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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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Alliance of Wound Care Stakeholders.

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

**Presentation – Dev Verma**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Presentation – Gary Chiang**

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

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

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

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

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

(Pause.)

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

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

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

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

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

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

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

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

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

(Pause.)

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

(Pause.)

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

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

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

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

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

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

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

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

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

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

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

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

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

(Pause.)

DR. VERMA: Alright, everyone. Sorry for

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

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

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

If partial wound healing is studied, it

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

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

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

**Presentation – Allan Guan**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

PMAs rely on an independent demonstration of the safety and effectiveness of the product seeking approval.

Like for de novo, sponsors must demonstrate a reasonable assurance of safety and effectiveness, and this is typically supported by clinical data. In addition, PMAs have additional controls, including post-approval requirements such as annual reporting and stricter oversight of manufacturing and design changes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Presentation – Rosa Sherafat-Kazemadeh**

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

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

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

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

CBER's products indicated for wound healing

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Presentation – Jennifer Bai**

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

help improve wound healing for patients.

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

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

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

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

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

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

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

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

should consider measuring volume or surface area. Signs of infection are also important to document.

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

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

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

In general, clinical outcomes associated

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

sponsors and stakeholders can discuss endpoints with FDA.

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

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

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

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

**FDA Introductory Comments – Dev Verma**

DR. VERMA: Thank you, everyone.

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

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

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

Orthopedic Surgery;

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

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

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

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

tissue healing and regeneration; and

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

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

**Presentation – Kenneth Fan**

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

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

suffered from chronic wounds, with costs ranging from $28.1 billion to $96.8 billion yearly. Chronic wounds are generally defined as wounds failing to progress through the normal wound healing phase process within one month. More than 90 percent of chronic wounds fall into venous ulcers, diabetic ulcers, and pressure ulcers.

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

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

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

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

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

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

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

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

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

again can be exacerbated by local tissue infection.

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

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

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

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

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

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

modalities and multidisciplinary care access. Thank you very much for your time and attention.

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

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

**Presentation – Lisa Gould**

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

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

of patients that are 80 years and older.

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

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

The prevalence of peripheral arterial

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

Other etiologies of arterial insufficiency include Buerger's disease, which is a vasospastic condition, which is primarily due to smoking. Sickle cell disease is not often thought of as an arterial insufficiency, but that is what's causing the wounds and vasculitides, which also are an arterial insufficiency that result in open wounds.

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

You can imagine they're pressure ulcers, but

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

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

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

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

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

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

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

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

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

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

helpful for patients who show a response to supplemental oxygen and can't otherwise be revascularized, and is being used for diabetic foot ulcers with low $TcPO_2$'s. Intermittent pneumatic compression also has some data. I will be honest; I haven't kept up on that data, but that's one modality.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Because of that, compression is the primary therapy because what that's doing is compressing those vessels so that the calf muscle pump can work and move the blood flow back to the heart. Elevation can work because it decreases the edema but, again, compression being the primary therapy.

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

One of the major problems is that patients

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

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

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

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

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

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

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

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

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

contributing to the stasis dermatitis.

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

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

**Presentation – Paul Kim**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Presentation – Caroline Fife**

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

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

(Pause.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

the same way regardless of what we call that.

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

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

**Panel Discussion**

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

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

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

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

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

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

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

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

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

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

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

but their wounds heal.

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

DR. VERMA: Thank you.

Dr. Gould, you have your hand raised.

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

When I was at the Tampa VA, we were looking

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

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

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

DR. VERMA: Dr. Tomic-Canic?

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

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

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

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

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

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

(No response.)

DR. VERMA: You may be muted.

DR. GARCIA: I apologize for that.

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

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

wounds are not going to progress towards healing.

DR. VERMA: Great.

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

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

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

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

actual way that they go away.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

That being said, I understand that in an

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

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

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

facilitate that coordinating of efforts.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. FIFE: Our payment reimbursement models

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

DR. VERMA: Thanks, everyone.

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

Dr. Fan, you mentioned in your talk that the U.S. really focuses on wound size and not as much on recurrence and function as Europe does. Dr. Kim, you also mentioned recidivism, and 20 percent of diabetic foot ulcers may recur.

Could the panelists speak a little bit more

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

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

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

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

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

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

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

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

(Laughter.)

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

I'm asking somebody who's had a pressure

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

let everyone take a stab at that.

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

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

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

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

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

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

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

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

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

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

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

patients and trying to heal these wounds.

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

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

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

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

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

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

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

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

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

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

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

(Video played.)

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

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

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

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

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

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

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

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

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

(Video played.)

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

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

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

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

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

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

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

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

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

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

(Video played)

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

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

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

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

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

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

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

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

The challenges I found were that not much is offered in wound care for home health. There are a lot of restrictions on home health, where there are many more opportunities and options in a wound care clinic, in-clinic care, and if you have a diabetic or vascular wound. But for those of us with pressure ulcers who have failed at prevention for whatever reason, we don't have the options. I beg you to give us options, to open up options for those of us in home care that are suffering months and years with these wounds. Thank you.

**Panel Discussion**

CAPT BENT: Great. Thank you.

We planned to have a live testimony take place at this point, but we're having some technical difficulties for that panelist, so we may have her join us in a little bit once we straighten that out.

I hope that hearing from some of our panelists about the impacts of their chronic wounds really reminds all of us of why we're here today and tomorrow, and why it's important for us to

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

Go ahead and say hello. Thanks.

MARTHA: I'm Martha Bednar.

CAPT BENT: Thank you, Martha.

Amy?

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

CAPT BENT: Thank you, Amy.

Dana?

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

CAPT BENT: Let me ask you to start it.

DANA: There we go.

CAPT BENT: Okay. Great.

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

CAPT BENT: Thank you.

Eric?

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

CAPT BENT: Alright.

Laurie?

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

CAPT BENT: Thank you.

Ollie?

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

CAPT BENT: Thanks, Ollie.

Peter?

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

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

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

CAPT BENT: Alright. Let me see.

RICHARD: There we go.

CAPT BENT: There we go.

RICHARD: Okay.

CAPT BENT: Great. Thank you so much.

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

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

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

PETER: Sure.

CAPT BENT: Thank you.

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

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

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

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

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

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

CAPT BENT: Great. Thank you.

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

(No response.)

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

MARTHA: Am I muted?

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

MARTHA: Okay.

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

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

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

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

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

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

AMY: Quality of life, definitely quality of

life.

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

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

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

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

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

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

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

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

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

AMY: Can I also add?

CAPT BENT: Yes, please.

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

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

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

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

Eric?

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

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

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

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

CAPT BENT: Thanks, Eric.

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

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

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

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

Dana?

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

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

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

CAPT BENT: Great. Thanks, Dana.

Richard, go ahead.

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

In the meantime, the pain was just

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

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

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

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

Amy, did you raise your hand?

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

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

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

CAPT BENT: Thanks, Amy.

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

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

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

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

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

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

CAPT BENT: Thanks.

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

JOE: I'm going to let Martha speak.

For me, it's the restriction on life.

CAPT BENT: Okay.

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

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

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

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

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

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

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

CAPT BENT: Thanks, Martha.

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

Go ahead, Dana.

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

Currently, I have a pressure wound on my

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

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

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

CAPT BENT: Thanks, Dana.

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

LAURIE: Thank you, Robyn.

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

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

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

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

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

CAPT BENT: Great. Thank you.

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

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

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

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

CAPT BENT: Thanks, Amy.

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

(No response.)

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

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

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

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

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

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

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

DANA: Do you mind?

CAPT BENT: No, sure.

DANA: Sorry. Thank you.

CAPT BENT: Martha, go ahead.

MARTHA: I should press something down to talk.

CAPT BENT: I can hear you.

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

JOE: Right.

MARTHA: Oh. You should see my drive; it

gets better.

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

(Laughter.)

MARTHA: I try. Anyway --

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

(No response.)

CAPT BENT: Did you get the request to unmute?

MARTHA: Unmute?

CAPT BENT: There we go.

MARTHA: Now I can just talk.

JOE: Yes.

CAPT BENT: Yes, ma'am.

MARTHA: Alright.

To me, complete healing would be the answer. If I was told it's only partially healed, I would find that unacceptable. The reason being, I was told by my vascular doctor that I need to wear compression stockings that are 30 to 40 milligrams

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

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

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

It's in my sneaker. Why is this not a wound?" "Oh, that's only plasma, and if you just have plasma coming out, it's not considered a wound yet."

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

CAPT BENT: Thank you.

Let me turn to Dana.

DANA: Thanks. Sorry.

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

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

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

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

CAPT BENT: Thanks.

Laurie?

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

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

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

CAPT BENT: Thanks, Laurie.

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

or less odor, or things like that?

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

Go ahead.

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

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

Again, this is just a hypothetical question.

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

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

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

CAPT BENT: Thanks, Laurie.

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

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

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

CAPT BENT: Great. Thanks, Ollie.

Does anyone else have any thoughts about this?

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

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

JOE: Oh, there we go.

CAPT BENT: Okay.

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

CAPT BENT: Great. Thank you.

Anybody else? I don't know, Eric or

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

Sorry, Amy.

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

CAPT BENT: Great. Thank you, Eric.

Amy?

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

The thing is, for many of us with chronic

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

CAPT BENT: Dana?

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

CAPT BENT: Great.

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

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

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

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

DANA: Yes.

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

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

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

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

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

CAPT BENT: Great. Thank you.

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

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

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

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

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

above the knee.

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

RICHARD: No.

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

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

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

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

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

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

ahead and get started.

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

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

(Video played.)

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

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

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

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

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

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

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

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

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

(Video played.)

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

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

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

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

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

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

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

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

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

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

(Video played.)

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

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

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

It's also a very expensive thing because gas

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

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

I recently was told I needed to be

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

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

(Video played.)

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

experienced as I've dealt with chronic wounds.

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

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

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

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

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

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

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

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

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

(No response.)

CAPT BENT: Well, Eric, I might still stick

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

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

CAPT BENT: Okay. Yes, you are.

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

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

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

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

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

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

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

CAPT BENT: Great. Thank you.

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

Laurie?

(No response.)

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

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

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

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

If I was going to put a new product on the

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

CAPT BENT: Thanks, Laurie.

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

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

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

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

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

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

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

CAPT BENT: Great. Thank you.

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

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

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

Dana?

(No response.)

CAPT BENT: I think you might be muted.

DANA: I'm muted.

CAPT BENT: There you go.

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

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

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

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

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

CAPT BENT: Great. Thank you so much.

Let me move on to our next question, which

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

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

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

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

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

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

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

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

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

MARTHA: Right.

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

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

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

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

CAPT BENT: Great. Thanks, Martha and Joe.

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

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

I think for me it's treatments with evidence

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

CAPT BENT: Thank you.

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

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

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

much more limited.

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

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

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

CAPT BENT: It does. Thank you.

Before I move on to the next question, is

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

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

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

CAPT BENT: Great.

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

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

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

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

CAPT BENT: Great. Thank you.

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

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

CAPT BENT: Great. Thank you.

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

Amy?

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

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

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

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

AMY: Yes, definitely.

CAPT BENT: Great. Thank you.

Richard?

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

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

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

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

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

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

DANA: With clinical trials, I would do it

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

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

CAPT BENT: Great. Thanks.

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

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

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

PETER: Can I comment on that?

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

CAPT BENT: Thanks.

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

want us to run over.

But go ahead, Laurie.

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

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

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

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

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

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

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

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

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

we would very much like to hear them.

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

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

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

**Introductory Comments - Maryjoy Mejia**

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

As we've heard today, the development of

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

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

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

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

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

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

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

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

With that, Dr. Kirsner?

**Presentation – Robert Kirsner**

DR. KIRSNER: Thank you.

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

I use the example of cancer, and wound healing has been compared to cancer over the years for a lot of different reasons. While the FDA is certainly different than the NIH and other governmental organizations, it is worthy to note that investment in cancer through the National Cancer Act in the '70s and NCI investment in molecular biology in the '80s has led to a really dramatic increase in the number of therapies that

have changed patients' lives.

During that time, of the last 50 years or so, in cancer technology, we've had the landmark paper by Winter talking about occlusive dressings. We've had dressings being developed in the '80s and beyond. But since then, as was noted earlier in the day, really just one drug and several cell- and tissue-based products have gone through the FDA process of approval, and there's ample evidence that as a public health concern, the wounds are underfunded by the NIH.

So while we're going to focus on clinical trials related to the FDA, and I know the FDA does not obviously have oversight over the NIH, whispering in your friends' ears is certainly important because good basic science and clinical research will lead to products for our patients down the road.

Now, I want to highlight one example of some data from clinical trials. This was a publication by the American Diabetes Association a couple of years ago that I was lucky enough to be part of

this publication. Within this publication, we looked at evidence-based advanced therapies for diabetic foot ulcers.

In this table, there are growth factors that are reported. There are cellular constructs, there are acellular constructs, placental membranes, and some other products as well. You can see the category of the products up top from platelet-derived growth factor, platelet release; human skin equivalent; dermal skin substitute; dermal template; submucosa small intestine; various acellular placental membranes; negative pressure; and HBO, and the sample sizes associated with those. There are relatively healing rates at the various time points in the second row; the time to closure; whether the product is FDA-approved; the study quality; whether there were additional RCTs; and whether there was real-life data.

The thing I want to highlight here using this table is that you can see that the products that went through the FDA review process -- not a 510(k) which we heard about earlier, but more

advanced Pathways with the FDA -- that process was associated with higher study quality, so there's a direct link between the study quality of the RCTs that are performed in wound healing and going through the FDA process.

A number of years ago, we published this paper in seminars in Cell & Developmental Biology, looking at the FDA and designing clinical trials for chronic cutaneous ulcers. The things we highlighted in this paper remain true even after nearly a decade in press.

What I want to highlight, though, over the next few minutes is some of the critical issues in wound healing clinical trials, and very importantly for the audience that's listening, some of the common pitfalls and the reasons why trials fail even if they have a good scientific rationale and a good product that they're studying.

Now, what I do want to tell you is that across all of medicine, even outside of wound healing itself, most high-quality trials are done for regulatory purposes with the aim of getting

approval or reimbursement. As I showed you in that table, the higher quality studies were associated with FDA approval, but this is not unique to wound healing. And, really, that's why it's so critical that as we think about FDA trials, it really not only is going to lead to more products for our patients, but improve the quality of the clinical trials that are carried out in our space, something we all definitely want.

So what are some critical issues in trial design? Of course, it starts with inclusion and exclusion criteria in determining who will be in a clinical trial. This is very important, choosing who should be enrolled and who should be excluded. There's a balance between enrollment expectations, how many patients per site, and how many sites you should have, which may increase cost and the speed of enrollment, and I'll talk a little bit more about that in just a few minutes.

Part of inclusion and exclusion criteria is whether you want a very generalizable or very homogeneous population, and oftentimes a trial will

start with a very homogeneous population, but if enrollment expectations are not met, they may broaden the entry criteria. And it really changes the trial itself, and then you have a hodgepodge of patients that are enrolled in the trialmetalloproteinases, and you can't get a clear answer from the results.

Companies or sponsors that are looking for FDA approval like the idea of generalizability because more patients will have access to their products, but when you're looking to perform an experiment, which a randomized-controlled trial is, having a tightly-controlled more homogeneous population is often preferred.

One of the key elements of this generalizability versus homogeneous population is whether or not all-comers are going to be studied, meaning all patients with venous leg ulcers, or all patients with diabetic foot ulcers, or is it going to be a refractory population. Clearly, this should be based on the science -- that is what the product does for that patient or that

disease -- but oftentimes marketing and other factors come into play when a trial is designed.

A refractory population might be defined by how long the wound has been there, how large the wound is, or in many trials, a run-in period to exclude those patients with excellent standard of care that are on a healing trajectory.

The second major issue in clinical trials -- and this is certainly going to be discussed throughout the day and then tomorrow -- is the outcomes that are chosen. Then finally is what are the critical issues in standard care in designing clinical trials.

I want to talk about enrollment expectations and speed, and share with you unpublished data that we're in the process of completing and submitting for a couple publications. The Diabetic Foot Consortium is a group of academic centers in the United States, starting with six academic centers, carrying out clinical research in diabetic foot ulcers. As part of this consortium, a project was undertaken to look at how fast diabetic foot ulcers

enroll patients historically.

Without going into great detail, data was taken over a 30-year period from clinicaltrials.gov and from PubMed, and after duplicates were removed, there were 765 records. Of those 765 records, 289 records met inclusion criteria for a systematic review. I just want to highlight some of the data related to speed of enrollment.

On your right, which I'm not going to go into, you can see how we divide it into U.S. versus outside of U.S., number of sites; the start dates; duration of enrollment and follow-up; what type of study it was; who it involved; and what FDA phase or non-applicable was the study. One of the take-home messages is the enrollment rate per month, but importantly, the enrollment rate in patients per month per site and the median is 1.67 across all studies for patients per month per site, and that's critical as trials are being designed.

Now, every trial is not the same, and when we began to kind of drill down, the Diabetic Foot Consortium is an observational study, so we looked

at that. The observational studies, in general, enrolled higher than the median. They enrolled 2.65 patients per site per month. In the U.S., where 30 percent of the data comes from, it's 0.53 patients per site per month, which is less than the median I showed you before.

The data before 2010 and after 2010 is quite similar, although 70 percent of data comes from after 2010, 1.68 patients per month. Faster enrollment was seen, in general, with shorter enrollment time, more than one year of follow-up in behavioral studies and in phase 1 studies, and those in percentages were the number of studies of the total that had those characteristics.

So you can see it's very important to understand what the expectations are, and if you thought that you were going to enroll 10 patients per site per month, you're going to be widely disappointed.

The other issue I just wanted to make sure we touch upon, and I mentioned it a little bit, is this generalizability versus homogeneous

population. It has very important factors in how fast the enrollment will be and what the expectations should be, and of course what is really accomplishable, where a study may be positive, and then what you could finally say about the study once that study is complete, even if it is positive.

Now I want to go on to outcomes. A few years ago, Bill Eaglstein, Marty Robinson, and myself looked at the FDA drug approval endpoints for chronic cutaneous ulcers, and in this paper we said what maybe other people were thinking; that really we need to re-evaluate the endpoints of chronic cutaneous ulcer studies. This paper really spurred a movement to increase options for FDA approval, and I think I'm proud to say that that paper, probably in no small part, led to a lot of work done by a lot of people that eventuated in this conference to look at some of these issues.

Finally, I want to talk a little bit about standard of care. There are some critical issues in trial design with standard of care because in

designing any experiment, it's very important to make sure that all factors are controlled, and you're only studying one variable, and in the case of a clinical trial, maybe some type of intervention.

For venous leg ulcers -- and we heard a little bit about venous leg ulcers -- compression is critical, and having exactly defined the type of compression is going to be very, very important for venous leg ulcers. This turns out not to be as challenging as other standard of care issues, but one of the most contentious is the use of offloading for diabetic foot ulcers.

Everyone on this call would agree that offloading for diabetic foot ulcers is critical, but when studies are carried out and they look for what's best, the real question is, what's best for the patients, or what's best for the company or the sponsor, or what's best for the investigators? As an example, somebody will say that putting someone in a contact cast is best, but investigators know that only a minority of patients will agree to

being in a contact cast in the study, so that may slow enrollment at your site and may have a financial impact on your being involved in the study.

We also know that the sponsor or the company that's looking to do an investigation is really trying to find the delta between their product and standard of care. The better the standard of care is, the higher the threshold they have to reach to show a difference. These become critical issues, designing a study that's valid and reliable, but also giving an opportunity for a product to work in this experimental setting.

The last issue to standard of care that I want to just mention in this relatively short talk is debridement because, really, there's a general lack of standardization, and also it's critically important to understand what the product that is being studied does.

Does it work to reverse the chronic environment of a non-healing wound or does it speed the healing of an acute wound? If you do large

debridement in a chronic wound, well, that wound looks a little bit -- not completely, but a little bit -- like an acute wound, and does the product work in that setting or does it work by different mechanisms?

So understanding what type of debridement gives the intervention the best chance to work. Also, if you're going to have debridement, make sure it's done consistently across all sites so that there's only one variable being studied, not the variable of debridement, but the intervention that is being targeted.

Then finally, I just want to mention in this last slide about some common issues that often derail sponsored clinical research, and I've seen this over, and over, and over again. And interestingly, it's regardless of whether we're talking industry, or even NIH, or federal sponsorship of trials.

The first one, of course, doesn't reflect federal sponsorship, but oftentimes trials are derailed because marketing considerations are taken

into effect to direct clinical trial design. This is a huge mistake because once you veer from preliminary scientific or clinical evidence that suggests the best scenario in which an intervention will work and begin to think about having more patients use an intervention, then you effectively reduce the sample size of the patients that could respond to the intervention. This is a huge problem where good products are given to people who won't respond to them because they're part of the market, and subsequently the trial will fail.

Important, is underestimating the cost and time of carrying out clinical research. I showed you some data about how fast clinical trials enroll, but undeniably, every sponsor -- whether it's the federal sponsors or industry sponsors -- always is looking at the top number, or listening to people who could say they can enroll lots of patients into a trial as opposed to seeing the data I showed or the clinical experience of many investigators.

What happens with this is that the study

then becomes undercapitalized, and this creates stress from top to bottom of the organization that's sponsoring this and often leads to changing of the trial design and going from a very homogeneous scientific-based protocol to a heterogeneous non-scientific-based protocol.

Part and parcel with that and very important is overestimating subject enrollment. Part of that has to do with poor site selection and understanding that even if you get a hundred percent good sites, something always comes up. An investigator gets sick, or an investigator changes locations, and all of a sudden you're down a good enrolling site, and it puts tremendous pressure on the study itself, tremendous pressure on the people that are administering the study, and the study will be longer and will be undercapitalized.

For many interventions, they were studied in small sample sizes by start-up companies, and oftentimes a start-up company has to go from a start-up to a manufacturing company to carry out high-quality clinical research. Oftentimes they

think that it's going to be easy, but there are problems with manufacturing, and even during the study progress, those manufacturing challenges will come to light and will interrupt. In the worst-case scenario, the study will have to be stopped, or the products that are being studied are inconsistent, or the study will be delayed. So making sure that the manufacturing processes are in place, going from a research start-up to manufacturing for a larger phase trial, is critical so that trials can be completed effectively.

Then finally, many of these things that I mentioned above lead to an overuse of protocol changes. The major reason is to speed enrollment, but there are other reasons, as I already mentioned here, with manufacturing issues, for example, or marketing considerations.

What happens is a well-designed study that's well thought out in a homogeneous population with strict inclusion and exclusion criteria to get a positive result, that then could be taken to patients, by making these protocol changes, the

population that's being studied changes, and the study is underpowered. Even if you have a good product, it doesn't reach statistical significance. This is a critical issue; that many studies have failed because of overuse of protocol changes because of the issues I stated.

I want to stop here and not abuse my time, and just to tell you that thoughtful scientific and evidence-based approach to trial design, dealing with some of the critical issues that I briefly mentioned here, and avoiding the common pitfalls will help improve quality and outcomes of clinical research for chronic wounds. I want to thank you very much for your attention.

(Pause.)

DR. MEJIA: Dr. Bearden, you're muted.

DR. BEARDEN: Can you hear me now?

DR. MEJIA: Yes.

DR. BEARDEN: Perfect.

**Presentation – Robert Bearden**

DR. BEARDEN: Thank you, Dr. Kirsner. It's always a difficult follow-up, but I think what

we'll capitalize here is some of the industry perspective to the challenges that you've noted.

As we go to the next slide here, what we've discussed today and what we've been hearing throughout these sessions is really the stress and strain that gets put on the entire ecosystem from the healthcare perspective, not only from the patients that we heard in the previous session, but also from the clinicians that we heard this morning.

There's increasing pressures from the hospitals to improve our outcomes and to improve our patients' satisfaction while limiting and reducing our costs. Again, this happens with restrictions in our policies, procedures, and our abilities to really adequately train the staff that ultimately end up treating those patients.

As we go to the next slide here, we see the prevalence of chronic wounds continuing to increase with huge inconsistency of clinical practice. Again, we made leaps and bounds in the last 20 to 25 years in how we standardize that practice, but

the care of wounds continues to be the wild wild west. And while we may see one individual clinician have a certain interpretation, as we heard in the previous session, the internet has provided a whole new avenue and data resources to where patients are starting to self-diagnose and even take the next steps to self-treatment.

Time is precious. It's those interventions and the approach to those interventions that ultimately change the impact to that prognosis. On average, a patient sees about 2.5 clinicians before receiving the appropriate care for that specific wound.

As we move to the next slide here, we understand that there are pressures on the system, and how should industry take those into account? We're streamlining in industry. We see disenfranchising of our clinicians to where they're more accountable to the hospital facilities that they're employed by. So we're standardizing our practice and we're trying to improve our patient outcomes, all with the burdens of reducing our

costs and lowering our readmissions.

As we go to the next slide, that holistic approach doesn't just happen with the individuals involved in the frontline care, but that also happens through the continuum care and site of care. We see that in the outpatient centers, and we see that all the way to the home health centers.

The ability to impact each one of these sites of care and maintain the standardized care approach becomes continually difficult. Again, with that, we have to adjust to create multimodality treatments, and the FDA has to be more accepting of those multimodality treatments as we continue to understand the scientific rationale and the pathophysiology and outcomes associated with these treatment therapies.

As we go to the next slide, it provides you a little bit of insight to industry's views and how we execute to these ideas and these inventions. As we come out of an ideation phase in which we're understanding feasibility and we're doing the bench-top understanding that Dr. Kirsner just

described and ultimately leading into a clinical trial, we go through each one of these validation steps.

Those validation steps include a multitude of functions: quality, regulatory, operations, manufacturing, clinical, and financial. So where we see the smaller start-up companies fail or they need earlier support is in these other functions in which one person may be required to wear two or three hats.

With the interpretation of the FDA, are there opportunities that industry can better partner with the FDA; chaperones or having objective inputs? FDA is largely kept at arms length in saying, "Provide all your data at once due to our resource constraints," however, there's an opportunity for increased collaboration and increase communication between the two parties.

As we go forward, I give you a deeper dive into what each phase really looks like. In ideation and the feasibility stage, the holistic approach doesn't just apply to the healthcare

system; it also applies to the industry partners and how are we evaluating.

How are we being able to engage our clinicians and their inventorship? These inventions come from the frontline. These inventions to solving a problem and realizing a patient need through that patient care have to be categorized and then evaluated.

Is it real? Do we have an IP landscape and freedom to operate there? Is the technology feasible from a scale-up and manufacturing component? Do we meet regulatory and reimbursement restrictions to maintain our budgetary thresholds? Is there an unmet need or is this an individual development? Can we see this from our previous inventions? One example is the Foley catheter, but we're not seeing as much of that in today's development.

As we go to the next slide, I think we'll describe more of the challenges as it relates to industry and building the pipeline to these new products. From a clinical angle, we see this

disenfranchising that I've mentioned in which the hospitals are pushing for production pressure. So the conflict of interest is, if there's inventorship happening, does that take away the opportunity for patient care? Are they losing that opportunity for increased patient enrollment?

Additionally, from a hospital perspective, there's a shift from therapeutic advancements. We see increased submissions for diagnostics rather than product therapies. While it's important that we be able to better understand and diagnose specific wounds, we can only impact the changes to that with increasing therapies.

What are the budgetary pressures? In combination with clinicians and inventing a specific product, we have to be mindful of the costs that come into that because that clinician, or the developing clinician, may come to the hospital committee, and they'll refer to that committee or the PNC committee to have it added to their formulary and to give access. We have limited multimodal modal products. Is there an

opportunity to expand those indications more easily? Can we minimize the faculty conflict of interest?

I think the solutions are yes. Right? It starts with collaborations. It starts with reducing policy and allowing for engagement of those government agencies more readily, and reducing our risks, through universities, through those government agencies, to really drive those trials and development.

But there's also an increased opportunity for FDA industry engagement, as well as with the clinicians, in which there is oversight where we limit the inherent bias that we see in these randomized-controlled trials. There is third-party objective oversight in review of that documentation to ease some of the challenges that Dr. Kirsner just mentioned so that we're not adjusting protocols inappropriately or that the inclusion and exclusion criteria are appropriately met. But in that earlier participation in the data review, as we continue to move through those ideation,

definition, and development phases, getting feedback at each step, rather than waiting for the full submission.

As we go to this next slide, please, we understand that chronic wounds are increasing in prevalence, and they have an impact to the patient care, and industry is constantly attempting to adjust to that. However, we've seen a shift in diagnostics and away from the therapies. We need to get back to those therapies and ultimately supporting the clinicians that are treating on the frontline.

There has to be product and strategic development there, creating a holistic approach so that we don't price ourselves out of the market and take us back to Polaroid. Polaroid pictures, they were the first to give you the picture, immediately. However, when they tried to take a product called Polavision, creating short video clips similar to their pictures, they priced themselves out of the market. We saw that with Apple. We've seen that with other technologies

very early on in their development stage. It wasn't until they've come back to the market with refined strategic development, to a product that is more affordable, that they ultimately had greater access.

How do we reduce the barriers to benchmark progress? Again, it's increased collaboration. It's reducing the barriers between, to where we're peer-to-peer interaction rather than teacher-to-student; where guidelines are, yes, we can do this or, no, you can't do this, but you can do it in this way.

I'm optimistic because prior to COVID, those challenges continued to ring true, and the obstacles and the thresholds were continuing to be higher and higher. However, what we saw with the development and, ultimately, accessibility to the products on the market through COVID, there's an opportunity to expedite and there's a willingness to expedite. Can we build off of that success? Can we continue that conversation ultimately to allow and influence change more directly?

I think the answer is yes, and as we go to this closing slide, I think it's about being together, not only from the clinicians, but to industry and to our government agencies that help to support and regulate these policies. We can address the complex problems together; we just have to be willing and we have to be in communication.

I think with that, Dr. Mejia, I will kick it back over to you for questions, answers, or any other comments.

MR. TETLOW: Thank you, Dr. Bearden.

We will now have our final debrief and Q&A of the day.

**Q&A – Kendall Marcus**

DR. MARCUS: Hi. Thank you, everybody who's participated today. It has been very informative workshop on day 1, and I want to give people the opportunity to ask any questions.

(No response.)

DR. MARCUS: Okay. Well, I guess it's been a long day, and everybody has taken in a lot of information that's given them a lot to think about.

I don't see any questions coming up in the question and answer box. If everybody is agreeable, I think we can end a few minutes early.

Any other comments or questions?

(Pause.)

MR. TETLOW: It looks like we do have some questions in the Q&A.

DR. MARCUS: Okay. I'll take the question directed at the agency. Has the agency considered following the approaches of other countries like Israel to develop new products?

We are bound by regulations and guidances for operation of the Food and Drug Administration to regulate product and drug development in the United States, and we adhere closely to our model of drug development. So the answer is certainly not within Dermatology and Dentistry have we considered adopting approaches of countries like Israel.

Dr. Kirsner, it looks like there is a question for you in the question and answer box.

DR. KIRSNER: Great. The question asks,

what is your view of the value of companion diagnostics to select the cohort patients most likely to benefit from the specific treatment, and therefore improve the statistics?

Any way you can create a more homogeneous population, meaning that group of patients that will actually respond to a therapy, the smaller the sample size you're likely to need. So it will make clinical trials, quote/unquote, "simpler," simpler in the fact that they would have smaller sample sizes.

It may take longer to find those patients, meaning that there may be less patients that would meet that criteria of the companion diagnostic, but once those patients meet the criteria, it's likely that the sample size would be smaller and your likelihood of success is probably going to be higher with that kind of improved homogeneous population.

(Pause.)

MR. TETLOW: Dr. Marcus, I think you might have been on mute.

DR. MARCUS: Oh, yes. I just said, "Thank you for answering that question."

Are there other additional questions?

MR. TETLOW: It looks like we do have one more point, one more question in the Q&A. The question reads --

DR. MARCUS: It looks like it's -- go ahead.

MR. TETLOW: I was just going to say the question reads, "A great perspective on the clinical issues, but the solutions seem distant. Perhaps there's a vital need for agents to have a relatively universal impact on tissue repair." It seems more like a comment.

DR. MARCUS: Yes, it looks more like a comment.

(Pause.)

DR. MARCUS: Okay. If we have no more questions, I would propose that we end a few minutes early today. I want to thank everybody again and ask if there are any -- one final question. It looks like this is a question for CDRH.

DR. CHANG: Hello. This is Cynthia Chang. I'm from CDRH, and the question is, would anyone like to elaborate about the huge difference between very few treatments versus hundreds of 510(k) devices?

As you may have seen from the presentations this morning, the 510(k) pathway is really to evaluate substantial equivalence to products that were either marketed prior to 1976 or for other class II devices. For most of those 510(k) devices that have been cleared, they are indicated for wound management basically to cover a wound, protect it, keep it moist, and essentially not to delay the natural wound healing process.

We understand that there are a number of products that are needed as part of wound care, and not all of them will be indicated for treatment or for accelerating wound healing. Nonetheless, devices are needed to cover the wound, keep it moist, and be part of the overall management process.

Hopefully that provides a little bit of

insight. If you look at the information on our website, there will be more context and resources for explaining what went into each of those 510(k) cleared and de novo granted devices. Thank you.

(Pause.)

MR. TETLOW: Dr. Marcus, you're muted again.

DR. MARCUS: Yes. I see there's a comment in the question and answer box about FDA's requirements for granting marketing approvals to new wound care products; "510(k) are too onerous to warrant expensive clinical development for this small market."

I think we've heard today that the market is anything but small. There are anywhere from 6 to 10 million people in the United States with chronic wounds, and it's costing health care billions of dollars every year. So I guess I would like to push back on the idea that this is a small market.

We do have regulations for demonstrating efficacy and safety that guides our requirements for drug development. We are having this wound care healing workshop today in order to attempt to

begin dialogue in addressing the many challenges that exist for successfully conducting clinical trials and getting products to market.

I think we've heard about many challenges in enrolling clinical trials that have little to do with FDA's requirements for demonstrating efficacy and safety, and that would be enrolling patients at clinical sites. I think we've heard a lot about the pathophysiology of chronic wounds; that there are a wide variety of wounds even though the healing process is the same; that within a diabetic wound ulcer, you may have different pathophysiologies in play so that perhaps even labeling a diabetic wound may not accurately describe the pathophysiology of the wound.

I've heard calls for basic research into patients that heal despite uncontrolled diabetes and basic research of patients who do not heal in the context of diabetes when most patients heal. I also hear some calls for more basic research that could inform clinical trial development and product development. I think that there are many factors

at play that are making this sector of drug development difficult.

Is there anyone from CDRH or CBER who would like to also comment?

DR. CHANG: This is Cynthia Chang from CDRH. I think what we've learned, as Dr. Marcus said, from the discussions today is really that there's a collaboration needed across all of the stakeholders in the wound care arena to try and find solutions to this very important problem.

We've discussed a number of different marketing pathways for CDRH that are not just 510(k) specific, and we've also heard from CDER and CBER as well. I think there's a lot of momentum now to make some positive progress in this arena, so thank you for participating in the discussion.

DR. MARCUS: I see a comment in the question and answer box that having a pathway to market based on safety of new products will facilitate bringing new products to the market, and that evidence of clinical efficacy can be built over time once the product is in the market.

That's not currently a pathway for drugs or biologics that can be followed. There needs to be a demonstration of efficacy and safety demonstrated before a product is marketed. We have a guidance that's available on our website on demonstrating efficacy that people can review to understand the different ways that efficacy can be demonstrated prior to marketing of drugs.

(Pause.)

MR. TETLOW: Dr. Marcus, you're muted again. Sorry.

DR. MARCUS: That's ok.

Thank you. I think we'll end now. I want to thank everybody who participated today. I want to thank our speakers. I want to thank our patients for sharing their experiences and conveying to us important aspects of wound care, and I want to thank everybody who was involved in organizing this workshop, so thank you.

Do we have any administrative things to wrap up before we end?

DR. VERMA: No, just that I will see

everyone tomorrow morning at 9 a.m. Thank you, everyone.

(Whereupon, at 3:30 p.m., the meeting was adjourned.)

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