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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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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

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

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

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



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

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

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

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

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

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

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

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

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

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

19 Welcome, Dr Herman.

20 **Presentation - Ira Herman**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 cells.

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

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

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

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

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

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



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

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

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

22           It is this conversation that takes place

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

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

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

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

11 **Presentation - Robert Kirsner**

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

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

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

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

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

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

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

10 The first was that on the first tissue  
11 culture, it met criteria, and the second was that  
12 the first culture was elevated, but then you could  
13 reduce the number of bacteria by any mechanism  
14 possible, and then re-culture and have less than  
15  $10^5$ . Interestingly, it was healing differences  
16 based on how patients enrolled in the study. If  
17 they enrolled with the first culture, 29 out of  
18 42 patients healed at 40 percent, while if they  
19 enrolled needing a second culture, that is the  
20 first culture at more than  $10^6$  and then it was  
21 subsequently lowered, only 9.3 percent of patients  
22 healed.

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

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

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

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

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

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

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

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

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



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

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

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

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

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

22 Perhaps these ideas related to bacteria may

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

5                               **Presentation - Geoffrey Gurtner**

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

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

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

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

5 No successful drug approval has occurred in  
6 wound healing for the past 25 years. The last drug  
7 that was approved was PDGF in 1997, and no small  
8 molecule has ever been approved, and a small  
9 molecule is different from a growth factor like  
10 PDGF because it's essentially a chemical. This  
11 chart just shows this graphically, that the  
12 likelihood of approval when you get from phase 1 to  
13 having an approved drug is zero percent in wound  
14 healing, and the overall FDA average is about  
15 10 percent.

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

1 in the context of biomarkers every week.

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

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

22 I think many of the products are certainly

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

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

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

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

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

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

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

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

16           We've been looking at this, again, for  
17    15 years, trying to understand how different  
18    disease states compare; new blood vessel formation.  
19    We've looked at aging. We've looked at diabetes.  
20    We've looked at a variety of diseases.

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



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

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

1 and tissues to survive tissue ischemia.

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

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

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

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

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

22           We have been focusing on small molecules as

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

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

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

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

1 can penetrate transdermally without significant  
2 technology innovation.

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

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

1       theoretically have some impact on secondary  
2       diabetic foot ulcer formation.

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

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

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

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

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

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

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

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

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



1       thalassemia.

2               This patient has had an ulcer for three  
3       years. This is anecdotal, and I fully admit that,  
4       but it's an interesting case study. The patient  
5       has received HBO, Apligraf, and all the advanced  
6       technologies. Again, in the expanded access  
7       context, we've had this patient, and the patient is  
8       now healed after 16 weeks. She's been an internal  
9       crossover control because during Thanksgiving she  
10      didn't want to come in and stopped using the  
11      polymer, and the wound got bigger. This was the  
12      end of our initial expanded access period, and we  
13      petitioned the FDA and got approval for another  
14      6 weeks, during which time the patient healed.  
15      This just shows the patient. I think you can see  
16      this works by decreasing the iron. You can see the  
17      hemosiderosis, which has almost completely  
18      resolved.

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

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

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

11 One of my mentors at the Boston Shriners  
12 Hospital is Matt Donelan, who made the offhand  
13 comment that "scars form where there's tension,"  
14 and that led me to work in this area for about  
15 20 years, trying to understand, how is it that  
16 tension forms scars and fibrosis? As a surgeon, we  
17 all know that's true. These are Langer's lines,  
18 and surgeons are taught to orient our incisions  
19 parallel, not perpendicular, to these lines because  
20 they're lines of minimal skin tension.

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

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

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

16 Unfortunately, this device, although it's  
17 very good for scars and incisions, isn't going to  
18 help the patient that we started this journey on,  
19 which this is the same patient 6 months earlier  
20 when he was in the emergency room, and after  
21 6 months of having famous Harvard professors take  
22 care of him, obviously a dismal result.

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

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

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

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

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

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

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

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

14 **Panel Discussion**

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

22 Just as a reminder, the public attendees can

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

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

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

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

17 DR. GERECHT: Maybe I can get started.

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

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

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

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

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



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

6 I'll tell it Marjana comment.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1       there are different circumstances and there are  
2       unique characteristics.

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

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

16               Dr. Sen, would you like to start?

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

19               DR. JONES:   For you, yes.

20               DR. LEWIS:   You can go ahead, sir.

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

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

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

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

22               Today the definition of wound closure is



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

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

13 So in this particular case, the TEWL study,  
14 or the transepidermal water loss study, is looking  
15 at those cases where the wound is closing as  
16 currently and taken to be the marker of closure,  
17 which is covering of the wound and no discharge for  
18 2 weeks. And in those cases where this is  
19 happening without the restoration of barrier  
20 function, we are then looking at the wound records.  
21 And in this case, according to the pilot study data  
22 that we have seen, wound transepidermal water loss

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

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

16           Dr. Jones?

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

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

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

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

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

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

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

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

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

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

4 Dr. Herman, you had some thoughts?

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

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

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

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

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

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

20                 Dr. Tomic-Canic, you have some thoughts?

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

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

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

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

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

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

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

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

19 Dr. Kirsner?

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



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

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

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

14 Dr. Sen, you also have some comments.

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

22 As we talked about this, the reason I bring

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

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

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

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

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

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

7 Having dealt with different branches of the  
8 agency, I think there needs to be maybe more of an  
9 equipoise about risk and benefit to try to take  
10 care of these patients because, again, no small  
11 molecules -- I've dealt with other branches, and  
12 clearly the cancer branch is much more aggressive.  
13 Cancer is a disease that everyone understands kills  
14 people and is very dramatic, but these diseases are  
15 also non-trivial; and I guess, for me, having an  
16 evolution in our ability to kind of get things into  
17 the clinic, and not just things that come through a  
18 369 human tissue exemption because we have hundreds  
19 of those, and it's kind of like practicing medieval  
20 medicine right now as a clinician.

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

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

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

7 Dr. Herman?

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

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

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

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

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

15 Any last thoughts? We have a minute.

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

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

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

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

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

1 precise way to actually help the wound heal.

2 That's one of the issues.

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

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

18           With this, we are now going to move into a  
19 10-minute break, and we'll look forward to coming  
20 back at 10:40. Thank you very much.

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

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**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. 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



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

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

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

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

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

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

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

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

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

13           Dr. Lisa Gould has been practicing plastic  
14 and reconstructive surgery with an emphasis on  
15 difficult wound problems since 1999. Dr. Marissa  
16 Carter is a biostatistician-epidemiologist,  
17 spending a great deal of time designing,  
18 monitoring, and analyzing clinical studies in the  
19 fields of wound care and quality of life.

20 Dr. Caroline Fife is a professor of geriatrics at  
21 Baylor College of Medicine in Houston and the chief  
22 medical officer of Intellicure, LLC, a health

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

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

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

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

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

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

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

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

18 **Presentation - Lisa Gould**

19 DR. GOULD: Thank you, Maryjoy.

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

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

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

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

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

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

11 In this leg wound, initially it was not  
12 closed, and then it had a small skin graft, and  
13 8 days later it was described as closed, and you  
14 can see the difference between the two.

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

1 some issues where cosmesis is certainly a big  
2 problem.

3 But complete closure is really one of the  
4 most theoretically objective and clinically  
5 meaningful endpoints, and the FDA definition is  
6 skin re-epithelialization without drainage or  
7 dressing requirements -- and the way I read  
8 it -- confirmed at 2 consecutive study visits  
9 2 weeks apart. In my reading, that's a month;  
10 that's 2 visits. But most people interpret it as  
11 it's closed, and then we'll see them 2 weeks later,  
12 and if it's still closed, that's healed.

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

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



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

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

22 In a recent clinical trial, we intended to

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

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

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

1 back and continue the trial for another week or  
2 two.

3 We were concerned that this rigorous  
4 definition would delay our outcomes, and then this  
5 trial would look very strange to everyone because  
6 of the delay in healing, but it did give us really  
7 strong confidence in the outcome. And indeed, if  
8 you look at the results with the number healed with  
9 the topical product, it was similar to what we see  
10 in other trials, where in the control, about  
11 40 percent of the patients healed, and then in the  
12 product application, 74 percent healed in 54 days,  
13 with mean time of healing to 54 days. So it wasn't  
14 out of the realm of what we usually see, and we had  
15 very good confidence that those wounds were  
16 actually closed.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

1 and better accepted by patients for early breast  
2 cancer.

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

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

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

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

8           (Pause.)

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

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

13                           **Presentation - Marissa Carter**

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

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

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

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

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

1 more, for the first time. We looked at  
2 17 randomized-controlled trials for indications of  
3 diabetic foot ulcers and venous foot ulcers, in  
4 which interventions -- and we call them high tech,  
5 but they were mostly drugs, devices, and biologics,  
6 and so forth, and what we were trying to figure out  
7 is the eligibility in the general population in  
8 those specific trials.

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

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

1 20 years, from '98 to 2018. These authors -- and  
2 they come from Europe -- focused primarily on the  
3 generalizability, but they were looking at things  
4 like socioeconomic status, ethnicity, other patient  
5 parameters, recording and reporting of medications,  
6 and comorbidities, and some of the things they  
7 found were kind of shocking.

8           Let's start by looking at screening rates.  
9 Only a third actually reported them, which means  
10 that two thirds did not report any kind of  
11 screening data. We don't even know how many people  
12 were actually eligible for the trial.

13 Surprisingly, 13 percent only reported patient  
14 ethnicity; 42 percent reported comorbidities, but  
15 these were very selective and they were certainly  
16 nowhere near comprehensive; and shockingly, small  
17 numbers reported things like current medication  
18 use -- we know lots of medicines affect wounds  
19 healing -- and socioeconomic factors. That's a  
20 huge issue. Lots of patients don't have access to  
21 good wound care, but don't know anything about who  
22 they are.

1           Even when we look at something like major,  
2           or I would say macroischemia, which we can define  
3           by ABPI, it's less than 0.8; still, only 40 percent  
4           didn't even bother to look at that. A shocking  
5           40 percent didn't even report on any adverse  
6           events. You know, that's a primary thing, right?  
7           We want to know if something is safe. Fifty  
8           percent only reported BMI.

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

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

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

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

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



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

3           Finally, I would say in the real world, the  
4 more complex the wounds in others, the more serious  
5 it is, the more severe it is, and so on like that,  
6 the harder it is, actually, to define standard of  
7 care because we know typically as wound care  
8 practitioners what standard of care is for a fairly  
9 simple wound like wound care management; moist  
10 wounds; debridement; offloading where appropriate;  
11 compression for VLU's; and so on like that.

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

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

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

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

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

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

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

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

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

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

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

1 things like that.

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

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

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

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

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

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

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

20           DR. MEJIA: Okay.

21                           **Presentation - Caroline Fife**

22           DR. FIFE: Thank you for letting me talk

1 about patient registries and real-world evidence.

2 It's a great segue thanks to Dr. Carter.

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

22 Now, that's an opportunity and a problem

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

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

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

22           In 2014, the U.S. Wound Registry

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

9 I see you, Tom. Hey.

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

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

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

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

19 **Panel Discussion**

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

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

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

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

14 DR. FIFE Yes. I'm excited to report there  
15 are some innovative thinking manufacturers that  
16 have done two or three interesting things. The  
17 first one is they've asked us to tell them what the  
18 likely loss of recruitment will be based on a list  
19 of exclusion criteria. So even though they may  
20 have to use certain exclusion criteria, they want  
21 to go into it knowing we're going to lose  
22 10 percent of people because of renal failure;

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

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

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

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

22 The other way the Wound Healing Index has

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

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

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

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

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

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

12             DR. CARTER:  Yes.

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

18             DR. FIFE:  Yes.

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

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

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

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

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

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

1 understand, really, what its limitations are. In  
2 that paper where we looked at the wound closure and  
3 wound healing, in the real-world evidence that we  
4 looked at, there were 901,000 wounds, and no study.  
5 used the FDA definition of wound closure, and  
6 89 percent didn't even define their assessment  
7 method.

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

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

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

1 DR. GOULD: Yes. How do you get to the  
2 problem of the diagnosis? I'm in clinic, and it's  
3 a square peg in a round hole. So I have the  
4 86 year old who banged her leg on the dishwasher  
5 door, but her real problem is that she has venous  
6 insufficiency and also some arterial insufficiency.  
7 But it gets classified as a traumatic wound, and I  
8 don't usually reclassify those because that was the  
9 etiology, although I know some people do because  
10 then they can put their product on it.

11 DR. FIFE: Yes, it's more likely that it's  
12 coded to coverage, so our bigger challenge is  
13 taking all the venous ulcers and figuring out the  
14 50 percent of them that are venous. That is about  
15 the reality, half of things coded as venous, or  
16 venous, and we know that from photo analysis, as  
17 well as from asking things like can you see bone or  
18 tendon? Because you shouldn't do that in a venous  
19 ulcer.

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



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

6 Real-world evidence is incredibly a messy  
7 business

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

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

1 bad news in the discussion so far.

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

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

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

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

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

1       figured it out.

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

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

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

17              DR. MEJIA: Thank you, Dr. Carter.

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

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

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

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

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

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

6 DR. GOULD: AMA.

7 DR. SERENA: That is the AMA.

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

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

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

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

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

1 continuum; it's a spectrum [indiscernible].

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

6 DR. MEJIA: Great. Thanks for that  
7 discussion.

8 Dr. Gould, did you want to comment further?

9 (Dr. Gould gestures no.)

10 DR. MEJIA: Okay. Alright.

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

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

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



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

6 DR. SERENA: Well, thank you, Nico.

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

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

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

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

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

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

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

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

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

1 study, comparative results, historic results,  
2 et cetera.

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

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

22 So I see in trial work, especially over the

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

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

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

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

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

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

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

22           We wished the pandemic didn't happen, and it

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

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

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

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

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

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

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



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

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

15 DR. MEJIA: Thank you for your comments.

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

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

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

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

22           We'll have almost a hundred nurse

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

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

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

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

22 DR. CARTER: What I actually say is what do

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

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

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

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

7 DR. FIFE: Lisa, your hand is up.

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

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

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

18 So we can use the real-world evidence to  
19 help us understand at what point does a wound stall  
20 when something has been used 6 weeks, 8 weeks,  
21 12 weeks, and then when should it be changed, and  
22 then also looking at some of the intermediary

1 endpoints.

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

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

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

1 DR. MEJIA: Dr. Banerjee?

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

10 Medicare is trying to figure out that there  
11 is a lot of overuse and abuse of a lot of these  
12 products. How do we determine that this product  
13 should be used 3 times or 4 times, or is it not  
14 enough? Do you waste money if you're restricted to  
15 2 or 3 applications or should we use it for more?

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

1 clinical decisions.

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

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

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



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

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

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

1 15 times for one wound. That's not how it works.  
2 So I think that's another insight that we get from  
3 the real-world data that's problematic when you  
4 look at claims.

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

17 They're just getting ready to publish now  
18 the main reason people screen fail in trials with  
19 4-week run-in periods, and you'd be surprised, or  
20 you wouldn't be surprised; they heal too quickly.  
21 Even at that standard of care for 4 months, when  
22 you put them in a trial and really control the

1 standard of care rigorously, they heal.

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

4 DR. SERENA: Yes, exactly.

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

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

15 MR. ROLLEY: Yes. Thanks for that.

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

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

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

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

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

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

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

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

12 I think, good God, one of the things I see  
13 all the time when I peer review trials is only  
14 20 years ago we had consult criteria for RCTs.  
15 None of the major wound care journals and studies  
16 insist that we have to have these for each  
17 peer-reviewed paper that comes through the door.  
18 Why not? This is not rocket science. It's not  
19 hard. We don't take care of the standards that  
20 many organizations within wound care actually put  
21 out and spend a lot of time and money on. It's  
22 like we just ignore them. How can we fix that?

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

13 That gets to the issue of this 12-week  
14 episode of care, which Medicare payers are wanting  
15 to put on us if a real patient is in service for  
16 7 months. Could we use some real-world data to get  
17 some reality check on the distance between these  
18 applications, and why it is what it is, and how  
19 many months it really takes to get all the wounds  
20 healed?

21 DR. MEJIA: Dr. Banerjee?

22 DR. BANERJEE: Also, I just wanted to follow

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

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

20 DR. MEJIA: Great. Thank you so much.

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

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

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

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

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

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



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

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

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

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

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

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

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

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

1 thoughts and input. Thank you.

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

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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

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

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

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

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

1 development and validation, including  
2 considerations for clinical trial design, conduct  
3 analysis, interpretation and reporting for  
4 regulatory determinations. Prior to joining FDA in  
5 2015, Dr. Daniels worked in the Health Economic and  
6 Outcomes Research Group at Allergan.

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

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

17 **Presentation - Julia Ju**

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

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

3 Patients are experts in their disease. With  
4 this recognition, FDA's Patient-Focused Drug  
5 Development Initiative, PFDD, began in the early  
6 2000s to incorporate the patients in the  
7 development of clinical trial endpoints for medical  
8 products. The goal is to use a systematic approach  
9 to capture patient experience and perspectives here  
10 in a way that can inform regulatory decision making  
11 and can be described in labeling accurately and  
12 informative to healthcare decision making.

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

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

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

1 treatment.

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

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



1 for a medical product.

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

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

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

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

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

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

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

1 the challenges in pain assessment in wound healing  
2 trials.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9                           **Presentation - Vickie Driver**

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

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



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

5           Following this extensive research, that I'm  
6 going to be discussing, and three publications, and  
7 a very wide-based outreach program, the FDA asked  
8 us to consider developing a wound care  
9 collaborative community, and this was done in just  
10 16 months ago, actually, after developing a charter  
11 of the tools program that was actually developed by  
12 the FDA.

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

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

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

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

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

1           Now, as part of this initiative, our  
2 research study, a robust research study, was  
3 conducted involving 628 multidisciplinary wound  
4 clinicians and researchers from four different  
5 groups. In 2016 and 2017, from the analysis of  
6 this survey, we confirmed 22 content-validated  
7 wound care endpoints by an independent  
8 biostatistician that were relevant in supporting  
9 clinical practice and relevant to or making a  
10 difference in patients' lives. Now, the survey not  
11 only incorporated 629 clinicians, but it was from  
12 13 specialties and represented nine different  
13 settings of care.

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

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

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

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

1           Then in 2018 and 2020, we conducted a  
2 patient survey via an IRB process that yielded  
3 451 responses from patients in 26 states, and it  
4 showed us that patients primarily agreed with  
5 clinician survey, and this was also published in  
6 the Wound Repair and Regeneration.

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

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

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

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

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

22 We also suggested new secondary endpoints.

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20                           **Presentation - Anne Klassen**

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

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

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

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

1 the WOUND-Q also will be qualified.

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

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

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



1 mixed methods, multiphase, and iterative.

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

11 This is our qualitative phase. We spent a  
12 lot of time here. We had an interview guide with  
13 topics that we wanted to explore, and then we did  
14 60 in-depth patient interviews. Some of these  
15 interviews lasted up to 2 hours. We tried to  
16 recruit a maximum variation sample in terms of age  
17 and gender, four different countries, wound type,  
18 and how long somebody had had their wound.

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

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

8           So this was coded, and you can see that  
9 there were multiple themes for social and  
10 psychological impact of the wound. We did this for  
11 all 60 of our interviews, and at the end of the  
12 process, we had close to 3,000 codes from the  
13 60 transcripts, and we were able to look at our  
14 major themes and subthemes in terms of wound type  
15 to see what is common and what can we develop that  
16 would work for different types of wounds.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

#### 15 **Panel Discussion**

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

1 assessments or COAs

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

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

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

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

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

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

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

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

7 DR. DANIELS: Thank you for that.

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

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

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

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

5 DR. DANIELS: Got it.

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

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

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

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

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

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

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

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

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

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

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

19 DR. JU: This is Julia, and if I may start.  
20 From the limited applications that we've seen, the  
21 10 [indiscernible] COA measures for wound healing,  
22 the most common type we've seen are pain and itch,

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

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

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

21 DR. DANIELS: Thank you.

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



1 add anything or not.

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

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

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

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

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

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

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

22 I don't know if anyone else wanted to add

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5 DR. PUSIC: No, you go ahead.

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

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

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

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

9 DR. DANIELS: No, those are great points.

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

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



1 going to measure frequency, severity, and impact.

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

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

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

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

1 other problems. They have many other problems.

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

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

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

1 obtain from patients?

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

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

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

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

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

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

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

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

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

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

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

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

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

16               DR. JU: Yes.

17               DR. DANIELS: Got it.

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

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

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

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

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

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

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

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

21 DR. DANIELS: Thank you, Dr. Fritsch.

22 I don't know if we have any responses from

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

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

13 So how do you incorporate those data into a  
14 randomized clinical trial? You have to have a much  
15 longer follow-up period than what we've been able  
16 to establish in our RCTS. They're typically only  
17 12 weeks, and we know that in critical ischemia and  
18 looking at other diseases, musculoskeletal,  
19 et cetera, we have to look at these patients for a  
20 long period of time to really gather the data that  
21 shows, yes, these patients have been able to go  
22 back to their lives, and these changes have



1 occurred.

2 DR. DANIELS: Those are excellent points.

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

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

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

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

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

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

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

6 DR. DANIELS: Thank you for that.

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

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

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

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

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

17 DR. DANIELS: Yes, most definitely.

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

20 (No response.)

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

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

9 So with that, thank you.

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

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

18 **FDA Introductory Comments - Dev Verma**

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

22 Our next and final session will focus on a

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

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

14 We'll be hearing from Dr. James Rollins, who  
15 is one of the medical officers in the coverage  
16 analysis group in the Center for Clinical Standards  
17 and Quality at CMS. He's worked at CMS for  
18 15 years, where he's been involved with coverage  
19 decisions, including those related to the  
20 management of chronic wounds. While at CMS, he's  
21 also director of the Division of Items and Devices.

22 We'll be hearing from Marcia Nusgart, the

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

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

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

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

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

6 **Presentation - James Rollins**

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

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

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



1 advancement with a potential major clinical impact.  
2 An NCD also can be externally requested; for  
3 example, when a current national non-coverage  
4 policy is in place and when there is substantial  
5 variation amongst LCDs. Also, external requests  
6 can be initiated by patients, advocacy groups,  
7 providers, specialty societies, vendors, but they  
8 must follow the instructions as stated in the  
9 Federal Register.

10 At the beginning of the NCD process, there  
11 is usually an informal discussion between the  
12 requester and CMS. This is followed by the  
13 submission of the formal request, a benefit  
14 category determination, and this is done because if  
15 the item does not fall within one of the benefit  
16 category groups, it cannot be covered.

17 There is a review of the evidence by CMS,  
18 which is known as an internal technology review.  
19 There also may be an external technology review in  
20 the form of a technology assessment, which is done  
21 by an evidence practice center or done by a MEDCAC  
22 committee.

1           The proposed determination is posted,  
2 followed by the final determination, which is  
3 posted. In order for CMS to get public input,  
4 there are two comment periods, one at the time the  
5 formal request is posted, and the second when the  
6 proposed determination is posted.

7           This is a cartoon of the NCD process, and it  
8 usually takes a total of 9 months. Depending on  
9 whether or not an external review is performed, it  
10 may last as long as a year.

11           I briefly mentioned MEDCACs. CMS often  
12 convenes MEDCAC committees on controversial topics.  
13 MEDCACs vote only on the quality of the evidence  
14 and not on the coverage determination. Not all  
15 MEDCAC findings result in an NCD. MACs use  
16 information from MEDCAC meetings to make LCDs.

17           In the past, a decision or determination has  
18 resulted in one of three actions: coverage,  
19 non-coverage, or left to a back [indiscernible]  
20 discretion. Innovators of new products felt that  
21 the denial of their new product stifled innovation.  
22 Some of these new products were promising, but the

1 studies had low numbers of Medicare-age  
2 participants; thus unable to generalize these  
3 findings to the Medicare population.

4 This led to a paradigm shift, the creation  
5 of coverage with evidence development, also known  
6 as CED, which began in 2005. In the CED paradigm,  
7 an item or service is only reasonable and necessary  
8 when it is provided within a research setting where  
9 there are added safety, patient protections, as  
10 well as monitoring and clinical expertise. CED  
11 research studies range from randomized clinical  
12 trials to registries.

13 In CED, Medicare covers items and services  
14 on the condition that they are furnished in the  
15 context of an approved clinical trial or the  
16 collection of additional clinical data. Coverage  
17 with evidence development allows for positive  
18 coverage when the evidence is insufficient for a  
19 more favorable decision.

20 These two slides represent a cartoon of the  
21 coverage process under coverage with evidence  
22 development. As noted in the slide, some outcomes

1 are more relevant to CMS than others. Improved  
2 function and participation is an outcome of  
3 interest that is important to CMS, and that's  
4 important because we'll talk about that in a  
5 minute.

6 Now we will take a look at the use of CED  
7 and how it has been incorporated in policy decision  
8 making. In 2003, CMS posted the NCD 190.0  
9 Autologous Blood-Derived Products for Chronic  
10 Non-Healing Wounds. At the time, CMS felt that the  
11 evidence was insufficient and found it not to be  
12 reasonable and necessary.

13 Based on additional input from the wound  
14 care community, a reconsideration of the NCD was  
15 performed in 2012. The decision was to cover  
16 autologous platelet-rich plasma, or PRP, for  
17 patients with chronic non-healing diabetic pressure  
18 and/or venous wounds if they participated in a CED  
19 study. The CED question that CMS wanted to know  
20 was, does the use of PRP result in complete wound  
21 healing; ability to return to previous function and  
22 resumption of normal activities; or reduction in

1 wound size or healing trajectory, which results in  
2 the patient's ability to return to previous  
3 function and resumption of normal activities?

4 CMS received and approved a number of  
5 protocols. Some of these approved protocols  
6 resulted in peer-reviewed published studies. CMS  
7 also reviewed other studies in the medical  
8 literature. They looked at guidelines. We  
9 consulted with medical and professional societies  
10 and had a technology assessment performed by one of  
11 our evidence practice centers.

12 In 2021, based on the published CED studies  
13 and other information, CMS was able to alter its  
14 position. In their new policy, CMS would  
15 nationally cover PRP for non-healing diabetic  
16 wounds and allow MACs' discretion to cover all  
17 other chronic non-healing wounds.

18 In summary, through the CED process, CMS was  
19 able to change its non-coverage position of PRP to  
20 national coverage of PRP for non-healing diabetic  
21 wounds, and allow the MACs to make discretionary  
22 PRP coverage of all other chronic non-healing

1 wounds. Thank you. That's it.

2 **Presentation - Marcia Nusgart**

3 MS. NUSGART: Good afternoon. This is  
4 Marcia Nusgart. I'm the executive director of the  
5 Alliance of Wound Care Stakeholders, and with me is  
6 Dr. Caroline Fife. You heard from her both  
7 yesterday and today, but actually the hat she's  
8 wearing today is as being the co-chair for the  
9 Alliance of Wound Care Stakeholders.

10 The Alliance is the united voice of the  
11 wound care community. We advocate on public policy  
12 issues that might create barriers to patient access  
13 to treatments or care. There are different areas  
14 we actually focus on: coding, coverage, and  
15 payment for wound care products and services;  
16 quality measures; and wound care research, and we  
17 serve as a resource both to the Food and Drug  
18 Administration and the Centers for Medicare and  
19 Medicaid Services on issues related to wound care.  
20 We are a multidisciplinary trade association, and  
21 our members are physician specialty societies,  
22 clinical and non-clinical associations, patient

1 organizations, and business entities.

2 Here's a list of the various clinical  
3 associations, and we talked yesterday about  
4 multidisciplinary. Well, I think this shows a  
5 wonderful representation of all the different  
6 clinical associations whose members treat patients  
7 with chronic wounds, and we're very proud to say  
8 that there are our members who help us.

9 So you heard today and yesterday about some  
10 wonderful conversations, and we invite you to  
11 Solution-Build, the payers at the Alliance's Wound  
12 Care Evidence Summit, where we invite you to  
13 connect and collaborate with public and private  
14 payers such as Humana, United Healthcare, Aetna,  
15 Blue Cross and Blue Shield, as well as CMS.

16 Those of you who've ever tried to be able to  
17 talk to commercial payers about the type of  
18 evidence and how they make their clinical decision  
19 making, you'll find them to be speakers at our  
20 conference. You'll be able to hear what they have  
21 to say because they, along with federal agencies  
22 and evidence analysis experts and researchers,

1 medical specialty societies, wound care clinics,  
2 and manufactures, we're all going to be able to get  
3 together to have a small meeting to talk about how  
4 much and what type of clinical evidence do  
5 regulators and payers need to give a positive  
6 coverage approval and decision for wound care  
7 products and services. So we invite you to attend.  
8 It's going to be a fabulous conference and  
9 synergistic to this wonderful FDA workshop.

10 By the way, Dr. Verma, congratulations.  
11 You've knocked it out of the ballpark over the past  
12 few days, you and your FDA staff. So I want to  
13 congratulate you on a fabulous meeting today. And  
14 you'll see Dr. Verma and some other FDA staff at  
15 our meeting also.

16 In terms of this FDA healing workshop, we  
17 did submit preliminary comments on the issues that  
18 the FDA did request, which did include a PowerPoint  
19 presentation when we met with the FDA in 2015 to  
20 talk about some of the issues regarding the 2006  
21 guidance document. And when I looked at some of  
22 these issues, it was amazing to me that some of



1 those issues are still relevant today.

2 One of those issues that I just wanted to  
3 mention is our concerns with the current FDA  
4 terminology for product classifications, because  
5 currently 510(k) and PMA biological CTP, or  
6 cellular and/or tissue-based products, for skin  
7 wound products have been placed in these FDA  
8 product classifications, indicating that they are  
9 wound dressings.

10 This terminology used for these product  
11 categories is outdated and really can't represent  
12 the true nature of these products, because the  
13 unattended consequences is that payers have been  
14 confused with FDA labeling of CTPs as wound  
15 dressings, so the payers thus believe that they're  
16 topically applied protective covers, and paid them  
17 as part of an office visit or an E&M service.

18 So our recommendation for FDA is to update  
19 the classification for CTPs to match the current  
20 terminology, to differentiate it from wound  
21 dressings.

22 Our paper today, it was so interesting the

1 way that we came up with this, because we were  
2 actually writing comments to CMS and Dr. Samuel  
3 Nussbaum, who helped us with this article, had said  
4 to me, "Marcia, well, do you actually know how much  
5 Medicare is actually paying for chronic or  
6 non-healing wounds?" And I'm like, "No, I really  
7 don't know; so let me go research it," and I  
8 couldn't find any really relevant type papers on it  
9 at that point in time, many years ago. And the  
10 reason for that being is because the research had  
11 focused on hospital long-term care settings instead  
12 of recognizing that so much wound care had been in  
13 the outpatient area.

14 So we crafted this article, and I'm so  
15 pleased to say that it has been quoted many times.  
16 I think even yesterday some people quoted the  
17 statistics from here, on this particular paper. We  
18 are going to be updating it this year to use the  
19 2019 and 2020 Medicare data, so stay tuned for  
20 that.

21 I'd like to turn it over to my colleague,  
22 Dr. Caroline Fife, that will talk through the

1 methodology and a number of different issues  
2 related to this fabulous paper, and it can be found  
3 in 2018 Value in Health, as well as on our website,  
4 and you can see also the link below.

5 **Presentation - Caroline Fife**

6 DR. FIFE: Thanks, Marcia.

7 What we did that was different in this  
8 analysis is that rather than going into it assuming  
9 that all wound care is represented by venous  
10 pressure and diabetic ulcers, we said, "No, wait a  
11 second. Let's find out what people go to wound  
12 centers for."

13 So we actually looked at 130 hospital-based  
14 outpatient wound centers and got the complete set  
15 of ICD-9, at the time, codes that were the reasons  
16 people showed up in wound centers. Then we threw  
17 that against the Medicare claims data set, and  
18 that's when we began to see surprising things,  
19 which is all of these nameless ulcers that we  
20 talked about yesterday: traumatic wounds; surgical  
21 infections; and infections of every type of ulcer.

22 One of the huge results was the

1 understanding that the majority of the cost is on  
2 the outpatient side. That was a surprise to  
3 everybody except the people involved in the paper.  
4 But the other thing that surprised even us was if  
5 you look inside that green circle, which are the  
6 diabetic ulcers, venous ulcers, and pressure  
7 ulcers, which we've had people say, "That's  
8 90 percent of what we see." Okay. It isn't.

9           The yellow arrows there demonstrate the  
10 nameless chronic ulcers, the various types of skin  
11 disorders, traumatic wounds that never heal, and  
12 surgical complications; that, in fact, in terms of  
13 prevalence, the DS [ph] surgical wound is perhaps  
14 the most common wound experienced by Medicare  
15 beneficiaries.

16           I don't think anybody really understood  
17 that, but by the time you layer infections of all  
18 of these things on top of that, then we're looking  
19 at an enormous number of problems that people are  
20 going to seek help for in the outpatient setting,  
21 primarily that are not venous, diabetic, and  
22 pressure.

1           When we then started to look at cost, we  
2 looked at the cost and if the principal diagnosis  
3 was a specific wound type. But then you can look  
4 at the cost if it's a secondary diagnosis because  
5 there were other reasons that the patient may have  
6 been hospitalized. Then if you multiply that by  
7 the prevalence rate, you begin to see what the real  
8 approximated costs are for some of these  
9 conditions.

10           So because of its prevalence, pressure  
11 ulcers represent a big portion, but look at that  
12 surgical wound; 24 billion is our estimation.  
13 Where is the research and innovation on those?  
14 Then if you look at the nameless wounds, the  
15 chronic ulcers and the traumatic wounds that never  
16 close, we've got nearly \$10 billion in those. So  
17 it is very worrisome to us that the investment that  
18 is in technology is missing at such an enormous  
19 cost in other wound types.

20           The other thing that we realize as we begin  
21 looking at these claims is that we can see claims  
22 on ulcers that lasted for a year. Now, one of the

1 things that was brought up in the panel is that  
2 when you look at claims, the claims conflate all of  
3 the wounds into the same diagnosis, so you can't  
4 tell looking at claims that the patient may have  
5 3 venous ulcers or 3 diabetic foot ulcers. But  
6 when you look at registry data, and you see the  
7 experience of the patient, then there may be times  
8 they have 5 wounds, times they have one wound,  
9 times they have 3 wounds. But they're getting  
10 wounds in crops, and 30 percent of the time they're  
11 getting a new wound while they're in service for  
12 the wound they've already got.

13 So it's not just that a wound comes back,  
14 which had a lot of discussion, but they get new  
15 ones in other places maybe of the same type, maybe  
16 of a different type, and they have more than one.  
17 That's also contributing to the cost, even though  
18 all of our research is wound focused, not patient  
19 focused.

20 We looked at this trying to get a little bit  
21 more understanding of the longitudinality of it,  
22 and a decade ago, Marissa Carter and I looked at

1 five years of data, 5,000 patients-ish,  
2 7000 wounds, and in about 100,000 visits; and not  
3 surprisingly, we could identify patients who  
4 continued to be seen year, on year, on year after,  
5 and the cost of those individual cases continued to  
6 escalate as each year went by.

7 That's not surprising, but what is often  
8 surprising is the fact that so many patients will  
9 be seen for years. That's one of the reasons that  
10 the cost accumulates on the outpatient side,  
11 because they have wounds for a long time, and they  
12 may get new ones by the time that we finish the one  
13 that we were starting them for.

14 So we looked at 5,200 patients who had an  
15 estimated cost of \$29 million, and we estimated  
16 that if you just looked at the prevalence rates of  
17 the wound types that we saw, we could see  
18 25 billion on the outpatient side alone. And we  
19 estimated that a decade before we did the study  
20 that Marcia was alluding to at the beginning, so we  
21 were really spot-on in our estimation of what the  
22 national expenditure would be, just looking at a

1 small slice of patients.

2 Non-healing wounds are more expensive than  
3 the ones that do well; that's not surprising to  
4 anyone. But the other thing that shocked people  
5 was that the healing rates that we were seeing  
6 using registry data were not as good as those in  
7 our RCTs, or those as good as marketing would  
8 suggest, so we needed to look a little bit more  
9 closely at healing rates to understand this cost.

10 We then went and looked at the controls for  
11 RCTs, and if you look only at the controls -- this  
12 was discussed a little bit yesterday -- you're  
13 seeing healing rates less than 50 percent in the  
14 controls of RCTs, where you've already said most of  
15 the patients enrolled in those RCTs are relatively  
16 healthy.

17 When you look at similar time frames, like  
18 12 weeks at the U.S. Wound Registry, the healing  
19 rates are much worse than they are in the controls  
20 of an RCT. Remember, we've got sicker patients in  
21 the registry. We've talked about that a lot. But  
22 even when you give an infinite period of



1 time -- that is don't put any limitations on the  
2 length of time to look for healing in the registry;  
3 let them play out as long as needed -- we still see  
4 that healing time frames are 33, 36, and 48 weeks,  
5 which tells you something about the duration of  
6 clinical trials when they're limited to 12 weeks;  
7 that part of the problem may be that there's just  
8 not enough time for those wounds to heal. But even  
9 when you give it as much time as it takes, we still  
10 only have about a 50 percent healing rate if you  
11 look at all-comers.

12 To personalize it a little bit, this is a  
13 man that I've continued to see. He's 80 years old.  
14 He's got severe bilateral, lower extremity  
15 lymphedema with venous insufficiency. He has CHF.  
16 He has COPD on oxygen. He has renal insufficiency.  
17 Every time he gets edematous and we increase his  
18 diuretic dose, his kidneys get in trouble. He has  
19 underlying diabetes. He gets hospitalized every  
20 month for volume overload, and often for wound  
21 infections and colonization. What keeps happening  
22 with him is that as he gets acute on chronic heart

1 failure, his legs just split open, and there's no  
2 amount of compression we can put him in that will  
3 control that.

4 This is not an unusual case. I didn't just  
5 pick the worst possible patient. This is just to  
6 give you insight into the challenges that we have  
7 with these folks.

8 In fact, when we looked at the CMS data on  
9 the prevalence of diseases in 500-ish physicians  
10 who were working full-time in wound centers, you  
11 look at the CMS data on their populations, and  
12 about 60 percent of those patients that are seen in  
13 hospital-based outpatient clinics have chronic  
14 kidney disease. More than half have diabetes.  
15 Half of them have heart failure. Half of them have  
16 ischemic heart disease, and lots of them have  
17 atrial fibrillation, which means they're also  
18 chronically anticoagulated.

19 Interestingly, those aren't the six of the  
20 most expensive conditions that Medicare is  
21 concerned about; those are the ones who have  
22 wounds. So I think the fact is the contribution of

1 chronic wounds to the cost of these underlying  
2 diseases has really not been understood.

3           Wound care is expensive because it's bigger  
4 than DFUs, VLU, and pressure ulcers. Chronic  
5 wounds are symptoms of expensive underlying medical  
6 conditions. Real-world healing rates are  
7 50 percent or less. When wounds do heal, it takes  
8 more than 36 weeks to heal them. The average  
9 patient has at least two of them, and they keep  
10 coming back or they get new ones.

11           Sadly, the basic interventions that work  
12 well are often neglected, in part due to challenges  
13 with coverage policy. Nutritional supplements  
14 aren't reimbursed at all, and other types of things  
15 we know that are basic interventions are reimbursed  
16 poorly for the amount of effort it takes to do  
17 them, like total contact casting. Then we have all  
18 of these expensive therapies; that we never really  
19 look at the real-world effectiveness or the cost  
20 effectiveness.

21           All those things contribute to the fact that  
22 we end up with a challenging environment where we

1 don't understand why cost ratchets up, but it has  
2 to do with the complexity of the patient, and that  
3 many of those are downstream implications from  
4 coverage policy. Dr. Rollins described the process  
5 of creating coverage policy that keeps Marcia and  
6 me, and all the other folks in the Alliance, very  
7 busy making responses to proposed coverage policy.

8 We'll just make one last pitch to ask you  
9 all to join us at the evidence summit, which will  
10 be an in-person meeting in Washington, and thanks  
11 again for having this meeting. It's been  
12 tremendously successful. I have watched every  
13 minute of it, and I thank you for the opportunity  
14 to listen, as well as speak.

15 DR. VERMA: Great. Thank you all for those  
16 great presentations. We will now start the panel  
17 led by Dr. Rochelle Fink.

18 **Panel Discussion**

19 DR. FINK: Thank you very, very much for  
20 inviting me to moderate this panel today. It is a  
21 really, really exciting subject. I had a few  
22 questions for the panelists. Some are more for the

1 industry and the associations, and then some we're  
2 going to point directly to Dr. Rollins from CMS.

3 But first I'm going to put industry and  
4 other stakeholders, non-governmental stakeholders,  
5 on the spot. Some of that stems from -- and I  
6 appreciate the Alliance of Wound Care Stakeholders  
7 filed a comment in the Federal Register notice  
8 today. So I read it, and that's where some of  
9 these questions stem from.

10 The first question that I have is there's  
11 been some back-and-forth; should the payers just  
12 look at real-world evidence, and I know the payers  
13 have asked to see clinical endpoints, and it seems  
14 like some of the difficulty is sort of coming to a  
15 place where both sides are happy.

16 My question for industry and stakeholders  
17 is, what clinical endpoints do you think CMS should  
18 look at when determining coverage? Also along with  
19 that, what type of a prospective clinical trial  
20 design, apart from real-world evidence, do you  
21 think would assist CMS in making a coverage  
22 decision? So endpoints, and what type of a

1 clinical trial do you think would be appropriate?

2 MS. LAW: I'll just start with the endpoints  
3 question, and I want to thank everybody for,  
4 really, a fabulous conference.

5 On the endpoints, obviously complete wound  
6 closure or complete wound healing -- we have all  
7 commented on it -- it doesn't necessarily make  
8 sense. I think we heard Dr. Gould say, really,  
9 wound treatment is often multiple products at once,  
10 and you want to step down as quickly as you can.

11 We've been leaning a bit more towards  
12 percent area reduction, which I believe was on  
13 Dr. Driver's list. We're still struggling with the  
14 question that was brought up earlier around volume  
15 and how to really accurately measure that. So the  
16 percent volume reduction, although we love that  
17 endpoint, really we are not quite there yet with  
18 the technology.

19 DR. FIFE: Can I jump in and say that I also  
20 think we ought to be mindful of what the device is  
21 designed to do? Pressure doesn't allow a wound to  
22 epithelialize. I don't have a dog in this fight;

1 I'm just as a clinician saying, you stop it in  
2 order to get the skin to grow. Its purpose is to  
3 fill in the hole.

4 So it's always been frustrating to me when  
5 you want to look at the impact of something that  
6 causes vascularity but maybe actually stops  
7 epithelialization; that the endpoint is  
8 epithelialization. Can we just have endpoints that  
9 are relevant to what the device is supposed to  
10 accomplish?

11 MS. NUSGART: I did not pay her to say that,  
12 but thank you very much.

13 DR. FIFE: You can send me a check later.

14 MS. NUSGART: Because we always mention  
15 something such as negative pressure wound therapy,  
16 which may have not been created to be able to have  
17 complete wound closure, as well as so many other  
18 medical devices. But there are other things  
19 that --

20 DR. FIFE: There are others.

21 MS. NUSGART: -- that do phenomenally well  
22 and that patients really do appreciate, so it's

1 something to be able to keep in mind.

2 MR. ROLLEY: I would agree with --

3 DR. FINK: So you have mentioned --

4 MR. ROLLEY: I'm sorry.

5 DR. FINK: Well, so far I think we have  
6 things that patients would appreciate, although it  
7 would be interesting to dive into that a little bit  
8 more. We have "not complete wound closure," and I  
9 guess the question is, how much of a wound closure?  
10 "It has to be designed for the purpose." Yes, that  
11 is true.

12 Also, nobody's touched on yet what type of a  
13 prospective clinical study do you think could be  
14 done?

15 MR. ROLLEY: My comments on a retrospective,  
16 it's a bit difficult because your products aren't  
17 on the market yet to really have data to go back  
18 through. Prospectively, I think if anything came  
19 out of the last couple of days, it is the  
20 complexities of these wounds. And with all the  
21 underlying conditions, the comorbidities, the  
22 wounds that Dr. Fife just showed, those are really



1       difficult -- as Amy was saying -- to have total  
2       wound closure as your only endpoint. You have to  
3       look at other endpoints besides that, the  
4       trajectory of healing.

5               Some of the things we talked about earlier  
6       today in terms of some of the patient-reported  
7       benefits, pain is particularly one. There are  
8       other endpoints you have, and a pressure ulcer  
9       patient, for example, is terminal. The chances of  
10      you ever healing somebody like that is slim to  
11      none. So would they be in your study? Well, maybe  
12      not necessarily. But pressure ulcer patients in  
13      particular pose a real difficulty because of the  
14      state that they may be in, in terms of end of life,  
15      so we have to be open-minded about that.

16             I think, though, again, from CMS'  
17      perspective, most of the devices and most of the  
18      products on the market are 510(k). So when we talk  
19      about clinical evidence, we're really talking about  
20      PMA products that really have to require the data,  
21      the studies to be done, because these products are  
22      510(k), and they're going into generic HCPC codes.

1 Oftentimes, they're policies that aren't really  
2 issued. They're not SCDs; they're all LCDs, for  
3 the most part.

4 So from a company perspective, the risk of  
5 doing the study sometimes is higher, and if I don't  
6 have to do it, I'm not going to do it. But --

7 DR. FIFE: I also just wanted to say -- and  
8 I'm sorry. I didn't mean to cut you off, Joe. But  
9 there are some things that matter in terms of cost  
10 like rehospitalization rates, also free days.  
11 Those are things that that I think really do  
12 matter, and they certainly track a cost. Even  
13 though most of our costs are outpatient  
14 hospitalization, it's an expensive thing we'd like  
15 to avoid for many reasons.

16 But I think we say that CMS doesn't look at  
17 cost in determining coverage policy, but nobody  
18 believes that CMS doesn't look at cost in creating  
19 LCDs or NCDs. We feel it because they read like  
20 things that are designed to control utilization,  
21 maybe abuse, although we never know exactly what  
22 the data behind it are. So maybe it's time for us

1 to talk about cost in a more open way, as a way to  
2 measure whether something's working.

3 I used to feel uncomfortable with the idea  
4 that cost was a surrogate for whether something  
5 worked, but I have reconsidered that position. If  
6 stuff really works, it ought to decrease the cost  
7 of health Care.

8 DR. FINK: Thank you very much. That's very  
9 interesting. I can see if Dr. Rollins wants to  
10 speak more on the coverage side, that might be  
11 difficult since CMS does not have statutory  
12 authority to do that.

13 I also appreciated, Mr. Rolley, that that  
14 was an interesting statement that you had, where  
15 basically FDA, 510(k), you're looking at  
16 substantially equivalent, where CMS has different  
17 statutory authority; again, you're looking at  
18 reasonable and necessary for the Medicare  
19 beneficiary population, which means that you have  
20 two agencies that might be looking at different  
21 things.

22 Alright. Number two, my second question, is

1 when companies produce products, what endpoints and  
2 what type of clinical studies, if any, are  
3 companies doing in order to decide what to release  
4 to the market?

5 MR. OLMSTEAD: Rochelle, I'll take that.  
6 Mark Olmstead with Smith & Nephew.

7 Really, when you look at industry, it  
8 depends upon what product or solution that we're  
9 looking at. So dependent upon the outcomes  
10 necessary, it might be an RCT or it might even be  
11 real-world evidence like we were talking about  
12 earlier today. It all depends upon what are the  
13 outcomes that we're looking for and what can we  
14 provide that would actually have the best outcomes  
15 that we can actually show in regards to the healing  
16 of the wound or the change of the wound in size or  
17 depth.

18 So that's an area that definitely Smith &  
19 Nephew works very closely with many stakeholders to  
20 try to do the right evidence for the right types of  
21 solutions, and it's all dependent upon those  
22 solutions; so many different things that we

1 actually utilize for our evidence, including  
2 real-world evidence and registries.

3 DR. FINK: No, I appreciate that. And just  
4 to keep putting you on the spot, the clinical  
5 evidence that you generate, whatever it is, do you  
6 end up publishing it, or putting it in  
7 peer-reviewed journals so that others can see it,  
8 or is that more kept within the company?

9 MR. OLMSTEAD: Yes. So it all depends upon  
10 what it is that you're actually trying to show as  
11 an endpoint. Sometimes there isn't enough patients  
12 to actually produce an outcome, so that you don't  
13 have that evidence to be published. But oftentimes  
14 it will be, and then you decide which journal you  
15 might put it in, as an example, or what  
16 publication, or even what entity you might share it  
17 with.

18 So it's all just really important to  
19 determine what is it that you're trying to solve  
20 for, and then do you have the number of patient  
21 lives and the right specific types of patients that  
22 you're trying to solve for in your outcomes, and

1       whether or not that is something that is even  
2       publishable. So it's sometimes also dependent upon  
3       the agency that you're sending in the information  
4       to.

5               MS. LAW: I would just like to comment on  
6       the prospective registry idea. We are just getting  
7       into that area, so that's fairly new.  
8       Historically, it's always been RCT, but I think  
9       some of the comments that we heard from Dr. Fife  
10      and others yesterday, to the extent that  
11      CMS/Medicare could standardize some of the  
12      out-of-hospital documentation, whether it's  
13      incentivizing, might be an option that Dr. Fife had  
14      for the quality measures.

15              To the extent we can have more consistent  
16      data or a risk stratification score that we could  
17      use, such as WHI that would have individuals put in  
18      age of wound at the beginning of treatment, that  
19      type of data could really help us build more  
20      powerful evidence. And it might make it a little  
21      easier and less expensive in the registry, in the  
22      prospective registry, because obviously there's so

1 much data we want to capture, but helping with  
2 those shortcuts might be a way to make that a  
3 little bit less cumbersome for industry.

4 DR. FINK: Thank you. I appreciate it.

5 Dr. Rollins, do you have anything to add to  
6 the discussion?

7 DR. ROLLINS: Yes. Actually, I had myself  
8 on mute.

9 I agree. The CED, coverage with evidence  
10 development, I think was an excellent tool that can  
11 be used, and has been used, to get additional  
12 information to help to prove that a particular  
13 technology is reasonable and necessary for the  
14 Medicare population.

15 Prior to the initiation of CEDs, I think  
16 that new companies with new products, when they  
17 approached CMS, there was probably a 50/50 approval  
18 rate and denial rate. But with CEDs, the number of  
19 outright denials have plummeted because, now, even  
20 though they did not meet the standard definition of  
21 reasonable and necessary, the information was  
22 promising, and that allowed for more research to

1 take place.

2 Now in terms of the protocols, the protocols  
3 that were submitted to CMS were developed by the  
4 vendors, as well as the researchers. We worked  
5 with vendors who had the protocols and gave them  
6 specific information in terms of what we considered  
7 important in terms of reasonable and necessary from  
8 the patient's perspective; not necessarily from the  
9 researcher's perspective, but from the patient's  
10 perspective. And the endpoints that we looked at  
11 were complete wound healing, as well as reduction  
12 in wound size, wound trajectory. But we also  
13 coupled it with improved quality of life,  
14 resumption of normal activities.

15 I think that the 15 endpoints that  
16 Dr. Driver mentioned earlier today, I think those  
17 are excellent endpoints to look at. Had they been  
18 incorporated in the protocols that we reviewed and  
19 approved, I think that would make the study much  
20 more meaningful. We did approve, as I said, a  
21 national coverage for non-healing diabetic wounds,  
22 but as I said, perhaps if some of those other 15



1 endpoints were included in protocols, we possibly  
2 could have nationally covered non-healing venous as  
3 well as pressure wounds. We did not, but we left  
4 that up to contractor discretion. But as I said,  
5 with other endpoints, that definitely would have  
6 helped to tip CMS into perhaps national coverage of  
7 those other two, besides the ones for diabetes.

8 DR. FINK: Thank you. That's very helpful.

9 Dr. Rollins, I have a follow-up question for  
10 you, and that is real-world evidence. There's been  
11 a lot of discussion about real-world evidence, and  
12 there might be the thought that the information  
13 submitted to CMS is only real-world evidence.

14 Do you believe that all real-world evidence  
15 could justify a policy decision, and if not, what  
16 along with real-world evidence would be helpful?

17 DR. ROLLINS: Well, there was a lot of  
18 discussion this morning about real-world evidence,  
19 and as one of the speakers said, there's pros and  
20 cons.

21 I look at real-world data and I look at  
22 real-world evidence, and I think that it's sort of

1     like in business, they use the term, "I'm drowning  
2     in data, but I'm starving, looking for  
3     information," especially useful information. And  
4     hopefully, over time, real-world data will  
5     transition into real-world evidence.

6             Currently, CMS, we do use real-world  
7     evidence in the sense that we have two cardiac  
8     NCDs. One uses registry data, the second one uses  
9     administrative data. So CMS is open to the idea of  
10    using real-world evidence, but as I said, over  
11    time, hopefully real-world data will evolve into  
12    real-world evidence, which we can use to help us in  
13    terms of our coverage policies for other topics.

14            I'm currently not aware of any NCD that  
15    specifically addresses wounds or wound healing in  
16    terms of using real-world evidence in making a  
17    decision.

18            DR. FINK: This is interesting, and I have  
19    to say, one of the things is I was happy to  
20    moderate this panel, as before COVID, I did a talk  
21    once, and one of the things I really enjoyed about  
22    it -- there were a number of podiatrists

1       there -- is that nobody was afraid to say what was  
2       on their mind. So it was actually a whole lot of  
3       fun, and I thought it was super helpful.

4               So that's why I'm hoping we can have the  
5       same spirit here. And let's hear; what does  
6       everybody think of what Dr. Rollins just said?

7               DR. FIFE: I am accused all the time of not  
8       being able to keep from speaking my mind. The one  
9       comment I'd make about coverage with evidence,  
10      which was an exciting opportunity, is that it was  
11      challenging because you had to run it like a  
12      clinical trial and bill it like you'd bill anything  
13      else. It's not an easy thing from the standpoint  
14      of the clinician. It hurts. The fact that you  
15      have now created a system that requires both things  
16      for research and for clinical use is very  
17      difficult, but it's exciting to think that there's  
18      a window.

19              The other thing that I think is important is  
20      I focused for years on trying to leverage stuff  
21      that clinicians have to do to things you need to  
22      know. So whenever you tie something to payments or

1     you tie something to quality, assuming they have to  
2     report it, you can end up with data that you might  
3     be able to rely on.

4             The cardiologists have been successful, in  
5     part, because they have really expensive devices.  
6     They get paid well enough that they can be really  
7     focused on their registry. It's a little tougher  
8     in wound care, where it's very hard to do a  
9     registry for something you get \$4 dollars for, so I  
10    think that disconnect is problematic. But it is  
11    exciting to think that there's a new opportunity.  
12    I do think we need to make it easier.

13            MS. LAW: It's really exciting. The CED, it  
14    is incredibly hard. There are other things that  
15    Medicare has in place, like consolidated billing  
16    that make it difficult for us to do registries  
17    around some of these lower levels, but still  
18    important products that are used for patients in  
19    home health, as well as in the wound care clinic,  
20    because the incentives are not always aligned to  
21    have the study performed. So that's just one  
22    thing.

1           I am curious if CMS will use real-world  
2 data. I think one of its biggest values could also  
3 be in reconsiderations for LCDs. We've been  
4 understandably wary to reconsider some of the LCDs,  
5 but I think the real-world evidence to see how  
6 things are actually being used could help us  
7 improve some of our policies.

8           I think one of the things is, as a  
9 manufacturer, we're reluctant to do multiple  
10 clinical studies on different wound types. That's  
11 just so expensive. We talked about the duration.  
12 Our last RCT for negative pressure took us  
13 8 and a half years, and that was on one wound type,  
14 so we really can't be thinking about multiple wound  
15 types. So knowing that there is a way to get LCDs  
16 or NCDs revisited using real-world evidence would  
17 be incredibly valuable, for the patients, I  
18 believe.

19           MR. FERROS: Rochelle, if I can comment,  
20 too, my background is mostly dealing with FDA, FDA  
21 policy and such, and I actually applaud FDA for, I  
22 think, taking the lead on real-world evidence.

1 You've published quite a few, a number of guidance  
2 documents to help industry in the use of real-world  
3 data, and thus real-world evidence.

4 I think what's important is for all  
5 government agencies and all of us to be advocates  
6 of real-world evidence. It's powerful. It's  
7 powerful data; it's powerful information. I know  
8 that the gold standard has been for many  
9 years -- just traditionally, the gold standard has  
10 been RCT, and that's fine.

11 We all understand the power of that. But  
12 real-world evidence is also powerful. It shouldn't  
13 be looked at as inferior, but I think it should be  
14 looked at as different. It has certain advantages  
15 to it, and the advantages of real-world evidence  
16 are things like generalizability and the fact that  
17 we've probably got a much wider geography, and the  
18 fact that you have typically long-term types of  
19 studies relative to the shorter-term RCTs. All  
20 these are positives that shouldn't be discounted.

21 So I applaud a FDA, and I think we should  
22 probably all be on that same boat of looking at

1 real-world evidence and seeing how it can be used.

2 (Crosstalk.)

3 DR. FINK: And I appreciate that  
4 statement --

5 DR. FIFE: And there are ways that payers  
6 can incentivize us --

7 DR. FINK: Caroline, I'm going to cut you  
8 off.

9 If I can just say, though -- and this is  
10 just from my novice personal thought -- we're sort  
11 of on two ends. How can there be both real-world  
12 evidence and clinical data that could work for the  
13 Wound Healing Association, or the wound healing  
14 companies, I should say?

15 DR. ROLLINS: If I can make a quick comment,  
16 as I said, we use an evidence-based medicine  
17 approach when we write our policies. Basically, at  
18 the top of the hierarchy of evidence, we use  
19 meta-analysis, as well as systematic reviews of  
20 randomized clinical trials. At the very bottom of  
21 that spectrum you've got single case reports.

22 It would be interesting if through that

1 continuum of different types of research design,  
2 there could be some type of correlation between any  
3 of those components and this real-world evidence.  
4 And it's possible that maybe real-world evidence  
5 could be equivalent to some type of cohort study in  
6 terms of the evidence development, or perhaps it  
7 could be at an equivalent level of crossover study,  
8 or something like that.

9 So even though the policies are currently  
10 driven using evidence-based medicine, it's possible  
11 that in the future, as I said, with the use of  
12 real-world evidence, it can supplement what we  
13 currently have. Whether or not it would act as a  
14 substitute, I don't know, but as I say, currently  
15 our focus is using evidence-based medicine.

16 MR. ROLLEY: From my perspective, I would  
17 agree that I'm not sure the RCT is going to go  
18 away, especially for approval, but I can see where  
19 real-world evidence would be useful as an adjunct  
20 to build the body of knowledge, the body of  
21 evidence; perhaps to expand indications beyond what  
22 your current labeling is.



1           I think it might have been said earlier that  
2 a lot of times you're getting approval for just  
3 diabetic foot ulcers, and then will have to do an  
4 entire new study just for a venous leg ulcer or for  
5 a pressure ulcer. As we've heard, and Dr. Fife  
6 will say, these are artificial categories to begin  
7 with. So leveraging real-world evidence to say,  
8 look, if it's working well in the original RCT with  
9 a DFU, and we've got good results and other  
10 indications, why not expand the indication? I  
11 don't see it replacing RCT anytime soon.

12           DR. FIFE: And let's not forget safety.  
13 That's a great opportunity for real-world data.  
14 Safety is so important, and we forget about it.

15           The other thing I was going to say is there  
16 are ways that payers can incentivize better data  
17 collection. Right now, you can do a good job with  
18 data or a bad job with data; you get paid the same,  
19 but it doesn't have to be that way.

20           DR. FINK: That's actually, if I can say, a  
21 very good point.

22           I have another question, though. I know we

1 keep going to RCTs, and we keep saying whenever we  
2 talk about clinical trials, it seems there's been  
3 discussion of RCTs. But I was wondering, is there  
4 any sort of clinical trial that isn't an RCT?  
5 Because I have to say through my experience at  
6 Medicare, we sat around in a room, and I'd say,  
7 "Yes, RCT is the gold standard, but it's not  
8 practical," and at least in my personal opinion it  
9 seems that Medicare understands that.

10 So what would be practical, do you think?

11 DR. FIFE: I'll dive into something. We  
12 designed a trial that wasn't carried out. The  
13 sponsor decided against it. But the trial was to  
14 have the patients consent for the active agent, and  
15 then on the back end we used the Wound Healing  
16 Index to create matched cohorts. And then the  
17 prospective arm, only the patients getting the  
18 treatment had to be consented; you didn't have to  
19 consent patients who weren't going to get  
20 treatment, who were just going to get standard of  
21 care, and then we could make sure that we had  
22 enough patients that were matched as a cohort.

1           I really think that that kind of operational  
2 design has a lot of potential, and we have the  
3 ability to do it right now if we just have the  
4 courage to step forward in that direction.

5           MR. OLMSTEAD: I believe there might be an  
6 opportunity to work with CMMI for a public-private  
7 partnership to kind of think about some of these  
8 different things that we're talking about today,  
9 and yesterday. It's just an opportunity to say  
10 we've done it a certain way before, but we know  
11 during COVID, we've come together in a completely  
12 different way, and have been able to solve a lot of  
13 big problems together.

14           So I'm just wondering if it's an opportunity  
15 for us to consider maybe looking at a different  
16 payment model that might come out of CMMI, where  
17 industry and government together could work on  
18 something that would make sense for the right  
19 patient and the right specific area that we're  
20 looking for in a clinical evidence, and a health  
21 economic evidence as well.

22           DR. FIFE: That could include quality

1 measures.

2 DR. FINK: Dr. Rollins, what do you think of  
3 that? I know you're in CCSQ, not CMMI, but what  
4 are your thoughts on that?

5 DR. ROLLINS: I think that's a good idea,  
6 specifically because a CMMI would set up  
7 specifically for that purpose, looking at different  
8 types of payment models for different types of  
9 situations. Now, I know for a fact that CMMI has  
10 been successful in putting in those types of  
11 activities. So as I said, I think it's something  
12 worth pursuing.

13 MS. LAW: I love that idea because as  
14 manufacturers, we are sometimes disincentivized to  
15 come up with products that require fewer treatments  
16 because we know they're going to fit into a code.  
17 We know what the payment is. We can't invest in  
18 it, although we know it would help the patient from  
19 going into the wound clinic each week.

20 So there are a lot of barriers where I think  
21 CMMI -- I was very excited when it first  
22 launched -- was really just the opportunity to look

1 at a total cost to treat and a longer duration, and  
2 really allow more flexibility, and as I said  
3 before, multiple treatment modalities, not just  
4 one, in sort of a safe environment to really  
5 look -- we have many hypotheses that we don't  
6 pursue because of the disincentives in payment, so  
7 I love that idea.

8 MS. NUSGART: Something else to think about,  
9 too -- a little bit different on the subject -- is  
10 that Dr. Rollins represents CMS that really deals  
11 with more the national coverage decision, but for  
12 so many of the wound care products, they really are  
13 governed under the LCDs that have the medical  
14 directors that are on the local level.

15 So it would be interesting to be able to  
16 understand the A/B MACs and the DME MACs in terms  
17 of how they view evidence, and hopefully they take  
18 their lead from Dr. Rollins and those at the CMS  
19 office in Baltimore, but many times -- I just was  
20 speaking earlier today at a public meeting for  
21 Novitas and First Coast, and many times some of  
22 these policies, and these LCDs, and the draft ones

1 aren't necessarily based on the evidence.

2 So it was something to be able to think  
3 about. It's a little bit different ringer than  
4 what we're talking about, Dr. Fink, but again,  
5 recognizing that the technologies right now that  
6 govern wound care are more on the local coverage  
7 area rather than the national coverage decisions.

8 DR. FINK: And I appreciate that. That was  
9 a very helpful comment. I just want to clarify one  
10 thing that, then I will turn it to Dr. Rollins to  
11 see what he says. But the national level does not  
12 direct the local level. The local level, they are  
13 independent.

14 MS. NUSGART: Absolutely.

15 DR. FINK: Yes. I just wanted to clarify  
16 that.

17 Dr. Rollins?

18 DR. ROLLINS: Yes, that is true. There are  
19 national coverage determinations and there are  
20 local coverage determinations. But when it comes  
21 to reviewing evidence, evidence is evidence, and I  
22 would hope that a reviewer would use the same

1 principles that other reviewers would use.

2 Now, as I said on the previous slide, one  
3 reason why a NCD might be initiated is because of  
4 discrepancies or multiple inconsistencies amongst  
5 LCDs. So if that's a situation that exists, the  
6 CMS would hopefully intervene to try to make sure  
7 that we're all on the same side in terms of what  
8 the evidence shows.

9 DR. FINK: Well, thank you very much. I  
10 don't know if we get to keep going or not. I've  
11 had fun on this panel. I hope that the rest of you  
12 have, too. I think the benefit of this panel is it  
13 seems, first of all, people are willing to have  
14 direct discussions so that everybody knows where  
15 the other one stands, and also, there were some  
16 really, really good ideas. We talked about CMMI;  
17 and we talked about clinical trials; the use of  
18 real-world evidence; whether costs could come in.  
19 Maybe it doesn't come into a coverage decision, but  
20 then we brought up CMMI.

21 So I want to really thank everybody on this  
22 panel, and thank you for asking me to moderate.

1 (Chorus of thank yous.)

2 DR. VERMA: Thank you, everyone, for a very  
3 lively and productive panel, and also a great  
4 two-day workshop. We'll now be hearing closing  
5 remarks from our division director of the Division  
6 of Dermatology and Dentistry, Dr. Kendall Marcus.

7 **FDA Closing Remarks - Kendall Marcus**

8 DR. MARCUS: Thanks, Dev.

9 Over the last two days, we've heard from FDA  
10 representatives, translational researchers,  
11 patients, academia, physicians, NIH, CMS, and  
12 industry. We've heard from FDA center  
13 representatives about the regulatory considerations  
14 that go into the review of products for the  
15 treatment of non-healing chronic wounds, with an  
16 emphasis that stakeholders should engage with the  
17 agency early in development for feedback.

18 We've heard the significant burden  
19 non-healing chronic wounds may have on many aspects  
20 of patients' lives; the complex pathophysiology of  
21 wound healing; possible therapeutic targets; the  
22 possible utility of patient registries and



1 real-world evidence; the importance of clinical  
2 outcome assessments that are context relevant for  
3 patients; a perspective from CMS on how coverage is  
4 determined; and challenges faced by industry in  
5 bringing products to market.

6 This workshop has been very helpful in  
7 gathering stakeholders together and having open  
8 dialogue, and I'm sure the work will continue well  
9 beyond this workshop.

10 Going forward, FDA will continue to interact  
11 with stakeholders to help ensure safe and effective  
12 products are available to patients with non-healing  
13 chronic wounds. We will summarize the lessons  
14 learned from this two-day workshop in a publicly  
15 available summary report. In the meantime, we  
16 encourage stakeholders to continue to submit  
17 comments to the public docket at the Federal  
18 Register, which is open until June 28th. The link  
19 for this is in the chatbox.

20 Thank you to all the speakers, panelists,  
21 patients, and organizers who have helped make this  
22 workshop a success. This concludes our 2022 Wound

1 Healing Scientific Workshop. Thank you.

2 (Whereupon, at 3:25 p.m., the meeting was  
3 adjourned.)

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