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U.S. FOOD AND DRUG ADMINISTRATION

Wound Healing Workshop

Virtual Workshop Via Zoom

Day 1

Thursday, April 28, 2022

9:00 a.m. to 3:30 p.m.

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3 Medical Officer, CDRH, FDA

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P R O C E E D I N G S

(9:00 a.m.)

Opening Remarks - Kendall Marcus

DR. MARCUS: Good morning. I'm Dr. Kendall Marcus, director of the Division of Dermatology and Dentistry in the Office of New Drugs in the Center for Drug Evaluation and Research at FDA. It's a pleasure to welcome you to our FDA Wound Healing Scientific Workshop. What we will be discussing over the next two days are not straightforward scrapes, cuts, or abrasions, but non-healing chronic wounds, which are often complex in their pathophysiology, management, and treatment.

On an individual level from a patient perspective, non-healing chronic wounds, like many conditions that affect the largest organ of the body, are not just skin deep. They can be painful, burdensome to take care of for both patients and their caregivers, and in some cases even limb and life-threatening. We are fortunate to be hearing directly from patients later today.

On a broader level from a public health

1 perspective, non-healing chronic wounds present a
2 significant public health burden. Over 6 million
3 patients are affected annually in the U.S., and
4 billions are spent annually on treatment. The
5 segments of the population who are older or who
6 have obesity or diabetes, all at higher risks of
7 developing such wounds, are increasing.

8 The mission of FDA is to protect and promote
9 the public health, and given the significant public
10 health burden of non-healing chronic wounds, we
11 understand the importance of having safe and
12 effective treatments available to patients with
13 such wounds.

14 Despite the public health burden, the number
15 of innovative products aimed at the treatment of
16 non-healing chronic wounds is currently limited.
17 Although patients have access to dozens of skin
18 substitute products and hundreds of dressings that
19 allow for wound management so that the natural
20 healing process can take place, such products are
21 not intended for treatment. Currently, three
22 devices to cell-based therapies -- one biologic and

1 no small-molecule drugs -- have FDA marketing
2 approval for treatment of the non-healing chronic
3 wounds.

4 Patients are in need of more innovative
5 treatment options, and the reason we're having this
6 two-day workshop is to communicate current FDA
7 thinking, seek external input, and facilitate
8 discussions on the current barriers to innovative
9 product development.

10 The barriers to innovative product
11 development for non-healing chronic wounds may
12 include a dearth of preclinical models that can
13 mimic human non-healing chronic wounds: challenges
14 with drug delivery; challenges with clinical trial
15 execution; and complex reimbursement
16 considerations. Given the complexity of non-
17 healing chronic wounds and the multiple possible
18 barriers to innovative product development, over
19 the next two days we will be hearing from a variety
20 of thoughtful speakers and panelists.

21 The FDA may regulate a wound care product as
22 a drug, device, biologic, or a combination product,

1 which is important because the way a product is
2 regulated will typically affect the center at FDA
3 that takes the lead on the product.

4 Generally, drugs are reviewed in the Center
5 for Drug Evaluation and Research, devices are
6 reviewed in the Center for Devices and Radiological
7 Health, and biologic products are reviewed in the
8 Center for Biologics Evaluation and Research.
9 Combination products may be regulated in any of
10 these centers.

11 This morning, we'll be hearing directly from
12 FDA representatives from each of the three centers
13 to discuss each center's role in product
14 development and issues which may arise during
15 review and regulation of wound care products.
16 Later this morning, speakers and panelists will
17 help us understand the pathophysiology of
18 non-healing chronic wounds.

19 This afternoon, we will hear perspectives
20 from patients to help understand what changes in
21 signs or symptoms are clinically meaningful to
22 them. We'll learn about their experiences with

1 clinical trials and hear their thoughts on the
2 current approaches to treating non-healing chronic
3 wounds. This afternoon will conclude with a
4 discussion of clinical trial issues, industry
5 perspective, and a brief end-of-day question and
6 answer session.

7 Tomorrow morning, we will discuss current
8 areas of research in wound healing and how current
9 research may be applied for innovative product
10 development. Later in the morning, we will discuss
11 possible solutions to overcoming challenges
12 identified on Day 1, to implementation of
13 successful clinical trials. In the afternoon, we
14 will discuss clinical trial endpoints and clinical
15 outcome assessments, and we will conclude our
16 workshop with a CMS and industry perspective
17 session.

18 We have an ambitious agenda and a tremendous
19 diversity of attendees participating in this
20 workshop: FDA; patients; academia; translational
21 researchers; industry; CMS; and representatives
22 from the Wound Care Collaborative Community and the

1 Alliance of Wound Care Stakeholders.

2 I look forward to a productive workshop with
3 informative talks and insightful panel discussions,
4 so that ultimately patients may benefit by having
5 access to safe and effective treatments. Thank
6 you.

7 **Presentation - Dev Verma**

8 DR. VERMA: Good morning. My name is Dev
9 Verma. I'm a plastic surgeon and medical officer,
10 and clinical reviewer in the Division of
11 Dermatology and Dentistry in the office of New
12 Drugs, Center for Drug Evaluation and Research at
13 FDA. This morning, I'll be providing an
14 introductory overview to FDA identified barriers
15 for product development for non-healing chronic
16 wounds.

17 I will briefly summarize the public health
18 burden of non-healing chronic wounds and the lack
19 of innovative effective products available to
20 patients; discuss FDA identified barriers that may
21 be impeding innovative product development; and
22 discuss FDA efforts to address these barriers.

1 Regarding the public health burden of
2 non-healing chronic wounds, the public health
3 burden of non-healing chronic wounds is
4 significant, both globally and in the United
5 States. Since FDA's mission is to protect and
6 promote public health of Americans, this is a
7 disease area FDA is acutely aware of and interested
8 in.

9 For the purposes of this talk and from a
10 regulatory perspective, non-healing chronic wounds,
11 also referred to as chronic cutaneous ulcers, are
12 defined as those that have failed to proceed
13 through an orderly and timely series of events to
14 produce a durable, structural, functional, and
15 cosmetic closure. These include pressure-related
16 ulcers; diabetic foot ulcers; venous and arterial
17 ulcers, but may also include other wounds that do
18 not neatly fit into these categories, including,
19 but not limited to, chronic post-surgical wounds;
20 chronic wounds secondary to genetic disorders of
21 the skin such as epidermolysis bullosa; chronic
22 wounds secondary to underlying inflammatory and

1 autoimmune mediated condition such as pyoderma
2 gangrenosum; and chronic wounds secondary to
3 vasculitis.

4 A large number of patients are affected
5 annually by non-healing chronic wounds in the U.S.
6 A large amount is spent on treatment, and given the
7 rising rates of obesity, diabetes, and the aging
8 population, the public health burden is expected to
9 increase.

10 Despite the public health burden, innovative
11 products aimed at the treatment of non-healing
12 chronic wounds are currently lacking. Greater than
13 800 products, including wound dressings, are
14 cleared by FDA for the management of wounds so that
15 the natural healing process can take place. Human
16 cells, tissues, and cellular- and tissue-based
17 products are also available, however, these
18 products are not intended for treatment.

19 FDA representatives from CDER, CBER, and
20 CDRH will be speaking after me this morning in more
21 detail, but on a high level, there are no approved
22 small-molecule drugs for the treatment of

1 non-healing chronic wound subtype. A single
2 biologic, which is a recombinant human
3 platelet-derived growth factor, received FDA
4 approval in 1997 for the treatment of a non-healing
5 chronic wound subtype. Only two moderately
6 effective cell-based therapies and three devices
7 have FDA marketing authorization for the treatment
8 of the non-healing chronic wound subtype.

9 Clearly, the public health burden of
10 non-healing chronic wounds does not align with the
11 number of treatments with FDA marketing
12 authorization. The number of patients affected is
13 high, the cost of care is high, and the number of
14 invested stakeholders is high. Yet there are zero
15 small-molecule drugs, only one biologic, two
16 cell-based therapies, and three devices authorized
17 for treatment.

18 The question then arises, why is there a
19 lack of innovative effective treatments for chronic
20 wounds? The most obvious broad answer points
21 initially to the complexity of wounds, the
22 stakeholders involved, and of the FDA itself.

1 Chronic wounds have varying etiologies with
2 cellular complexity. There are varying standards
3 of care, and wound care requires comprehensive
4 wound management, including appropriate control of
5 complicating factors such as unrelieved pressure;
6 infection; vascular issues; uncontrolled metabolic
7 derangement; and nutritional deficiency, in
8 addition to appropriate debridement when necessary.

9 There are multiple stakeholders invested in
10 the space, each often with varying interests, and
11 FDA itself with its multiple centers, associated
12 regulations, guidance documents, and multiple
13 pathways for clearance, approval, and
14 authorization, may be perceived as complex.
15 Therefore, rather than focusing on broad
16 complexities, in an effort to identify specific
17 barriers to innovative product development for
18 non-human chronic wounds, FDA engaged in an
19 internal science strategies program.

20 From 2020 to 2021, the Division of
21 Dermatology and Dentistry, through this internal
22 science strategies program launched by the Office

1 of New Drugs, collaborated with experts from CBER,
2 CDRH, and OND's Division of Clinical Outcome
3 Assessment to assess areas of unmet need and
4 activity in the product development pipeline for
5 wound healing.

6 OND's science strategies program develops
7 tools and resources to systematically assess the
8 drug development landscape by therapeutic area to
9 identify barriers for drug development in areas of
10 unmet patient needs. Due to high unmet need with
11 relatively limited research and funding,
12 non-healing chronic wounds was identified as an
13 area of priority.

14 Through the OND science strategies group,
15 the specific FDA identified barriers to innovative
16 product development for non-healing chronic wounds
17 are outlined here. Regarding a dearth of
18 biological models, though a tremendous body of
19 basic science research on wound healing exists, the
20 pathophysiology remains complex, and chronic wounds
21 are uncommon in animals and challenging to
22 simulate. A lack of optimal preclinical models

1 that are capable of properly recapitulating human
2 wounds remains a significant translational
3 challenge.

4 Regarding challenges in drug delivery, the
5 hostility of the wound environment presents unique
6 complexities such as degradative enzymes, bacterial
7 infection, and a critical role played by
8 inflammatory cells, which are obstacles to
9 developing therapeutics which maintain efficacy in
10 such a hostile environment.

11 Challenges in clinical trial-related issues
12 and execution are discussed in the next slide and
13 will also be expanded on during a session tomorrow.
14 And regarding reimbursement and commercial
15 viability, reimbursement for wound care is highly
16 complex and dependent on a multitude of factors
17 which may impede patient access to products and
18 discourage sponsors from innovative wound care
19 product investment and development.

20 Of these identified barriers, challenges in
21 clinical trial-related issues and execution are
22 barriers which FDA is most likely able to impact.

1 Such challenges include, but are not limited to,
2 difficulties with subject enrollment; heterogeneous
3 study designs with varying standard of care
4 protocols and study populations often
5 non-representative of real-world patients; and
6 difficulty achieving the most commonly utilized
7 primary efficacy endpoint of complete wound.
8 healing.

9 Given the FDA identified barriers to
10 innovative product development for non-human
11 chronic wounds and recognizing the high public
12 health burden, we are undertaking efforts to help
13 address these barriers going forward. Over the
14 next few days, we will be discussing these barriers
15 and what FDA can help impact, and what external
16 stakeholders can help impact, including discussion
17 of barriers that have not been identified here.
18 The workshop is being transcribed and will be made
19 publicly available, including a summary report.

20 In addition to this workshop, FDA will
21 continue to interact with key wound healing
22 stakeholders, including the Wound Care

1 Collaborative Community, many of whom are
2 participating in this workshop as speakers and
3 panelists. Hearing directly from patients is
4 important in helping FDA understand what is
5 clinically meaningful to patients, and later this
6 morning we are fortunate to be hearing directly
7 from patients.

8 Future patient-focused drug development
9 meetings and/or dedicated patient listening
10 sessions are likely to also be helpful in
11 determining what outcomes are clinically meaningful
12 to patients and what products they would like to
13 see on the market.

14 Education on the purpose of guidance
15 documents is vital. Later this morning, we'll have
16 a presentation discussing the 2006 guidance on
17 non-healing chronic wounds, which reminds
18 stakeholders the guidance documents are a set of
19 recommendations and that stakeholders can propose
20 alternate approaches to FDA for feedback.

21 Encouraging data sharing across stakeholders
22 is also important, as sharing knowledge amongst

1 industry, academia, translational researchers, CMS,
2 and other key stakeholders will help foster
3 innovation. And finally, soliciting public
4 comments via the Federal Register is an important
5 way in which FDA can hear directly from the public.

6 Over the next few days, we'll be hearing
7 from a variety of stakeholders, speakers, and
8 panelists, but we realize we may not be able to
9 address all issues or hear all perspectives.
10 Therefore, we would like to hear from as many
11 stakeholders as possible and have a request for
12 specific public comments in the Federal Register
13 notice associated with this workshop.

14 We encourage patients or caregivers of an
15 individual with a non-healing chronic wound,
16 healthcare providers, product developers, industry,
17 researchers, and those involved in the
18 reimbursement landscape to access the Federal
19 Register notice, read Section 3 which outlines
20 specific comments we are seeking, and then click
21 the green "submit a formal comment button" to
22 submit their comments. Outlined here are steps you

1 may take to access the Federal Register notice and
2 submit comments regarding this workshop, with
3 comments open until June 28th 2022.

4 I'm optimistic that with an open dialogue
5 and persistence -- [inaudible - together we can
6 bring into balance the discrepancy between the high
7 public health burden and low number of effective
8 treatments, and help ensure that patients have
9 access to safe and effective treatment options for
10 non-healing chronic wounds. Thank you.]

11 **Presentation - Gary Chiang**

12 DR. CHIANG: Good morning. My name is Gary
13 Chiang, and I'm an internist, and I serve as
14 medical officer and clinical reviewer in the
15 Division of Dermatology and Dentistry in the Center
16 for Drug Evaluation and Research at the FDA.

17 This morning I will be discussing CDER's
18 regulation of wound healing products, and I will
19 provide an overview of the drug development
20 process; discuss the benefit-risk assessments that
21 the FDA takes into consideration when making
22 regulatory decisions; discuss the types of wound

1 healing products regulated by CDER; and discuss
2 some developmental challenges that may arise.

3 This is a graphic of the drug development
4 process from the initial stages through the
5 postmarketing. The agency's role in safety review
6 typically begins with the submission of an
7 investigational new drug or IND. FDA's involvement
8 in the process is as early as possible. The
9 applicant may request a pre-IND meeting. The
10 agency generally remains involved throughout the
11 entire drug development process, and if approved,
12 safety review continues into postmarketing. Let's
13 go over some important aspects of drug development
14 for wound care products.

15 Product development is a stepwise process
16 involving an evaluation of both animal and human
17 efficacy and safety information. The goals of
18 nonclinical safety evaluation is key information to
19 estimating --

20 (Pause.)

21 DR. CHIANG: The goals of nonclinical safety
22 evaluations is key information to estimating an

1 initial safe dose and dose range for upcoming human
2 trials and to identify parameters for clinical
3 monitoring for potential adverse effects.

4 Building on the stepwise process, clinical
5 trials should be extended based on the
6 demonstration of adequate safety and previous
7 clinical trials. As long as clinical trials are
8 thoughtfully designed, reflect what developers know
9 about the product, safeguard participants, and
10 otherwise meet federal standards, FDA allows wide
11 flexibility in clinical trial designs.

12 Sponsors submit an investigational new drug,
13 and the division reviews the early protocol on a
14 30-day safety review and provides comments and
15 recommendations for study designs and endpoint
16 considerations. As the drug development process
17 proceeds, sponsors should get all the markers and
18 meeting requirements. The sponsors will make a
19 decision when they believe they're ready to submit
20 an application for marketing.

21 Products demonstrating a reasonable safety
22 profile may make it to an NDA, or new drug

1 application, or BLA, or a biologic license
2 application. We begin our review by assessing the
3 adequacy of the safety database. Is the size of
4 the population exposed to the study drug, and is
5 the duration of exposure adequate? Is there
6 appropriate use of pooled analysis? Is the
7 population sufficiently diverse to represent the
8 expected target population?

9 Hopefully, all these issues were fleshed out
10 in the presubmission meeting with the agency. The
11 review also includes a determination of adequacy of
12 the applicant's safety evaluations. Were all
13 reasonable applicable clinical evaluations
14 conducted to assess the safety of the drug?

15 The bulk of the pre-safety review involves
16 evaluating the data for important differences
17 between drug and comparator in order to assess the
18 likelihood of causality. For the majority of
19 products, the parameters shown here -- deaths,
20 adverse events, laboratory findings, vital signs,
21 cardiac testing -- are reviewed for causality.
22 Reviewers will base additional safety parameters

1 assessments based on nonclinical or mechanical
2 action, known drug class effects, or targeted
3 population. Submission-specific safety assessments
4 include tumor development such as immunomodulating
5 drugs, effects on reproduction, pregnancy, or
6 effects in pediatric [inaudible - audio lost].

7 (Pause.)

8 MR. TETLOW: One moment, everybody, while we
9 get Gary reconnected. Just a moment.

10 (Pause.)

11 MR. TETLOW: Gary, thanks for rejoining us.
12 Your slides are still up, and you should be able to
13 continue where we left off at.

14 DR. CHIANG: Okay. Let's go to slide 8.
15 Thank you.

16 The safety assessments often include an
17 evaluation of exposure-response by both intrinsic
18 and extrinsic factors. Intrinsic factors may
19 include drug-disease interactions, gender, age
20 race, and genetics. Extrinsic factors may include
21 drug interactions, diet, or pharmacodynamic drug
22 interactions. This benefit-risk assessment is the

1 basis of FDA's regulatory decision in the premarket
2 review. Reviewers rely on extensive evidence of
3 safety and effectiveness data provided by the
4 applicant. This assessment involves both
5 quantitative analysis and a subjective qualitative
6 weighing of the evidence.

7 Variations in clinical and scientific
8 judgments among FDA experts can lead to differing
9 individual opinions and conclusions regarding the
10 benefit-risk assessment. A regulatory action is
11 informed by deliberations with the entire review
12 team, supervisory staff, and may include
13 consideration of advisory committee
14 recommendations.

15 CDER regulatory territory of wound care
16 products includes small molecules, topical and
17 systemics, biologics, which are managed by both
18 CDER and CBER. While CBER regulates biologics such
19 as gene therapy, human tissue, blood and
20 plasma-derived products, CDER regulates DNA/RNAs,
21 immune modulators, proteins, and of course we can't
22 forget botanicals and combinations.

1 Despite this, the audience is aware that we
2 have a heavy public health burden, although we lack
3 innovative products, saying that treatment of
4 non-healing wounds are currently very lacking.
5 Despite the public health burden, only a single
6 biologic product, a recombinant human
7 platelet-derived growth factor, has received FDA
8 approval for the treatment of non-healing chronic
9 wounds, which was back in 1997, and there are
10 currently no approved small-molecule drugs.

11 In my review time here at the Division of
12 Dermatology and Dentistry, I've noticed the
13 following barriers to wound care product
14 development. In particular, sponsors face
15 development program challenges due to a lack of
16 nonclinical models or novel trial designs that make
17 determination of safety or efficacy more complex,
18 in addition to the challenge of having complete
19 wound closure as perceived to be the only
20 acceptable primary endpoint.

21 A lack of nonclinical models -- in
22 particular, botanicals -- may not have the required

1 nonclinical data for agency review. A guidance for
2 botanicals are available. In general, sponsors
3 should engage with the agency early in development
4 to obtain feedback about what nonclinical data is
5 necessary and what waivers may be obtained.

6 Regarding novel trial designs, the division
7 is open to working with sponsors on giving feedback
8 for novel trial designs with caveats that patient
9 safety is our priority. Sometimes novel trial
10 designs may not provide the data needed to ensure
11 safe and efficacious use of the drug product. In
12 particular, study designs in which subjects act as
13 their own control, crossover designs may be
14 discussed with the agency on a case-by-case basis
15 for feedback.

16 Certain designs may be acceptable
17 [inaudible - audio lost] --

18 MR. TETLOW: Alright. Please give us a
19 moment while we get Gary rejoined to the meeting.
20 Just a moment, please.

21 (Pause.)

22 DR. VERMA: Alright, everyone. Sorry for

1 the technical difficulties. I'll take over for
2 Gary's talk here. I think he's having some tech
3 issues. Gary was mentioning study designs.

4 In particular, study designs in which
5 subjects act as their own control, and crossover
6 designs, may be discussed with the agency on a
7 case-by-case basis for feedback. Certain study
8 designs may be acceptable earlier in product
9 development; for example, during proof-of-concept
10 trials to better understand the product.

11 Regarding endpoint development, the Division
12 of Dermatology and Dentistry currently recommends
13 complete wound closure as their most clinically
14 meaningful primary endpoint for the treatment of
15 non-healing chronic wounds. However, other
16 multicomponent endpoints such as debridements
17 coupled with reduction in pain, or decreased
18 dressing burden coupled with reduction in pain, may
19 be acceptable if such endpoints are validated as
20 being clinically meaningful and can be reliably
21 measured in clinical trials using validated tools.

22 If partial wound healing is studied, it

1 would also likely need to be part of a
2 multicomponent endpoint in order to be clinically
3 meaningful. In certain situations, it may be more
4 appropriate to use co-primary endpoints rather than
5 a multicomponent endpoint, and co-primary endpoints
6 would need to be robust. We encourage sponsors to
7 engage with the division early in product
8 development to discuss their proposed endpoints to
9 obtain feedback.

10 In conclusion, drug development is a
11 stepwise interactive process between the agency,
12 and stakeholders are reminded that we encourage
13 early communication with the agency in product
14 development to obtain feedback so that, ultimately,
15 patients have the best chances of having access to
16 safe and effective products.

17 That concludes the talk. Thanks so much,
18 and we can go on to the next one.

19 **Presentation - Allan Guan**

20 DR. GUAN: Good morning. My name is Allen
21 Guan, and I am a biomedical engineer in the Plastic
22 Surgery Skin and Wound Devices team at the FDA's

1 Center for Devices and Radiological Health. Today
2 I'll be presenting on the regulation of wound
3 dressing devices.

4 This presentation is divided into the
5 following topics, beginning with the general
6 categories of wound dressings, an overview of the
7 regulatory pathways for wound dressing devices, and
8 performance data considerations. I'll also go
9 through examples along the way to give you a
10 tangible sense of the types of products that fall
11 into the different regulatory pathways.

12 Wound dressings can be broadly classified
13 into three categories: solid dressings; gels,
14 creams, and ointments; and wound wash solutions.
15 This presentation will focus on the first two
16 categories, the solid wound dressings and the gels,
17 creams, and ointments. Please note that other
18 wound care devices such as negative pressure wound
19 therapy systems are outside the scope of this
20 presentation.

21 Solid wound dressings are composed of a base
22 material that could be synthetic, naturally

1 derived, biodegradable, or non-biodegradable, and
2 this base material provides structural strength in
3 the dressing, which allows it to function as a
4 scaffold or to be used in a single or multiple
5 layers.

6 Solid wound dressings are also commonly
7 combined with antimicrobial agents such as silver,
8 chlorhexidine, and PHMB, to inhibit the growth of
9 microorganisms within the dressing. Please note
10 that these antimicrobial agents are not intended to
11 act on the wound itself, but rather to protect the
12 device.

13 In contrast to solid wound dressings, gels,
14 creams, and ointments are amorphous and typically
15 have a high water content with thickeners to
16 enhance the viscosity to aid in application of the
17 product. These may also be in the form of
18 oil-in-water emulsions. Antimicrobials are also
19 commonly combined with these dressings to preserve
20 the product while on the shelf. Other chemicals
21 such as botanical extracts, honey, and skin
22 protectants may also be included in the

1 formulation. These products are typically packaged
2 in tubes or bottles and may be single or multiuse,
3 and may or may not be provided sterile.

4 How are these products regulated? FDA
5 regulates medical devices as class I, II, or III,
6 depending on their level of risk. Class I wound
7 dressing devices typically do not require premarket
8 review and do not contain drugs, biologics, or
9 animal-derived material

10 Class II medical devices utilize the 510(k)
11 pathway and are clear and based on establishing
12 substantial equivalence to a legally marketed
13 device. This is typically done according to
14 requirements that are set forth in special
15 controls. Novel medical devices for which there is
16 no appropriate existing regulation may be
17 classified into class I or class II through the
18 de novo pathway.

19 Class III devices utilize the PMA pathway
20 for approval. Wound dressing that fall under the
21 class III designation include those intended for
22 wound treatment to act as a skin substitute, or

1 those that are life-supporting or life-sustaining.
2 An exception to these three classifications are
3 wound dressings containing antimicrobials, drugs,
4 or other chemicals or animal-derived material,
5 which were on the market prior to the 1976 Medical
6 Device Amendments.

7 These are known as unclassified
8 pre-amendments devices, and they are currently
9 reviewed through the 510(k) pathway. These
10 dressings are intended for wound management, which
11 includes covering and protecting the wound,
12 absorbing exudate, and maintaining a moist wound
13 environment.

14 So now that we've established a high-level
15 overview of the different classes of wound
16 dressings, I'll spend the next slides describing
17 the different pathways through more detail and
18 provide some examples along the way.

19 We'll start with class I, which are
20 typically exempt from premarket review, and several
21 examples are shown here on the slide. Note that
22 all of these are intended for wound management that

1 are composed of non-resorbable material. They also
2 do not contain antimicrobials, drugs, chemicals,
3 biologics, or animal-derived material.

4 Now, let's move on to the premarket
5 notification. 510(k's) make up the largest share
6 of wound dressing submissions to CDRH. The purpose
7 of a 510(k) is to establish substantial equivalence
8 of a new device to a legally marketed device, known
9 as a predicate. Substantial equivalence is
10 determined by evaluating the intended use,
11 technological characteristics, and any applicable
12 performance testing. On the right-hand side of the
13 slide, I've included the 510(k) decision-making
14 flowchart, which you may find at the link at the
15 bottom of the slide.

16 The majority of wound dressings cleared
17 under the 510(k) pathway are currently
18 unclassified. A couple examples of unclassified
19 dressings that are reviewed through 510(k) are
20 wound dressings that do contain antimicrobials,
21 drugs, or other chemicals for wound management, and
22 these are under product code FRO, and extracellular

1 matrix dressings for wound management, which are
2 under product code KGN.

3 Next is the de novo process. This is a
4 mechanism by which novel medical devices for which
5 no appropriate regulation exists are classified
6 into class I or class II. A de novo is granted
7 when a sponsor can demonstrate reasonable assurance
8 of safety and effectiveness for the proposed
9 device. If the proposed device is classified as
10 class II, future devices of the same type will be
11 reviewed through the 510(k) pathway, where the
12 de novo may serve as a predicate.

13 Currently, there is only one category of
14 class II dressings, which are wound dressings with
15 DADMAC added to it, which was classified through
16 the de novo process. As of today, there's only one
17 dressing in this regulation, which is the NIMBUS
18 Barrier Gauze Dressing.

19 Lastly, class III devices, which constitute
20 the highest risk, are reviewed through the
21 premarket approval or PMA process. In contrast to
22 the comparative approach of the 510(k) pathway,

1 PMA's rely on an independent demonstration of the
2 safety and effectiveness of the product seeking
3 approval.

4 Like for de novo, sponsors must demonstrate
5 a reasonable assurance of safety and effectiveness,
6 and this is typically supported by clinical data.
7 In addition, PMA's have additional controls,
8 including post-approval requirements such as annual
9 reporting and stricter oversight of manufacturing
10 and design changes.

11 One example of a class III dressing is an
12 interactive wound and burn dressing. These
13 products are intended to actively promote the
14 healing of a wound or burn by physically
15 interacting with body tissues. The device is
16 intended to serve as a long-term skin substitute or
17 as temporary synthetic skin, and they may also be
18 intended to prepare a wound bed for autograft. One
19 dressing that falls under this category is the
20 Integra Dermal Regeneration Template.

21 Now that we've gone through the main review
22 pathways and some examples of wound dressings, I'll

1 use the next few slides to discuss some of the
2 testing that is done to support premarket
3 submissions for wound dressing devices.

4 Biocompatibility assessments play an
5 essential part in ensuring the safety of medical
6 devices. Regardless of classification, all medical
7 devices, including class I exempt, are expected to
8 be evaluated for biocompatibility. However, FDA
9 only reviews biocompatibility for medical devices
10 that are submitted through the 510(k), PMA, and
11 de novo pathways.

12 On this slide, I've highlighted the
13 biocompatibility endpoints, which are typically
14 needed for addressing wound dressing devices, and
15 you may find this table in Attachment A of our
16 biocompatibility guidance, which is linked at the
17 bottom of this slide.

18 In addition to biocompatibility, other bench
19 testing may be required to substantiate performance
20 claims. For example, solid wound dressings which
21 contain antimicrobial for the purposes of
22 inhibiting growth of microorganisms within the

1 dressing and to prevent penetration of organisms
2 through the dressing need to perform antimicrobial
3 effectiveness and barrier effectiveness testing.
4 Some dressings may contain animal-derived material
5 through which viral inactivation studies may be
6 needed to demonstrate products safety.

7 In addition to bench testing, animal testing
8 such as wound healing studies can provide important
9 information regarding the safety and performance of
10 a new wound dressing device. Generally, wound
11 dressings cleared under 510(k) do not require
12 animal study data, however, there are certain
13 situations where such information is needed.

14 The first is when the device is considered
15 cytotoxic according to ISO 10993.5, and this is
16 commonly seen in products containing antimicrobials
17 such as silver. In this scenario, an in vivo
18 evaluation is needed to determine whether the
19 in vitro cytotoxicity translates to delayed wound
20 healing. The second scenario is when the sponsor
21 elects to conduct a wound healing study to address
22 the implantation endpoint as part of

1 biocompatibility assessment. And lastly, a wound
2 healing study may be recommended when bench testing
3 alone is not sufficient to establish substantial
4 equivalence with the proposed predicate.

5 For animal wound healing studies, FDA
6 recommends the use of a pig model rather than small
7 mammals such as rabbit, guinea pig, rat, and mouse.
8 This is because pigskin is more similar to human
9 skin, both anatomically and physiologically, and
10 both heal partial-thickness wounds primarily to
11 re-epithelialization, whereas small mammals heal
12 wounds primarily through wound contraction.

13 We've just discussed cases where animal
14 studies are needed to establish safety and
15 effectiveness, but clinical data may also be
16 requested when bench and animal data are not
17 sufficient to demonstrate device safety or
18 effectiveness for the proposed indications for use.
19 The FDA expects that clinical data submitted in
20 support of a premarketing submission be valid
21 scientific evidence. Some examples include
22 prospective data from a protocol that's been

1 reviewed by FDA such as through an IDE; literature,
2 including systematic reviews and meta-analyses; and
3 also real-world evidence.

4 I hope this gives you a high-level overview
5 of the regulatory pathways for wound dressing
6 devices. Most wound dressings are handled through
7 the 510(k) pathway and are intended for wound
8 management. However, depending on risk and
9 intended use, some may be handled through the PMA
10 or de novo pathways, and many are class I exempt
11 from premarket review.

12 Lastly, I've included a list of the publicly
13 available databases on the FDA website, where you
14 can find more information on specific wound
15 dressing devices. Thank you, and that concludes my
16 presentation.

17 **Presentation - Rosa Sherafat-Kazemadeh**

18 DR. SHERAFAT-KAZEMADEH: Good morning. I'm
19 Rosa Sherafat from the FDA's Center for Biologics
20 Evaluation and Research, Office of Tissue and
21 Advanced Therapies or OTAT. Today I will provide
22 an overview of products regulated by OTAT, followed

1 by a brief discussion of regulatory pathways for
2 approval of OTAT regulating wound healing products;
3 then I will discuss regulatory standards for
4 approval of biologics and reviews, or recent
5 approval of StrataGraft as an example.

6 OTAT regulates a variety of products.
7 Examples of gene therapy products include ex vivo
8 genetically modified cells; non-viral vectors such
9 as plasmids; replication-deficient and
10 replication-competent viral vectors; microbial
11 vectors; and gene-editing products.

12 Cellular products range from stem cell and
13 stem cell-derived products and the functionally
14 mature and differentiated cells and cell
15 derivatives such as exosomes, cell lysates, and
16 conditioned media. OTAT also regulates therapeutic
17 vaccines and antigen-specific active immune
18 therapies; xenotransplantation products; certain
19 device and combination products; blood and
20 plasma-derived products; as well as certain human
21 tissues such as umbilical cord and birth tissues.

22 CBER's products indicated for wound healing

1 are generally reviewed in OTAT. A number of
2 products indicated in the realm of wound care are
3 investigated clinically under INDs or IDs,
4 depending on the type of the product. Here are
5 some examples of wound care products that are
6 approved or cleared such as StrataGraft and Epicel,
7 which are for treatment of geothermal burns.

8 CBER OTAT generally oversees tissue-
9 engineered medical products. As stated in the 2013
10 FR notice, the primary responsibility of overseeing
11 wound care products containing live cells has been
12 transferred to CBER OTAT.

13 OTAT regulated wound healing products may be
14 regulated as biological products under Section 351
15 of the PHS Act and the Food, Drug, and Cosmetic
16 Act, and applicable regulations. These products
17 are investigated under INDs. Substantial evidence
18 of effectiveness and safety are required to support
19 a marketing application such as biologic license
20 application, or BLA, for marketing approval.

21 Point of care devices indicated for wound
22 healing generally follow premarket approval, or

1 PMA, pathway due to the risk-based classification.
2 A combination product is regulated by OTAT when the
3 biological product constituent part such as live
4 cells, provides the primary mode of action. These
5 products are typically regulated under the IND/BLA
6 pathway. Tissue-engineered cell scaffold skin
7 substitutes are examples of such combination
8 products in the realm of wound healing products.

9 For CBER biological products to demonstrate
10 substantial evidence of effectiveness to support a
11 future BLA, we generally require more than one
12 adequate and well-controlled clinical trial. The
13 consistency of results across two adequate and
14 well-controlled trials greatly reduces the
15 possibility that a bias, chance, site-specific, or
16 fraudulent result will lead to an erroneous
17 conclusion that a product is effective.

18 Reliance on a single trial is generally
19 limited to situations in which a trial has
20 demonstrated a clinically meaningful effect on
21 mortality, irreversible morbidity, or in prevention
22 of a disease with a potentially serious outcome and

1 when confirmation of the result in a second trial
2 would be impractical or unethical.

3 Under certain circumstances, effectiveness
4 of a product can be established by one adequate and
5 well-controlled clinical investigation plus
6 confirmatory evidence. In such circumstances,
7 several factors will be taken into consideration,
8 which include the persuasiveness of a single trial;
9 the robustness of the confirmatory evidence; the
10 seriousness of the disease; the size of the patient
11 population; and whether it is ethical and
12 practicable to conduct more than one adequate and
13 well-controlled clinical investigation.

14 Here, I will provide an example of a
15 recently approved product for treatment of deep
16 partial-thickness burns.

17 StrataGraft is an allogeneic cellularized
18 scaffold product indicated for the treatment of
19 adults with deep partial-thickness thermal burns,
20 which contain intact dermal elements for which
21 surgical intervention or autograft is clinically
22 indicated. StrataGraft is one example of such

1 regulatory flexibility when substantial evidence of
2 effectiveness was provided by one adequate and
3 well-controlled phase 3 clinical trial with
4 persuasive evidence of effectiveness and safety,
5 plus confirmatory evidence of safety and
6 effectiveness from a phase 1b trial.

7 The safety and effectiveness of StrataGraft
8 in adults with thermal burns were evaluated in four
9 multicenter clinical trials. All four trials had
10 an open-label, which was subject to a
11 randomized-controlled design with 12 months
12 duration of follow-up.

13 Two trials, Strata 2016 and Strata 2011,
14 evaluated deep partial-thickness thermal burns. In
15 both trials, autograft served as the intra-subject
16 control. For each subject, following excision of
17 non-viable tissue, two treatment sites of
18 comparable depth that contained intact dermal
19 elements and had similar potential for experiencing
20 mechanical shear forces post-grafting were
21 identified and randomized to receive either topical
22 application of StrataGraft or autograft.

1 Results from the phase 3 trial were
2 persuasive and provided the primary evidence of
3 effectiveness for the BLA. Results from the
4 phase 1b trial provided supporting evidence of
5 effectiveness. For evaluation of safety, in
6 addition to these two trials, data from two earlier
7 randomized-controlled trials in adults with full-
8 thickness complex skin defects, were also analyzed
9 and [indiscernible].

10 The phase 2 trial met both of its predefined
11 co-primary endpoints. Co-primary endpoint 1 was
12 the difference in the percent area of the
13 StrataGraft treatment site and control autograft
14 treatment site that required autograft by month 3.
15 Achievable wound closure at 3 months was defined as
16 wound closure at 2 consecutive study visits at
17 least 2 two weeks apart. Wound closure of the
18 treatment site was defined as complete skin
19 re-epithelialization and the absence of drainage.

20 Among 71 StrataGraft-treated sites, only
21 three required autografting to achieve wound
22 closure by month 3. Among 71 autograft treatment

1 sites, two needed repeated autograft to achieve
2 wound closure by month 3. Therefore, by 3 months,
3 102 percent of the autograft treatment sites were
4 autografted, while only 4 percent of the
5 StrataGraft treatment sites required autograft.

6 The difference in the percent area of the
7 StrataGraft and control autograft treatment sites
8 that required autograft by 3 months was
9 98 plus-minus 17 percent, with a p-value of less
10 than 0.0001. In other words, donor site harvest
11 was eliminated in 96 percent of the
12 StrataGraft-treated deep partial-thickness burns.

13 Co-primary endpoint number 2 was the
14 proportion of subjects achieving durable wound
15 closure at the StrataGraft treatment site at
16 3 months without autograft replacement. By
17 3 months, approximately 83 percent of StrataGraft
18 treatment sites and 86 percent of autograft
19 treatment sites achieved wound closure. The lower
20 bound of the 95 percent confidence interval for
21 StrataGraft treatment sites was 74.4 percent, which
22 was above the predefined null threshold of

1 50 percent. Therefore, this study also met second
2 co-primary endpoints.

3 The phase 1b study provided confirmatory
4 evidence of effectiveness on the basis of the
5 percent area of a StrataGraft treatment site
6 autografted by 28 days after StrataGraft treatment,
7 and the proportion of treatment sites had achieved
8 complete wound closure by 3 months.

9 By day 28, no StrataGraft site required
10 autografts. Between 28 days and 3 months, one
11 patient had both the StrataGraft treatment site and
12 the autograft site subsequently treated with
13 autograft, and a second patient had 25 percent of
14 the StrataGraft treatment site autografted.
15 Therefore, at 3 months, approximately 93 percent of
16 StrataGraft treatment sites and 100 percent of
17 autograft treatment sites achieved complete wound
18 closure.

19 All the StrataGraft treatment sites that
20 achieved complete wound closure at 3 months also
21 remained closed at 6 and 12 months after treatment.
22 These two clinical trials provided substantial

1 evidence of effectiveness of StrataGraft for the
2 treatment of deep partial-thickness thermal burns,
3 demonstrating a meaningful clinical benefit
4 regarding achieving durable complete wound closure
5 and reducing the need for an autograft and
6 associated donor-site morbidities.

7 In summary, CBER biological products are
8 generally regulated under Section 351 of the PHS
9 Act and the Food, Drug, and Cosmetics Act. For
10 drugs and biologics, statutory requirements of
11 substantial evidence of safety and effectiveness
12 are generally fulfilled by more than one adequate
13 and well-controlled clinical trial. However, in
14 certain cases such as for rare diseases, one
15 adequate and well-controlled clinical investigation
16 plus confirmatory evidence may be considered
17 sufficient to establish effectiveness.

18 Therefore, to maximize the use of valuable
19 patient resources for rare conditions, even in the
20 early-phase clinical trials, we recommend that the
21 investigators and sponsors design and conduct
22 randomized concurrent controlled trials with

1 appropriate blinding because the early-phase trials
2 can potentially provide confirmatory evidence of
3 effectiveness of the product.

4 CBER devices for wound healing generally
5 follow premarket approval for the PMA pathway to
6 provide reasonable assurance of safety and
7 effectiveness. This concludes my presentation, and
8 this slide includes contact information and CBER
9 resources for questions regarding CBER regulatory
10 products, and thank you for your attention.

11 **Presentation - Jennifer Bai**

12 DR. BAI: My name is Jennifer Bai, and I am
13 a medical officer from the Center for Devices and
14 Radiological Health at the FDA. My background is
15 in plastic surgery, and I will be discussing the
16 FDA wound healing guidance that was published in
17 2006. I will be presenting the CDRH perspective on
18 how we typically use the guidance document in
19 reviewing wound care devices. Product development
20 for wound healing is a collaborative effort, and
21 the FDA guidance is a set of recommendations to
22 facilitate the development of devices and drugs to

1 help improve wound healing for patients.

2 While I'm speaking today on behalf of CDRH,
3 where we oversee medical devices, FDA has published
4 a cross-cutting guidance that is used across
5 multiple centers with recommendations for
6 evaluating products with proposed indications to
7 treat wounds. The official name of the guidance is
8 Chronic Cutaneous Ulcer and Burn Wounds -
9 Developing Products for Treatment, which was
10 published in June 2006.

11 The purpose of the guidance is to provide
12 recommendations to industry and sponsors for the
13 development of drugs, devices, and biologics to
14 treat wounds. Again, I wanted to emphasize that
15 the guidance represents the FDA's current thinking
16 on wound healing at the time of publication and
17 contains recommendations, which are not
18 prescriptive or set in stone. The FDA is open to
19 considering a variety of potential clinical
20 endpoints that are clinically meaningful to
21 patients, and I will be describing this guidance
22 through a CDRH lens.

1 One of the important components of device
2 labeling is the indications for use statement.
3 From a CDRH perspective, the indication for use is
4 based on substantial evidence and is reflective of
5 the safety and effectiveness of the product and is
6 a key component of medical device labeling.

7 Some wound devices may require clinical
8 studies, and if so, the clinical study should
9 support the indication for use statement. It
10 should identify the condition; in this case specify
11 the type of wound and patient population for which
12 the device is to be used and be clinically
13 meaningful to patients.

14 I will briefly go over some of the
15 preclinical considerations that are discussed in
16 the guidance document. Animal wound models are
17 important, as they can establish pharmacologic
18 responses, assess potential toxicities, and provide
19 data on in vivo biodistribution and
20 pharmacokinetics. Toxicology studies are also
21 important to conduct to assess the safety of
22 products for wound care.

1 This slide lists some of the important
2 aspects that should be considered when designing a
3 clinical study. As for any clinical trial,
4 randomization, having a comparator arm, and
5 blinding are important factors for helping reduce
6 bias.

7 For clinical studies for wounds
8 specifically, proper wound assessment and
9 quantification is important to document at the
10 beginning of the study and throughout the study.
11 The population chosen should also optimize the
12 study's ability to detect treatment effect and
13 reflect the population for which the product will
14 be indicated and used for.

15 Assessment and characterization of the type
16 of wound is critical, as different types of wounds
17 have unique considerations and standard of care.
18 On this slide, you can see examples of a diabetic
19 foot ulcer, venous stasis ulcer, and a pressure
20 ulcer. Important factors include ulcer
21 classification and size of the wound, including
22 depth and undermining. If the wound is deep, you

1 should consider measuring volume or surface area.

2 Signs of infection are also important to document.

3 Standard care is also an important factor to
4 consider. Standard care is the generally accepted
5 wound care procedures used in a clinical trial.
6 Varying standards of care can confound the outcome
7 of a study. Standard care should optimize
8 conditions for healing and be prospectively defined
9 in the protocol.

10 The FDA does not have specific guidelines
11 for standard care, but we recommend all sites agree
12 to use the same standard care for wound care. The
13 rationale for the standard care chosen should be
14 provided, and the protocols should provide details
15 to ensure uniform application across study centers.

16 Moving on to a discussion on the potential
17 efficacy endpoints for wound treatment products,
18 here is an overview of possible efficacy endpoints
19 from the wound healing guidance. There may be
20 different approaches from different centers and for
21 different products.

22 In general, clinical outcomes associated

1 with the use of a wound treatment product can be
2 broadly grouped into two efficacy categories,
3 improved wound healing and improved wound care.
4 Each outcome category includes a variety of
5 potential endpoints for clinical trials, and
6 suggestions for possible outcome measures and
7 clinical trial endpoints are offered in the
8 guidance.

9 Complete wound closure is an example of an
10 efficacy endpoint for improved wound healing.
11 Improved wound care endpoints can include treatment
12 of wound infection, debridement, and pain control.
13 The guidance also provides recommendations on
14 possible endpoints for temporary dressings and
15 other wound care claims. In the next few slides, I
16 will go over each of these.

17 Under improved wound healing, one of the
18 most objective and clinically meaningful wound
19 healing endpoints is complete wound closure.
20 Complete wound closure is defined as skin
21 re-epithelialization, without drainage or dressing
22 requirements, confirmed at two consecutive study

1 visits 2 weeks apart. This endpoint should measure
2 incidence of complete wound closure in the
3 treatment group and the control group by a
4 specified time, which is called landmark analysis.

5 According to the guidance, other possible
6 endpoints can be used in addition to complete wound
7 closure but need to be clinically meaningful. The
8 guidance mentions accelerated wound closure as
9 another possible endpoint for improved wound
10 healing. This is defined as a clinically
11 meaningful reduction in the time to healing using a
12 time-to-event analysis, with event being complete
13 closure.

14 For improving wound healing, the guidance
15 notes that partial healing would not suffice as a
16 primary endpoint because the clinical benefit of
17 incremental wound size changes has not been
18 established.

19 Other center specific talks will discuss in
20 more detail how partial wound healing may be
21 utilized as a multicomponent endpoint or co-primary
22 endpoint, however, partial healing that facilitates

1 surgical wound closure can be a measurable trial
2 endpoint of clinical benefit. In addition, studies
3 that evaluate improvement in the quality of wound
4 healing, such as cosmesis or function, present
5 other potential endpoints.

6 Products for wound management may still
7 provide important patient benefit without improving
8 the incidence or timing of wound closure relative
9 to standard of care. In terms of improved wound
10 care, examples of possible endpoints for wound
11 treatment products include treatment of wound
12 infection, debridement of necrotic tissue, and
13 wound pain control. When wound closure is not the
14 chosen primary efficacy endpoint, wound closure
15 should be evaluated as a safety outcome for all
16 products with a wound care claim.

17 A third type of endpoint is for temporary
18 dressings, which may provide short-term benefit
19 without having any long-term deleterious effects.
20 Temporary dressings function as a barrier and are
21 intended to provide supportive care until a
22 definitive closure can be accomplished. In

1 addition to healing, possible endpoints for
2 temporary dressings include improved barrier
3 functions and reduced infection rates.

4 Clinically significant improvement in
5 certain aspects of daily living may also support a
6 labeling claim. The trial endpoints should measure
7 a direct clinical benefit, and the endpoints
8 assessed should be done with a clinically relevant
9 validated instrument.

10 Patient-reported outcomes are important, as
11 patient perspectives are very valuable and provide
12 future patients with patient-centered information
13 on the product. This is an area for great
14 potential for growth, as there are very few
15 validated patient-reported outcomes for wound
16 healing.

17 Finally, a brief discussion on safety
18 considerations. Some safety considerations for
19 clinical trials of wound care products are listed
20 on this slide. Immune reactions are important to
21 assess for biologics and drugs. Stopping rules for
22 the study are especially critical because this

1 patient population often has a high background
2 incidence of serious adverse events, and the
3 product may have a deleterious effect on wound
4 healing. Therefore, it is important to have
5 stopping rules in the study.

6 We are looking to make sure the wounds are
7 not worsening, increasing in size, having higher
8 infection rates, or increased amputation rates. If
9 there are signs or symptoms to suggest wound
10 deterioration, these patients should be
11 discontinued from study treatment, however, they
12 should remain in the study for safety assessment
13 and efficacy analysis. Absorption through the
14 wound and irritation and contact sensitization
15 studies are also important in evaluating safety in
16 these products.

17 When developing a new product for marketing,
18 we encourage sponsors to engage with the FDA. The
19 FDA is open to collaboration with sponsors,
20 stakeholders, and companies in discussing the
21 clinical endpoints for their products. Outlined
22 here are just some of the mechanisms through which

1 sponsors and stakeholders can discuss endpoints
2 with FDA.

3 To conclude, the wound healing guidance is
4 meant to provide recommendations based on current
5 thinking at the time of publication for the
6 development of devices, drugs, and biologics for
7 wound healing. The FDA is open to considering a
8 variety of endpoints for wound care studies,
9 however, they must demonstrate clinical benefit to
10 patients.

11 As discussed in the previous slides, some of
12 the additional endpoints mentioned in the guidance,
13 in addition to complete wound closure, include
14 cosmesis, improvement in function, reduction in
15 infection, among other things. Again, different
16 endpoints may be appropriate for different products
17 and indications, so we encourage you to discuss
18 your specific product with FDA.

19 The process of encouraging innovation and
20 improvement in the realm of wound healing is a
21 collaborative process, and this conference is a
22 useful platform to help facilitate communication to

1 improve patient care. The FDA is committed to
2 working together to bring safe, high-quality, and
3 innovative wound care products to patients. Thank
4 you for your time.

5 **FDA Introductory Comments - Dev Verma**

6 DR. VERMA: Thank you, everyone.

7 Our next morning session will focus on the
8 diagnosis and natural healing of chronic wounds.
9 Our objectives for this session are outlined here.
10 We hope to identify the factors that disrupt normal
11 wound healing and lead to non-healing chronic
12 wounds; describe the subtypes of non-healing
13 chronic wounds; and identify gaps in current
14 treatment options.

15 We'll be hearing from Dr. Kenneth Fan,
16 associate professor of plastic surgery in the
17 Georgetown University School of Medicine and
18 scientific director of plastic surgery at the
19 MedStar Health Research Institute;

20 Dr. Paul Kim, the medical director of the
21 Wound Program at UT Southwestern Medical Center and
22 professor in the Departments of Plastic Surgery and

1 Orthopedic Surgery;

2 Dr. Lisa Gould, a plastic surgeon who is
3 past president of the Wound Healing Society and is
4 affiliate professor in the Department of Molecular
5 Pharmacology and Physiology at University of South
6 Florida, and clinical associate professor of
7 medicine at Brown University;

8 Dr. Aimee Garcia, the acting section chief
9 of Geriatrics and Palliative Care and associate
10 professor in the Department of Medicine,
11 Geriatrics, at Baylor and past chair of the
12 American College of Certified Wound Care
13 Specialists;

14 Dr. Caroline Fife, a professor of geriatrics
15 at Baylor College of Medicine, the chief medical
16 officer of Intellicure, LLC, a health information
17 technology company, and the executive director of
18 the U.S. Wound Registry;

19 Dr. Sharon Gerecht, professor in the
20 Department of Biomedical Engineering at Duke and a
21 global expert in vascular and stem cell biology and
22 engineering, whose lab develops biomaterials for

1 tissue healing and regeneration; and

2 Dr. Marjana Tomic-Canci, who is the chair in
3 wound healing and vice chair of research and
4 professor of dermatology, and the director of the
5 Wound Healing and Regenerative Medicine Program in
6 the Department of Dermatology at the University of
7 Miami Miller School of Medicine.

8 After the talks, I'll be moderating a panel
9 discussion and posing questions to the panelists,
10 and we'll start now with hearing Dr. Fan's talk.

11 **Presentation - Kenneth Fan**

12 DR. FAN: Hello. I'm Kenneth Fan, associate
13 professor and 4th-year clerkship director of
14 Georgetown University's School of Medicine,
15 Department of Plastic Surgery, and scientific
16 director at the MedStar Health Research Institute.
17 Thank you for the opportunity to talk about wound
18 healing stages and how acute and chronic wounds
19 differ.

20 Chronic wounds represent a significant
21 burden to the U.S. health system. In 2018,
22 Medicare identified 8.2 million beneficiaries who

1 suffered from chronic wounds, with costs ranging
2 from \$28.1 billion to \$96.8 billion yearly.

3 Chronic wounds are generally defined as wounds
4 failing to progress through the normal wound
5 healing phase process within one month. More than
6 90 percent of chronic wounds fall into venous
7 ulcers, diabetic ulcers, and pressure ulcers.

8 Wound healing is a complex process involving
9 cells, cytokines, growth factors, and matrix
10 elements. Generally, acute wound healing can be
11 split into hemostasis, inflammatory, proliferative
12 and remodeling phases. The hemostasis phase is
13 hallmarked by platelets exposed to collagen,
14 releasing content in the granules leading to the
15 coagulation cascade, causing a fibrin platelet
16 matrix to control hemorrhage and support wound
17 healing.

18 Inflammation is hallmarked by a wide variety
19 of factors of cytokines, neutrophils, and
20 macrophages to phagocytized debris and bacteria,
21 which secrete growth factors. Prolonged or intense
22 inflammation leads to chronic wounds. The

1 proliferative and remodeling phases are hallmarked
2 by re-epithelialization, fibroblast migration, and
3 conversion of immature type 3 collagen to type 1
4 collagen. This occurs in regular wound healing.

5 Although the causes of chronic wounds are
6 numerous -- diabetic, arterial, venous, and
7 pressure ulcers constitute the majority of chronic
8 wounds -- despite unique pathophysiology, factors
9 contributing to the chronicity of non-healing
10 wounds become similar with time.

11 Driven by proinflammatory cytokines, the
12 prolonged and overactive neutrophil response leads
13 to increase protease activity, mainly matrix
14 metalloproteinases. In some cases, protease
15 activity has been found to be over a hundred times
16 higher in chronic compared with acute wounds.
17 Increased metalloproteinase leads to degradation of
18 growth factors, their receptors, and adhesion
19 proteins such as fibronectin and vitronectin,
20 preventing cell adhesion for normal wound closure.

21 Wounding also damages the blood supply,
22 leading to hypoxia along with decreased oxidative

1 burst and microbicidal activity by
2 polymorphonuclear leukocytes. The uncontrolled
3 polymorphonuclear leukocytes respond to low oxygen
4 tension by releasing proteinases and toxic oxygen
5 metabolites, which damage endothelial cells. This
6 leads to cellular destruction, deposition of
7 fibrin, and further decreased delivery of nutrients
8 and oxygen, propagating a vicious cycle of
9 non-healing.

10 The inflammatory state is also prolonged by
11 the presence of bacteria, leading to increased
12 metabolic demand and protease levels in the wound.
13 The mere presence of bacteria in a chronic wound
14 does not affect wound healing. Definitions used
15 for overt clinical infection include microorganism
16 density greater than 10^5 to 10^6 colony-forming units
17 or gram, as these levels are used for thresholds
18 for delayed -- [inaudible - audio lost.]

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20 chronic wounds. The proliferative and remodeling
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8 The inflammatory state is also prolonged by
9 the presence of bacteria, leading to increased
10 metabolic demand and protease levels in the wound.
11 The mere presence of bacteria in a chronic wound
12 does not affect wound healing. Definitions used
13 for overt clinical infection include microorganism
14 density greater than 10^5 to 10^7
15 colony-forming units, or gram, as these levels are
16 used for thresholds for delayed wound healing and
17 disease.

18 Systemic conditions exacerbate chronic wound
19 inflammation, which the following panelists will
20 discuss. These systemic conditions lead to local
21 tissue hypoxia and reperfusion injury. With aging,
22 there's an impaired stress response, and these

1 again can be exacerbated by local tissue infection.

2 The chronic wound leads to significant
3 burden to the patient, particularly in low
4 extremity disease. Diabetic low extremity disease
5 has a 13.8 percent prevalence amongst diabetic
6 patients. Diabetic foot ulcers have surpassed
7 diabetic coma as the primary cause of mortality
8 amongst diabetic patients. For new onset ulcers,
9 the 5-year mortality is 43 to 55 percent. After
10 amputation due to deconditioning, the 5-year
11 mortality on systematic review is 62.6 percent.

12 The organization of care in the United
13 States for low extremity disease remains fragmented
14 at best. Evidence-based, multidisciplinary team
15 approach, despite their proven efficacy to limb
16 salvage, remain highly underutilized.

17 In the United Kingdom, limb salvage teams
18 are strategically organized, and 85 percent of
19 primary care physicians are able to recall referral
20 centers less than 12 miles away, leading to a
21 70 percent reduction in major amputation in the
22 United Kingdom. However, in the United States, our

1 research is more focused on decreasing wound size
2 rather than recurrence or function. This leads to
3 the use of expensive dressings and biologics, which
4 is a \$3.1 billion dollar market in the United
5 States as of 2019.

6 The analysis of the National Inpatient
7 Sample done at our institution indicate multiple
8 patient level and hospital level factors affecting
9 access to wound salvage modalities and
10 multidisciplinary care. For example, white and
11 non-Hispanic patients had the highest proportion of
12 lower extremity reconstruction, whereas black
13 patients had the lowest. Access to urban teaching
14 hospitals in competitive environments was the
15 strongest protective factor against amputation and
16 predictor of receiving wound salvage.

17 Preservation of limb length is critical for
18 mobility. The more joints preserved, the more
19 mobile a patient can be. However, when amputations
20 are indicated, limb length preservation mainly
21 occurs in urban environments. Further studies are
22 needed in quality and distribution of limb salvage

1 modalities and multidisciplinary care access.

2 Thank you very much for your time and attention.

3 DR. GOULD: I was told that Dr. Kim isn't
4 there yet, so this is Dr. Gould. I was going to go
5 next.

6 MR. TETLOW: Lisa, no worries. We're
7 pulling up your slides now.

8 **Presentation - Lisa Gould**

9 DR. GOULD: Hi. I'm Lisa Gould. I'm a
10 plastic surgeon, and I've been tasked to give you
11 an overview of arterial and venous ulcers, and I
12 will preface this with saying that as a plastic
13 surgeon, I'm rarely involved in the arterial
14 ulcers, but I certainly know about them.

15 You've already heard that we are facing a
16 rise in older adults, and that projected rise will
17 certainly affect our field of wound healing.
18 Chronic leg wounds affect at least 3.6 percent of
19 people older than 65 years of age. And you can see
20 in the graph on the bottom left, what we call the
21 silver tsunami, the rise in the number of people 65
22 and older, and particularly the rise in the group

1 of patients that are 80 years and older.

2 We also have a large number of patients who
3 are obese, and in that population, 65 and over, 65
4 to 74 years of age, and that's not going to go away
5 as these patients age, so we have about 30 percent
6 of patients that are over 75 years older considered
7 obese. Accompanying that is the rise in diabetes
8 and, again, that doesn't go away as the patients
9 age. So we have what I call the perfect storm of
10 aging, obesity, and diabetes, making wound healing
11 a really major problem.

12 With arterial insufficiency, that goes along
13 with all of those factors. Usually it's a large
14 and small vessel disease problem in patients who
15 have atherosclerosis, and it encompasses about
16 10 to 30 percent of all lower extremity ulcers; so
17 a smaller problem, but a major problem. When it's
18 combined with diabetes, there's a 9-fold increase
19 in the prevalence or incidence of arterial
20 insufficiency, also increased with age, with being
21 male, and in Afro Americans.

22 The prevalence of peripheral arterial

1 disease is about 15 percent in those who are over
2 45 and rises slightly in those who are over 70, but
3 is projected to increase dramatically over the next
4 couple decades. The top five risk factors are
5 smoking, diabetes, hypertension, hyperlipidemia,
6 and obesity. When peripheral arterial disease is
7 combined with diabetes, there's a 15-fold greater
8 likelihood of requiring an amputation.

9 Other etiologies of arterial insufficiency
10 include Buerger's disease, which is a vasospastic
11 condition, which is primarily due to smoking.

12 Sickle cell disease is not often thought of as an
13 arterial insufficiency, but that is what's causing
14 the wounds and vasculitides, which also are an
15 arterial insufficiency that result in open wounds.

16 We have to know what we're seeing. It's
17 usually wounds on the distal extremities with a
18 deep punched-out appearance and scant granulation
19 tissue often located between the toes, on the toe
20 tips, on the outer ankle, or wherever there's
21 trauma or friction from walking.

22 You can imagine they're pressure ulcers, but

1 because the inflow is so low, that skin is much
2 more sensitive to pressure, so it's an arterial
3 ulcer, as you can see in that middle
4 slide -- middle photo -- where it's on the outer
5 area of an extremity maybe due from pressure in the
6 bed, maybe due from footwear, or bracing. All of
7 those things can cause the arterial ulcers.

8 I teach the students to be really aware of
9 the difference between dry gangrene and wet
10 gangrene. We can often leave a dry gangrenous
11 extremity in place as long as it remains dry, but
12 then if there is moisture or any signs of infection
13 at the junction between the skin and the eschar,
14 that can be a surgical emergency, and patients need
15 to be acutely aware of watching for that, and
16 hightail it in to get it taken care.

17 The standard of care is absolutely a
18 multidisciplinary team, and that includes vascular
19 surgeons primarily, but also podiatrists;
20 cadorsists [ph] [indiscernible]; physical
21 therapists; the primary care physician; diabetes
22 management with endocrinology and diabetic

1 educators; pain management; sometimes plastic
2 surgeons; and a host of others. Putting all that
3 team together can be a little bit of a challenge.

4 There are validated risk stratifications.
5 The WIFI is a very good one actually because it
6 stands for Wound, Ischemia, and Foot Infection. It
7 was developed by the Society for Vascular Surgery
8 in 2014, and it's really designed specifically to
9 estimate the amputation risk but encompasses
10 varying degrees of the ischemia, tissue loss, and
11 also a score for presence and severity of
12 infection; so you can get a numerical score that
13 helps you understand the patient better. But the
14 primary goal is to optimize perfusion, which falls
15 on the shoulders of the vascular surgeon but,
16 unfortunately, as our patients get older and have
17 diabetes, sometimes that perfusion cannot be
18 optimized.

19 In addition, there's local wound care, and
20 that just follows the basic principles of
21 cleansing, debridement, although with arterial
22 insufficiency, we avoid debridement of stable black

1 eschars, and unless there's an acute infection that
2 needs to be addressed, we avoid debridement prior
3 to revascularization.

4 As always, we're managing the bacterial
5 balance. There are bacteria in all open wounds,
6 but we don't want it to become an infection, and
7 managing the moisture. Although in this case, most
8 of these wounds are dry, and we tend to keep them
9 dry because we don't want excess bacteria causing
10 an infection and raising the eschar.

11 Pharmacotherapy is usually based on
12 antithrombotic agents and statins, but also
13 diabetes management, hypertension control, and
14 lipid-lowering. There are advanced therapies for
15 arterial ulcers, but they so far are poorly
16 studied. But when we have patients who can't be
17 revascularized, or their wounds don't heal despite
18 revascularization, there may be some options in the
19 future.

20 This shows the list of things that have been
21 studied. Electrical stimulation needs further
22 study. Hyperbaric oxygen therapy may actually be

1 helpful for patients who show a response to
2 supplemental oxygen and can't otherwise be
3 revascularized, and is being used for diabetic foot
4 ulcers with low TcPO₂'s. Intermittent pneumatic
5 compression also has some data. I will be honest;
6 I haven't kept up on that data, but that's one
7 modality.

8 Negative pressure wound therapy has to be
9 used with extreme caution because, as I showed,
10 excess pressure can cause a wound, so we would have
11 to really watch it. Ulcers tend to be painful, so
12 patients may not tolerate the negative pressure
13 wound therapy.

14 Spinal cord stimulation has been used
15 primarily for pain rather than increasing blood
16 flow, and stem cell and gene therapy have been
17 studied but still needs further work. Topical
18 oxygen therapy has recently had some good studies
19 for diabetic foot ulcers, but not for just primary
20 arterial ulcers at this time, although I suspect it
21 will be coming. Ultrasound therapy has one RCT
22 that concluded that ~~the missed~~MIST therapy, which

1 is a topical delivery of ultrasound non-contact,
2 had a higher rate of healing at 12 weeks for
3 ischemic ulcers.

4 That's really the wrap-up on arterial
5 ulcers. I think there's one more slide about
6 arterial. It seems like something was missing, but
7 we'll get to it.

8 We'll go on to venous ulcers. The venous
9 leg ulcers are really the most frequently occurring
10 chronic leg wound, and it's primarily an outpatient
11 disease with 2 and a half million patients per year
12 in the U.S. But a lot of these patients actually
13 do get hospitalized, at least one inpatient
14 admission for infection over a year's time, and
15 that doubles the cost of treating patients with
16 venous leg ulcers.

17 These are some examples, and I'll go through
18 them. The one on your left is a patient who is a
19 worker who spent a lot of time on a hard floor and
20 had very serious venous insufficiency. She had an
21 exquisitely painful ankle ulcer, which looks fairly
22 small, but it was unable to be touched. She

1 actually got better with a series of venous
2 ablations, which took away her pain and helped the
3 ulcer to heal.

4 The photo in the middle is one of a patient
5 who had a traumatic injury which damaged his veins,
6 and he had very, very severe venous insufficiency;
7 very small ulcers but very difficult to heal and
8 required high-level compression once he did heal in
9 order to remain healed and not recur.

10 On the right you can see a very, very
11 typical venous ulcer with superficial wound
12 sloughed in the surface, ragged edge, and
13 hemosiderin staining around the surface. You
14 notice that in people of dark skin, that dark skin
15 gets very dark, and many patients are taken aback
16 because they've learned that skin that is that
17 black is gangrenous, and we have to reassure them
18 that that's not what's happening to their leg.

19 On the bottom is a pretty severe venous
20 ulcer. Again, you can see the ragged edges.
21 They're not nice, neat wounds, usually fairly
22 superficial, but when they're over the medial

1 malleolus, they can be more painful and harder to
2 heal. You can also see the edema in that leg and
3 the poor quality of the skin.

4 This is my artist rendition of what's going
5 on. In the normal venous system, you have intact
6 valves, so there's a deep system, a superficial
7 system and perforators between the two, and the
8 goal is to have one-way flow back to the heart,
9 through the arteries and up through the veins.

10 When there's venous insufficiency, which
11 usually happens when we stand on two legs but
12 sometimes happens with trauma or with blood clots
13 in legs, you get damage to those valves. It can be
14 either or both, the deep system -- the superficial
15 system -- and the perforators.

16 Most often it's in the superficial system,
17 and you can see that you get two-way flow. You get
18 leaky vessels. The red cells escape out into the
19 periphery and leave behind their heme. The
20 macrophage has recognized that as being foreign,
21 and macrophages eat that up, and then they become
22 what's called heme-laden macrophages. They're also

1 recognized as foreign, and other macrophages come
2 in and try to take care of that problem, and that
3 sets up the huge inflammatory response, which leads
4 to ulceration.

5 Because of that, compression is the primary
6 therapy because what that's doing is compressing
7 those vessels so that the calf muscle pump can work
8 and move the blood flow back to the heart.

9 Elevation can work because it decreases the edema
10 but, again, compression being the primary therapy.

11 When a patient has an open wound, multilayer
12 compression is the gold standard. Unfortunately,
13 some of our patients don't tolerate it well,
14 especially our older adults, and if there is a
15 combined arterial insufficiency, we have to modify
16 the compression as well. In those cases, sometimes
17 pneumatic compression may be an answer for them,
18 and then when the wound heals, we can go to
19 compression garments as shown with the stockings or
20 in the lower right, the velcro applied device,
21 which is easier to don.

22 One of the major problems is that patients

1 can't get these on and off, and especially as they
2 get older they have arthritic hands, they can't
3 reach their toes, and it really becomes a problem
4 and that's why they have recurrent wounds. So we
5 have to modify what we would apply ideally with the
6 mantra that any compression is better than no
7 compression, but it can be a real problem.

8 The other problem that we're running into in
9 the wound clinic is the cost of applying the
10 compression and buying the multilayer compression
11 systems. They are bundled in with debridement and
12 with application of products, so we eat the entire
13 cost of the whole thing. They're really treating
14 two different things. We're treating the venous
15 insufficiency, which is separate from treating the
16 wound. FDA doesn't usually get involved in
17 payment, but I think it's important to understand
18 that some of these payment issues are impeding
19 ability for patients to get what they need.

20 Very few of our patients these days have
21 just one disease. On the left, you can see a
22 patient who has mixed arterial and venous

1 insufficiency. You see the hemosiderin staining.
2 You see that he's had a saphenectomy, which isn't
3 healing well, and then a severe ulcer over the
4 medial malleolus, which is actually an arterial
5 ulcer.

6 On the right, you can see what happens with
7 diabetic peripheral arterial disease. The vessels
8 below the trifurcation get very ratty. It's hard
9 to revascularize these patients. They tend to
10 dwindle as it gets toward the ankle. Although they
11 may be able to re-establish inline flow for a short
12 period of time, that inline flow may not actually
13 get to the wounds that we need to heal.

14 Also, we need to be aware of BLEE. BLEE
15 sounds like something that is exciting and good for
16 spring, but it's not. It's actually bilateral
17 lower extremity erythema and edema, and we see it a
18 lot in people with venous insufficiency and with
19 swollen legs. From good studies in the literature,
20 particularly from dermatology, it's been documented
21 that cellulitis is frequently misdiagnosed about
22 30 percent of the time, which may account for some

1 of those admissions of patients with venous
2 insufficiency. Bilateral cellulitis is rare. It's
3 not a systemic disease, and stasis dermatitis
4 improves with leg elevation.

5 Patients come in with red, swollen legs.
6 They get put on antibiotics. They elevate their
7 legs while they're in the hospital, and everything
8 gets better. So people think that it was from the
9 antibiotics when in fact it was because the stasis
10 dermatitis got better. They also present with
11 multiple comorbid illnesses that result in red,
12 weepy legs. Patients with congestive heart
13 failure, obesity, chronic edema, lymphedema, and
14 immobility all can present with red, weepy legs.

15 In the figure, you can see on the top, the
16 one that's labeled A, that patient may have
17 actually had stasis dermatitis. It's kind of in
18 the pattern of the dressing that was applied. In
19 B, after a period of time with the legs up and some
20 rest, now you can see three ulcers that are more
21 distinct. The redness has gone away, and you can
22 see the hemosiderin deposition that was probably

1 contributing to the stasis dermatitis.

2 In the lower left is our typical patient who
3 is obese and has some element of lymphedema,
4 bilateral equivalent erythema, which is probably
5 not cellulitis but will get better with
6 compression. The bottom right is a true
7 cellulitis. This patient had an open wound and had
8 a swollen red, weepy leg that was on one side. The
9 other side was completely normal, and that one
10 responded appropriately to antibiotics.

11 In conclusion, I want to emphasize that most
12 of our patients have multiple diseases, but we can
13 help them by understanding what those diseases are
14 and treating them with appropriate standard of
15 care. Thank you.

16 **Presentation - Paul Kim**

17 DR. KIM: Good morning. Hopefully, you all
18 can hear me. I want to thank Dr. Verma and the FDA
19 for sponsoring this event. I think it's very
20 important to share our knowledge with those that
21 are making some very important decisions.

22 I'm assigned the diabetic foot ulcer. It's

1 been a passion of mine for the last 20 years of
2 practice. I started my career at Georgetown
3 University Hospital, with some very prominent
4 people there that published a lot of good work. I
5 went on to University of Texas Southwestern, where
6 I lead the wound program as the medical director.
7 I have nothing relevant to disclose for this
8 lecture.

9 I always start with this slide because I
10 think it's important to understand. It's been
11 reviewed now by a couple of people that have talked
12 about this, but I think I wanted to try to
13 objectify this a little bit in an equation.

14 Whenever I'm faced with a diabetic foot
15 ulcer, for example, I think about their healing
16 potential. In the numerator there's a 1 and in the
17 denominator there's bacteria perfusion and tissue
18 mechanics. These three things, we can impact
19 change on, but the major driver of healing
20 potential of our patient is the host, and these
21 host factors are numerous, and they're diverse,
22 including their genomic profile, their nutritional

1 status, or access to health care, and so on and so
2 forth.

3 So it's very difficult problem. I think we
4 focus in on things that we can change, but the
5 things that we can't change or impact very little
6 are things that I think may be driving healing
7 overall.

8 There is a pathway to limb loss. This is
9 why we fight for the ulcer and try to heal that
10 ulcer as a simple toe ulcer but, unfortunately,
11 they tend to progress to digital amputation;
12 transmetatarsal amputation; ~~show parts~~Chopart
13 amputation; below-knee amputation; and above-knee
14 amputation.

15 When you think about the foot, it's a
16 remarkable and -- pun intended -- feat of
17 engineering because it has to be mobile adaptor.
18 If you think about your own feet, has to be able to
19 absorb shock and adjust to the terrain. But it
20 also has to be rigid, and that combination really
21 promotes problems, especially in the diabetic
22 patient.

1 We're going to talk about the pathogenesis
2 of the diabetic foot ulcer but, essentially, here
3 are some examples that can occur, really, anywhere
4 on the foot, not necessarily the weight-bearing
5 surface. In those extreme cases like Charcot
6 neuroarthropathy, which occurs in anywhere between
7 1 to 4 percent of the diabetic neuropathic
8 population, it's a significant fracture or
9 dislocation and subluxation most predominantly in
10 the mid-foot that causes chronic ulcers, and you
11 get this rocker-bottoming effect of the wound,
12 again, that's due to pressure with ambulation.

13 We know this is a big problem. It's not
14 just a big problem here, it's a pandemic in
15 the -- and I use that word very specifically
16 because the growing rate, the incidence and
17 prevalence, is just astounding globally, and in the
18 United States as well.

19 The cost of these can exceed \$245 billion
20 dollars to take care of diabetes, and the subset of
21 that is for diabetic foot ulcers. One in five
22 healthcare dollars in the United States are spent

1 on diabetes-related disease and the most common
2 cause of non-traumatic amputations, and the
3 exponential rise in this problem is not going away.

4 The risk of a patient developing a diabetic
5 foot ulcer, a patient with diabetes, is about
6 25 percent over their lifetime, which is pretty
7 significant; so 1 in 4 patients will develop a
8 chronic, non-healing ulcer. The prevalence in the
9 United States is between 4 and 10 percent, and
10 80 percent of non-traumatic amputations are
11 preceded by a foot ulcer.

12 These are hard problems, and Dr. Gould
13 really elegantly talked about, in a very short
14 period of time, the ischemic or vascular issues.
15 Here's an example of a superficial femoral artery
16 that's been occluded. You can see the attempt for
17 revascularization that failed and some below-knee
18 amputation.

19 Here's another problem where there's bony
20 destruction. This is not osteomyelitis, but this
21 is Charcot neuroarthropathy. And again, this is
22 just on the side of the OR, dissecting through the

1 bone, and see how completely destroyed and how poor
2 that tissue quality actually is.

3 If you have overlying soft-tissue infection
4 and an underlying bone problem, again, this is not
5 a salvageable limb. It's unfortunate, and this
6 happens way too often. Often our patients present
7 with a combination of things like ischemia,
8 underlying bone infection, overlying soft-tissue
9 infection, and again, it's not a salvageable foot.

10 I've showed you a bunch of amputation cases,
11 and I'm not saying that I'm a pro amputation
12 person -- in fact, I'm not -- but I can argue that
13 in some cases that's absolutely the right thing to
14 do for our patients. I'm reminded, though, every
15 day, from a patient and a friend of mine who's an
16 amputee, and he wrote this in a book he gave me.
17 "We're born with two feet, and one is not a spare."
18 As the limb loss occurs, the healthcare costs
19 increase, and the impairment and function quality
20 of life all drop, so you start with an at-risk
21 diabetic patient.

22 This is some work by Neil Barshes, who's a

1 vascular surgeon at Baylor. He's a very good
2 friend of mine. He is a very thoughtful person,
3 and he's able to pictorially show you that there is
4 this stairway -- or elevator in some cases -- to
5 limb loss.

6 One of the problems, and one of the
7 challenges that we have in the United States -- and
8 across the globe, actually -- is there's a
9 disparity of care, and we know that now due to our
10 recent experience during the pandemic. This is how
11 scary it is. It depends on where you show up in
12 the emergency department whether your leg can be
13 saved or not, and there are these regional
14 differences. In the south, you're more likely to
15 get an immediate below-knee amputation versus
16 attempted limb salvage in some of these other
17 states. Often this is dictated by physician style
18 and what specialist is seeing that patient for the
19 first time in the emergency department.

20 I was just talking about the acute setting
21 just a few minutes ago, but in the outpatient
22 setting, often these patients have no idea where to

1 go first. What happens is patients are bounced
2 around between specialists and specialists, and
3 what that does is it delays care, and the wound
4 becomes even harder to heal.

5 We see this often with patients that are
6 referred to us who have seen 10 other specialists.
7 It doesn't even matter what specialist it is. It
8 varies from dermatology, to family practice, to
9 podiatry, to PM&R, and they ultimately end up in a
10 place that has some significant experience, and
11 hopefully we can improve their care.

12 There is a quadrad that leads to ulceration
13 and amputation. One is peripheral neuropathy;
14 second is ischemia; and third is foot deformity.
15 As part of this foot deformity, there are soft
16 tissue changes. And we have to understand, as the
17 diabetes disease process continues, there's fat pad
18 atrophy and immobility that occurs.

19 What happens with that is that that puts
20 that patient's foot at risk. Imagine half your
21 body weight, and with every step placed -- or even
22 just standing -- the step is on one location. And

1 if there's a deformity, a bony deformity, that soft
2 tissue will break down.

3 There's also another way to think about
4 this, the pathway to ulceration amputation. There
5 could be a callous that presents, or just a minor
6 or major trauma creates an ulcer that fails to
7 heal. Then infection sets in, and then amputation.
8 The patient cycle, it's amazing to me to watch
9 patients that I've taken care of over many years,
10 and they just start to lose more and more of their
11 limb, and they switch from one side to another.

12 How do we manage these problems? These are
13 some fundamental things: Offloading debridement;
14 edema control; biofilm; moisture management; drugs;
15 biologics; and devices. Each of these topics is a
16 6-hour lecture, but all of these things are very
17 important.

18 I alluded to this earlier. I think it
19 really does take a consolidated, true
20 multidisciplinary effort, but there are some core
21 people that are involved in the care of the
22 diabetic foot ulcer. Certainly plastic surgery,

1 vascular surgery, and podiatric/orthopedic surgery
2 create that central nidus of absolutely a required
3 specialist in diabetic foot ulcer management, but
4 it doesn't preclude the need for all of these other
5 specialists that's really important in the
6 long-term care for that patient.

7 When I look at the literature -- and I don't
8 have time to talk about every little thing -- what
9 we want to do is think about this as a pyramid. At
10 the bottom there's a chronic ulcer or diabetic foot
11 ulcer. At the top, we want to get to the top of
12 that pyramid of a healed ulcer. How do we do that?
13 Well, you maximize perfusion, address the tissue
14 mechanics, the biofilm, infection control, as we
15 discussed just a few minutes ago.

16 But if you look at the literature, about
17 50 percent of the patients will heal primarily
18 doing these three things, and I know that because
19 I've looked at the control group of randomized
20 comparative or controlled trials. And if you look
21 at just the standard of care group, you'd get about
22 a 50 percent healing rate within 12 weeks. What

1 happens with these adjunctive therapies, including
2 devices, biologics, and drugs, is you can elevate
3 that as far as healing rate, but if you look at the
4 literature and the critically appraised -- the good
5 studies, if you will -- you clearly see this
6 ceiling effect, and that's about a 80 percent
7 healing rate. So the top 20 percent of diabetic
8 foot ulcers will never heal, and that's
9 unfortunately what happens with these patients that
10 end up in amputation.

11 To that, this idea of recidivism is very
12 important as far as diabetic foot ulcers are
13 concerned. Whenever I see a patient and they
14 heal -- I'm able to heal them or they're able to
15 heal themselves, primarily -- I always talk to them
16 and say, "Your foot's at tremendous risk." And
17 depending on what the literature says and which
18 literature you read, the pooled estimate is that
19 about 22 percent of these patients will reoccur
20 within one year.

21 So that's what so important, is not
22 necessarily the primary healing. I think if we do

1 the right things, we can get them to heal, but then
2 after that, we want to prevent them from
3 reoccurring.

4 In conclusion, the DFU is a manifestation of
5 an underlying systemic disease as diabetes. We
6 have to remember that diabetes has not stopped once
7 you heal the wound. The diabetes, unfortunately,
8 continues, and the patient gets older and sicker.
9 Remember, the skin is an organ, and that organ is
10 dysfunctional because of diabetes, so,
11 unfortunately, the pathway is not stopped as far as
12 trying to prevent amputation; it just continues.

13 We have to also remember the foot is a high
14 demand -- I think about it as an end organ. It's
15 anatomically isolated and it's certainly at risk.
16 It can be healed, but there is a high rate of
17 recidivism, and there's unfortunately not a lot of
18 data looking at long-term outcomes after primary
19 healing, and I think we need to think about that.
20 Thank you.

21 **Presentation - Caroline Fife**

22 DR. FIFE: Hello. I'm going to talk about

1 one of the elephants in the room, which is what I
2 refer to as the nameless wounds. We have this
3 perception that diabetic foot ulcers, venous
4 ulcers, and pressure ulcers are the primary types
5 of problems that we treat.

6 (Pause.)

7 DR. FIFE: We have this perception that
8 diabetic foot ulcers, venous ulcers, and pressure
9 ulcers are the entities that we're treating, but
10 when we look at prevalence rates from Medicare
11 claims data, you may be surprised to realize that
12 surgical wounds are far more prevalent than
13 diabetic foot ulcers, venous ulcers, and pressure
14 ulcers. And then there is another category that
15 gets really no press, and that is the traumatic
16 wounds that never heal, generic chronic ulcers,
17 which I refer to as the wounds with no name.

18 This entity we keep talking about, and even
19 saying represents 90 percent of our problem, is
20 really a prevalence of about 3.8 percent -- or
21 5.1 percent -- are the wounds with no name; that
22 is, "I hit my leg on the coffee table and it never

1 healed," or "I have a surgical complication." So
2 it troubles me deeply that with this being such a
3 large category, there's so little investment in
4 technology or attention.

5 Just to understand an additional challenge,
6 it also has to do with how we code these. In
7 general, there's no English term that encompasses
8 the concepts of both wounds and ulcers. In coding
9 language, wounds and ulcers are quite different,
10 with wounds being surgical complications or
11 traumatic injuries, and ulcer is relating to your
12 underlying medical condition, like pressure ulcers,
13 venous, otherwise coded as chronic non-pressure
14 ulcers.

15 It may surprise people to realize that there
16 is no ICD-10 code for a diabetic foot ulcer. There
17 are many codes for venous ulcers and none for a
18 diabetic foot ulcer. When you're seeing a patient
19 with a diabetic foot ulcer, the only option you
20 have is to code them as a chronic non-pressure
21 ulcer, and then try to make a connection between
22 that and their diabetes.

1 This is an additional problem when we're
2 trying to do research in the area, but another
3 interesting factor that has to do with coding is
4 that wounds, which are due to accidents with
5 surgical complications, as I mentioned, are
6 required to have an additional related-to code
7 attached to them, and these are some of my personal
8 favorites, which also include being hit by falling
9 space debris, a code that I aspire to use before I
10 retire, or being sucked into a jet engine as a
11 subsequent encounter.

12 However, the chronic non-healing pressure
13 ulcers, the ones that we say have no names, do not
14 have to be and, in effect, can't be coded with any
15 subsequent etiology code. So they really remain a
16 question mark as to what they really are.

17 Just to give you a perspective on this, Lisa
18 Gould, Dr. Gould, just talked about arterial
19 ulcers, and in fact there's no code for those.
20 Neither of these patients are diabetics. It is
21 possible to code their underlying medical condition
22 as atherosclerosis, including with gangrene. But

1 if I'm seeing the patient and I have to apply a
2 diagnostic code to the wound itself, I really don't
3 have a way to do that, except to say it's a chronic
4 non-healing ulcer, when in fact, and particularly
5 the lady on the right -- who has 3-vessel blockage
6 below the knee that's unrevascularizable, at least
7 by endovascular procedures -- had grossly ischemic
8 wound, and I can only code it as a chronic ulcer.

9 The other challenge for us is all of these
10 are traumatic wounds where the patient hit their
11 leg on something. I think I could run an entire
12 clinic off the open dishwasher door traumatic
13 wounds. We have some guidance from CMS that we
14 should re-code those as chronic ulcers if they fail
15 to heal for 30 days, but in fact most people don't
16 bother to do that, and they continue to be coded as
17 a traumatic wound even though they persist for
18 months at a time, and all of them are due to the
19 underlying medical conditions of the patient, as
20 Dr. Kim indicated, the host factors.

21 Then there are all the problems that we have
22 a diagnosis for but, again, we can only attribute

1 the underlying medical condition. And we think
2 they're rare, but as Dev indicated earlier,
3 Dr. Verma, really are not that rare. I have three
4 calciphylaxis patients in my practice right now. I
5 have 8 people with pyoderma gangrenosum. I
6 commonly have people with inflammatory ulcers
7 associated with autoimmune diseases like lupus and
8 sarcoid. These are not infrequent problems, at
9 least in chronic wounds centers.

10 We know what's going on with these patients.
11 The one on the left has an iliac artery thrombosis.
12 This patient has a T-cell lymphoma. This is a
13 vasculitis. And yet, they're all going to be coded
14 as a chronic non-pressure ulcer, even though we are
15 not uncertain of their etiology.

16 There are lots of chronic ulcers that are
17 due to drug problems, various types of injections,
18 chemotherapy extravasation, intentional injection,
19 and off-label use of certain medications. That's
20 also not an uncommon category, and a huge problem
21 that we now have are wounds that are due to
22 radiation for cancer. I would like to start a

1 campaign to stop irradiating shins of elderly
2 people for skin cancer.

3 We also have overlap in categories. This is
4 a heal ulceration in a diabetic who has peripheral
5 arterial disease. So now, would you in your mind
6 attribute this as a pressure ulcer injury? And by
7 the way, pressure ulcers are still called ulcers.
8 In ICD-10, there's a movement to call them
9 injuries, but ulcers is how they're coded. So are
10 they pressure ulcers, a diabetic foot ulcer, which
11 is really a chronic ulcer that is not due to
12 pressure, or an arterial ulcer, which is a chronic
13 ulcer not due to pressure? In other words, it is
14 all three of these things, but we have to pick a
15 lane.

16 Then there are the acute wounds that are
17 going to be coded as chronic ulcers because as
18 Dr. Gould mentioned, we have challenges for
19 payment. These are all blisters that are acute
20 that are due to acute chronic heart failure in
21 patients with or without sleep apnea. They're all
22 going to be coded as venous ulcers because that's

1 the only way that compression bandaging, which they
2 desperately need, is going to be covered.

3 When we look at registry data, we find that
4 the average patient in a wound center has
5 10 comorbid conditions, which are really the cause
6 of their problem; malnutrition was rampant, and the
7 average patient takes 12 medications. This is the
8 bag of medicines that an illiterate patient brought
9 in and asked me to help him understand what he was
10 taking all of these medicines for. He can't read
11 the labels. I drew pictures on the bottle to try
12 to help him understand their purpose. Many drugs
13 significantly impact wound healing, but that's
14 another thing that we haven't had much discussion
15 around.

16 The last point that I'll make is that even
17 though wounds have names, they are really not
18 representing distinct pathophysiologic entities.
19 All of these are diabetic foot ulcers. They're
20 clearly not all due to the same pathophysiologic
21 process; some are neuropathic, some are ischemic.
22 One of these patients has diabetes and the other

1 doesn't. One of these patients has idiopathic
2 peripheral neuropathy, which by the way is
3 relatively common. They look the same. Their
4 treatment is largely the same, although the
5 patients who don't have diabetes do not have
6 coverage for appropriate footwear because they're
7 not diabetic.

8 Yet, the presence of diabetes does not make
9 the wound diabetic. About half the patients with
10 venous ulcers have diabetes and many patients with
11 pressure ulcers have diabetes. So even talking
12 about pressure ulcers, we have some that are
13 outside and due to friction and sheer, and some
14 that are inside and out due to what are effectively
15 vascular infarctions, and yet we give one name to
16 those regardless of the process.

17 Despite all of the confusion in terminology,
18 all wounds really heal the same way. They heal by
19 the creation of vascular tissue, which we call
20 granulation, and then subsequent epithelialization.
21 So it is not apparent that because we give certain
22 types of categories names, that their resolution in

1 terms of healing happens by any different factor,
2 except that pressure has to be controlled and edema
3 has to be managed.

4 So if you think about the universe of the
5 chronic ulcers that we're dealing with, diabetic
6 foot ulcers, pressure ulcers, and venous ulcers
7 represent a relatively small portion of it, with
8 the wounds with no name far exceeding them in
9 frequency, and then diabetes affecting all of the
10 diabetic foot ulcers, of course, but about half of
11 all the others. Yet, there is also substantial
12 overlap in many of these types, and I put in dark
13 green the only ulcer types that are really involved
14 in FDA prospective clinical trials.

15 I submit to you that the largest category of
16 problems that I see on a daily basis are wounds
17 that have no name, although it's not that we don't
18 know what has caused them; we just don't have any
19 research directed at them. The ulcers that do have
20 names conflate different pathophysiologic processes
21 and, thus, I feel that makes the name almost
22 clinically meaningless. All of the healing happens

1 the same way regardless of what we call that.

2 DR. VERMA: Thank you, Dr. Fife and all the
3 speakers for your excellent talks. We're just
4 going to take a few minutes break until 11:05, and
5 then we'll be back to start our panel discussion.

6 (Whereupon, at 11:01, a recess was taken.)

7 **Panel Discussion**

8 DR. VERMA: Alright. Welcome back,
9 everyone. Thanks again to all the speakers for
10 your excellent presentations.

11 I'll be moderating this panel discussion and
12 posing questions to our speakers and panelists, but
13 the public attendees are also welcome to type in
14 any questions you may have in the Q&A box. If we
15 have time, we'll address them in the panel today,
16 and any questions we can't address, we hope to
17 summarize in a post-meeting summary.

18 This is the first question I would like to
19 ask our panelists.

20 Non-healing chronic ulcers are often
21 referred to as a symptom of an underlying disease,
22 and sometimes this can lead to dismissing them as

1 secondary to the underlying disease. Physicians
2 and patients may see a small wound, considerate it
3 related to their underlying disease, and allow it
4 to get bigger before it becomes a serious actual
5 condition that requires more complicated treatment

6 Are non-human chronic ulcers a sign or
7 symptom of an underlying disease, distinct disease,
8 or do they have elements of both? I know Dr. Fife,
9 you had mentioned this in your talk, and I think I
10 know what your answer will be, but I'd love to hear
11 a little bit more of your perspective first.

12 DR. FIFE: Well, I think they are a symptom,
13 but if you are worried that they're dismissed by
14 the patient, yes, that may be true. They're often
15 also dismissed by sometimes the primary care docs
16 because we don't really do any education in medical
17 schools about the wound process.

18 But I think wounds are a symptom of disease,
19 and that makes them far more complicated for us to
20 try to develop clinical trials around because we
21 end up in this bizarre situation where wounds are a
22 symptom of underlying disease. In order to do a

1 clinical trial, we look for the healthiest people
2 we can find, and we exclude the majority of the
3 diseases that cause the wound in the first place,
4 and then look for totally healthy people with
5 chronic ulcers, which just doesn't happen. When
6 somebody has a chronic wound, it's because
7 something's wrong with them, and I think we don't
8 figure out how to talk about that.

9 DR. VERMA: Dr. Kim or Dr. Fan, do you have
10 any other thoughts? Do you agree with this, that
11 chronic ulcers are a symptom?

12 DR. KIM: Yes. I just have a couple of
13 comments, Dr. Verma. You know, it's interesting,
14 because on the face of it, it seems like a pretty
15 easy answer. It's secondary, I think; in many
16 cases secondary to some etiology, some disease,
17 including diabetes for diabetic foot ulcers. But
18 having said that, what I often find are patients
19 that have diabetes that's uncontrolled -- let's say
20 they live at a fasting blood sugar of 400, a
21 hemoglobin A1c of 12 -- and their wounds heal. So
22 I did nothing to impact their underlying diabetes,

1 but their wounds heal.

2 So it seems to me there should be a
3 relationship right there, and there often is. The
4 better blood sugar control, then you kind of
5 decrease the likelihood of problems, including
6 infection. But the reality is these patients have
7 long-standing diabetes, whether it's controlled or
8 uncontrolled. We can't really do anything about
9 that, but we can affect change locally or
10 regionally in that wound space. So I can answer
11 that both ways. I'm not sure. I think it's
12 probably a little bit of both.

13 DR. VERMA: Thank you.

14 Dr. Gould, you have your hand raised.

15 DR. GOULD: Yes. I agree, again, with both
16 sides. The problem is we have such a compendium of
17 underlying diseases, and then we have the wound,
18 and it's not necessarily related to just one
19 disease. So I think we have to start looking at it
20 as its own disease, but we also have to look at the
21 flip side.

22 When I was at the Tampa VA, we were looking

1 at pressure ulcers, and there are people who do
2 everything that we would ask them to do, and yet
3 they don't heal their wound. On the other hand, we
4 have a group of patients who we would say do
5 everything wrong, and they don't get a wound. So
6 it would behoove us to study the super healers and
7 the people who heal despite the uncontrolled
8 diabetes, and find out what part of that disease
9 they have that is helping them to heal.

10 So I think we could dissect it apart and try
11 to figure out is there a genetic disposition to
12 being able to heal? Is there a genetic disposition
13 to having wounds that don't heal?

14 DR. FIFE: My bias is we're missing
15 nutritional pieces.

16 DR. VERMA: Dr. Tomic-Canic?

17 DR. TOMIC-CANIC: Yes. I would like to echo
18 everything that's being said. I think even though
19 they might be a symptom, I think we have to
20 approach it from the understanding of the
21 pathophysiology of wounds itself. We need to
22 approach it as a distinct disease.

1 Again, something that Dr. Fife just touched
2 upon in her presentation, and you mentioned this,
3 too, is there is an orderly restoration of these
4 chronic wounds when they actually start healing, so
5 there is something common about the process that
6 needs to be implemented, regardless of how the
7 tissue has arrived to the non-healing, as a symptom
8 of maybe uncontrolled diabetes, or pressure, or
9 whatever else might be contributing.

10 But when you look at the pathways, at least
11 from the research perspective, when you look at the
12 pathways that contribute to pathophysiology, there
13 are common threads; again, not necessarily like
14 with a list of molecules that are the same in all
15 of these wounds, but more of how the tissue is
16 responding, and how the tissue looks on a cellular
17 level, based on the non-healing pathways.

18 They might be common, even though the
19 molecules are not necessarily identical in all of
20 these tissues. Therefore, this is actually
21 distinct disease in the context of pathophysiology,
22 and also prospectively looking at what are the

1 paths to intervene to actually get them to heal and
2 not reoccur. So again, all inclusive, it may be
3 distinct disease but are the symptoms of more
4 complications that are systemically present.

5 DR. VERMA: Dr. Garcia, we'll hear from you,
6 and then I'll move on to the next question.

7 (No response.)

8 DR. VERMA: You may be muted.

9 DR. GARCIA: I apologize for that.

10 I just wanted to start by apologizing to
11 everyone for my tardiness. I had an emergency on
12 the floor with one of our nursing staff. But what
13 I wanted to say in terms of pressure injuries,
14 obviously, most of the time the issue with pressure
15 injuries is pressure, and despite the underlying
16 medical issues, if you remove the pressure, the
17 patient progresses towards healing.

18 But clearly, in none of these chronic wounds
19 is the wound in a vacuum. All of the underlying
20 medical conditions, and external factors as well,
21 are going to play a part in the healing process,
22 and if we don't address those underlying issue, the

1 wounds are not going to progress towards healing.

2 DR. VERMA: Great.

3 If we can actually move on to slide 7, we're
4 going to skip a question.

5 The question, while we're getting it up, is,
6 basically, Dr. Fife mentioned in her talk that
7 regardless of the contributing factors, that all
8 wounds heal via an identical process, so all
9 healing involves the same physiological process,
10 regardless to what we call a wound or ulcer. This
11 kind of touches upon what Dr. Tomic-Canic was
12 saying as well, and I said in our symptom versus
13 disease discussion.

14 Do the panelists agree that regardless of
15 the etiology, all wounds ultimately heal via an
16 identical process?

17 DR. FIFE: I love being an iconoclast, so I
18 still say they all have to granulate and
19 epithelialize. I think that's the other
20 fascinating elephant in the room. It's not that
21 there aren't individual factors you have to control
22 like pressure and edema, but it doesn't change the

1 actual way that they go away.

2 DR. TOMIC-CANIC: I would add that, again, I
3 think that what we might have to do to a given
4 wound might be different, but in the sense of
5 reactivating, in the essence what you need to do is
6 really shift a phenotype from a non-healing to
7 acute wound healing like phenotype.

8 How you achieve that might be different for
9 venous, or pressure, or even a subset because,
10 again, not every type of wound is identical. Not
11 all diabetic foot ulcers are the same. So I think
12 that our intervention might be wound specific, but
13 the pathway to healing is kind of following the
14 basic biological principle of the evolutionary
15 process, and that is acute wound healing, and once
16 this pathway gets reactivated, then the process
17 kind of takes on its own.

18 DR. FIFE: We have a fascinating window in
19 some of the chemotherapy drugs that are
20 anti-neovascular agents. So as cancer becomes a
21 chronic illness, patients come in with drugs, the
22 specific goal of which is to prevent the growth of

1 vascular tissue, and then they get a wound, and
2 people want me to fix it. We are missing a great
3 opportunity to understand some of the aberrancies
4 in the process, based on what some of our drug
5 therapies do.

6 DR. GOULD: I'm a surgeon, so I hit
7 everything with cold steel, almost everything, and
8 I do see that things heal when taking -- the wounds
9 respond similarly when taking care of appropriately
10 with debridement and then topical wound therapies.
11 Most of them do heal. Obviously, there's going to
12 be a small percent, but maybe that's because we
13 don't understand part of the disease.

14 As we understand the wound bed, which
15 Dr. Tomic-Canic is helping us do, we may know
16 what's missing, actually, in the wound bed around
17 the wound edges that are preventing some of those
18 wounds from responding.

19 DR. FIFE: They still make granulation
20 tissue and epithelialize, everyone of them.

21 DR. KIM: Well, I disagree a little bit
22 here. What we're talking about are the

1 non-responders, the chronic wounds. Those are the
2 wounds that have not healed.

3 So yes, all wounds should heal. They don't
4 heal. That's why we're having this discussion.
5 These are the non-responders that we need to focus
6 in on, and I think they are different. I think
7 that population is different, and it's driven by
8 lots of factors. It's both external and internal.

9 The basic process of healing certainly is
10 universal, but those are for patients that heal.
11 The question is about the ones that don't heal, and
12 this is why it's reflected in our treatment
13 approach. We throw everything against the wall and
14 hope something sticks because we just don't know,
15 and that's really, to me, the biggest treatment
16 challenge.

17 It's not the healers. Those are easy. The
18 non-healers are the challenge. It's the top
19 20 percent that I'm challenged with, and we put
20 labels on them. We call them hospice or palliative
21 wound patients. Those are chronic wounds patients.
22 That's the population that we need to focus in on.

1 And as Dr. Fife mentioned earlier, that's not where
2 the studies are designed around, so we'll maybe
3 never know.

4 DR. FIFE: It would be nice to see us talk
5 about etiologies instead of diabetes, but
6 neuropathy infection. Those are the real
7 etiologies. Diabetes is too blunt of a term.
8 There are specific interventions we have for CVS
9 and specific interventions for neuropathy. It
10 would be nice to talk about those more
11 pathophysiologic than we do.

12 DR. KIM: I just never see those, Dr. Fife.
13 I never see those patients early on where I can
14 impact change on their neuropathy. It's too late
15 by the time I see them, and those are,
16 unfortunately, the patients that are the most
17 challenged to heal.

18 DR. FIFE: Yes. But I would say it's still
19 a more precise term to say that some of the
20 problems are neuropathic opposed to just saying,
21 oh, it's diabetes, because, as you indicated, it's
22 very hard to show that A1C level impacts healing

1 directly. It does impact the development of
2 neuropathy, but we ought to know the answer of A1c
3 because we use A1C levels as exclusion
4 [indiscernible] criteria in clinical trials, and we
5 really don't know how much the A1C level itself
6 affects the healing process. We don't actually
7 know the answer to that, I don't think.

8 DR. VERMA: Great. Yes. We have a whole
9 session tomorrow on clinical trial issues, and we
10 certainly understand that for clinical trials, the
11 study population needs to be really well defined.

12 In order to enroll subjects who are
13 non-responders, it would be best likely to do a
14 run-in period in the trials and really only involve
15 the sick patients who don't respond to good
16 standard of care. We need to enroll patients who
17 have more comorbidities and real-world patients
18 also. We have a whole session on that tomorrow,
19 but thank you for raising those points now.

20 One thing I wanted to touch upon was
21 multidisciplinary care. This is something that
22 came up in a lot of the talks. As everyone

1 mentioned, wound care really is interdisciplinary.
2 Several different people and services may be
3 involved, and this just increases the risk of
4 communication problems or treatment failure at so
5 many different time points, and it seems that's
6 often where patients can be let down.

7 Dr. Kim, you also talked about disparate
8 care in different parts of the country, and that
9 delayed care can lead to wounds that are even more
10 difficult to heal. So I'd just like to hear from
11 the panelists, how do you think multidisciplinary
12 care could be improved for wound healing?

13 DR. GARCIA: I can speak from the long-term
14 care standpoint. We have interdisciplinary team
15 meetings, and that involves all the different
16 players in terms of nursing staff, dietary,
17 physical therapy, as well as the providers who are
18 taking care of the residents. Having some type of
19 communication like that and the management of
20 patients is helpful because all of the different
21 players are in one forum.

22 That being said, I understand that in an

1 outpatient clinical practice, that's not going to
2 be feasible. So clearly in the outpatient aspect
3 it's more of a communication with the primary care
4 provider who was the consultant that sent the
5 patient to you, but I think having members of those
6 teams as part of your platform and taking care of
7 the resident or the patient is going to be helpful.

8 For example, ordering a wheelchair cushion
9 for a patient is helpful, but if that wheelchair
10 cushion is not adequately mapped to the patient's
11 needs and they're just ordering a standard
12 wheelchair cushion for someone who needs offloading
13 on their ischium, but the patient is sliding down
14 because that wheelchair cushion is not wide enough
15 for the chair or is not the right type of cushion,
16 then you've done nothing for the patient. So that
17 patient really needs to have that physical therapy
18 evaluation for that wheelchair cushion.

19 DR. GOULD: I think the systems of care are
20 really beneficial, and I'm talking about the
21 non-profit systems of care, not the for-profit
22 systems of care, because that really does

1 facilitate that coordinating of efforts.

2 We have our hospital, our outpatient wound
3 center, our visiting nurses, and several of the
4 skilled nursing facilities all interconnected along
5 with our primary care doctors, and that helps
6 communication. We can communicate in the
7 electronic medical record. We have a texting
8 system. We can really follow those patients from
9 place to place and get them the things that they
10 need.

11 That needs to be better coordinated. I used
12 to be in the VA. I loved it because it was one
13 system. One VA is not one VA, but at least you
14 knew what you were getting. You get into the
15 private world, and it's completely different and
16 disconnected. So we need some better systems, and
17 we need wound centers that are in those systems and
18 not just out on their own.

19 DR. KIM: Yes. I just want to make a
20 comment on that, too.

21 As you know, Dr. Kapil -- and Dr. Fan is on
22 at Georgetown, and I think is truly one of the

1 great representatives of a multidisciplinary
2 approach, but I have concerns because when I'm at
3 different lectures and conferences, these terms are
4 bantered around quite a bit. They use terms like
5 "interdisciplinary," "multidisciplinary,"
6 "transdisciplinary," "pan-disciplinary."

7 I don't know what any of that means because,
8 honestly, now having served at two different
9 academic institutions, it seems like everybody is
10 multidisciplinary. But when you start to delve
11 into that, you realize that they may have one
12 specialist with one that you can call when you need
13 them, and they call that multidisciplinary.

14 I think the key is -- what's been mentioned
15 here already by Dr. Gould and Dr. Garcia -- there
16 are two major concepts that make it
17 multidisciplinary. It doesn't matter what the
18 disciplines are by the way. It's communication and
19 cohabitation. The problem is that the
20 communication through the EMR is a great way if you
21 work within a system, but it doesn't mean they're
22 cohabitating. We use Epic, and I have access to

1 all kinds of specialists. It doesn't mean they're
2 readily available to see my patients.

3 I think the cohabitation model that
4 Georgetown exemplifies is the ideal. It has to be
5 the office next to your office with a different
6 discipline working on the same patient. I think
7 that is truly multidisciplinary. Unfortunately, if
8 you look at the papers on multidisciplinary
9 approach and you see them globally, they're not
10 truly multidisciplinary. They're still
11 consultative services and, to me, I think the
12 outcomes can be even further improved if it was
13 truly, in my definition, multidisciplinary.

14 DR. FAN: Yes, I agree with everything that
15 Dr. Kim has said. I have the luxury of working at
16 Georgetown, so if there's a patient that comes in
17 with a chronic wound, you have a vascular surgeon,
18 you have a rheumatologist, and you have hyperbarics
19 down the hall.

20 I think coordinating that, especially for
21 the chronic wound patient who may not be so mobile,
22 who may be elderly, going to all these different

1 private practice clinics, that's how things fall by
2 the wayside. And even with great communication
3 amongst the providers, you also have to consider
4 the patient factor. So I completely agree that
5 communication and cohabitation is critical for
6 multidisciplinary care.

7 DR. TOMIC-CANIC: I would also like to add
8 one more thing to all of that, which is research,
9 which is typically in the background and kind of a
10 side project, mostly back to volunteering or very
11 involved clinics and/or surgeons for that matter.

12 I don't think that any wound center is
13 really truly built to have the research arm already
14 implemented that interventional clinical trials, or
15 any kind of clinical trials, or even research
16 projects can be built on and be directly
17 implemented. It's mostly high-energy people who
18 are really willing and caring to participate, and
19 engaging. But I don't think that, in general,
20 wound centers are even considering that kind of arm
21 from the get-go as they are being set up.

22 DR. FIFE: Our payment reimbursement models

1 disincentivize communication. There are very few
2 ways in which we are incentivized in any way. The
3 communication level is almost exclusively based on
4 the commitment and devotion of the clinician. We
5 like to think that we're altruistic, but altruism
6 just does not work as a framework for good clinical
7 care.

8 DR. VERMA: Thanks, everyone.

9 I'd like to talk next about wound
10 recurrence. Part of the reason non-healing chronic
11 wounds are called chronic, it's not just the length
12 of time it takes them to heal, but the fact is it's
13 their kind of condition, and they may recur. For
14 that reason, a lot of clinicians have advocated,
15 saying that chronic wounds shouldn't be considered
16 healed but rather in remission.

17 Dr. Fan, you mentioned in your talk that the
18 U.S. really focuses on wound size and not as much
19 on recurrence and function as Europe does.

20 Dr. Kim, you also mentioned recidivism, and
21 20 percent of diabetic foot ulcers may recur.

22 Could the panelists speak a little bit more

1 about how helping prevent recurrence of the wounds
2 may be as equally as important as actually getting
3 the wounds to heal, and what kind of strategies you
4 take in your practice to help prevent wound
5 recurrence?

6 DR. FIFE: One of the things I'd like to
7 point out is that sometimes when we talk about
8 recurrence, I'm often asked, when we're looking at
9 registry data, "Is that the same one that came
10 back?" as if they happen always at the exact
11 location where they previously happened.

12 So I'd like to make sure when we talk about
13 recurrence, we made another boo-boo; not
14 necessarily the wound that just closed that
15 reopened again because it's not that easy to say,
16 "Oh, exact spot." For venous ulcers, it's a region
17 that usually breaks down, and for diabetic foot
18 ulcers with their Charcot deformities, their feet
19 keep changing shape, so that's one issue.

20 But the thing that I'm most burdened about
21 is that we keep talking about all of this from the
22 perspective through the lens of the wound. The

1 average patient has two of them, and depending on
2 what disease process you're looking at, they may
3 have three or four. So we do not approach this
4 through the patient lens. It's not just that the
5 wound occurs; it's that I got the left one healed,
6 and they still have the right one, and they're
7 still in treatment for the right boo-boo, and then
8 30 percent of the time while I'm seeing them for
9 one wound, they develop another one.

10 So it's way bigger than just the issue of
11 recurrence. It's multiple wounds, and it's the
12 crops of them that keep coming up.

13 DR. GOULD: We also ask our patients to do
14 things that are nearly impossible.

15 DR. GARCIA: That's what I was going to say.

16 (Laughter.)

17 DR. GOULD: I'm asking an 80 year old to
18 wear compression every single day, and to apply
19 moisturizers to their legs, and all sorts of
20 things, and not run into the dishwasher door.
21 That's where we run into problems.

22 I'm asking somebody who's had a pressure

1 ulcer and telling them that that area that broke
2 down is never going to have normal strength again,
3 and therefore you have to protect it, and you have
4 to stay off of it, and you can't sit for 8 hours
5 and do the work that you originally intended to do.

6 So we're really condemning them to a life
7 that's completely altered than the life I have, and
8 I'd say that you have as well, but I don't know
9 your history. But it's really hard. So I think we
10 have to expect recurrence because they have scar.
11 They have underlying problems. Scar tissue is
12 never normal. The vascularity is never going to be
13 normal. It's really hard.

14 Aimee, you have stuff to add to that?
15 Because you do it all the time.

16 DR. GARCIA: Yes. I was going to say that
17 we have to work within the construct of the
18 patient's reality because in an ideal world, all of
19 the things that we tell the patient to do magically
20 make them not recur. But if this is a patient who
21 has, for example, a diabetic foot wound, but he's
22 the breadwinner for his family, he's got to go to

1 work; there are no ifs, ands, or buts, and he can't
2 go to work as a construction worker with a boot, a
3 DH Walker.

4 So we as providers need to work within the
5 construct of the patient's reality and try to focus
6 our care to what the patient needs as well, not
7 just healing the wound, but healing the wound
8 within their reality.

9 DR. FIFE: That I think has implications for
10 endpoints because maybe the endpoint ought to be
11 that they don't have to get rehospitalized, so
12 healing becomes an unrealistic goal for some of
13 those folks.

14 DR. GARCIA: Yes. It will keep them from
15 getting an amputation.

16 DR. TOMIC-CANIC: I wanted to add that there
17 are a lot of research efforts really ongoing into
18 that arena and the understanding of biology on why
19 the wounds really -- what are the pathways that
20 lead to recurrence.

21 I will just mention, because I think it's
22 going to be discussed tomorrow with Dr. Jones and

1 Dr. Sen, that in terms of the activities of the
2 Diabetic Food Consortium, we're actually trying to
3 look, and test, and validate the biomarkers that
4 can predict reoccurrence. So there are efforts on
5 the research side that are going along the lines
6 because this is obviously recognized as a
7 significant problem, and to understand why it
8 happens and whether we can predict how that
9 happens.

10 DR. KIM: This has been mentioned many times
11 from this section of the question. When I think
12 about recidivism and recurrence, at least in the
13 diabetic foot ulcer world, this is a social issue
14 once it's healed. All of these things, including
15 trying to get payment for their diabetic shoes and
16 inserts, the issue of trying to have close
17 surveillance of these patients, where their access
18 to health care is limited, these are so -- and this
19 is especially true with Dr. Garcia's population of
20 sacral and ischial ulcers. That's a social
21 problem. That's not a medical problem; that's a
22 social problem.

1 I think those are the bigger challenges.
2 And I don't know how you can, from the design
3 perspective, study these social problems. It's not
4 like you're measuring wounds to see what rate or
5 percent healed. That's easy. It's hard to try to
6 figure out what their barriers of care are. That's
7 hard. If you want to get to the root of the
8 problem, I think that's the root of the problem.
9 The healing is not the root of the problem; it's
10 their environment that create these barriers to
11 heal, and we've yet to identify those.

12 DR. FIFE: And let's face it. We see people
13 at the end of a series of unfortunate events that
14 may have taken place for two decades, and then
15 we're supposed to fix that. That's an unrealistic
16 expectation that we can fix risk factors that have
17 taken two decades to evolve.

18 DR. TOMIC-CANIC: And I would like to add to
19 that, that there is really a biological cause on
20 the reoccurrence. For example, bacteria can be
21 actually hiding inside epidermis, and even though
22 that epidermis closes, that intracellular bacteria

1 can actually cause reoccurrence of infection and
2 will open that wound regardless of what's being
3 done to it externally.

4 So you have to acknowledge that, again, not
5 all reoccurrences are going to be the same; that
6 there might be some biological underlying issue, or
7 the epidermal barrier has not been fully formed,
8 and therefore there is a penetration of
9 microorganisms through that skin, even though it
10 looks closed.

11 So we cannot dismiss the biology here. I
12 just have to speak from the research world because
13 the more we look, the more causes we find for
14 reoccurrence that actually are inherent in that
15 tissue that actually we perceive as closed.

16 DR. FIFE: Although, I don't know if
17 they're different than the reason they happen in
18 the first place. I think that's a fair question.
19 When you talk about recurrence, the factors are
20 different than the reason they had the first wound.

21 DR. GOULD: Also, some of the secondary
22 healing, if you secondarily heal a very, very large

1 area, that's going to remain unstable, whereas if
2 we had something and understood the biology better,
3 we could get that revascularized in a better
4 quality tissue that doesn't have such propensity to
5 break down, and then we might not have so much
6 recidivism. I'm going to put that on Marjana's
7 shoulders to figure out.

8 DR. VERMA: I'd like to close the panel with
9 one final question. What I've heard is wound care
10 really does require a holistic approach. We
11 shouldn't be just looking just at the wound in
12 isolation. Healing wounds requires the right
13 provider, the right standard of care, and you need
14 the right coordination of care, whether it's
15 multidisciplinary or interdisciplinary, and the
16 right treatment. All that's required to heal a
17 wound.

18 In an ideal world, if everything else is
19 taken care of, here at the FDA, we're focused on
20 treatments, on products. So in the panelists'
21 opinion, what would be an ideal product for
22 treatment of non-healing chronic wounds? And I'll

1 let everyone take a stab at that.

2 DR. FIFE: I think we're missing nutrition.
3 I think some of the products we need are things we
4 swallow.

5 DR. VERMA: Just to follow up, is that a
6 product that's necessary or is that education for
7 patients about --

8 DR. FIFE: I think it's probably
9 supplements, and I think some of them we know about
10 like l-arginine that are available, but we don't
11 take them, so it's left up to the patient to figure
12 out how to get them. I think that's an enormous
13 gap because there is generally a focus on the stuff
14 you put on the boo-boo. I'm not convinced that
15 that's where the answer is going to be in some of
16 these systemic illnesses.

17 DR. GOULD: I think it's going to be a
18 drug-device combination. That's been one of the
19 stumbling blocks for basic science researchers, is
20 they see a multitude of factors that they see are
21 problematic in what we know about the basic science
22 of a wound, and they say I want to address these

1 factors. It's a combination of those, plus a
2 device to do delivery, and then they look at how
3 can I get this through from my basic science to
4 product development and say, "It's too hard; not
5 gonna do it."

6 So I think that what we need are pathways
7 that allow that to transform better, where we can
8 look at combinations, we can look at time to
9 delivery, and get wounds to heal because our
10 clinical trials, as we'll talk about tomorrow,
11 they're designed with one thing that's supposed to
12 heal a wound in 12 weeks, and that's not how wounds
13 work. So we need to understand the combination.

14 DR. TOMIC-CANIC: Yes. I think that's a
15 major challenge in general because I think it's not
16 a single factor. I think it's the combination of,
17 simply because there are, as we talked about,
18 multiple ways of how the wound arrives to the
19 non-healing point, and to reactivate that and
20 switching that wound into an acute healing wound,
21 it's not going to be simple. I think once you
22 approach this, again, as a multiple components

1 approach, I think it's becoming costly and almost
2 cost prohibitive to approach it as a multifactorial
3 delivery or multifactorial drug targets.

4 I want to say -- and I think somebody will
5 touch upon this in these two days -- is that unlike
6 the cancer field that has so many small molecules
7 and so many different types of approaches,
8 treatment approaches, ours currently are very
9 limited.

10 I think the more we have them approved, I
11 think we are going to have a lot more combinations
12 available. Approvals, again, are restricted by
13 this single primary outcome because they think
14 there are much more benefits to patients than just
15 having it closed. Once we have these kind of
16 therapies approved, I think then the combinations
17 will be in place.

18 DR. KIM: I think what we're talking about
19 is such a complex system. There are such huge gaps
20 in our knowledge. I feel like after 20 years, I
21 know less than when I first started. I thought I
22 had it all figured out. I know so little about my

1 patients and trying to heal these wounds.

2 To your question, Kapil, I think, first of
3 all, I don't know if diagnostics is part of the
4 FDA. You were talking about more interventions and
5 treatments, but if we can identify wounds and the
6 specific particular characteristics of wounds, that
7 can drive your intervention and the most
8 appropriate treatment.

9 Right now, we need to try to cater our
10 therapies more specifically to specific patients,
11 and we just don't take that approach.

12 DR. FAN: I agree. I don't think there's a
13 mechanism for us to have a one fix all because
14 wounds are just so complex and so multifactorial.

15 DR. VERMA: Thank you all for the great
16 panel discussion and your great talks. We have a
17 lot to mull over. As other questions come in, in
18 the chat box, public questions, we'll be answering
19 them either today or over the course of the next
20 two days.

21 I'll give everyone the next five minutes of
22 their time back, we'll have a lunch break, and

1 we'll come back at 12:30 for a patient's voice
2 session. Thanks, everyone.

3 (Whereupon, at 11:41 a.m., a lunch recess
4 was taken.)

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

(12:31 p.m.)

Patient Voice Session - Robyn Bent

CAPT BENT: Good afternoon, everybody, and welcome back. I hope you had an excellent lunch. My name is Robyn Bent. I'm the director of Patient Focused Drug Development within the Center for Drug Evaluation and Research here at the FDA. I'll serve as the discussion facilitator for this session.

Patient-focused drug development is really a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation. As experts in what it's like to live with their condition, patients are uniquely positioned to inform the understanding of the therapeutic context for medical product development and evaluation.

Today we are fortunate to have with us nine patients who have lived with a variety of different

1 types of wounds. They volunteered their time to
2 share with us their perspectives on dealing with
3 these wounds. We will have two hours for our
4 discussion today. Many of our panelists have
5 pre-recorded videos that we're going to share with
6 you. During their videos, our panelists will
7 provide a high-level overview of their experiences,
8 then we'll move on to our panel discussions.

9 We'll have two panel discussions. Our first
10 session will focus on the health effects and daily
11 impacts of chronic non-healing wounds that matter
12 most to individuals, and our second panel
13 discussion will focus on panelists' thoughts and
14 approaches to managing their wounds. Between the
15 two panel sessions, at approximately 1:30 Eastern
16 time, we'll take a 10-minute break, returning at
17 1:40 to see the remaining four videos from our
18 panelists. Our session will end at 2:30 and will
19 be followed up by another break.

20 We're looking forward to our conversations,
21 so we'll go ahead now and start the videos.

22 (Video played.)

1 ERIC: Hi there. My name is Eric Donovan.
2 I'm a functional nutritionist from Boston,
3 Massachusetts. I'm going to be briefly detailing
4 my experience as a patient who suffered a chronic
5 wound. I will quickly detail my experience, and
6 I'm open to any further dialogue pertaining to my
7 comments, but to begin, I will highlight the health
8 effects, daily living, approaches to care, and
9 challenges with access.

10 My wound was the result of a pressure
11 injury. I have a C5 quadriplegic diagnosis and use
12 a wheelchair for mobility. The injury was acquired
13 from improper and faulty medical equipment. The
14 health effects that accompanied my wound were
15 amplified due to the pre-existing spinal cord
16 injury. My ability to care for the wound was
17 limited, so I required extra attention for my care
18 team, which through the pandemic proved
19 challenging.

20 Subsequently, daily life was heavily
21 affected. Hours of my day were solely focused on
22 wound care and wound healing practices; for

1 example, offloading and pressure relief. Stress
2 and depression were of special concerns due to the
3 amount of time that I was required to stay in bed.
4 Additionally, connecting with and feeling
5 encouraged with proper treatment was challenging,
6 as there were differing opinions on how to treat my
7 wound.

8 One thing I look for in my practitioners is
9 their ability to see beyond a diagnosis, symptom,
10 or condition, and to be seen as a human
11 experiencing those conditions. So I was careful on
12 how I chose to move forward, and fortunately was
13 able to connect with my wound care specialist, who
14 was the last physician I saw before continuing with
15 any protocol and wound healing.

16 The approaches offered to me were surgery,
17 donated tissues, and tending to my body's ability
18 to try and close the wound. Because of my colorful
19 medical history, surgery for me was the last
20 resort. After deciding on a therapeutic
21 partnership with my wound care specialist,
22 Dr. Gould, we began treating my chronic wound with

1 wound care supplies and healing techniques and
2 spending time off the wound, and because of its
3 location meant bed for me.

4 I was written orders for supplies that were
5 not always accessible and needed shipping time,
6 which means orders could be impacted and were not
7 readily available. Availability of such supplies
8 added to the stress of the wound. Due to the
9 location of my wound and bony anatomy, I ultimately
10 needed to have a surgical intervention which was a
11 flap surgery, which I was mentally and physically
12 prepared for, and will note that the trust between
13 my physician and I had a great deal of weight in my
14 recovery.

15 I'm happy to report that this particular
16 wound has been classified as healed, and I hope
17 that my comments today can help others meet their
18 own goals in chronic wound healing. Thank you.

19 (Video played.)

20 MARTHA: Hi. My name is Martha Bednar [ph].
21 On June 22, 2007, I experienced my first venous
22 stasis ulcer while on vacation with my husband Joe

1 in Hawaii. My husband and I found a podiatrist who
2 treated it. It was a very painful process. After
3 two weeks, he sent me to the Wound Center at
4 Queen's Hospital, where I was treated by a surgeon.
5 When we returned to New Jersey, I had follow-up
6 care at St. Peter's Hospital with another surgeon.
7 By the end of August, my wound was closed, and I
8 was able to return to teaching for the next year.
9 Finally in 2008, I retired.

10 I didn't know then, but I know now, that my
11 venous stasis ulcers are a chronic problem. In
12 2013, I got my second one on the inner side of my
13 left ankle, and my third one on the outer side of
14 the same ankle. In 2016 and 2017, I got the 4th
15 and 5th ulcers on the inner-left ankle.

16 February 15 2018, I got the 6th one on the
17 inner side of my right ankle. In February 25,
18 2019, I got the 7th one on my inner-left ankle. On
19 September 16, 2020, I got the 8th ulcer on the
20 inner-left ankle, and on October 16, 2020, I got
21 the 9th ulcer on the outer-left ankle. On
22 October 6, 2021, I got the 10th ulcer on the

1 inner-left ankle. On December 15th of 2021, I got
2 the 11th and current ulcer on my inner-left ankle.

3 I'm 76 years old, Caucasian, of Italian and
4 Polish heritage, and live in a suburban community.
5 My wounds do affect my quality of life. The almost
6 continuous pain feels as if someone took a
7 cigarette and burned my skin. The only time I
8 don't feel any pain is when I sleep.

9 In addition, I can't walk as fast as I would
10 like. My husband needs to cook breakfast and
11 supper, and also he drives me to my medical
12 appointments since I can't drive. He also does the
13 grocery shopping and certain household chores since
14 I can't stand for long periods of time.

15 My current medical care is overseen by
16 Dr. Granick at University Hospital, Newark, New
17 Jersey. When he's not there, Tom the nurse
18 practitioner is in charge with Frances [ph] the
19 nurse. They treat me with triad, a sponge to
20 absorb the drainage and Unna's boot, and a 4-layer
21 compression wrap from my toes to my knee. The
22 triad and bandages are changed on a weekly basis.

1 My husband and I have been trained to change the
2 bandages in case we are able to travel once the
3 pandemic restrictions are lifted and knowledge of
4 care cannot be arranged or is not available where
5 we plan to visit.

6 My most challenging experience is trying to
7 lead a normal life without the pain of these
8 wounds. I'm looking forward to being healed for a
9 longer time between wounds

10 (Video played)

11 LAURIE: Hi. My name is Laurie Rappl. I'm
12 a physical therapist, I'm a certified wound
13 specialist, and I'm a T12 paraplegic. I incurred
14 my injury in June of 1980, so I've been a complete
15 spinal cord injury for the last 42 years. Over
16 those years, I've had several ischial pressure
17 wounds. I probably spent probably a total of five
18 or six years in bed with various wounds always on
19 the same spot.

20 Most recently, I spent all of 2021 in bed
21 with a pressure ulcer, trying to offload it as much
22 as possible in order to heal it and avoid surgery.

1 During that time, I was seen at a wound clinic, a
2 local wound clinic, which claims to be
3 multidisciplinary, and they are as far as they have
4 nurses and doctors and podiatrists, and they do
5 have HBO.

6 As a certified wound specialist, I'm aware
7 of many treatment options that are on the market.
8 However, when I went to the wound center, and they
9 only see a handful of spinal cord injured at this
10 particular center, I was offered a general surgeon,
11 a very good general surgeon who oversaw my care and
12 was there once a week. He did debridement and put
13 me on the VAC, and I was on the VAC for a total of
14 about 4 months.

15 On the VAC, the wound progressed, and then
16 it regressed, and then I was not able to improve it
17 any further than that, but all I was offered was
18 continuing the VAC, and I was allowed to pack it
19 with either Promogran or with silver. Despite the
20 fact that that wasn't working, that's what I was
21 offered unless I wanted to go to flap surgery. I
22 eventually did go have a mini flap -- I saw a

1 plastic surgeon -- and I was in the hospital for a
2 total of six weeks, from November 9th to
3 December 24th of last year.

4 In that time, the way it affected my health
5 was profound. I had depression, which greatly
6 affected my family. I thought I was doing pretty
7 well, but now in hindsight my family tells me it
8 was a very, very difficult time for them. I felt
9 very much isolated because I was relegated to the
10 four walls of my bedroom unless I was going to a
11 doctor's appointment or the home health nurse was
12 coming in; a loss of appetite; pain everywhere.

13 You'd think in bed you wouldn't have pain,
14 but it's very painful to lay in bed 24/7, in my
15 shoulders, in my back, my neck, my gut, everywhere.
16 I can't describe to you how much pain that is; a
17 complete loss of strength. When I was done with
18 bed rest and came out of the hospital, I could
19 barely transfer myself. I have to use a sliding
20 board now, which for a person as a T12, that's like
21 going back to training wheels. It's a great loss
22 of ability.

1 identify and find a way to address the current
2 barriers to product development for non-healing
3 chronic wounds. Before we start our panel
4 discussion, I'd like to invite our other panelists
5 to turn on their videos and unmute, and just
6 briefly say hello.

7 Go ahead and say hello. Thanks.

8 MARTHA: I'm Martha Bednar.

9 CAPT BENT: Thank you, Martha.

10 Amy?

11 AMY: I'm Amy Ellickson [ph] from Wisconsin.

12 CAPT BENT: Thank you, Amy.

13 Dana?

14 DANA: I'm Dana Davis. I can't seem to
15 unhide my video, and I'm from Denver, Colorado.

16 CAPT BENT: Let me ask you to start it.

17 DANA: There we go.

18 CAPT BENT: Okay. Great.

19 DANA: Sorry. I'll start my video. Great.
20 I'm 54, and I'm from Colorado.

21 CAPT BENT: Thank you.

22 Eric?

1 ERIC: Hi there. My name is Eric. I am 33,
2 and I'm from Boston.

3 CAPT BENT: Alright.

4 Laurie?

5 LAURIE: I'm Laurie Rappl. I am in
6 Greenville, South Carolina.

7 CAPT BENT: Thank you.

8 Ollie?

9 OLLIE: Ollie Simpson. I live in the state
10 of New York.

11 CAPT BENT: Thanks, Ollie.

12 Peter?

13 PETER: I'm Peter Fisher [ph]. I'm 75 years
14 old. I reside in the Houston area of Texas.

15 CAPT BENT: Thank you. Dr. Maddy? Rick?

16 RICHARD: Yes. I'm Richard Maddy. I reside
17 in a suburb of Houston, and I'm currently having
18 problems getting my video to start.

19 CAPT BENT: Alright. Let me see.

20 RICHARD: There we go.

21 CAPT BENT: There we go.

22 RICHARD: Okay.

1 CAPT BENT: Great. Thank you so much.

2 As we mentioned, and on the screen you can
3 see Topic 1, which will focus on the Health Effects
4 and Daily Impacts of Chronic Wounds. On this slide
5 you'll see some of the questions that we're going
6 to discuss during the session.

7 Now maybe what I'd like to do is turn back
8 to our panelists, and we'll start the panel
9 discussion portion of the meeting. Let me start by
10 asking you, what aspects of the non-healing or
11 chronic wounds have had the most significant impact
12 on your quality of life?

13 I wonder, Peter, if you'd be willing to
14 maybe start off the question and answer session?

15 PETER: Sure.

16 CAPT BENT: Thank you.

17 PETER: Sure. I suffered the wound during
18 surgery for my lung back in December of 2021. From
19 the hospital, I was moved to a rehab center, and
20 from the rehab center, home. I saw a specialist,
21 Dr. Fife, for the wound healing. She prescribed
22 traditional medications and treatment of the wound,

1 and my first meeting with her was January 31st, and
2 the last was in April, the end of April of this
3 year.

4 I found that the most arduous aspect of the
5 whole process was the changing of the medication at
6 the wound and the limitation that the wound
7 produced in terms of my active life. I was
8 limited, not severely, but to a certain extent, and
9 was unable to do some of the functions that I had
10 been doing.

11 This process, I'm almost embarrassed to be
12 on this panel given the length and duration of many
13 of the panelists' conditions. Let me just say that
14 the one thing that I found most important, and it
15 was Dr. Fife that pointed this out, was nutrition,
16 nutrition, nutrition. She loaded me up with
17 vitamins. She directed me on my diet. And as soon
18 as she did that and I began to follow her
19 instructions, I began to heal.

20 When I first visited her, she said it would
21 be a 6-month process. It actually took about 3 and
22 a half months for healing to occur, and she was

1 amazed at the speed. But it was all a function of
2 that nutritional benefit of the supplements and
3 good eating, and that's about all I had to say on
4 that.

5 CAPT BENT: Great. Thank you.

6 Martha, I see that you have your hand up, so
7 let's turn to you.

8 (No response.)

9 CAPT BENT: If you're speaking, you may be
10 muted.

11 MARTHA: Am I muted?

12 CAPT BENT: No. We can hear you now. Thank
13 you.

14 MARTHA: Okay.

15 I wanted to ask Peter, what specific
16 vitamins did she put you on, and what new diet
17 contributed to your success? Because I'm very into
18 nutrition, and I think I eat well, but in spite of
19 that, I've gotten 12 of these venous stasis ulcers.

20 PETER: The most important, I think, single
21 pill that I'm taking is lots of vitamin D3. She
22 put me on 10,000 units a day. I had been taking

1 vitamin D3 on the order of 500 units. And while
2 that 10,000 units seems like a huge amount, it had
3 no effect on my digestive system, but it had a
4 tremendous effect on the healing process.

5 As far as the diet was concerned, the first,
6 second, and third thing she said was, "Lay off the
7 liquor, lay off the liquor, and lay off the
8 liquor," and I finally got that through my head.
9 And when I started that and started eating a good
10 nourishing diet and the vitamin supplements that
11 she recommended, I found the improvement in the
12 wound to be dramatically fast. And as she said,
13 she was shocked at how quickly I recovered.

14 CAPT BENT: Great. As a spoiler, we're going
15 to have a few questions about nutrition in the
16 second panel topic, so we'll dive a little bit
17 deeper into the impacts of nutrition in just a
18 little bit.

19 Let me see. Amy, I don't know if you would
20 be willing to talk to us a little bit about the
21 most significant aspects of the non-healing wound.

22 AMY: Quality of life, definitely quality of

1 life.

2 Until last week, I was traveling twice a
3 week to Rochester, Minnesota. For me, that's an
4 hour and a half each way, which gets to be costly.
5 As you know, gas is not cheap and parking isn't
6 cheap, so spending a lot of time taking care of
7 this. Also, I'm on biologic drugs right now, so my
8 immune system is severely compromised. Not just
9 COVID, but anything out there I have to be really
10 careful of, so I can't be around a lot of people.

11 My niece is graduating in a couple weeks
12 with her doctorate in nursing. I can't go because
13 it's being held at the Kohl Center. It's going to
14 be packed with people, so family things that I
15 can't attend, and that's hard to do.

16 It also affects my quality of life. It's a
17 very time-consuming thing, the amount of time that
18 you put into wound care. People have mentioned
19 pain, and I think we can all attest to what that
20 does to your quality of life. I'm really lucky
21 that my previous wound care doctor emphasized pain
22 management, but I know for a lot of people that can

1 be a problem. But even though I'm on pain
2 medicine, it really impacts what I do. It impacts
3 my mobility. It hurts to move, but it hurts more
4 if I don't move, so I move. I move around.

5 It also affects my quality of life as far as
6 trying to get everybody on the same page. When I
7 first started this journey, doctors were clueless.
8 My condition is called pyoderma gangrenosum, which
9 is an autoimmune system problem. It's a
10 neutrophilic dermatosis thing. It's a very rare
11 disease, so doctors don't know how to treat it.
12 They often will use a traditional wound care
13 approach, which can make the condition worse.

14 In the beginning, I was getting
15 debridements, which would make the wounds larger
16 and more painful, and you just don't do that to PG.
17 The [indiscernible] makes it worse. But I am in
18 good care. I was lucky enough that I've known
19 other family members who have had rare things and
20 ended up going to the Mayo Clinic to get them dealt
21 with. So I was like, "Ok. If my doctor doesn't
22 know what's going on, that's where I'm going to

1 go," and I did. And I will give them credit
2 because they know what they're doing there. Things
3 started to turn around for me once I went there,
4 but I've tried a bunch of different treatments that
5 haven't worked, or they've worked, then they've
6 stalled, so I'm kind of at a standstill right now.

7 Someone else mentioned depression. I will
8 definitely hype on that one, too, because having
9 chronic wounds, when it interferes with your daily
10 functioning, and your family life, and your friend
11 life, depression sets in. So I would urge anyone
12 that is dealing with chronic wounds to take care of
13 your mental health as well, because mental health
14 and physical health go together.

15 CAPT BENT: Thanks, Amy. I think that
16 that's an important point, and I think that we'll
17 hear that from a number of our panelists. It seems
18 like that's across the board.

19 AMY: Can I also add?

20 CAPT BENT: Yes, please.

21 AMY: One thing I was very fortunate to run
22 across is a PG support group. It's an online

1 support group, and it has been a blessing for me.
2 Because this disease is rare, I get the experience
3 of other people around the world who are dealing
4 with this, and what's worked for them and what
5 hasn't, and we build each other's moral up all the
6 time. Since this is a global support network, no
7 matter what time of day or night it is, there's
8 always someone you can talk with, so that's been a
9 big help.

10 CAPT BENT: Great. Thank you. I think
11 that's really very helpful information.

12 Let me see. Before we move on to the next
13 question, are there any others on the panel who'd
14 like to share a little bit about which aspects of
15 the non-healing wounds have the most significant
16 impact on your quality of life? If there's anybody
17 else, you can either go ahead and try and raise
18 your hand or you can just unmute and speak.

19 Eric?

20 ERIC: Can everyone hear me? I'm not muted,
21 am I?

22 CAPT BENT: Yes. No, we can hear you.

1 ERIC: Okay. Great. I just wanted to
2 comment. I don't disagree with anything anyone
3 said. I think there is validity to all the
4 comments made, depression, pain management, and all
5 those things. I think at the core of that,
6 communication is really the main thing there, and
7 communicating. I think everyone wants to feel seen
8 at the end of the day, and you want to be seen by
9 your family, your peers, and your physicians.

10 Having that open line of communication,
11 whether that be for more resources -- like someone
12 just said, support groups, options. I think
13 everyone is on point with my experience, and just
14 to highlight, the communication I think is really
15 at the core of everyone's comments.

16 CAPT BENT: Thanks, Eric.

17 Let me turn to Ollie, and then Dana, and
18 then we'll move on to the next question.

19 OLLIE: This is Ollie. I just wanted to say
20 that pain was very much a part of my wound, and I
21 think maybe it wasn't the wound, but the treatment
22 that I was given. The debridement that I had

1 initially, I had a lot of inflammation around the
2 wound area, and it certainly affected my mobility.
3 Instead of living an active lifestyle, I
4 became -- how do I say it? -- kind of like a couch
5 potato. I laid down and I sat down most of the
6 time, and I had to take advantage of things that I
7 had not before, such as getting someone to rake my
8 leaves, or to use a wheelchair when I was in the
9 airport, and things of that type. So the pain
10 really affected my quality of life.

11 CAPT BENT: Thanks, Ollie. That is an
12 important component.

13 Dana?

14 DANA: I just want to add -- and I agree
15 with what everybody has said. The depression, I
16 think, really comes from the fact that everything I
17 loved to do and do has been taken away, or I've
18 been told I've had wounds for over 31 years. I
19 can't just take my dog for a walk.

20 I've been in a wheelchair, but I live in
21 Colorado, so trying to either get a Roll-A-Bout to
22 offload or a wheelchair in ice and snow, there are

1 factors that people don't think about when you're
2 trying to be a really good patient and offload, but
3 then, basically, all you can do is stay home and
4 try to find something where you can find joy, and I
5 do think that wounds take away your joy. It's hard
6 to find things that you used to love to do to still
7 be able to do them, and that, I think, is a really
8 difficult part of it.

9 CAPT BENT: Great. Thanks, Dana.

10 Richard, go ahead.

11 RICHARD: Yes. This is not a problem now,
12 but looking back on when I had my wounds, the main
13 problem, as they were getting worse, was pain
14 control. There was a great deal of hesitancy on
15 the part of the doctors that were treating me at
16 the time to prescribe pain medication. My primary
17 care physician said that he did not prescribe
18 opioids, and I should see my pain specialist.
19 Well, the pain specialist that I was going to at
20 the time said that he didn't prescribe opioids; I
21 should see my primary care physician.

22 In the meantime, the pain was just

1 excruciating. I was sleeping maybe 2 hours a
2 night, and this went on for about a year. And the
3 only way I could get any sleep was when the pain
4 got so bad that I would actually pass out. And
5 when I passed out, I could sleep for about 2 hours,
6 and then I got up again.

7 So pain management is something that I think
8 we're going to have to address one way or the other
9 in this climate that we have. I know we have an
10 opioid crisis, but individuals are going to find a
11 way, if they're in enough pain, to deal with that
12 pain, and sometimes the measures that they take to
13 deal with the pain are dangerous and they're
14 permanent.

15 CAPT BENT: Thank you. I think that's also
16 a really important point.

17 I'd like to move on now to talking a little
18 bit about the specifics of your wound care and
19 maybe if there were any challenges to that. Are
20 there any specific aspects of caring for the wound
21 that you've found the most challenging? Maybe it
22 was being trained to care for the wound.

1 Amy, did you raise your hand?

2 AMY: Right away, I'm going to say
3 insurance. Insurance has been the biggest barrier
4 as far as wound care supplies. As you all know,
5 they have their codes, and if it doesn't fall under
6 this code, then we don't cover it; or one of my
7 wound care supplies, we will cover it, but we only
8 cover it for this lot. So I get one package, and
9 it's one thing and, well, that's good for 7 days
10 out of the 28, but it doesn't cover the other
11 3 weeks. So I'm paying for a lot of wound care
12 supplies out of pocket.

13 The other thing is when I first started with
14 wound care supplies, it was finding someone who
15 knew what they were doing and knew what to
16 prescribe. So the biggest things would be finding
17 someone who knows what they're doing as far as
18 prescribing those wound care supplies, and then
19 having them covered. A lot of my supplies I buy on
20 Amazon because even though I have Medicare,
21 Medicare doesn't cover a lot of it, so I'm left to
22 other devices or rationing. I'm supposed to do my

1 wound care every day. I often do it every other
2 day to make the supplies last further.

3 CAPT BENT: Thanks, Amy.

4 Martha? And I know Joe might have some
5 thoughts on this as well.

6 JOE: Well, yes. My father hated me, so my
7 name is my Martha right now.

8 No. I just have to agree with two of the
9 things that were said. Number one, finding
10 available, competent, knowledgeable wound care is
11 difficult. At least in Martha's case, she had
12 venous stasis ulcers, and there were surgeons and,
13 quote/unquote, "wound care specialists" who were
14 going to treat it like any other wound, and it
15 literally took a couple years to identify
16 appropriate care and treatment.

17 Secondly, as Martha said in her video, she
18 has been watching her ankles be taped and treated
19 for a number of years. Sitting in the treatment
20 rooms, it's almost impossible not to learn how to
21 do it, and then get a little bit more education.
22 So we are hoping that when we can travel, we're

1 going to pack an extra suitcase and just bring
2 medical supplies along with us in case we cannot
3 find competent, available wound care wherever we
4 go. There are lots of people who say, yes, we've
5 got wound care centers, and we can take care of
6 everything, and then you show up and they look at
7 you, and they kind of scratch their head, so we've
8 got to prepare for it.

9 One last comment, Amazon, say what you want,
10 but from the perspective of the wound care supplies
11 we need, they're fantastic.

12 CAPT BENT: Thanks.

13 If I can ask a follow-up question; of all of
14 the challenges like the logistics of caring for the
15 wound, the burden of doing the wound care, access
16 to treatment, the emotional stress, which of those
17 would you consider kind of the most challenging?

18 JOE: I'm going to let Martha speak.

19 For me, it's the restriction on life.

20 CAPT BENT: Okay.

21 JOE: And not one of those things is more
22 important than the other. If you can get

1 materials, and you don't have people who teach you
2 how to use them, they're useless, so it's kind of a
3 package deal. And as someone else said, we spend
4 more time taking care of wounds and going to
5 doctors now than we ever imagined.

6 MARTHA: We're both retired, and we didn't
7 think that this is what retirement would be. I am
8 grateful when I can walk a few steps without pain,
9 but my foot, it's unfortunate that the left foot is
10 worse than the right.

11 I also have another problem, which is called
12 posterior tibial tendon dysfunction with flat
13 collapsing feet due to arthritis. My podiatrist
14 says you don't want to do surgery. "You won't be
15 able to tolerate it. They'll put bolts in your
16 foot," and don't even do it. Then I went to this
17 Dr. Q in New York, and she said the same thing;
18 "You don't want surgery."

19 So my question is, well, how do I walk
20 better? Because sometimes I feel like the foot's
21 just going to give out. And I thought maybe a
22 brace, so Joe went on the internet, and he got

1 three braces. We brought it to the plastic surgeon
2 who oversees this wound center that I go to, and
3 decided that none of them are good for me. Maybe
4 we should go back and see Dr. Q. Maybe she can
5 make a brace.

6 But then I listened to this morning's
7 discussion, and they were saying the brace can
8 actually cause your skin to break down, and my
9 skin's already broken, so I don't know because I'm
10 not a medical person; I'm learning. I'm a teacher,
11 a retired teacher, not a specialist of anything. I
12 know a lot of little things.

13 CAPT BENT: Thanks, Martha.

14 I feel like I watched Dana nod, but not a
15 lot, when you said that. So let me turn to Dana
16 and see if she has any comments. And it may be
17 building on what you said or it might be something
18 completely different.

19 Go ahead, Dana.

20 DANA: It's two things, totally about the
21 brace.

22 Currently, I have a pressure wound on my

1 heel that was caused by the offloading boot I was
2 put on to help the wound that was on my toe. So
3 the wound on my toe has healed, but now for two
4 years I've had this wound on my heel. And like
5 you, trying to find care has been so difficult.

6 I am so blessed to have Dr. Driver, who I
7 met 20 years ago. I don't live in the same place
8 as her. I send her constant texts of wounds. If
9 people look through my phone, they would think I'm
10 insane because I'm constantly sending her pictures
11 going, "Should I be worried about this? They've
12 sent me home." And she's like, "Nope. You need to
13 be on antibiotics. You need to go back."

14 So I find it so helpful to have somebody
15 that I can trust so much, but so frustrating that
16 in the state that I live in, I can't get them to
17 listen to me. I'm either too healthy for insurance
18 to get what I need, and by the time I'm actually
19 really sick, it's too late, and I have to go in the
20 house, and I'm on a PICC line. So I completely
21 relate to what you're saying.

22 CAPT BENT: Thanks, Dana.

1 Let me turn to Laurie to hear maybe about
2 the specific aspects of caring for your wounds that
3 you've found the most challenging.

4 LAURIE: Thank you, Robyn.

5 I'm speaking as a spinal cord injured
6 person, and the daily impacts were the complete bed
7 rest, which is totally isolating. You're just
8 stuck in your room. And as much as we all felt
9 like we were isolated from COVID, you don't know
10 what those mobility restrictions are like until you
11 have to be in bed in your bedroom 24/7. I think
12 one of our panelists can speak to that. That was
13 extremely difficult.

14 The wound care itself, I had home health
15 coming in every other day, but there was cure
16 around that. And I would say I spent at least an
17 hour a day doing something with the wound. Health
18 effects, I said in my video, were multiple,
19 including depression, but just the pain all over my
20 body.

21 The most challenging thing for me was not
22 just trying to keep my spirits up and be happy when

1 other people came in to visit, because I didn't
2 want to be a grouch because then they wouldn't come
3 and visit anymore -- so there's that little social
4 dynamic -- but it was the frustration of only being
5 given extremely limited treatment options. Even
6 though they weren't working, those are the only
7 options I was given.

8 For a pressure ulcer, it's different than
9 for some of the vascular ulcers that are being
10 addressed. I didn't feel like I had caregivers who
11 were knowledgeable about my kind of wound and what
12 else they could do for it, short of VAC and
13 surgery.

14 CAPT BENT: Great. Thank you.

15 Let me see. Amy, did you have something you
16 wanted to add before we moved on?

17 AMY: Yes. It has to do with treatments
18 and, again, insurance. Again, what I have is rare.
19 It's PG, so a lot of treatments are not approved by
20 insurance for it, and we're fighting quite the
21 battle. It's basically the doctors versus the
22 insurance companies.

1 I was recently doing an ultrasound
2 treatment, and it was making a difference. I was
3 getting a decrease in wound size, which has since
4 stalled. Also, the rolled edges have eliminated
5 and the hypergranulation has decreased. Those are
6 signs of wound healing, but the insurance doesn't
7 consider that good enough. So there's not a
8 medical necessity according to the insurance
9 company for that treatment to continue, so that
10 treatment is being denied.

11 Also, I had a provider who recommended
12 hyperbaric treatment, and there are some studies to
13 back this up for being effective for PG, but there
14 aren't enough studies. And because there aren't
15 enough studies, Medicare is saying, "No. We're not
16 going to approve this treatment for you." So I
17 have doctors who are fighting to try to get the
18 right treatment for me, but we keep running up
19 against insurance that says, "No. We're not going
20 to do this," and that's really frustrating, and
21 that gets on you emotionally, too.

22 CAPT BENT: Thanks, Amy.

1 Before I move on to our next question, is
2 there anyone else who wanted to touch on the most
3 challenging aspects of caring for their wounds?

4 (No response.)

5 CAPT BENT: Okay. I don't see anybody, so
6 let me move on to the next question. This is kind
7 of a complicated question.

8 At the beginning of the session, we heard
9 from you all about the aspects of having a wound
10 that had the most impact on your life, and we've
11 obviously just heard about how this wound has
12 impacted your abilities to do the things that you
13 want to do. As you know, FDA regulates wound care
14 products, so I wanted to kind of build on what you
15 told us earlier and ask you a question about how
16 you would define an effective treatment.

17 When you had a wound, would you have
18 considered anything other than complete wound
19 healing of the wound to be a successful treatment?
20 For example, if you had a wound, would partial
21 healing have been acceptable to you? What if there
22 was a treatment that decreased the pain from the

1 wound, or allowed for easier wound care, or maybe
2 less frequent dressing changes? I wonder if
3 anybody wanted to speak to that.

4 I know, Dana, we touched on this briefly
5 during our call, and you had some thoughts, so I
6 don't know if maybe you'd be willing to start off,
7 and then we can turn to Martha once you're done?

8 DANA: Sure. I wasn't ready. I saw Martha
9 was ready to go.

10 CAPT BENT: Oh, sorry. I can turn to
11 Martha, and then to you.

12 DANA: Do you mind?

13 CAPT BENT: No, sure.

14 DANA: Sorry. Thank you.

15 CAPT BENT: Martha, go ahead.

16 MARTHA: I should press something down to
17 talk.

18 CAPT BENT: I can hear you.

19 MARTHA: If I unpress it, then you can hear
20 me?

21 JOE: Right.

22 MARTHA: Oh. You should see my drive; it

1 gets better.

2 JOE: No, you don't want to see that. Never
3 do you want to see that.

4 (Laughter.)

5 MARTHA: I try. Anyway --

6 CAPT BENT: Martha, I'm going to click on
7 asking you to unmute, and then you should be able
8 to just click on that.

9 (No response.)

10 CAPT BENT: Did you get the request to
11 unmute?

12 MARTHA: Unmute?

13 CAPT BENT: There we go.

14 MARTHA: Now I can just talk.

15 JOE: Yes.

16 CAPT BENT: Yes, ma'am.

17 MARTHA: Alright.

18 To me, complete healing would be the answer.

19 If I was told it's only partially healed, I would
20 find that unacceptable. The reason being, I was
21 told by my vascular doctor that I need to wear
22 compression stockings that are 30 to 40 milligrams

1 of mercury, which are very difficult to get on. I
2 do it. It takes me about 10 minutes. I put this
3 cream on my leg first, and I get them on.

4 But I would like this wound -- that's the
5 soft wound that's on my left ankle -- to be healed
6 so I could shower without a plastic bag, and then
7 put this cream on, and get into my compression
8 stocking. That would be helpful. Then, of course,
9 each day, I have to check both legs, both ankles,
10 to make sure another one is not going to just
11 happen because these things happen as if I were a
12 living volcano, and it's hard for people who don't
13 have these venous stasis ulcers to understand that.
14 It's not like I'm standing and I bang my foot
15 against the table. It's like I'm sitting here
16 talking to you, and I look down, and I see drainage
17 out of my ankle.

18 Then I'll go to the wound center and I'll
19 say, "Okay. It's a wound, right?" And the latest
20 told to me is, "It's not a wound yet." I mean,
21 "It's not a wound? It's coming through my
22 compression stocking. It's coming through my sock.

1 It's in my sneaker. Why is this not a wound?"

2 "Oh, that's only plasma, and if you just have
3 plasma coming out, it's not considered a wound
4 yet."

5 So now we've got to wait until more stuff
6 comes out, a couple of weeks, I'm in pain, and
7 there's no pain medication that works for this
8 except sleeping. Thank God I can sleep because
9 that's the only thing. But you can't sleep
10 24 hours a day, plus my body wouldn't allow that
11 either, and that's not healthy. So yes, I would
12 want to be completely healed.

13 CAPT BENT: Thank you.

14 Let me turn to Dana.

15 DANA: Thanks. Sorry.

16 So for me, I agree, and also I agree with
17 you; I've lived half my life with a shower boot.
18 If I could take a shower without the blue shower
19 boot, I'd be so thrilled.

20 But for me, it's complete healing because
21 I'm a type 1 diabetic for 47 years. I have MS, and
22 I'm on a biologic, so I can't have tap water. I

1 can't have anything -- I can't do anything. My
2 wounds are on the bottom of my feet, and until
3 they're completely healed, and completely healed
4 with enough time that the skin gets time to
5 actually become viable skin again, for me that's
6 not healing.

7 I agree with Martha. So many times, again,
8 I'm going to say I'm not sick enough yet for them
9 to do a certain treatment or for me to be able to
10 get a skin graft that I need; or if I'm healed a
11 certain amount, I can no longer get a skin graft,
12 but yet I still have an open wound, and for me that
13 means I go on a PICC line if I have an open wound
14 for too long. So for me, it's got to be a hundred
15 percent healing.

16 CAPT BENT: Thanks.

17 Laurie?

18 LAURIE: The ultimate goal would be a
19 hundred percent healing. I can't see any way
20 around that. However, I will say that when I was
21 on the VAC, and the wound made progress, it
22 decreased in depth, and then it increased in depth,

1 and it just stayed there despite another 2 months
2 on the VAC. I would take just progress toward
3 healing. For me, it would have been a massive
4 benefit. I would take interim steps just to move
5 my wound forward.

6 I don't think there's just one answer to a
7 wound, and being a wound specialist, I have this
8 double perspective. But I know we probably won't
9 be able to use one thing through the whole course
10 of treatment, so for me, I would have taken
11 anything that would have just moved my wound
12 forward so that maybe the VAC could be started
13 again later, or something else would step in. But
14 just having 2 months of zero progress, despite
15 doing everything I was supposed to, literally, for
16 me would be beneficial.

17 CAPT BENT: Thanks, Laurie.

18 That's kind of what I'm asking. Obviously,
19 the ideal is that the wound heals completely, but
20 are there interim measures of healing that would be
21 acceptable to you, whether that would be less pain,
22 or a 50 percent decrease in the size of the wound,

1 or less odor, or things like that?

2 Ollie, right before I turn to you, let me
3 turn to my FDA colleagues and see if they had any
4 follow-up questions for either Laurie or just in
5 general.

6 Go ahead.

7 DR. VERMA: Yes. This is Dev. Thank you
8 all for sharing your time and volunteering. Your
9 stories are really appreciated.

10 I heard a lot of you talking about pain and
11 pain being a big factor in your wounds. A lot of
12 you have also mentioned that a hundred percent
13 healing is necessary. But could you envision a
14 product that could partially heal your wound and
15 improve the pain? Would that be something that
16 you'd be willing to accept, a potential product
17 that decreases your wound by, say, 50 percent, but
18 improves your pain by 85 percent?

19 Again, this is just a hypothetical question.

20 CAPT BENT: Laurie, if you just want to give
21 a quick answer before we turn back?

22 LAURIE: Yes. Well, I didn't have pain

1 because I'm a paraplegic, so my wound didn't hurt,
2 but I would have taken a decrease in depth. I know
3 some of the studies, when they look at partial
4 healing, they're looking at the outside edges of
5 the wound, which is kind of easy to measure, but
6 the depth was my problem. I had a small wound on
7 the outside, but depth, and that's a little harder
8 to measure. I don't know an objective way to do
9 that, but I would have taken any decrease in depth,
10 an increase in granulation tissue.

11 CAPT BENT: Thanks, Laurie.

12 Ollie, I don't know if you want to maybe
13 start off by answering the question, and then we
14 can continue on with anything else you have to say.

15 OLLIE: Okay. Well, what I wanted to
16 say -- and maybe I've missed some of the
17 points -- is that the decrease in pain was very
18 important as a beginning step to complete healing
19 of my wounds. I feel a lot of the pain, as I may
20 have mentioned, was due to the inflammation around
21 the wounds, and it needed the proper medicine to do
22 that. So I just wanted to say, complete healing

1 was my goal, but interim steps to reduce the pain
2 were very, very helpful.

3 CAPT BENT: Great. Thanks, Ollie.

4 Does anyone else have any thoughts about
5 this?

6 JOE: This is Joe Bednar. I have to agree
7 with Ollie. If in fact this is chronic, if in fact
8 it's going to continue for let's say
9 forever -- [inaudible - audio lost] --

10 CAPT BENT: Joe, I think we may have lost
11 you. Oh, you're muted. Let me ask you to unmute.

12 JOE: Oh, there we go.

13 CAPT BENT: Okay.

14 JOE: I mean, if this is chronic, if it's
15 going to go on for time after time, if you're going
16 to heal and then it's going to reoccur, then
17 clearly anything that could reduce the pain during
18 the treatment process I believe would be welcomed
19 as long as it is not accepted as the end of the
20 treatment process. That's it.

21 CAPT BENT: Great. Thank you.

22 Anybody else? I don't know, Eric or

1 Richard? Go ahead, Eric, and then we'll turn to
2 Amy.

3 Sorry, Amy.

4 ERIC: I agree. I think that, for me, a
5 hundred percent healing was my goal, but
6 understanding and having some acceptance around the
7 situation I think was the first step in allowing or
8 welcoming healing. But to answer -- forgive me the
9 doctor's name -- yes, I think steps towards the end
10 goal are welcomed, of course.

11 CAPT BENT: Great. Thank you, Eric.

12 Amy?

13 AMY: I was just going to say I agree with
14 that. Intermediate stuff would be nice. It's nice
15 to see that progress, say, if your wound has
16 decreased by 50 percent or the pain has decreased
17 by 80 percent. I'm not sure if that's the
18 percentage the doctor gave, but if there was a
19 wound care product that combined those, decreased
20 the wound size and dealt with the pain at the same
21 time.

22 The thing is, for many of us with chronic

1 wounds, one of the worst things is actually the
2 dressing change, so you actually need some pain
3 medicine in your system before you would do the
4 dressing change because that's the worst part. So
5 if you had a product that decreased the size and
6 had pain medicine in it, the pain medicine is being
7 used after the most painful part is already done.

8 CAPT BENT: Dana?

9 DANA: Really quickly on this, I feel sort
10 of guilty because I don't have pain because I have
11 total neuropathy. So I think one thing that you do
12 have to look at when you're looking at these kind
13 of treatments is if you have people that have
14 neuropathy, the pain is actually not really an
15 issue. And I feel bad, because I feel bad that
16 everybody has such bad pain, and that's not an
17 issue that I have.

18 CAPT BENT: Great.

19 Let me ask a follow-up question. Do you
20 feel like if your wound was in a different location
21 than it currently is, your perspective would be
22 different on healing?

1 Maybe, Dana, can I stick with you because
2 you're nodding your head?

3 DANA: A hundred percent. I mean, because
4 it's the bottom of my feet, if my wound isn't
5 completely healed, I can't walk. So if it was
6 somewhere else, maybe I would feel differently
7 about the steps towards healing because, for me,
8 until it's completely healed, I can't put pressure
9 on it.

10 LAURIE: You're in exactly the same position
11 as Eric and I are. When we have a wound on our
12 ischium, we can't sit up; no mobility.

13 DANA: Yes.

14 LAURIE: On your feet, no mobility, but the
15 advantage is no pain.

16 DANA: And that's an advantage, and I admit
17 that I feel very guilty, and I'm sorry that you all
18 have so much pain.

19 ERIC: Yes. I don't think my pain is
20 necessarily from the wound. I think that there are
21 surrounding factors because of the wound that I
22 experience pain. But again, I don't mean to take

1 anything away from everyone's unique experiences,
2 but they are unique to each individual.

3 Yes, I've got to collect my thoughts here
4 for a minute.

5 CAPT BENT: Great. Thank you.

6 I don't know if anybody else has any
7 comments that they want to share. I know we're
8 just a few short minutes away from a 10-minute
9 break, but if anyone has any additional thoughts on
10 this, or I don't know if any of my FDA colleagues
11 have any follow-up questions.

12 RICHARD: I think if you've had
13 functionality before, before you got your wound,
14 you wouldn't expect anything other than complete
15 healing because you didn't have a wound before; and
16 now you have a wound, and so you expect complete
17 healing. That would be the expectation.

18 Now, in my instance, I had a very unusual
19 situation. It was an autoimmune disease called
20 cutaneous polyarteritis nodosa, and it caused huge
21 lesions on my legs. It's a form of vasculitis, and
22 these grew, and grew, and grew.

1 The frustrating thing to me was I was in and
2 out of the hospital 16 times, and the hospital was
3 affiliated with a medical school, and there seemed
4 to be no professional curiosity on the part of the
5 physicians that saw me, and they would all come in,
6 in groups. You know, you'd have the senior
7 physician, and then you'd have the fellows and the
8 residents, and the whole group.

9 They would look at my lesions, and they
10 would make comments on them, but never once did
11 they seem like they were concerned with the
12 diagnosis. I was an interesting case, and as an
13 interesting case, I guess I was interesting to look
14 at. But when I asked them what do you think I
15 have, nobody knew. And the way we found out what I
16 had was through an internet search that my wife
17 did. She looked at some pictures and said, "I
18 think this is what you have." And I took it to the
19 chief rheumatologist that was overseeing my care at
20 the time, and he said, "Yeah, I believe that's it."
21 But by that time, it was too late, and the only
22 cure for it was the amputation of both my legs

1 above the knee.

2 CAPT BENT: Thanks, Richard. I know that
3 sounds like a horrible experience, and I know we've
4 talked about how no patient wants to be an
5 interesting case --

6 RICHARD: No.

7 CAPT BENT: -- or hear that they're
8 interesting.

9 We're at 1:31. Eric, I know you were saying
10 you were kind of thinking about things. If we can
11 come back to you at the beginning of our next panel
12 session just to kind of wrap it up.

13 But right now, we'll move on to a 10-minute
14 break -- well, 9-minute break -- reconvening at
15 1:40 Eastern time, where we'll start off with our
16 last four patient videos, and then move into the
17 second panel discussion.

18 Thanks so much, everybody. See you in a few
19 minutes.

20 (Whereupon, at 1:31 p.m., a recess was
21 taken.)

22 CAPT BENT: It's 1:41, so we're going to go

1 ahead and get started.

2 Welcome back, everyone. I hope you had an
3 excellent break. We have limited time, so we're
4 going to move straight to our next set of panel
5 videos, our final set of panels videos, the last
6 four, and then we'll turn back to our panelists and
7 ask them a few more questions.

8 We'll go ahead and get those videos started.
9 Thank you.

10 (Video played.)

11 RICHARD: My name is Dr. Richard Maddy, and
12 I experienced chronic wounds that were related to
13 an autoimmune disease called cutaneous.
14 polyarteritis. nodosa. The wounds themselves were
15 quite painful, and the main health effects that I
16 experienced from them in the beginning were the
17 pain, the pain itself. As the wounds continued to
18 get worse, the pain became worse, and it came to
19 the point where it was really intractable pain,
20 pain that couldn't be relieved by normal analgesia.
21 It was pain that required very strong measures in
22 order just to control it.

1 It affected my life greatly. I was unable
2 to sleep most of the time that I had the wounds.
3 In fact, out of the 24-hour day, I probably got
4 about 2 hours of sleep per day. What would happen
5 was I would have to live with the pain until the
6 point where the pain literally caused me to pass
7 out, and I would pass out for 2 hours, and then I
8 would wake up again in pain.

9 The treatment that was offered to me was
10 varied, and most of the physicians that I saw, up
11 until the very end, weren't sure of what I had.
12 They really weren't sure of the disease. And the
13 frustrating thing about it was that many of them
14 didn't seem all that concerned about finding out
15 what type of disease I had.

16 I was in and out of the hospital a total of
17 16 times. I had gone to an initial wound care
18 specialist who offered palliative care in the form
19 of different types of dressings, but really no
20 consequential care of the wounds to speak of. The
21 treatments in my way of thinking were suboptimal.
22 They really just didn't address the problem at all

1 and, again, this caused the wounds to further
2 affect my activities of daily living. I got to the
3 point where I was unable to walk, the pain was so
4 great, and it caused many challenges in just my
5 daily life.

6 It wasn't until the very end that a
7 prognosis -- or a diagnosis, excuse me, was made,
8 and this was made, interestingly enough, after a
9 medical research foray by my wife, who had gotten
10 on the internet and looked for different
11 possibilities. She came across cutaneous
12 polyarteritis nodosa, and showed this to one of the
13 lead rheumatologists who was treating my case in
14 the hospital, and he agreed that this was probably
15 what it was.

16 At this point, it was too late. It was
17 impossible to treat at this point, and the only
18 remedy for it was an amputation of both legs above
19 the knee because at this point I had gone septic,
20 and the disease was about to kill me.

21 So I did not have a positive experience as
22 far as the treatment goes. I did not have a

1 positive experience as far as my contact with many
2 medical professionals went. My final wound care
3 physician was really the one that helped save my
4 life, and I owe a great deal to her, Dr. Caroline
5 Fife. But apart from that, I was somewhat
6 disappointed with the way that our medical system
7 is going. Thank you.

8 (Video played.)

9 OLLIE: I am Ollie Simpson, 79 years old. I
10 had venous ulcers on both legs, just above the
11 ankle, over a period of five years. Sometimes I
12 had just one; sometimes I had it on both legs. The
13 health effects that I experienced were mental
14 health and pain. I often felt lethargic. I lacked
15 interest in trying to do the things I had once
16 enjoyed. I did not sleep well at night. I laid
17 down and took naps during the day. I became
18 discouraged about the wounds healing and
19 disappointed when they got worse.

20 My hope was renewed on my first visit to the
21 second clinic, when the program director said, "I
22 have never met a venous ulcer that I could not

1 heal." About the pain, my thought is that the
2 wound itself was not painful, but things done to
3 try to heal the wound caused pain. The most
4 pervasive pain was caused by inflammation around
5 the wound. Until I went to the second clinic,
6 information was not treated properly. Compression
7 wrappings sometimes were too tight or too loose,
8 and slid down. The covering directly over the
9 wounds often dug into the surrounding area.

10 How the wound affected my daily life, the
11 pain caused changed my way of living. I could not
12 walk far. I had to get someone to mow my yard in
13 the fall and clear the snow in the wintertime. My
14 vegetable garden had more weeds than vegetables. I
15 got a handicapped parking tag so I could park
16 closer to business entrances. I appreciated the
17 stores that had electric carts. I used the airline
18 wheelchair services whenever I flew.

19 Since I could not get the compression
20 wrapping wet, I took sponge baths; shoes, the
21 compression wrappings are bulky, so I bought a pair
22 of knock-off Crocs at the dollar store and slit the

1 tops so I could insert my foot. On wet days, I
2 would put a plastic bag over my foot before putting
3 on the Crocs. Overall, my life changed from very
4 active to sedentary, much sitting and lying down.

5 I relied on the medical professionals. The
6 first wound clinic used debriding and a moist
7 medication over the wound. It got worse. The
8 dermatologist recommended hyperbaric oxygen
9 treatment. It made no difference in my wounds.
10 The second wound clinic, a vascular study was done
11 on my left leg about 3 months before it healed. It
12 was determined that the VenaSeal procedure was
13 appropriate. I continued to wonder if that helped
14 the healing. An MD at the second clinic asked what
15 I thought was the best medication for my left leg
16 wound. He'd listen to my answer. I strongly
17 believe that medication and the expert compression
18 wrapping by the program director was key to my
19 wound healing.

20 With one exception, obtaining necessary
21 supplies was no challenge. The supplies were
22 available at the facility and covered by Medicare.

1 An exception was an MD at the second clinic refused
2 to use the elasticized wrapping that was most
3 effective over the Unna boot. It was part of a
4 multilayer package, and she'd have to toss the
5 unused layers. My wound got worse under her care.

6 My care providers were determined by
7 referrals. First was the first wound clinic; my
8 wound got worse. Next was a dermatologist; a
9 little progress. Next was the second wound clinic.
10 The dermatologist had heard the program director
11 speak at a conference. On my next visit, she said,
12 "You have to see him." He healed my wounds and
13 gave me back a pain-free life. It took the right
14 person, correct medication on the wound, and expert
15 compression wrapping to heal my wounds.

16 (Video played.)

17 AMY: Hi. My name is Amy Ellickson. I'm a
18 58-year-old female from Wisconsin. I've had a
19 chronic open wound due to pyoderma gangrenosum for
20 the last 2 and a half years. It's affected my
21 quality of life in many ways. The biggest thing
22 probably has been emotional mental health.

1 It's really draining in that regard because
2 there are a lot of professionals who don't know how
3 to deal with this disease because it's so rare, so
4 it's really hard because I've had some
5 professionals who have caused more harm to the
6 wound than good, but once I got hooked up with some
7 medical professionals who knew what they were
8 doing, that really helped. Also, with support, I'm
9 in a PG support group. It's a virtual support
10 group, but it is very beneficial because of the
11 emotional support, plus the experience of the other
12 members in the group. The open wound has affected
13 my quality of life.

14 As far as pain, PG is a very painful
15 condition. I do take pain medication for it. It
16 also affects my mobility. It affects my time
17 because wound care is a very time-consuming
18 process. Also, until yesterday, I was traveling
19 twice a week, an hour and a half each way, to
20 receive MIS therapy, which is a type of treatment
21 for PG, so that's a time-consuming thing.

22 It's also a very expensive thing because gas

1 prices are high, and paying for gas doing those
2 trips twice a week, plus parking, gets to be
3 expensive. It's also expensive financially because
4 of insurance barriers. Because PG is so little
5 known, a lot of research has not been done, so
6 there are not a lot of treatments that are approved
7 specifically for this disease, and that also
8 includes a lot of medications not being approved
9 yet. So insurance turns down a lot of things that
10 the doctors want to be able to do to treat the PG,
11 so that has been a barrier as well, fighting the
12 insurance companies.

13 We've tried various treatments for the PG
14 wounds, everything from prednisone, to dapsone, to
15 colchicine [indiscernible], to MIS therapy, which
16 we just discontinued yesterday because that has
17 stalled. I am doing infliximab infusions. That
18 suppresses the immune system, which again also
19 affects your quality of life because I get
20 infections very easily not having a working immune
21 system.

22 I recently was told I needed to be

1 hospitalized because I had an infection that my
2 body just couldn't fight, so it's affecting my
3 quality of life. The side effects from the
4 medicine affect my quality of life, plus that
5 interferes with what I can do socially because I
6 just can't be around people. I have to watch my
7 infection risk.

8 So the biggest things affecting the quality
9 of life, just to sum it up, would be the emotional
10 mental health, the financial burden, the time
11 restraints, and the social constraints.

12 (Video played.)

13 DANA: Hi. My name is Dana Davis. I am
14 54 years old, and I have type 1 diabetes and MS. I
15 have been a type 1 diabetic since I was seven, and
16 I have had chronic wounds, pressure wounds, on my
17 feet since I was 21. I have a very high arch and
18 short Achilles, and from the time I was 21, I had a
19 wound that started on my big right toe, which has
20 now since been amputated, along with the first
21 digits of the two toes next to it because of my
22 weird gait that I have; the health effects I've

1 experienced as I've dealt with chronic wounds.

2 I have been on PICC lines about 8 or
3 9 times. I have suffered osteomyelitis 2 times and
4 became very, very sick. I had a wound on my left
5 heel that I was put into a contact cast, and ended
6 up getting a septic knee, and almost lost my leg
7 because the doctor at the time didn't believe me
8 that something wasn't right. They refused to
9 culture.

10 I'm going to say that's a big thing. I
11 don't present like anybody else with wounds, and I
12 know when I'm infected, and I don't have a
13 temperature always. It's not red, it won't get
14 pussy, but I literally can go from zero to almost
15 dying in like 2 hours, and it's really frustrating
16 when the doctors don't listen to me when I know I
17 am really, really sick. Again, I've mentioned I've
18 come really close to dying twice because of chronic
19 wounds and doctors not realizing how sick I was.

20 The wounds have affected my daily life.
21 It's completely changed my life. I can no longer
22 walk my dog. I'm in a walking cast again. I was

1 in a wheelchair for 6 months most recently. I've
2 been in wheelchairs on and off for the last 10 to
3 15 years. A couple times a year, because
4 offloading is very difficult when you have MS
5 because you don't have the balance and you can't
6 use crutches and other things that everybody else
7 can do, it gets very depressing. It's hard to
8 shower with a shower boot. I feel like I've spent
9 60 percent of my life in a blue shower boot.

10 The approaches to treatment have been really
11 interesting. MediHoney and contact casts seem to
12 be everybody's favorite, and they really do not
13 work with me at all, and I am a little
14 vociferous [indiscernible] about what doesn't work
15 with me. Sometimes the doctors don't want to hear
16 it, and therefore I'm non-compliant and deemed a
17 little bit difficult, and I understand that. I
18 don't know if they know my frustration for how long
19 and how much pressure wounds have affected my life,
20 and it feels like most of my life.

21 Accessing care, I've been really fortunate
22 because I do have kind of a big mouth and I will

1 state what I need. I've had an opportunity to find
2 the best care that I can, and I think it's hard. I
3 feel really bad for those who can't find an access
4 that care or be an advocate for themselves because
5 wounds are awful and terrible, and we shouldn't
6 just be told if we lose a limb, it's ok, or just
7 don't walk. It's not ok.

8 CAPT BENT: Alright. Another big thank you
9 to our panelists for sharing these experiences, and
10 we know that dealing with chronic non-healing
11 wounds can really be traumatic, and we heard a lot
12 about the impacts that the wounds have on mental
13 health. We know that this can be hard to talk
14 about, and we really appreciate you sharing it with
15 us so that we can really work to move the science
16 forward. It really is very impactful.

17 As we move forward to the second topics, let
18 me loop back first to Eric to see if you had
19 anything else you wanted to add about acceptable
20 treatment responses.

21 (No response.)

22 CAPT BENT: Well, Eric, I might still stick

1 with you because my first question then is, what
2 impact do you think nutrition has had on your wound
3 and wound healing?

4 ERIC: Sorry about that. I should be
5 unmuted now.

6 CAPT BENT: Okay. Yes, you are.

7 ERIC: I have a special interest in
8 nutrition. I am a functional nutritionist, new to
9 the field, but I just want to take a moment to just
10 thank everyone that was involved in having this
11 event happen. My goal, in my career as a
12 functional nutritionist, is to insert myself into
13 filling these gaps between what everyone is saying.

14 Our physicians have this 10,000 foot
15 perspective of us. From way up high, they are
16 looking at us for ways to progress our situation
17 forward, while us as the patient, we are the
18 individuals in the tall grasses, trudging through
19 the symptoms and everything that comes with the
20 misfortune of having a chronic wound.

21 Being your own advocate would be my best
22 piece of advice, and be the squeaky wheel when you

1 have to. Our outcomes have a lot to do with our
2 willingness to be a part of that, and not just
3 handing over our care to physicians and expecting
4 them to fix that. If that was so easy -- everyone
5 wishes there was a magic wand there to make their
6 wound go away, so I think highlighting the
7 uniqueness of all of our situations and not
8 forgetting how important advocacy is.

9 But to answer your question in nutrition, I
10 found leaps and bounds of success in my wound
11 healing when my nutrition was a focal point. I am
12 pretty adventurous when it comes to trying new
13 food. So again, through my self-advocacy, I was
14 doing a lot of internet searching, seeing studies,
15 research into specific types of foods within the
16 macro groups, and proteins obviously are of high
17 importance.

18 I tried a lot of different things and see
19 what stuck, and through that, noticing protein was
20 a huge part of it, and just fiber and all the
21 micronutrients that go in with that. I could bore
22 you with all the protocols that I put myself on.

1 But yes, to answer your question, nutrition's a
2 huge piece of this.

3 CAPT BENT: Great. Thank you.

4 Does anyone else want to comment on the
5 impact of nutrition, or whether their providers
6 made any specific nutrition recommendations? I
7 feel like Peter had touched on this earlier, but
8 I'm not sure that we still have Peter, so let me
9 turn to Laurie.

10 Laurie?

11 (No response.)

12 CAPT BENT: You're muted. Oh, now you're
13 not.

14 LAURIE: I'm not a nutritionist, but I've
15 always had a strong interest in nutrition. I think
16 I did everything I was supposed to with my last
17 wound. I was eating 60 grams of protein a day,
18 which is not easy for someone who prefers a
19 vegetarian diet. But I did my eggs, and my
20 chicken, and I did my vitamin D3, and my zinc, and
21 my arginine, and all these adjuvant supplements
22 you're supposed to buy, which comes out of pocket.

1 I just think for a spinal cord injured
2 wound, we just don't know enough about wounds. I
3 think maybe I prevented mine from getting worse,
4 but it certainly didn't progress. So I think
5 nutrition is important, but I think, as was said
6 earlier this morning, in this morning sessions, we
7 just don't know what we're doing. I think there's
8 so much we just don't know, and that's the
9 frustrating part of, as somebody said, being in the
10 weeds, being in the tall grasses. We're the ones
11 in the trenches that are dealing with it.

12 I think a lot of our medical professionals
13 are frustrated as well. It's also hard to be your
14 own advocate when you're going to people who just
15 don't know what else to do with you. So how do you
16 find a knowledgeable care provider? A lot of our
17 multidisciplinary clinics -- multidisciplinary, it
18 seems to me, means doctor or nurse, but an electric
19 stimulation, as a physical therapist, electrical
20 stimulation is well documented for wounds. I
21 wasn't given access to it.

22 If I was going to put a new product on the

1 market, I would want to go where there's a big
2 market for it and big reimbursement, which means
3 vascular diabetic ulcers. But as Dana just said,
4 they don't work on all diabetic ulcers, so it's
5 maddening. It's maddening, being in the weeds.

6 CAPT BENT: Thanks, Laurie.

7 Did anyone else have anything they wanted to
8 add about nutrition and the impact that it may have
9 had on wound healing.

10 PETER: Yes. This is Peter Fisher. Can you
11 hear me?

12 CAPT BENT: Oh, great. Yes, sir, we can.

13 PETER: Just as has been said here, I can't
14 tell you how much the advocacy of a physician is,
15 how central it is, especially if they're wound care
16 specialists. It provides -- and I don't think it's
17 a false sense -- a real sense that you can overcome
18 or you can survive the condition you're in with
19 that kind of an advocate by your side. When you've
20 got the physician advocate, all sorts of doors open
21 to you. He was more responsive to me. My
22 cardiologist was more responsive. All these things

1 resulted from the advocacy of my wound care
2 specialist, so it's essential.

3 I hear these stories today, and they're
4 gut-wrenching. They make me sad and embarrassed to
5 even be on this panel because mine is such an
6 insignificant condition compared to all of the
7 others that spoke. But still, it's the support
8 that you get, and you've got to find the right kind
9 of physician. In my mind, that's what's essential.

10 Some of the other members have touched
11 on -- and not just touched on but have underscored
12 the importance of this -- their experience of being
13 bounced around from one provider to another
14 provider, to a provider that doesn't know what
15 they're doing, and on and on and on. If you get
16 the good help at the beginning, it's so much easier
17 to progress, and that's my comment.

18 CAPT BENT: Great. Thank you.

19 Let me ask you all. One of our panelists,
20 who was not able to join us today, during our prep
21 session had talked a little bit about the
22 challenges, knowing that she needed to have good

1 nutrition, and noting that when she was having
2 really good nutrition -- like when she was in a
3 rehab facility and they were able to provide her
4 with her meals 3 times a day, and well-balanced
5 meals, and good calories -- that she was able to
6 make good progress in her wound healing. But as
7 soon as she went home, it was much harder for her,
8 with the wounds, to provide that kind of nutrition
9 for herself.

10 Have you experienced having the wounds that
11 decrease your mobility and increase your pain, and
12 then not being able to provide yourself with the
13 optimal nutrition that you maybe should be having?

14 Dana?

15 (No response.)

16 CAPT BENT: I think you might be muted.

17 DANA: I'm muted.

18 CAPT BENT: There you go.

19 DANA: One of problems when you do have
20 osteomyelitis is you get extreme nausea, and then
21 the meds make you really nauseous. So every time
22 I've been on a PICC line, it is hard to get good

1 nutrition when I have a severe infection because I
2 can't keep anything down, and I'm so nauseous, and
3 I end up losing like 15 pounds when I end up
4 getting some kind of infection. So nutrition
5 becomes really difficult when you're home and
6 you're super nauseous. What do you do? I mean,
7 that becomes something that's really difficult.

8 CAPT BENT: Great. Thank you. I think
9 that's a really good point.

10 Does anybody else have anything they'd like
11 to add related to nutrition or any challenges
12 related to that?

13 LAURIE: Bed rest does that for me, too. It
14 totally decreases your appetite, and then with
15 limited mobility, you don't have the ability to get
16 up and eat as much as you should. So you really
17 depend on the service of others to bring you the
18 right food and to prepare it, but then you don't
19 feel like eating it. It's hard to do the right
20 thing.

21 CAPT BENT: Great. Thank you so much.

22 Let me move on to our next question, which

1 is, what factors would you consider when making
2 decisions about or selecting a course of treatment?
3 Are there things that you look for in a treatment,
4 things that you dislike about another treatment
5 that would make you want to use one treatment over
6 another? For example, would it -- oh, go ahead,
7 Martha.

8 MARTHA: Okay. One of the things that I
9 look for is I don't want the treatment to make the
10 treatment of the wound feel worse, because I did go
11 initially to a doctor who was a surgeon, who said
12 that I should be scrubbing a venous stasis ulcer.
13 And in the process of telling me to do that, I was
14 in such pain as he's debriding it, and then as a
15 result, I got a third ulcer.

16 I would literally cry from him treating me,
17 to going to a restaurant just because that's what
18 my husband and I wanted to do after the treatment,
19 because the pain was so excruciating. And I
20 actually thought I had cancer of the bone because I
21 said, "I can't do this anymore. I can't go to this
22 doctor." I said, "Maybe I do have cancer of the

1 bone. Let me go to Memorial Sloan Kettering," and
2 I did. And there I saw a dermatologist who showed
3 my husband and I on the internet a picture of a
4 venous stasis ulcer, and he said, "This is not the
5 kind of ulcer you should be scrubbing." He told me
6 to see Dr. Alvarez.

7 I don't know if any of you know him,
8 Dr. Oscar Alvarez, but he's a researcher in wound
9 care, and I call him -- and he doesn't like me to.
10 But I called him Saint Oscar. His name is Oscar
11 Alvarez. Because he's closed my second wound, all
12 the way up to I would say my eighth one when he
13 retired from the Wound Center. He'd still be
14 treating me, but he's not doing that anymore.

15 But he was awesome. He would even say to
16 somebody there, let's say a nurse, "No, you can't
17 treat her with this because she has sensitive skin,
18 and she won't be able to tolerate it" --
19 treatments -- because he kind of knew my skin and
20 how sensitive it was.

21 So if you can find a person like that -- I
22 know it's very hard -- you want to keep him. I

1 followed him to Calvary Hospital in New York, to
2 the Bronx, and then finally to University Hospital
3 in Newark, where he was until he retired. And when
4 you find a good doctor, you follow him.

5 JOE: Yes. The secret is finding a wound
6 care doctor who knows how to treat your wounds.

7 MARTHA: Right.

8 JOE: Okay? Now, there is no simple
9 solution to that, that we know of, because it took
10 us a couple years. But if you find such a doctor,
11 follow that doctor wherever that doctor goes. Just
12 follow them.

13 One of the frustrating things is there are
14 wound care clinics and wound care centers with lots
15 of fancy names, and lots of bariatric chambers, and
16 this and that, but then you see a doctor, and your
17 doctor says, "Well, this is what I'm going to do,
18 and I'm going to see if it works." And you need to
19 ask the question -- and sometimes it's an
20 embarrassing question -- "Have you ever dealt with
21 this before?" And if they say no, just say thank
22 you very much, and leave, and most of the time

1 they're going to say, "Yeah, yeah. We know how to
2 deal with this."

3 In the morning sessions, there was this
4 discussion of multidisciplinary treatment centers
5 and a bunch of terms like that. The real thing is,
6 if you see a doctor who doesn't necessarily have
7 lots of experience or really understand this, you
8 need to find a doctor who has enough humility to
9 ask other people for help.

10 CAPT BENT: Great. Thanks, Martha and Joe.

11 Let me let me turn to Dana. Did you have a
12 thought about what -- I mean, I know you have a
13 thought -- you consider when selecting a course of
14 treatment for your wound?

15 DANA: Absolutely. And just to springboard
16 off of them, I went from Chicago, to Boston, to
17 West Virginia to follow a doctor, and she was
18 somewhere where I couldn't see her for about
19 10 years, so I was desperate then. So I agree with
20 you. If you find somebody who knows your wound,
21 you've got to stick with them.

22 I think for me it's treatments with evidence

1 that match the biology, and it would be treatments
2 that are reimbursable as well. But that becomes
3 really difficult because, again, I have to be so
4 sick to get reimbursed, or I have to be so sick to
5 prove that I should have that treatment. But those
6 would be a couple things for me.

7 CAPT BENT: Thank you.

8 Did anyone else have a thought about
9 treatment priorities, whether it was fewer dressing
10 changes or something that you could do yourself at
11 home?

12 I feel like, Laurie, at one point you
13 mentioned the importance of resources for home
14 care. Would that kind of impact your choices for a
15 treatment plan?

16 LAURIE: Well, that goes back to
17 reimbursability, because there are things that are
18 reimbursed in the clinic that a doctor is supposed
19 to do, and there are probably a lot of reasons why
20 that happens. There are those kind of treatments,
21 and then there are things that are allowed in the
22 home that the home care nurse can do, and they're

1 much more limited.

2 I didn't have access to some things for that
3 reason. I didn't have access to some things
4 because they hadn't been studied for pressure
5 ulcers. So Dana makes a good point about wanting
6 studies on a product, but I would have tried
7 anything. Just give me something else, but at
8 least change your approach to me.

9 So if I was presented with something that I
10 would have an option to use, I think it would have
11 to be easy for me to use in the home. It can't be
12 a huge bulky thing. It's got to be something I'd
13 be able to use, that I'd be physically able to do
14 by myself.

15 I have tried a couple of modalities that
16 aren't available anymore that were very cumbersome,
17 and created noise, and created radio interference
18 with devices in the house. So people couldn't
19 watch TV or talk on phones when I was using them;
20 very difficult. I hope that answers your question.

21 CAPT BENT: It does. Thank you.

22 Before I move on to the next question, is

1 there anyone else who has a thought on what they
2 would look for when selecting a treatment?

3 RICHARD: Let me jump in real quickly. I
4 think this may be key to selecting a treatment
5 because most patients really don't know what they
6 need until a physician tells them, so they're
7 highly dependent on the physician.

8 Ninety-five years ago, an article appeared
9 in the Journal of the American Medical Association,
10 and it was written by a Harvard physician named
11 Francis Weld Peabody, and the name of the article
12 was called, The Care of the Patient. Dr. Peabody
13 said in that article, toward the end of it, "that
14 the secret to the care of the patient is in caring
15 for the patient." What you look for is a physician
16 who actually cares for you. They're very rare, and
17 they're difficult to find, but if you look hard
18 enough, you can find them.

19 CAPT BENT: Great.

20 Gosh. Richard, I kind of wish that was your
21 closing comment because that would be really an
22 excellent way for us to close this session. But we

1 do still have 10 more minutes, but I think that's a
2 really profound comment, and I think that is very
3 reflective of what we've been hearing here today,
4 and I know Eric has kind of touched on that a bit
5 as well.

6 Let me move on to our next question. It's
7 about clinical trials. If I remember correctly, I
8 don't think anyone on this panel was ever offered
9 the opportunity to participate in a clinical trial.
10 Is that correct? If you had the opportunity to
11 participate in a clinical trial, can you --

12 DANA: A long time ago; my God, it was in
13 the '90s. I don't remember what it was, but it was
14 for one of the first skin grafts that they did, and
15 I had to sign all these waivers and do all these
16 things, and it really didn't help, I think. I was
17 25, and I probably wasn't as great of a patient as
18 I should have been then, and they were doing all
19 the experimental stuff with the skin graft. First
20 it was fetal foreskin, whatever graft that was, a
21 long, long time ago.

22 CAPT BENT: Great. Thank you.

1 Aside from Dana, you haven't had the
2 opportunities or been offered participation in a
3 clinical trial, but if I could maybe just hear from
4 some of you, if you had the opportunity to
5 participate in a clinical trial, would you be
6 willing? Let me start with Martha.

7 MARTHA: I was asked to be in a clinical
8 trial, and the reason I declined was because it
9 meant putting things on your skin. And I have very
10 sensitive skin, so I don't want to try something
11 that could affect my skin and become maybe a wound
12 or something, so I declined it. Originally, I
13 thought it was a good idea to help, but then I
14 turned it down. I wouldn't do it just for that
15 reason. I'm interested in people who don't have
16 sensitive skin that would be willing to try things
17 like this, because I think it could be helpful to
18 other people.

19 CAPT BENT: Great. Thank you.

20 Is there anyone else who would speak to
21 their willingness or concerns about participating
22 in a clinical trial?

1 Amy?

2 AMY: I would do a clinical trial, just
3 anything to further research on this PG thing.
4 When I originally signed up for this, I hadn't done
5 a clinical trial, and while doing this I was
6 contacted by Dr. Ortega, who actually might be
7 listening right now.

8 It's not really a clinical trial, per se,
9 but it's filling out surveys and just trying to get
10 some criteria and domain. He might be able to
11 correct me on this. I filled out one survey
12 already, but criteria, domain for PG, and what we
13 consider important research topics for PG, and what
14 would be good determinants for it, for research in
15 it. So that's not really a trial, it's just
16 filling out surveys. But anything to help further
17 the research, I'm willing to do.

18 CAPT BENT: Before I move to Richard, let me
19 ask you a follow-up question, Amy. If you had the
20 opportunity to participate in a clinical trial that
21 was either virtual or decentralized, meaning that
22 you didn't have to travel to the clinic site for a

1 visit but instead your wound would be assessed at
2 home, would that be more appealing to you?

3 AMY: Yes, definitely.

4 CAPT BENT: Great. Thank you.

5 Richard?

6 RICHARD: Yes. When I was being treated by
7 my first wound care specialist -- before I was able
8 to find Dr. Fife -- he was a cardiothoracic
9 surgeon, and why he was a wound care specialist is
10 beyond me. But he was conducting a clinical trial
11 of I think it was venous return, or something like
12 that, and he felt that, based on his observations
13 of my legs, they would benefit from having a small
14 stent put in that he was conducting a trial in. He
15 was part of a nationwide trial.

16 This particular trial involved the placing
17 of the stent, and then I would have to take
18 pictures of it on a weekly basis and send those in.
19 The trial basically did nothing. I think he did
20 not understand what my disease actually was. It
21 was a form of vasculitis, and that's certainly not
22 going to be appropriate for that. But anyway,

1 that's my experience with clinical trials, and I
2 wasn't impressed.

3 CAPT BENT: I know that, obviously,
4 hopefully you're not in a position where you have
5 any more experience with wounds, but would that
6 experience kind of turn you off to future clinical
7 trials, or is that something you think you'd still
8 be interested or you'd still be willing to
9 participate in?

10 RICHARD: It would depend on the physician.
11 If the physician was actually looking for a cure
12 rather than just treating me palliatively on a
13 weekly basis, then I would think, yeah. If this
14 was a physician with professional curiosity, trying
15 to find out what it was that I had, that
16 continually asked, "We think it might be this, but
17 what else could it be?" and keep going on, and
18 going on until they found it, then yeah, that's the
19 kind of physician I would trust in a clinical
20 trial. But again, those are few and far between.

21 CAPT BENT: Thank you. Let me turn to Dana.

22 DANA: With clinical trials, I would do it

1 in a heartbeat. I've done it for MS and everything
2 else. I am willing to give my body to science.
3 The one problem I find with a lot of the wound
4 trials is they wouldn't include me. I don't
5 qualify or my wound is too bad. I think that the
6 clinical trials need to be widened, and then the
7 endpoints be a little more realistic to start with.
8 I think that it's kind of an all-or-none sort of
9 thing, and I think there needs to be an ability to
10 include us who have more severe wounds to see where
11 we could get in the steps.

12 I know I said I'm the one that wants it
13 cured and I want it closed, but I also feel like if
14 we're trying to help others, we need to be able to
15 widen what that approach is, and then bring in what
16 our expectations are to start with, so we can start
17 moving forward in that process.

18 CAPT BENT: Great. Thanks.

19 Building on this question, there's a
20 question in the question and answer session, which
21 is, would the panel comment on their willingness to
22 participate in clinical trials where they may be

1 randomized to a placebo? So it would be
2 potentially an investigational treatment, plus
3 standard of care -- guessing -- versus just
4 standard of care.

5 Is that something that you would be willing
6 to be randomized to?

7 PETER: Can I comment on that?

8 Richard mentioned, rather than care, caring.
9 And my sense of these clinical trials, especially
10 when you are offering a placebo -- I say offering;
11 you're exposed to the placebo -- would show, yeah,
12 we have some goals, but it doesn't sound like cure.
13 It sounds like maybe reducing the symptoms or
14 alleviating some of the pain. So as is he, as is
15 Richard, I'm a patient of Dr. Fife, and I can't
16 tell you how caring she is, and I would never swap
17 her for a clinical trial. It just wouldn't happen.
18 Thank you.

19 CAPT BENT: Thanks.

20 We only have two minutes left, so I'm going
21 to go to Laurie and Amy. And I'm sorry, I'm going
22 to have to ask you to keep it brief because I don't

1 want us to run over.

2 But go ahead, Laurie.

3 LAURIE: Sure. They both had the benefit of
4 stepping into treatment with one of the premier
5 doctors in the country, who most of us would love
6 to go to, Dr. Fife, and there's perfect example of
7 going to the right doctor is the right thing to do.

8 I would participate in a clinical trial if
9 they did one of those crossover things where you
10 have your two groups, and then at a certain point
11 you could cross over into the other group. I think
12 that would be great. And I do wish that they would
13 open up clinical trials to those who are not the
14 perfect patient because that's limiting our
15 clinical trials and that's limiting the application
16 of the results that they get.

17 CAPT BENT: Thanks, Laurie, a very important
18 point.

19 Let me turn to Amy for, no pressure, our
20 final comment of the day.

21 AMY: I'll just say very quickly, yes, I
22 would do a drug clinical trial specifically talking

1 about hyperbaric for PG because there aren't enough
2 studies done to have the insurance companies say
3 it's ok. I would not want to be in a placebo
4 group, however, because there are studies that back
5 up and that say it does work for PG. So I would
6 want to be receiving the hyperbaric for the PG, but
7 I would definitely be willing to be in a trial for
8 that.

9 CAPT BENT: Great. Thank you so much, Amy.

10 If we can go two slides ahead, I just want
11 to thank everybody for participating today. I
12 think we've learned a huge amount from you. It was
13 really a great session. I thank you so much for
14 taking your time and sharing your thoughts and
15 perspectives with us.

16 There is a Federal Register notice open
17 where you can submit any sort of comments or
18 feedback, or answer some of the questions about
19 wound healing. It's available. Here on this
20 slide, you can see that it's open until June 28th
21 of 2022. So if anybody out there has been watching
22 and has experiences that they would like to share,

1 we would very much like to hear them.

2 If we can go to the next slide, the next
3 slide contains the link. So if you are willing to
4 share your thoughts -- not just patients, but
5 caregivers or clinicians -- you can go to
6 federalregister.gov and search for the words,
7 "Wound Healing Workshop," and that is, again, open
8 through June 28th.

9 Thank you so much. I believe now you are on
10 a break until 2:40 p.m. Thank you, everyone, and
11 have a great break.

12 (Whereupon, at 2:31 p.m., a recess was
13 taken.)

14 **Introductory Comments - Maryjoy Mejia**

15 DR. MEJIA: Welcome back, everyone. Good
16 afternoon. I just want to get things started so we
17 can be respectful of everyone's time. I'm Joy
18 Mejia, a medical officer in the Division of
19 Dermatology and Dentistry, and I have the pleasure
20 of introducing this session on clinical trial
21 issues.

22 As we've heard today, the development of

1 wound healing products has yielded many failures.
2 The lack of new approved treatment interventions
3 largely reflects difficulties with designing and
4 implementing clinical trials for wound products.

5 As already conveyed by many of the
6 participants today, challenges exist due to the
7 complexity of wound healing at the cellular
8 molecular level, with recruitment of many cell
9 types that must timely coordinate a response of
10 tissue injury, as well as at the clinical level,
11 where patients who suffer with non-healing wounds
12 often have long lists of comorbidities.

13 Healthcare providers as well must undertake
14 multiple therapeutic paths to encourage wound
15 healing. When any single aspect of these various
16 complex factors is not adequately addressed, wounds
17 fail to heal.

18 Altogether, these issues impact the
19 execution of clinical trials, namely the
20 recruitment, enrollment, and exclusivity of
21 subjects, duration and expense of trials, and
22 selection of endpoints. These challenges are ones

1 that are familiar to many in attendance today and
2 ones that our speakers, Dr. Robert Kirsner and
3 Dr. Bearden will expand upon in more detail.

4 With that, I'd like to introduce our
5 speakers, Dr. Kirsner, who joins us from the
6 University of Miami where he dons many roles as the
7 chairman and the endowed Harvey Blank Professor in
8 the Dr. Phillip Frost Department of Dermatology and
9 Cutaneous Surgery. He's also a professor of public
10 health sciences at the University of Miami Miller
11 School of Medicine, chief of dermatology at the
12 University of Miami Hospital and Clinics and
13 Jackson Memorial Hospital, and director of the
14 University of Miami Hospital Wound Center.

15 Dr. Bearden, who will be speaking following
16 Dr. Kirsner's talk, leads the global team for
17 research, technology, and innovation in biologics
18 and regenerative medicine solutions at Smith &
19 Nephew. His research has focused on improving
20 understanding of disease pathophysiology, support
21 to healing cascade, and augmentation to current
22 standard of care practices. He leads a team of

1 researchers that support product development and
2 delivery to market in the wound, orthopedic, as
3 well as sports medicine specialties.

4 With that, Dr. Kirsner?

5 **Presentation - Robert Kirsner**

6 DR. KIRSNER: Thank you.

7 Hello, everyone. Thank you for that lovely
8 introduction, and I'm going to talk kind of in
9 broad strokes about overview of clinical trial
10 issues for chronic wounds. I know this audience,
11 in general, is a very experienced audience, so I'm
12 going to touch on some of the high points in the
13 next few minutes.

14 I use the example of cancer, and wound
15 healing has been compared to cancer over the years
16 for a lot of different reasons. While the FDA is
17 certainly different than the NIH and other
18 governmental organizations, it is worthy to note
19 that investment in cancer through the National
20 Cancer Act in the '70s and NCI investment in
21 molecular biology in the '80s has led to a really
22 dramatic increase in the number of therapies that

1 have changed patients' lives.

2 During that time, of the last 50 years or
3 so, in cancer technology, we've had the landmark
4 paper by Winter talking about occlusive dressings.
5 We've had dressings being developed in the '80s and
6 beyond. But since then, as was noted earlier in
7 the day, really just one drug and several cell- and
8 tissue-based products have gone through the FDA
9 process of approval, and there's ample evidence
10 that as a public health concern, the wounds are
11 underfunded by the NIH.

12 So while we're going to focus on clinical
13 trials related to the FDA, and I know the FDA does
14 not obviously have oversight over the NIH,
15 whispering in your friends' ears is certainly
16 important because good basic science and clinical
17 research will lead to products for our patients
18 down the road.

19 Now, I want to highlight one example of some
20 data from clinical trials. This was a publication
21 by the American Diabetes Association a couple of
22 years ago that I was lucky enough to be part of

1 this publication. Within this publication, we
2 looked at evidence-based advanced therapies for
3 diabetic foot ulcers.

4 In this table, there are growth factors that
5 are reported. There are cellular constructs, there
6 are acellular constructs, placental membranes, and
7 some other products as well. You can see the
8 category of the products up top from
9 platelet-derived growth factor, platelet release;
10 human skin equivalent; dermal skin substitute;
11 dermal template; submucosa small intestine; various
12 acellular placental membranes; negative pressure;
13 and HBO, and the sample sizes associated with
14 those. There are relatively healing rates at the
15 various time points in the second row; the time to
16 closure; whether the product is FDA-approved; the
17 study quality; whether there were additional RCTs;
18 and whether there was real-life data.

19 The thing I want to highlight here using
20 this table is that you can see that the products
21 that went through the FDA review process -- not a
22 510(k) which we heard about earlier, but more

1 advanced Pathways with the FDA -- that process was
2 associated with higher study quality, so there's a
3 direct link between the study quality of the RCTs
4 that are performed in wound healing and going
5 through the FDA process.

6 A number of years ago, we published this
7 paper in seminars in Cell & Developmental Biology,
8 looking at the FDA and designing clinical trials
9 for chronic cutaneous ulcers. The things we
10 highlighted in this paper remain true even after
11 nearly a decade in press.

12 What I want to highlight, though, over the
13 next few minutes is some of the critical issues in
14 wound healing clinical trials, and very importantly
15 for the audience that's listening, some of the
16 common pitfalls and the reasons why trials fail
17 even if they have a good scientific rationale and a
18 good product that they're studying.

19 Now, what I do want to tell you is that
20 across all of medicine, even outside of wound
21 healing itself, most high-quality trials are done
22 for regulatory purposes with the aim of getting

1 approval or reimbursement. As I showed you in that
2 table, the higher quality studies were associated
3 with FDA approval, but this is not unique to wound
4 healing. And, really, that's why it's so critical
5 that as we think about FDA trials, it really not
6 only is going to lead to more products for our
7 patients, but improve the quality of the clinical
8 trials that are carried out in our space, something
9 we all definitely want.

10 So what are some critical issues in trial
11 design? Of course, it starts with inclusion and
12 exclusion criteria in determining who will be in a
13 clinical trial. This is very important, choosing
14 who should be enrolled and who should be excluded.
15 There's a balance between enrollment expectations,
16 how many patients per site, and how many sites you
17 should have, which may increase cost and the speed
18 of enrollment, and I'll talk a little bit more
19 about that in just a few minutes.

20 Part of inclusion and exclusion criteria is
21 whether you want a very generalizable or very
22 homogeneous population, and oftentimes a trial will

1 start with a very homogeneous population, but if
2 enrollment expectations are not met, they may
3 broaden the entry criteria. And it really changes
4 the trial itself, and then you have a hodgepodge of
5 patients that are enrolled in the
6 trial metalloproteinases, and you can't get a clear
7 answer from the results.

8 Companies or sponsors that are looking for
9 FDA approval like the idea of generalizability
10 because more patients will have access to their
11 products, but when you're looking to perform an
12 experiment, which a randomized-controlled trial is,
13 having a tightly-controlled more homogeneous
14 population is often preferred.

15 One of the key elements of this
16 generalizability versus homogeneous population is
17 whether or not all-comers are going to be studied,
18 meaning all patients with venous leg ulcers, or all
19 patients with diabetic foot ulcers, or is it going
20 to be a refractory population. Clearly, this
21 should be based on the science -- that is what the
22 product does for that patient or that

1 disease -- but oftentimes marketing and other
2 factors come into play when a trial is designed.

3 A refractory population might be defined by
4 how long the wound has been there, how large the
5 wound is, or in many trials, a run-in period to
6 exclude those patients with excellent standard of
7 care that are on a healing trajectory.

8 The second major issue in clinical
9 trials -- and this is certainly going to be
10 discussed throughout the day and then
11 tomorrow -- is the outcomes that are chosen. Then
12 finally is what are the critical issues in standard
13 care in designing clinical trials.

14 I want to talk about enrollment expectations
15 and speed, and share with you unpublished data that
16 we're in the process of completing and submitting
17 for a couple publications. The Diabetic Foot
18 Consortium is a group of academic centers in the
19 United States, starting with six academic centers,
20 carrying out clinical research in diabetic foot
21 ulcers. As part of this consortium, a project was
22 undertaken to look at how fast diabetic foot ulcers

1 enroll patients historically.

2 Without going into great detail, data was
3 taken over a 30-year period from clinicaltrials.gov
4 and from PubMed, and after duplicates were removed,
5 there were 765 records. Of those 765 records,
6 289 records met inclusion criteria for a systematic
7 review. I just want to highlight some of the data
8 related to speed of enrollment.

9 On your right, which I'm not going to go
10 into, you can see how we divide it into U.S. versus
11 outside of U.S., number of sites; the start dates;
12 duration of enrollment and follow-up; what type of
13 study it was; who it involved; and what FDA phase
14 or non-applicable was the study. One of the
15 take-home messages is the enrollment rate per
16 month, but importantly, the enrollment rate in
17 patients per month per site and the median is 1.67
18 across all studies for patients per month per site,
19 and that's critical as trials are being designed.

20 Now, every trial is not the same, and when
21 we began to kind of drill down, the Diabetic Foot
22 Consortium is an observational study, so we looked

1 at that. The observational studies, in general,
2 enrolled higher than the median. They enrolled
3 2.65 patients per site per month. In the U.S.,
4 where 30 percent of the data comes from, it's
5 0.53 patients per site per month, which is less
6 than the median I showed you before.

7 The data before 2010 and after 2010 is quite
8 similar, although 70 percent of data comes from
9 after 2010, 1.68 patients per month. Faster
10 enrollment was seen, in general, with shorter
11 enrollment time, more than one year of follow-up in
12 behavioral studies and in phase 1 studies, and
13 those in percentages were the number of studies of
14 the total that had those characteristics.

15 So you can see it's very important to
16 understand what the expectations are, and if you
17 thought that you were going to enroll 10 patients
18 per site per month, you're going to be widely
19 disappointed.

20 The other issue I just wanted to make sure
21 we touch upon, and I mentioned it a little bit, is
22 this generalizability versus homogeneous

1 population. It has very important factors in how
2 fast the enrollment will be and what the
3 expectations should be, and of course what is
4 really accomplishable, where a study may be
5 positive, and then what you could finally say about
6 the study once that study is complete, even if it
7 is positive.

8 Now I want to go on to outcomes. A few
9 years ago, Bill Eaglstein, Marty Robinson, and
10 myself looked at the FDA drug approval endpoints
11 for chronic cutaneous ulcers, and in this paper we
12 said what maybe other people were thinking; that
13 really we need to re-evaluate the endpoints of
14 chronic cutaneous ulcer studies. This paper really
15 spurred a movement to increase options for FDA
16 approval, and I think I'm proud to say that that
17 paper, probably in no small part, led to a lot of
18 work done by a lot of people that eventuated in
19 this conference to look at some of these issues.

20 Finally, I want to talk a little bit about
21 standard of care. There are some critical issues
22 in trial design with standard of care because in

1 designing any experiment, it's very important to
2 make sure that all factors are controlled, and
3 you're only studying one variable, and in the case
4 of a clinical trial, maybe some type of
5 intervention.

6 For venous leg ulcers -- and we heard a
7 little bit about venous leg ulcers -- compression
8 is critical, and having exactly defined the type of
9 compression is going to be very, very important for
10 venous leg ulcers. This turns out not to be as
11 challenging as other standard of care issues, but
12 one of the most contentious is the use of
13 offloading for diabetic foot ulcers.

14 Everyone on this call would agree that
15 offloading for diabetic foot ulcers is critical,
16 but when studies are carried out and they look for
17 what's best, the real question is, what's best for
18 the patients, or what's best for the company or the
19 sponsor, or what's best for the investigators? As
20 an example, somebody will say that putting someone
21 in a contact cast is best, but investigators know
22 that only a minority of patients will agree to

1 being in a contact cast in the study, so that may
2 slow enrollment at your site and may have a
3 financial impact on your being involved in the
4 study.

5 We also know that the sponsor or the company
6 that's looking to do an investigation is really
7 trying to find the delta between their product and
8 standard of care. The better the standard of care
9 is, the higher the threshold they have to reach to
10 show a difference. These become critical issues,
11 designing a study that's valid and reliable, but
12 also giving an opportunity for a product to work in
13 this experimental setting.

14 The last issue to standard of care that I
15 want to just mention in this relatively short talk
16 is debridement because, really, there's a general
17 lack of standardization, and also it's critically
18 important to understand what the product that is
19 being studied does.

20 Does it work to reverse the chronic
21 environment of a non-healing wound or does it speed
22 the healing of an acute wound? If you do large

1 debridement in a chronic wound, well, that wound
2 looks a little bit -- not completely, but a little
3 bit -- like an acute wound, and does the product
4 work in that setting or does it work by different
5 mechanisms?

6 So understanding what type of debridement
7 gives the intervention the best chance to work.
8 Also, if you're going to have debridement, make
9 sure it's done consistently across all sites so
10 that there's only one variable being studied, not
11 the variable of debridement, but the intervention
12 that is being targeted.

13 Then finally, I just want to mention in this
14 last slide about some common issues that often
15 derail sponsored clinical research, and I've seen
16 this over, and over, and over again. And
17 interestingly, it's regardless of whether we're
18 talking industry, or even NIH, or federal
19 sponsorship of trials.

20 The first one, of course, doesn't reflect
21 federal sponsorship, but oftentimes trials are
22 derailed because marketing considerations are taken

1 into effect to direct clinical trial design. This
2 is a huge mistake because once you veer from
3 preliminary scientific or clinical evidence that
4 suggests the best scenario in which an intervention
5 will work and begin to think about having more
6 patients use an intervention, then you effectively
7 reduce the sample size of the patients that could
8 respond to the intervention. This is a huge
9 problem where good products are given to people who
10 won't respond to them because they're part of the
11 market, and subsequently the trial will fail.

12 Important, is underestimating the cost and
13 time of carrying out clinical research. I showed
14 you some data about how fast clinical trials
15 enroll, but undeniably, every sponsor -- whether
16 it's the federal sponsors or industry
17 sponsors -- always is looking at the top number, or
18 listening to people who could say they can enroll
19 lots of patients into a trial as opposed to seeing
20 the data I showed or the clinical experience of
21 many investigators.

22 What happens with this is that the study

1 then becomes undercapitalized, and this creates
2 stress from top to bottom of the organization
3 that's sponsoring this and often leads to changing
4 of the trial design and going from a very
5 homogeneous scientific-based protocol to a
6 heterogeneous non-scientific-based protocol.

7 Part and parcel with that and very important
8 is overestimating subject enrollment. Part of that
9 has to do with poor site selection and
10 understanding that even if you get a hundred
11 percent good sites, something always comes up. An
12 investigator gets sick, or an investigator changes
13 locations, and all of a sudden you're down a good
14 enrolling site, and it puts tremendous pressure on
15 the study itself, tremendous pressure on the people
16 that are administering the study, and the study
17 will be longer and will be undercapitalized.

18 For many interventions, they were studied in
19 small sample sizes by start-up companies, and
20 oftentimes a start-up company has to go from a
21 start-up to a manufacturing company to carry out
22 high-quality clinical research. Oftentimes they

1 think that it's going to be easy, but there are
2 problems with manufacturing, and even during the
3 study progress, those manufacturing challenges will
4 come to light and will interrupt. In the
5 worst-case scenario, the study will have to be
6 stopped, or the products that are being studied are
7 inconsistent, or the study will be delayed. So
8 making sure that the manufacturing processes are in
9 place, going from a research start-up to
10 manufacturing for a larger phase trial, is critical
11 so that trials can be completed effectively.

12 Then finally, many of these things that I
13 mentioned above lead to an overuse of protocol
14 changes. The major reason is to speed enrollment,
15 but there are other reasons, as I already mentioned
16 here, with manufacturing issues, for example, or
17 marketing considerations.

18 What happens is a well-designed study that's
19 well thought out in a homogeneous population with
20 strict inclusion and exclusion criteria to get a
21 positive result, that then could be taken to
22 patients, by making these protocol changes, the

1 population that's being studied changes, and the
2 study is underpowered. Even if you have a good
3 product, it doesn't reach statistical significance.
4 This is a critical issue; that many studies have
5 failed because of overuse of protocol changes
6 because of the issues I stated.

7 I want to stop here and not abuse my time,
8 and just to tell you that thoughtful scientific and
9 evidence-based approach to trial design, dealing
10 with some of the critical issues that I briefly
11 mentioned here, and avoiding the common pitfalls
12 will help improve quality and outcomes of clinical
13 research for chronic wounds. I want to thank you
14 very much for your attention.

15 (Pause.)

16 DR. MEJIA: Dr. Bearden, you're muted.

17 DR. BEARDEN: Can you hear me now?

18 DR. MEJIA: Yes.

19 DR. BEARDEN: Perfect.

20 **Presentation - Robert Bearden**

21 DR. BEARDEN: Thank you, Dr. Kirsner. It's
22 always a difficult follow-up, but I think what

1 we'll capitalize here is some of the industry
2 perspective to the challenges that you've noted.

3 As we go to the next slide here, what we've
4 discussed today and what we've been hearing
5 throughout these sessions is really the stress and
6 strain that gets put on the entire ecosystem from
7 the healthcare perspective, not only from the
8 patients that we heard in the previous session, but
9 also from the clinicians that we heard this
10 morning.

11 There's increasing pressures from the
12 hospitals to improve our outcomes and to improve
13 our patients' satisfaction while limiting and
14 reducing our costs. Again, this happens with
15 restrictions in our policies, procedures, and our
16 abilities to really adequately train the staff that
17 ultimately end up treating those patients.

18 As we go to the next slide here, we see the
19 prevalence of chronic wounds continuing to increase
20 with huge inconsistency of clinical practice.
21 Again, we made leaps and bounds in the last 20 to
22 25 years in how we standardize that practice, but

1 the care of wounds continues to be the wild wild
2 west. And while we may see one individual
3 clinician have a certain interpretation, as we
4 heard in the previous session, the internet has
5 provided a whole new avenue and data resources to
6 where patients are starting to self-diagnose and
7 even take the next steps to self-treatment.

8 Time is precious. It's those interventions
9 and the approach to those interventions that
10 ultimately change the impact to that prognosis. On
11 average, a patient sees about 2.5 clinicians before
12 receiving the appropriate care for that specific
13 wound.

14 As we move to the next slide here, we
15 understand that there are pressures on the system,
16 and how should industry take those into account?
17 We're streamlining in industry. We see
18 disenfranchising of our clinicians to where they're
19 more accountable to the hospital facilities that
20 they're employed by. So we're standardizing our
21 practice and we're trying to improve our patient
22 outcomes, all with the burdens of reducing our

1 costs and lowering our readmissions.

2 As we go to the next slide, that holistic
3 approach doesn't just happen with the individuals
4 involved in the frontline care, but that also
5 happens through the continuum care and site of
6 care. We see that in the outpatient centers, and
7 we see that all the way to the home health centers.

8 The ability to impact each one of these
9 sites of care and maintain the standardized care
10 approach becomes continually difficult. Again,
11 with that, we have to adjust to create
12 multimodality treatments, and the FDA has to be
13 more accepting of those multimodality treatments as
14 we continue to understand the scientific rationale
15 and the pathophysiology and outcomes associated
16 with these treatment therapies.

17 As we go to the next slide, it provides you
18 a little bit of insight to industry's views and how
19 we execute to these ideas and these inventions. As
20 we come out of an ideation phase in which we're
21 understanding feasibility and we're doing the
22 bench-top understanding that Dr. Kirsner just

1 described and ultimately leading into a clinical
2 trial, we go through each one of these validation
3 steps.

4 Those validation steps include a multitude
5 of functions: quality, regulatory, operations,
6 manufacturing, clinical, and financial. So where
7 we see the smaller start-up companies fail or they
8 need earlier support is in these other functions in
9 which one person may be required to wear two or
10 three hats.

11 With the interpretation of the FDA, are
12 there opportunities that industry can better
13 partner with the FDA; chaperones or having
14 objective inputs? FDA is largely kept at arms
15 length in saying, "Provide all your data at once
16 due to our resource constraints," however, there's
17 an opportunity for increased collaboration and
18 increase communication between the two parties.

19 As we go forward, I give you a deeper dive
20 into what each phase really looks like. In
21 ideation and the feasibility stage, the holistic
22 approach doesn't just apply to the healthcare

1 system; it also applies to the industry partners
2 and how are we evaluating.

3 How are we being able to engage our
4 clinicians and their inventorship? These
5 inventions come from the frontline. These
6 inventions to solving a problem and realizing a
7 patient need through that patient care have to be
8 categorized and then evaluated.

9 Is it real? Do we have an IP landscape and
10 freedom to operate there? Is the technology
11 feasible from a scale-up and manufacturing
12 component? Do we meet regulatory and reimbursement
13 restrictions to maintain our budgetary thresholds?
14 Is there an unmet need or is this an individual
15 development? Can we see this from our previous
16 inventions? One example is the Foley catheter, but
17 we're not seeing as much of that in today's
18 development.

19 As we go to the next slide, I think we'll
20 describe more of the challenges as it relates to
21 industry and building the pipeline to these new
22 products. From a clinical angle, we see this

1 disenfranchising that I've mentioned in which the
2 hospitals are pushing for production pressure. So
3 the conflict of interest is, if there's
4 inventorship happening, does that take away the
5 opportunity for patient care? Are they losing that
6 opportunity for increased patient enrollment?

7 Additionally, from a hospital perspective,
8 there's a shift from therapeutic advancements. We
9 see increased submissions for diagnostics rather
10 than product therapies. While it's important that
11 we be able to better understand and diagnose
12 specific wounds, we can only impact the changes to
13 that with increasing therapies.

14 What are the budgetary pressures? In
15 combination with clinicians and inventing a
16 specific product, we have to be mindful of the
17 costs that come into that because that clinician,
18 or the developing clinician, may come to the
19 hospital committee, and they'll refer to that
20 committee or the PNC committee to have it added to
21 their formulary and to give access. We have
22 limited multimodal modal products. Is there an

1 opportunity to expand those indications more
2 easily? Can we minimize the faculty conflict of
3 interest?

4 I think the solutions are yes. Right? It
5 starts with collaborations. It starts with
6 reducing policy and allowing for engagement of
7 those government agencies more readily, and
8 reducing our risks, through universities, through
9 those government agencies, to really drive those
10 trials and development.

11 But there's also an increased opportunity
12 for FDA industry engagement, as well as with the
13 clinicians, in which there is oversight where we
14 limit the inherent bias that we see in these
15 randomized-controlled trials. There is third-party
16 objective oversight in review of that documentation
17 to ease some of the challenges that Dr. Kirsner
18 just mentioned so that we're not adjusting
19 protocols inappropriately or that the inclusion and
20 exclusion criteria are appropriately met. But in
21 that earlier participation in the data review, as
22 we continue to move through those ideation,

1 definition, and development phases, getting
2 feedback at each step, rather than waiting for the
3 full submission.

4 As we go to this next slide, please, we
5 understand that chronic wounds are increasing in
6 prevalence, and they have an impact to the patient
7 care, and industry is constantly attempting to
8 adjust to that. However, we've seen a shift in
9 diagnostics and away from the therapies. We need
10 to get back to those therapies and ultimately
11 supporting the clinicians that are treating on the
12 frontline.

13 There has to be product and strategic
14 development there, creating a holistic approach so
15 that we don't price ourselves out of the market and
16 take us back to Polaroid. Polaroid pictures, they
17 were the first to give you the picture,
18 immediately. However, when they tried to take a
19 product called Polavision, creating short video
20 clips similar to their pictures, they priced
21 themselves out of the market. We saw that with
22 Apple. We've seen that with other technologies

1 very early on in their development stage. It
2 wasn't until they've come back to the market with
3 refined strategic development, to a product that is
4 more affordable, that they ultimately had greater
5 access.

6 How do we reduce the barriers to benchmark
7 progress? Again, it's increased collaboration.
8 It's reducing the barriers between, to where we're
9 peer-to-peer interaction rather than teacher-to-
10 student; where guidelines are, yes, we can do this
11 or, no, you can't do this, but you can do it in
12 this way.

13 I'm optimistic because prior to COVID, those
14 challenges continued to ring true, and the
15 obstacles and the thresholds were continuing to be
16 higher and higher. However, what we saw with the
17 development and, ultimately, accessibility to the
18 products on the market through COVID, there's an
19 opportunity to expedite and there's a willingness
20 to expedite. Can we build off of that success?
21 Can we continue that conversation ultimately to
22 allow and influence change more directly?

1 I think the answer is yes, and as we go to
2 this closing slide, I think it's about being
3 together, not only from the clinicians, but to
4 industry and to our government agencies that help
5 to support and regulate these policies. We can
6 address the complex problems together; we just have
7 to be willing and we have to be in communication.

8 I think with that, Dr. Mejia, I will kick it
9 back over to you for questions, answers, or any
10 other comments.

11 MR. TETLOW: Thank you, Dr. Bearden.

12 We will now have our final debrief and Q&A
13 of the day.

14 **Q&A - Kendall Marcus**

15 DR. MARCUS: Hi. Thank you, everybody who's
16 participated today. It has been very informative
17 workshop on day 1, and I want to give people the
18 opportunity to ask any questions.

19 (No response.)

20 DR. MARCUS: Okay. Well, I guess it's been
21 a long day, and everybody has taken in a lot of
22 information that's given them a lot to think about.

1 I don't see any questions coming up in the question
2 and answer box. If everybody is agreeable, I think
3 we can end a few minutes early.

4 Any other comments or questions?

5 (Pause.)

6 MR. TETLOW: It looks like we do have some
7 questions in the Q&A.

8 DR. MARCUS: Okay. I'll take the question
9 directed at the agency. Has the agency considered
10 following the approaches of other countries like
11 Israel to develop new products?

12 We are bound by regulations and guidances
13 for operation of the Food and Drug Administration
14 to regulate product and drug development in the
15 United States, and we adhere closely to our model
16 of drug development. So the answer is certainly
17 not within Dermatology and Dentistry have we
18 considered adopting approaches of countries like
19 Israel.

20 Dr. Kirsner, it looks like there is a
21 question for you in the question and answer box.

22 DR. KIRSNER: Great. The question asks,

1 what is your view of the value of companion
2 diagnostics to select the cohort patients most
3 likely to benefit from the specific treatment, and
4 therefore improve the statistics?

5 Any way you can create a more homogeneous
6 population, meaning that group of patients that
7 will actually respond to a therapy, the smaller the
8 sample size you're likely to need. So it will make
9 clinical trials, quote/unquote, "simpler," simpler
10 in the fact that they would have smaller sample
11 sizes.

12 It may take longer to find those patients,
13 meaning that there may be less patients that would
14 meet that criteria of the companion diagnostic, but
15 once those patients meet the criteria, it's likely
16 that the sample size would be smaller and your
17 likelihood of success is probably going to be
18 higher with that kind of improved homogeneous
19 population.

20 (Pause.)

21 MR. TETLOW: Dr. Marcus, I think you might
22 have been on mute.

1 DR. MARCUS: Oh, yes. I just said, "Thank
2 you for answering that question."

3 Are there other additional questions?

4 MR. TETLOW: It looks like we do have one
5 more point, one more question in the Q&A. The
6 question reads --

7 DR. MARCUS: It looks like it's -- go ahead.

8 MR. TETLOW: I was just going to say the
9 question reads, "A great perspective on the
10 clinical issues, but the solutions seem distant.
11 Perhaps there's a vital need for agents to have a
12 relatively universal impact on tissue repair." It
13 seems more like a comment.

14 DR. MARCUS: Yes, it looks more like a
15 comment.

16 (Pause.)

17 DR. MARCUS: Okay. If we have no more
18 questions, I would propose that we end a few
19 minutes early today. I want to thank everybody
20 again and ask if there are any -- one final
21 question. It looks like this is a question for
22 CDRH.

1 DR. CHANG: Hello. This is Cynthia Chang.
2 I'm from CDRH, and the question is, would anyone
3 like to elaborate about the huge difference between
4 very few treatments versus hundreds of 510(k)
5 devices?

6 As you may have seen from the presentations
7 this morning, the 510(k) pathway is really to
8 evaluate substantial equivalence to products that
9 were either marketed prior to 1976 or for other
10 class II devices. For most of those 510(k) devices
11 that have been cleared, they are indicated for
12 wound management basically to cover a wound,
13 protect it, keep it moist, and essentially not to
14 delay the natural wound healing process.

15 We understand that there are a number of
16 products that are needed as part of wound care, and
17 not all of them will be indicated for treatment or
18 for accelerating wound healing. Nonetheless,
19 devices are needed to cover the wound, keep it
20 moist, and be part of the overall management
21 process.

22 Hopefully that provides a little bit of

1 insight. If you look at the information on our
2 website, there will be more context and resources
3 for explaining what went into each of those 510(k)
4 cleared and de novo granted devices. Thank you.

5 (Pause.)

6 MR. TETLOW: Dr. Marcus, you're muted again.

7 DR. MARCUS: Yes. I see there's a comment
8 in the question and answer box about FDA's
9 requirements for granting marketing approvals to
10 new wound care products; "510(k) are too onerous to
11 warrant expensive clinical development for this
12 small market."

13 I think we've heard today that the market is
14 anything but small. There are anywhere from 6 to
15 10 million people in the United States with chronic
16 wounds, and it's costing health care billions of
17 dollars every year. So I guess I would like to
18 push back on the idea that this is a small market.

19 We do have regulations for demonstrating
20 efficacy and safety that guides our requirements
21 for drug development. We are having this wound
22 care healing workshop today in order to attempt to

1 begin dialogue in addressing the many challenges
2 that exist for successfully conducting clinical
3 trials and getting products to market.

4 I think we've heard about many challenges in
5 enrolling clinical trials that have little to do
6 with FDA's requirements for demonstrating efficacy
7 and safety, and that would be enrolling patients at
8 clinical sites. I think we've heard a lot about
9 the pathophysiology of chronic wounds; that there
10 are a wide variety of wounds even though the
11 healing process is the same; that within a diabetic
12 wound ulcer, you may have different
13 pathophysiologies in play so that perhaps even
14 labeling a diabetic wound may not accurately
15 describe the pathophysiology of the wound.

16 I've heard calls for basic research into
17 patients that heal despite uncontrolled diabetes
18 and basic research of patients who do not heal in
19 the context of diabetes when most patients heal. I
20 also hear some calls for more basic research that
21 could inform clinical trial development and product
22 development. I think that there are many factors

1 at play that are making this sector of drug
2 development difficult.

3 Is there anyone from CDRH or CBER who would
4 like to also comment?

5 DR. CHANG: This is Cynthia Chang from CDRH.
6 I think what we've learned, as Dr. Marcus said,
7 from the discussions today is really that there's a
8 collaboration needed across all of the stakeholders
9 in the wound care arena to try and find solutions
10 to this very important problem.

11 We've discussed a number of different
12 marketing pathways for CDRH that are not just
13 510(k) specific, and we've also heard from CDER and
14 CBER as well. I think there's a lot of momentum
15 now to make some positive progress in this arena,
16 so thank you for participating in the discussion.

17 DR. MARCUS: I see a comment in the question
18 and answer box that having a pathway to market
19 based on safety of new products will facilitate
20 bringing new products to the market, and that
21 evidence of clinical efficacy can be built over
22 time once the product is in the market.

1 That's not currently a pathway for drugs or
2 biologics that can be followed. There needs to be
3 a demonstration of efficacy and safety demonstrated
4 before a product is marketed. We have a guidance
5 that's available on our website on demonstrating
6 efficacy that people can review to understand the
7 different ways that efficacy can be demonstrated
8 prior to marketing of drugs.

9 (Pause.)

10 MR. TETLOW: Dr. Marcus, you're muted again.
11 Sorry.

12 DR. MARCUS: That's ok.

13 Thank you. I think we'll end now. I want
14 to thank everybody who participated today. I want
15 to thank our speakers. I want to thank our
16 patients for sharing their experiences and
17 conveying to us important aspects of wound care,
18 and I want to thank everybody who was involved in
19 organizing this workshop, so thank you.

20 Do we have any administrative things to wrap
21 up before we end?

22 DR. VERMA: No, just that I will see

1 everyone tomorrow morning at 9 a.m. Thank you,
2 everyone.

3 (Whereupon, at 3:30 p.m., the meeting was
4 adjourned.)

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