pursue because of the disincentives in payment, so I love that idea.

MS. NUSGART: Something else to think about, too -- a little bit different on the subject -- is that Dr. Rollins represents CMS that really deals with more the national coverage decision, but for so many of the wound care products, they really are governed under the LCDs that have the medical directors that are on the local level.

So it would be interesting to be able to understand the A/B MACs and the DME MACs in terms of how they view evidence, and hopefully they take their lead from Dr. Rollins and those at the CMS office in Baltimore, but many times -- I just was speaking earlier today at a public meeting for Novitas and First Coast, and many times some of these policies, and these LCDs, and the draft ones

aren't necessarily based on the evidence.

So it was something to be able to think about. It's a little bit different ringer than what we're talking about, Dr. Fink, but again, recognizing that the technologies right now that govern wound care are more on the local coverage area rather than the national coverage decisions.

DR. FINK: And I appreciate that. That was a very helpful comment. I just want to clarify one thing that, then I will turn it to Dr. Rollins to see what he says. But the national level does not direct the local level. The local level, they are independent.

MS. NUSGART: Absolutely.

DR. FINK: Yes. I just wanted to clarify that.

Dr. Rollins?

DR. ROLLINS: Yes, that is true. There are national coverage determinations and there are local coverage determinations. But when it comes to reviewing evidence, evidence is evidence, and I would hope that a reviewer would use the same

principles that other reviewers would use.

Now, as I said on the previous slide, one reason why a NCD might be initiated is because of discrepancies or multiple inconsistencies amongst LCDs. So if that's a situation that exists, the CMS would hopefully intervene to try to make sure that we're all on the same side in terms of what the evidence shows.

DR. FINK: Well, thank you very much. I don't know if we get to keep going or not. I've had fun on this panel. I hope that the rest of you have, too. I think the benefit of this panel is it seems, first of all, people are willing to have direct discussions so that everybody knows where the other one stands, and also, there were some really, really good ideas. We talked about CMMI; and we talked about clinical trials; the use of real-world evidence; whether costs could come in. Maybe it doesn't come into a coverage decision, but then we brought up CMMI.

So I want to really thank everybody on this panel, and thank you for asking me to moderate.

(Chorus of thank yous.)

DR. VERMA: Thank you, everyone, for a very lively and productive panel, and also a great two-day workshop. We'll now be hearing closing remarks from our division director of the Division of Dermatology and Dentistry, Dr. Kendall Marcus.

FDA Closing Remarks – Kendall Marcus

DR. MARCUS: Thanks, Dev.

Over the last two days, we've heard from FDA representatives, translational researchers, patients, academia, physicians, NIH, CMS, and industry. We've heard from FDA center representatives about the regulatory considerations that go into the review of products for the treatment of non-healing chronic wounds, with an emphasis that stakeholders should engage with the agency early in development for feedback.

We've heard the significant burden non-healing chronic wounds may have on many aspects of patients' lives; the complex pathophysiology of wound healing; possible therapeutic targets; the possible utility of patient registries and

real-world evidence; the importance of clinical outcome assessments that are context relevant for patients; a perspective from CMS on how coverage is determined; and challenges faced by industry in bringing products to market.

This workshop has been very helpful in gathering stakeholders together and having open dialogue, and I'm sure the work will continue well beyond this workshop.

Going forward, FDA will continue to interact with stakeholders to help ensure safe and effective products are available to patients with non-healing chronic wounds. We will summarize the lessons learned from this two-day workshop in a publicly available summary report. In the meantime, we encourage stakeholders to continue to submit comments to the public docket at the Federal Register, which is open until June 28th. The link for this is in the chatbox.

Thank you to all the speakers, panelists, patients, and organizers who have helped make this workshop a success. This concludes our 2022 Wound

Healing Scientific Workshop. Thank you.

(Whereupon, at 3:25 p.m., the meeting was adjourned.)