Driving Innovation in Wound Care Summit

SAWC Spring WHS | WCCC Wound Care Collaborative Community | WOUNDS A Compendium of Clinical Research and Practice

Connect to WiFi:

Network name:
Marriottbonvoy_Conference

Passcode:
ACCESS CODE (not case sensitive)

Driving Innovation in Wound Care Summit

SAWC Spring WHS | WCCC Wound Care Collaborative Community | WOUNDS A Compendium of Clinical Research and Practice

Summit Opening: Moderators' Remarks

WCCC Program Moderators:
Sharon Gabrielson RN MBA,
Board of Directors

Phalan Bolden MSN, MBA, FNP-C,
Business Committee

Breaking the Barrier: Discovery and Innovation In Wound Care

William W. Li, MD

President & Medical Director

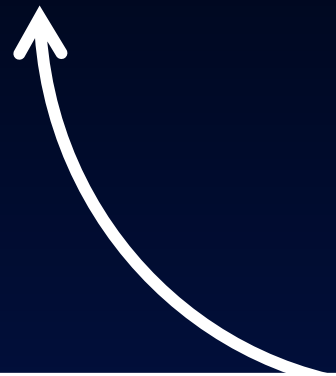
The Angiogenesis Foundation

INNOVATION

The development of breakthrough products and services that improve patient outcomes, care delivery, or operational efficiency

Not “more of the same”

“Unmet needs drive advances.”



“Products do not drive advances.”

WE NEED QUANTUM LEAPS

- Retinopathies: laser >>> anti-VEGF
- Cancer: chemotherapy >>> Immunotherapy
- Weight loss: dieting >>> GLP-1 agonists

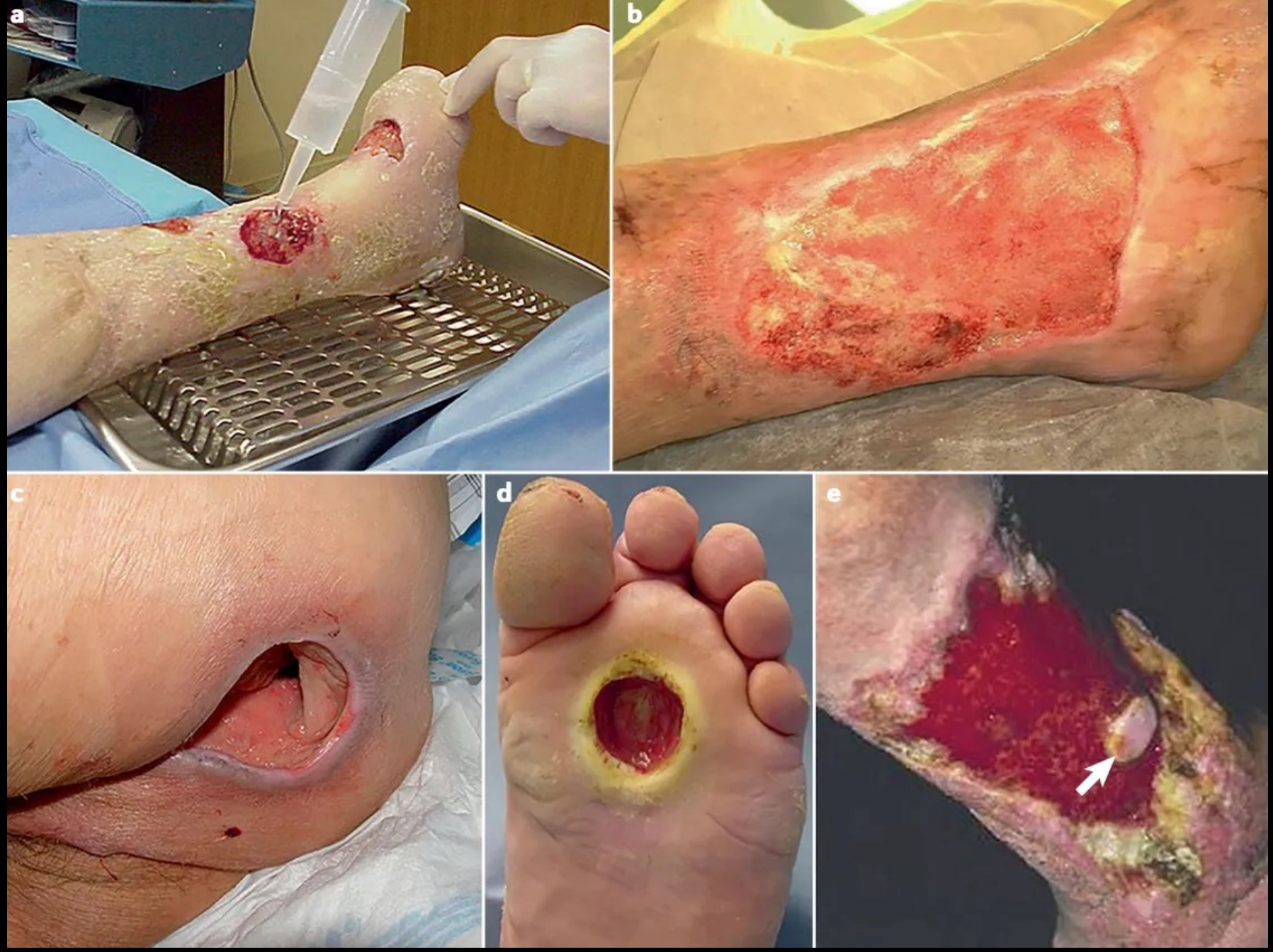
Wounds: dressings, debriders, tissue equivalents, HBO, NPWT >>> ???

WOUND CARE

WOUND THERAPY

WOUND CLOSURE

WOUND REPAIR



— Falange, et. al. Nat Rev Dis Primers 2022;8(21):50


Angiogenesis
Neurogenesis
Regeneration
Collagen Deposition
Epithelialization
Remodeling

THE (near) FUTURE

Startlingly different therapeutic strategies to activate wound healing process to achieve true wound repair

“Beyond the 3Cs: Cleansing, Covering, and Closure.”

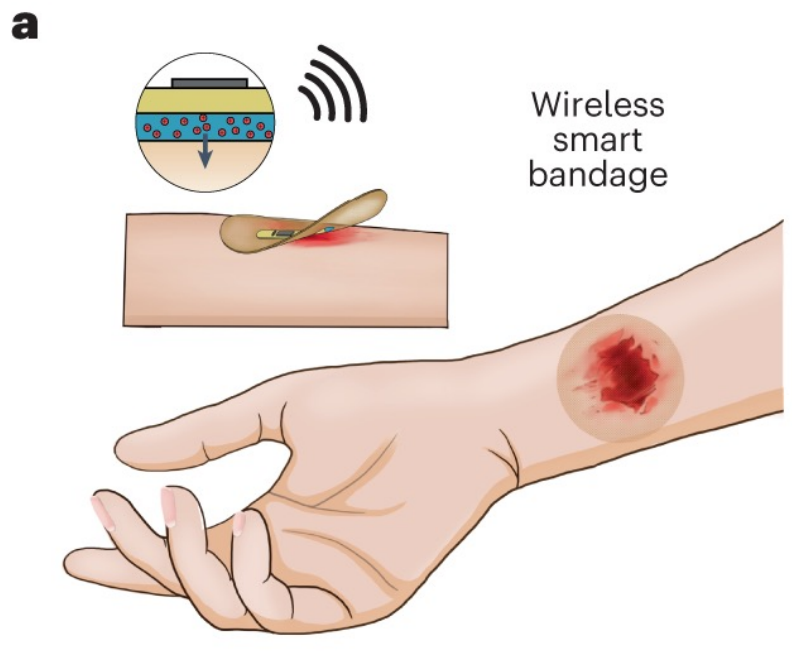
SOME FUTURE INNOVATIONS

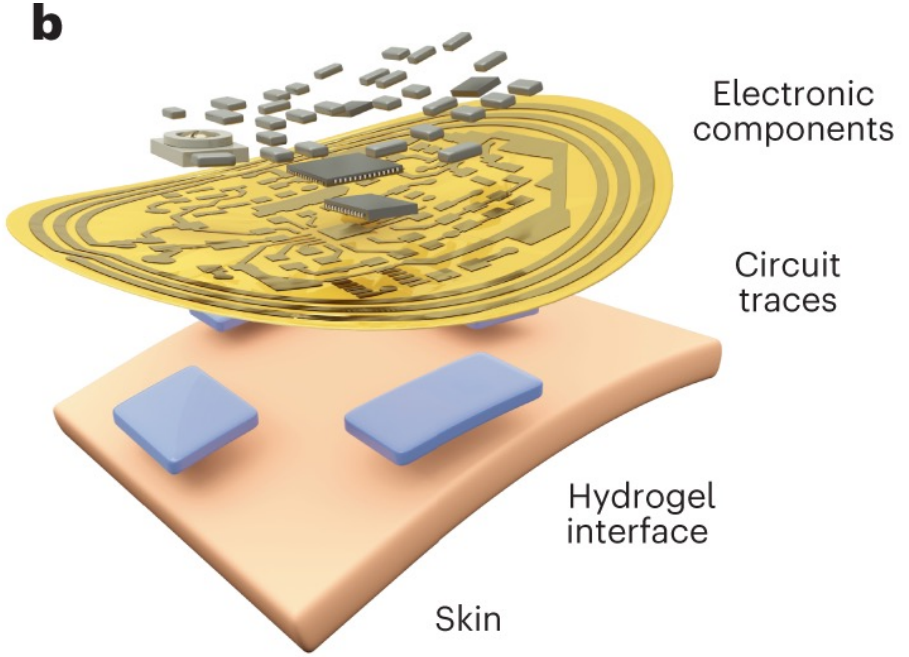
- Electroceuticals
- Dietary therapies
- Microbiome therapy

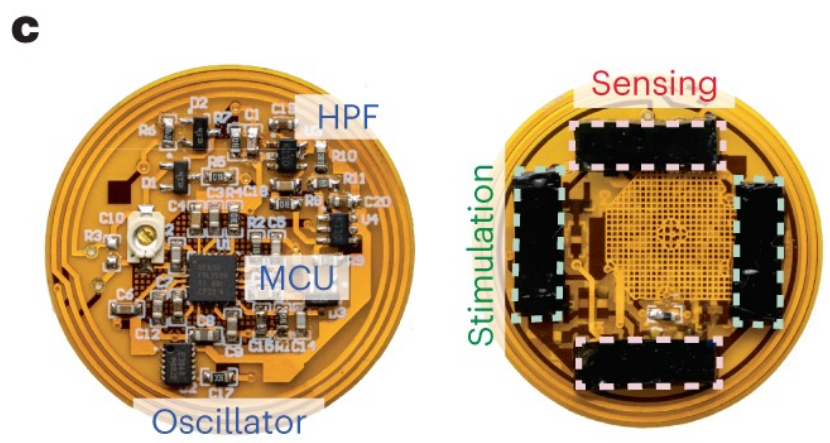
SOME FUTURE INNOVATIONS

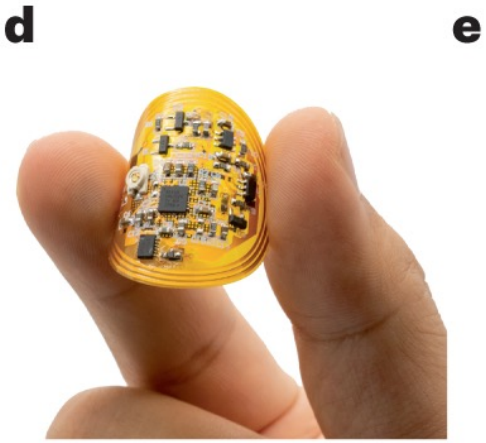
- **Electroceuticals**
- **Dietary therapies**
- **Microbiome therapy**

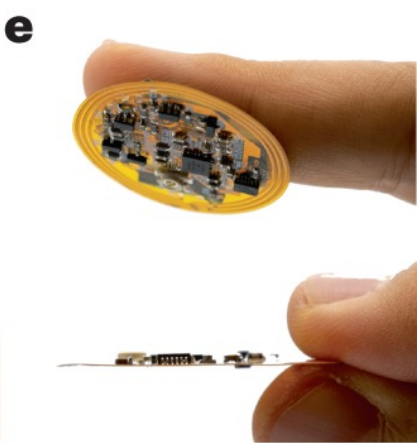
Electroceuticals











Besnier *et al. Trials* (2017) 18:373
DOI 10.1186/s13063-017-1997-1

STUDY PROTOCOL

The efficacy of tr nerve stimulatio walking distance arterial disease v claudication: stu randomised cont TENS-PAD study

Florent Besnier[1,2], Jean-Michel Sénard Thibaut Guiraud[1,2] and Marc Labrunée

Abstract

Background: In patients with periphe onset due to vascular claudication. It w as transcutaneous electrical nerve stim programmes, and thus improve their c 10-Hz TENS prior to walking. TENS sign patients with class-II PAD. We now see TENS for 3 weeks (5 days a week) on w

Methods/design: This is a prospective subjects with unilateral PAD (Leriche-F group (TENS group): the treatment will a pulse width of 200 μs, maximal inten exercise rehabilitation programme, for stimulation will be delivered according automatically falling to zero after 10 s outcomes: transcutaneous oxygen pres (VO_2 peak), endothelial function (Endo triglycerides), fasting glycaemia, HbA1c

(Continued on next page)

Microci
© 2001
www.na

Angiogenesis Induced Stimulation Is Mediated h and VEGF

SANDRA L. AMARAL, J. RUSSELL LINDER AND ANDREW S. GR
Department of Physiology, Medical College of V

ABSTRACT

Objective: Physiological angiogenesis in skeleta to physical training and electrical stimulation. T angiotensin II (Ang II) in regulating both angiog growth factor (VEGF) protein expression induc

Methods: The right tibialis anterior (TA) and ex muscles of Sprague-Dawley rats were stimulated The contralateral muscles served as controls. T throughout the stimulation protocol, the rats rec in their drinking water. Rats without any drug Immunohistochemistry and Western blot analysi source and quantify the VEGF protein express tionship between angiogenesis and VEGF exp VEGF-neutralizing antibody.

Results: Chronic electrical stimulation of the sk increases in vessel density (14% and 30% for EI 7 days. In addition, stimulation increased VEGF muscles. Both lisinopril and losartan blocked ele inhibited the angiogenesis induced by stimula inhibited angiogenesis, confirming the relationsh vessel growth.

Conclusion: The current study suggests a pa receptors (AT_1) and VEGF in electrically stimul

Am J Physiol Cell Physiol 317: C277–C286, 2019.
First published April 17, 2019; doi:10.1152/ajpcell.00474.2018.

RESEARCH ARTICLE

Electrical stimulation facilitates the angiogenesis of human umbilical vein endothelial cells through MAPK/ERK signaling pathway by stimulating FGF2 secretion

Kang Geng,[1] Jing Wang,[2] Pengfei Liu,[3] Xinli Tian,[1] Hongjun Liu,[1] Xue Wang,[1] Chunbing Hu,[4] and Hong Yan[1]

[1]*Department of Burns and Plastic Surgery, Affiliated Hospital of Southwest Medical University, Luzhou, China;* [2]*Southwest Petroleum University College of Mechanical and Electrical Engineering, Chengdu, China;* [3]*Department of Orthopedics, Aerospace 731 Hospital, Beijing,China; and* [4]*Department of Plastic Surgery, Yuehao Medical Beauty Hospital, Chengdu, China*

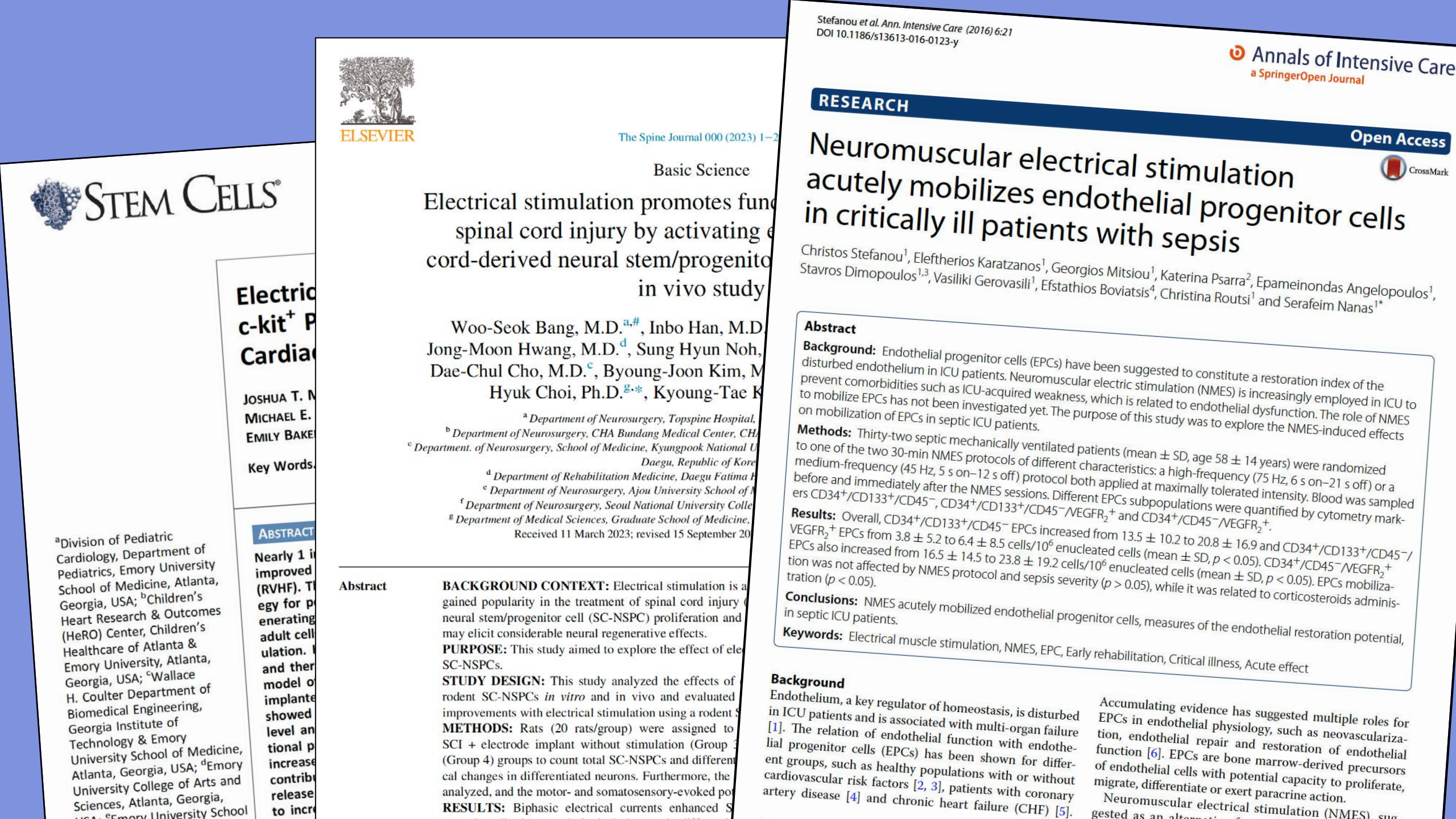
Submitted 26 November 2018; accepted in final form 2 April 2019

Geng K, Wang J, Liu P, Tian X, Liu H, Wang X, Hu C, Yan H. Electrical stimulation facilitates the angiogenesis of human umbilical vein endothelial cells through MAPK/ERK signaling pathway by stimulating FGF2 secretion. *Am J Physiol Cell Physiol* 317: C277–C286, 2019. First published April 17, 2019; doi:10.1152/ajpcell.00474.2018.—Electrical stimulation (ES) is able to enhance angiogenesis by stimulating fibroblasts. Fibroblast growth factor 2 (FGF2) is an independent angiogenesis inducer. The present study aimed to evaluate the role of ES-induced FGF2 secretion in affecting angiogenesis during wound healing via the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway. Fibroblasts and human umbilical vein endothelial cells (HUVECs) were exposed to ES, and the HUVECs were cocultured with ES-treated fibroblast culture solution. ES exposure showed no toxic effects on fibroblasts or HUVECs. ES led to enhanced growth of fibroblasts and HUVECs as well as FGF2 secretion, which is induced through the NOS pathway. ES-induced FGF2 secretion was shown to increase vascular endothelial growth factor (VEGF) protein and enhance migration, invasion, and angiogenesis of HUVECs. Also, ES-induced FGF2 secretion activated the MAPK/ERK signaling pathway. However, inhibition of the MAPK/ERK signaling pathway reversed the positive effects of ES-induced FGF2 secretion. In vitro experiments showed positive effects of ES on wound healing. Taken together, the findings suggested that ES promoted FGF2 secretion and then activated the MAPK/ERK signaling pathway by facilitating angiogenesis and promoting wound healing.

angiogenesis; electrical stimulation; fibroblast growth factor 2; MAPK/ERK signaling pathway; wound healing

to expedite recovery in cases of severe peripheral nerve injury by enhancing axonal regeneration and functional recovery (37). More importantly, ES has been demonstrated to induce angiogenesis by stimulating vessel tube formation in trophoblasts via induction of the angiogenic signaling pathway (36). Angiogenesis represents a crucial factor in the event of wound healing, with insufficient angiogenesis shown to result in impairment and permanent damage (8). ES is capable of accelerating the process of wound healing by promoting angiogenesis and stimulating fibroblasts and protein synthesis during the inflammatory response as well as during the proliferative and remodeling stages of healing (33). However, the finer molecular mechanism associated with the influence of ES in the promotion of angiogenesis remains largely unknown.

The fibroblast growth factor (FGF) family, consisting of 18 various FGF receptor ligands, has been reported to exert potent effects on angiogenesis, wound healing, and embryonic development (30). As a member of the FGF family, FGF2 has been highlighted as a critical angiogenic factor (39). Increased FGF2 secretion from astrocytes has been suggested to contribute to neurite outgrowth promotion (7). In injured vessels, FGF2 has also been demonstrated to increase endothelial cell proliferation and facilitate vessel repair (24). Moreover, FGF2 possesses the capacity to confer protection to human umbilical vein endothelial cells (HUVECs) against cytotoxic human immunodeficiency virus (HIV) protein via endothelial cell survival signaling pathways, including the extracellular signal-



STEM CELLS®

Electric
c-kit+ P
Cardiac

JOSHUA T. M
MICHAEL E.
EMILY BAKE

Key Words.

ABSTRACT

Nearly 1 i
improved
(RVHF). Th
egy for p
enerating
adult cell
ulation.
and ther
model o
implante
showed
level an
tional p
increase
contribu
release
to incr

[a]Division of Pediatric Cardiology, Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, USA; [b]Children's Heart Research & Outcomes (HeRO) Center, Children's Healthcare of Atlanta & Emory University, Atlanta, Georgia, USA; [c]Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology & Emory University School of Medicine, Atlanta, Georgia, USA; [d]Emory University College of Arts and Sciences, Atlanta, Georgia,

ELSEVIER

The Spine Journal 000 (2023) 1–2

Basic Science

Electrical stimulation promotes func
spinal cord injury by activating e
cord-derived neural stem/progenito
in vivo study

Woo-Seok Bang, M.D.[a,#], Inbo Han, M.D.
Jong-Moon Hwang, M.D.[d], Sung Hyun Noh,
Dae-Chul Cho, M.D.[c], Byoung-Joon Kim, M
Hyuk Choi, Ph.D.[g,*], Kyoung-Tae K

[a] Department of Neurosurgery, Topspine Hospital,
[b] Department of Neurosurgery, CHA Bundang Medical Center, CH
[c] Department. of Neurosurgery, School of Medicine, Kyungpook National U
Daegu, Republic of Kore
[d] Department of Rehabilitation Medicine, Daegu Fatima H
[e] Department of Neurosurgery, Ajou University School of M
[f] Department of Neurosurgery, Seoul National University Colle
[g] Department of Medical Sciences, Graduate School of Medicine,
Received 11 March 2023; revised 15 September 20

Abstract

BACKGROUND CONTEXT: Electrical stimulation is a
gained popularity in the treatment of spinal cord injury (
neural stem/progenitor cell (SC-NSPC) proliferation and
may elicit considerable neural regenerative effects.

PURPOSE: This study aimed to explore the effect of ele
SC-NSPCs.

STUDY DESIGN: This study analyzed the effects of
rodent SC-NSPCs *in vitro* and in vivo and evaluated
improvements with electrical stimulation using a rodent S

METHODS: Rats (20 rats/group) were assigned to
SCI + electrode implant without stimulation (Group
(Group 4) groups to count total SC-NSPCs and different
cal changes in differentiated neurons. Furthermore, the
analyzed, and the motor- and somatosensory-evoked po

RESULTS: Biphasic electrical currents enhanced S

Stefanou et al. Ann. Intensive Care (2016) 6:21
DOI 10.1186/s13613-016-0123-y

Annals of Intensive Care
a SpringerOpen Journal

RESEARCH

Open Access

Neuromuscular electrical stimulation acutely mobilizes endothelial progenitor cells in critically ill patients with sepsis

Christos Stefanou[1], Eleftherios Karatzanos[1], Georgios Mitsiou[1], Katerina Psarra[2], Epameinondas Angelopoulos[1], Stavros Dimopoulos[1,3], Vasiliki Gerovasili[1], Efstathios Boviatsis[4], Christina Routsi[1] and Serafeim Nanas[1*]

Abstract

Background: Endothelial progenitor cells (EPCs) have been suggested to constitute a restoration index of the disturbed endothelium in ICU patients. Neuromuscular electric stimulation (NMES) is increasingly employed in ICU to prevent comorbidities such as ICU-acquired weakness, which is related to endothelial dysfunction. The role of NMES to mobilize EPCs has not been investigated yet. The purpose of this study was to explore the NMES-induced effects on mobilization of EPCs in septic ICU patients.

Methods: Thirty-two septic mechanically ventilated patients (mean ± SD, age 58 ± 14 years) were randomized to one of the two 30-min NMES protocols of different characteristics: a high-frequency (75 Hz, 6 s on–21 s off) or a medium-frequency (45 Hz, 5 s on–12 s off) protocol both applied at maximally tolerated intensity. Blood was sampled before and immediately after the NMES sessions. Different EPCs subpopulations were quantified by cytometry markers $CD34^+/CD133^+/CD45^-$, $CD34^+/CD133^+/CD45^-/VEGFR_2{}^+$ and $CD34^+/CD45^-/VEGFR_2{}^+$.

Results: Overall, $CD34^+/CD133^+/CD45^-$ EPCs increased from 13.5 ± 10.2 to 20.8 ± 16.9 and $CD34^+/CD133^+/CD45^-/VEGFR_2{}^+$ EPCs from 3.8 ± 5.2 to 6.4 ± 8.5 cells/10^6 enucleated cells (mean ± SD, $p < 0.05$). $CD34^+/CD45^-/VEGFR_2{}^+$ EPCs also increased from 16.5 ± 14.5 to 23.8 ± 19.2 cells/10^6 enucleated cells (mean ± SD, $p < 0.05$). EPCs mobilization was not affected by NMES protocol and sepsis severity ($p > 0.05$), while it was related to corticosteroids administration ($p < 0.05$).

Conclusions: NMES acutely mobilized endothelial progenitor cells, measures of the endothelial restoration potential, in septic ICU patients.

Keywords: Electrical muscle stimulation, NMES, EPC, Early rehabilitation, Critical illness, Acute effect

Background

Endothelium, a key regulator of homeostasis, is disturbed in ICU patients and is associated with multi-organ failure [1]. The relation of endothelial function with endothelial progenitor cells (EPCs) has been shown for different groups, such as healthy populations with or without cardiovascular risk factors [2, 3], patients with coronary artery disease [4] and chronic heart failure (CHF) [5].

Accumulating evidence has suggested multiple roles for EPCs in endothelial physiology, such as neovascularization, endothelial repair and restoration of endothelial function [6]. EPCs are bone marrow-derived precursors of endothelial cells with potential capacity to proliferate, migrate, differentiate or exert paracrine action.

Neuromuscular electrical stimulation (NMES) sug-

Low-Frequency Ultrasound (20-40 kHz) as an Adjunctive Therapy for Chronic Wound Healing: A Systematic Review of the Literature and Meta-Analysis of Eight Randomized Controlled Trials

Jeffrey Voigt, MBA, MPH[1], Martin Wendelken, DPM, RN[2], Vickie Driver, MS, DPM, FACFAS[3], and Oscar M. Alvarez, Ph

Abstract

Ultrasound as a therapeutic agent in chronic wound healing has been studied
meta-analysis specifically examines low-frequency (20-30 kHz) ultrasound delive
objective of this review was to determine whether low-frequency ultrasound use
outcomes of complete healing and reduction of size of chronic lower limb wounds.
assessment, relevant wound-related journals, and clinical guidelines were searched
authors of relevant randomized controlled trials were completed. Searches focuse
in randomized controlled trials. Data were collected via a data collection form
coauthors. Meta-analyses and heterogeneity checks were performed using Mar
and random effects) statistical methods on studies with similar outcomes (co
reduction) over similar time periods. Single study results were reported via the
randomized controlled trials were identified. Results demonstrated that early
venous stasis and diabetic foot ulcers was favorably influenced by both high- a
low frequency—either via contact or noncontact techniques. However, the quali
low-frequency low-intensity noncontact ultrasound because of significant biases
stasis or diabetic foot ulcers (Wagner classification 1-3), early healing appears to
intensity noncontact ultrasound or low-frequency high-intensity contact ultras

Keywords

Low frequency ultrasound, chronic wound healing, wound debridement

Ultrasound Med Biol. 2014 June ; 40(6): 1177–1186. doi:10.1016/j.ultrasmedbio.2013.12.007.

LOW-INTENSITY PULSED ULTRASOUND PROMOTES CHONDROGENIC PROGENITOR CELL MIGRATION VIA FOCAL ADHESION KINASE PATHWAY

Kee W. Jang[*,†], **Lei Ding**[*], **Dongrim Seol**[*], **Tae-hong Lim**[†], **Joseph A. Buckwalter**[*,‡], and **James A. Martin**[*]

[*]Department of Orthopaedics and Rehabilitation, The University of Iowa, Iowa City, IA

[†]Department of Biomedical Engineering, The University of Iowa, Iowa City, IA

[‡]Veterans Affairs Medical Center, Iowa City, IA

Abstract

Low-intensity pulsed ultrasound (LIPUS) has been frequently studied for its beneficial effects on the repair of injured articular cartilage. Here, we hypothesized that these effects are due to stimulation of chondrogenic progenitor cell (CPC) migration toward injured areas in cartilage through focal adhesion kinase (FAK) activation. CPC chemotaxis in bluntly impacted osteochondral explants was examined by confocal microscopy and migratory activity of cultured CPCs was measured in trans-well and monolayer scratch assays. FAK activation by LIPUS was analyzed in cultured CPCs by western blot. LIPUS effects were compared with the effects of two known chemotactic factors; formylated-methionine peptides (fMLF), and high-mobility group box 1 (HMGB1) protein. LIPUS significantly enhanced CPC migration on explants and in cell culture assays. Phosphorylation of FAK at the kinase domain (Tyr 576/577) was maximized by 5 minute exposure to LIPUS at a dose of 27.5 mW/cm^2 and at a frequency of 3.5 MHz. Treatment with fMLF, but not HMBG1 enhanced FAK activation to a degree similar to LIPUS, but neither fMLF nor HMGB1 enhanced the LIPUS effect. LIPUS-induced CPC migration was blocked by suppressing FAK phosphorylation with a Src family kinases (SFKs) inhibitor that blocks FAK phosphorylation. Our results imply that LIPUS might be utilized to promote cartilage healing by inducing the migration of CPCs to injured sites, which could delay or prevent the onset of post-traumatic osteoarthritis (PTOA).

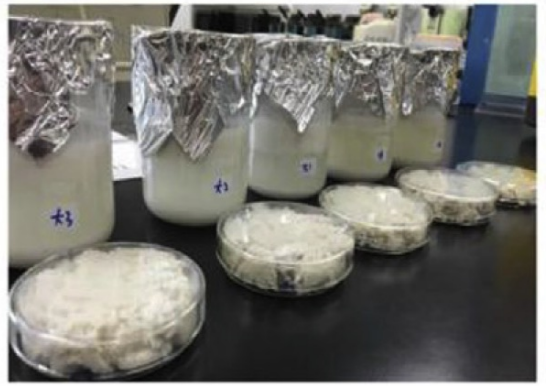
SOME FUTURE INNOVATIONS

- Electroceuticals
- Dietary therapies
- Microbiome therapy

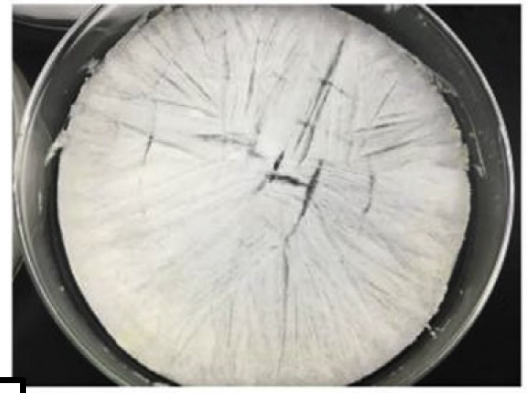
Steaming

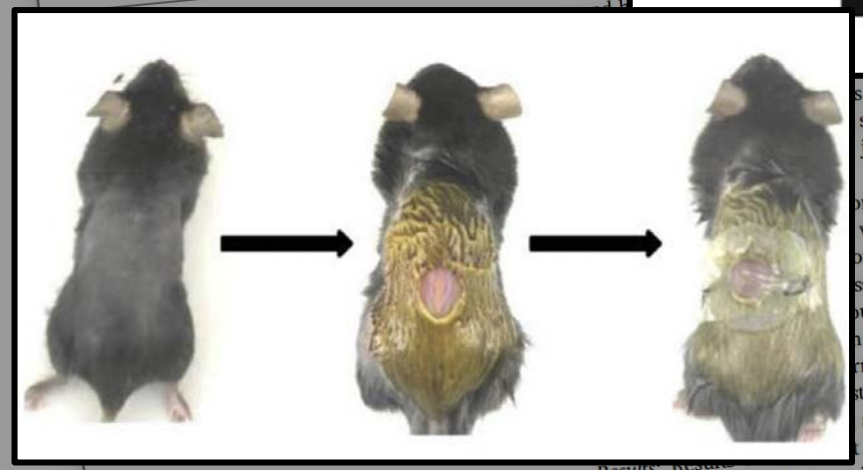
Size Reduction

Extraction and Sonication



Freeze-drying





Journal of Et

Conten

Journal

journal homepa

ELSEVIER

Sea bass (*Lateolabrax maculatus*) a
from inflammation to proliferatio

Jiali Chen[a,b], Muthukumaran Jayachandra

[a] Programme of Food Science and Technology, Division of Science and Tec
Zhuhai, China
[b] Centre for Cancer and Inflammation Research, School of Chinese Medic

ARTICLE INFO

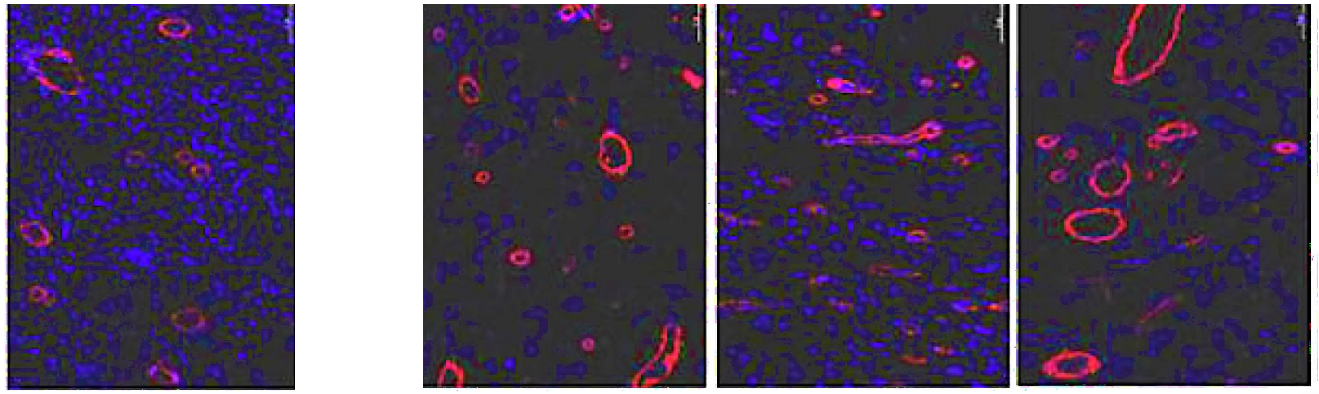
ABST

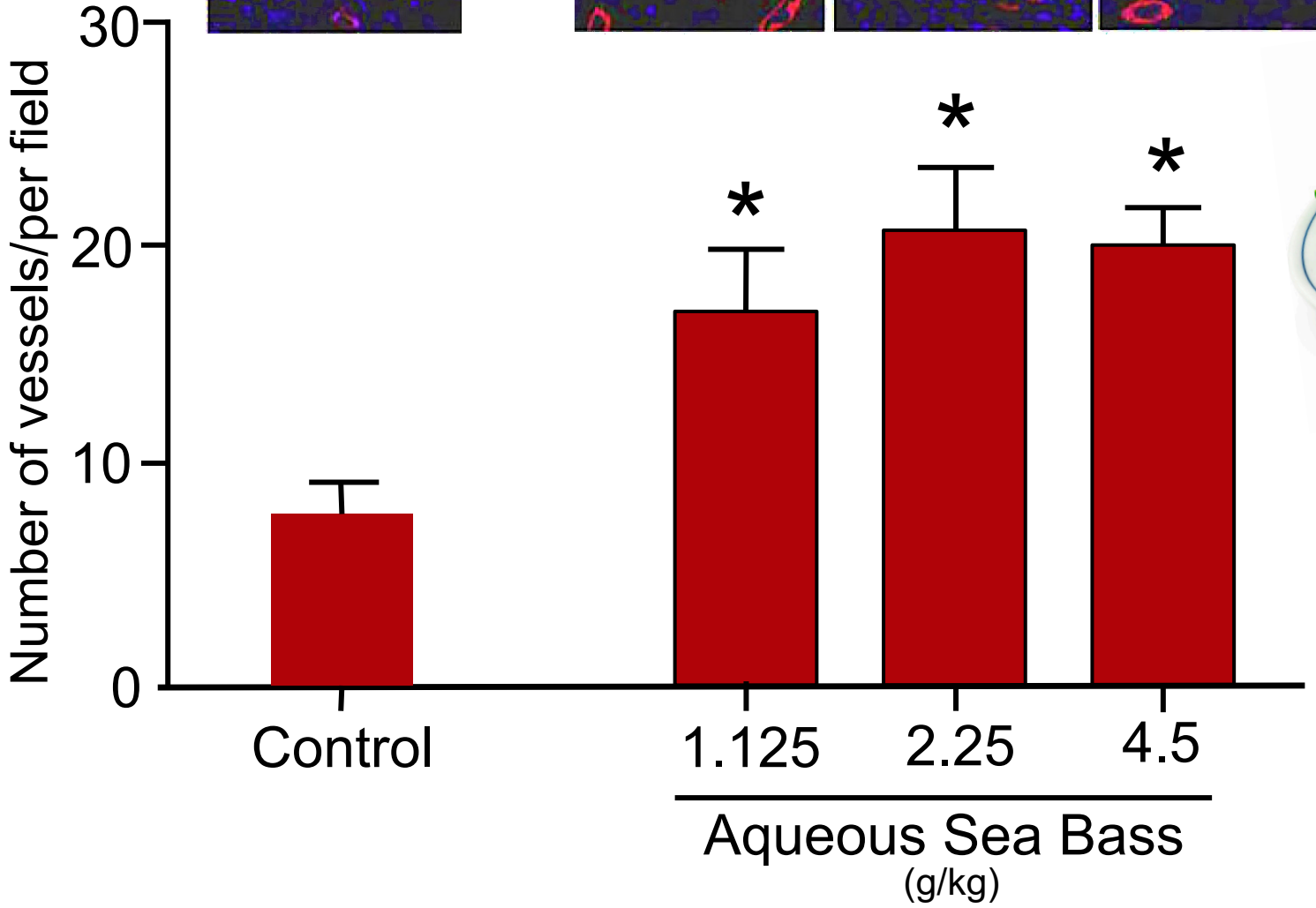
Ethnopha

s of wound healing
study is to investigate the molecular mechanisms of
justification for clinical application of aqueous extract of sea bass (ASB) in

on from inflammation to proliferation phase treated as the critical step in wound
via *in vitro* and *in vivo* study. A series of inflammatory mediators associated with
on effects of fibroblasts upon treatments were studied via Western blotting, en-
ssay (ELISA), real time reverse transcription-polymerase chain reaction (RT-PCR)
ous wound model was applied on skin wound healing study to observe the healing
n ASB treatments. Hematological parameters and tumor necrosis factor-α (TNF-α)
rmined. Histopathological examinations were conducted by hematoxylin and eosin
staining. Immunofluorescence were performed to identify infiltrating neutrophils
actin (α-SMA).
ASB significantly reduced the production of inflammatory mediators cycloox-
ygenase-2 (COX-2), nitrite oxide (NO) production and TNF-α. The phosphorylation and nuclear protein levels of
factor nuclear factor-κB (NF-κB) in toll-like receptor 4 (TLR4) signaling were decreased by ASB
cyclin D1 expression level of fibroblasts were significantly increased
presented many similarities in ap-

Results:





SEA BASS COLLAGEN PEPTIDES:

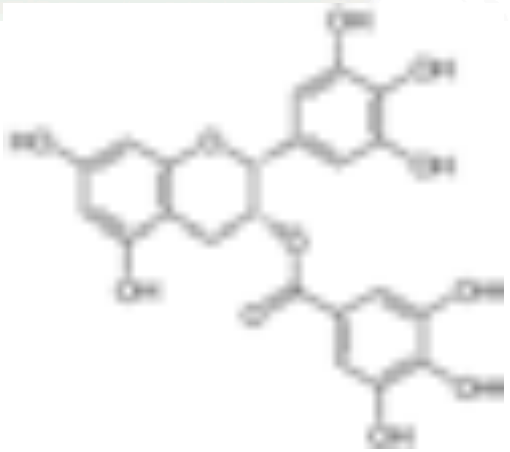
+ Angiogenesis

- Inflammation

+ Fibroblast proliferation

+ Collagen deposition

GREEN TEA



Clin Exp Pharmacol Physiol 2016;43:1

ORIGINAL ARTICLE

Epigallocatechin-3-gallate augments therapeutic effects of mesenchymal stem cells in skin wound healing

Min Li[1] | Jingxing Xu[1] | Tongxin Shi[2] | Haiyang Yu[1] | Jianping Bi[1] | Guanzhi Chen[2]

[1]The Affiliated Qingdao Municipal Hospital of Qingdao University, Qingdao, China

[2]The Affiliated Hospital of Qingdao University, Qingdao, China

Correspondence
Guanzhi Chen, The Affiliated Hospital of Qingdao University, Qingdao, China.
Email: guanzhichenz@sina.com

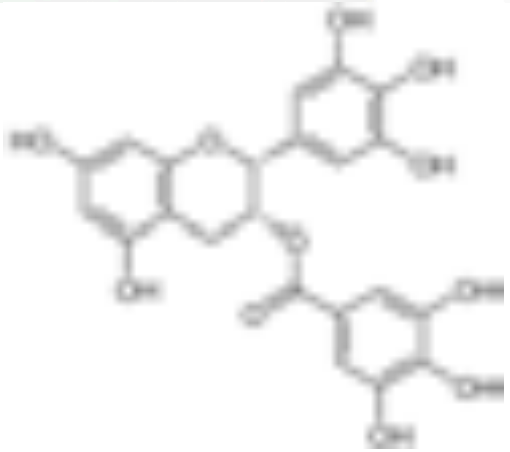
Summary

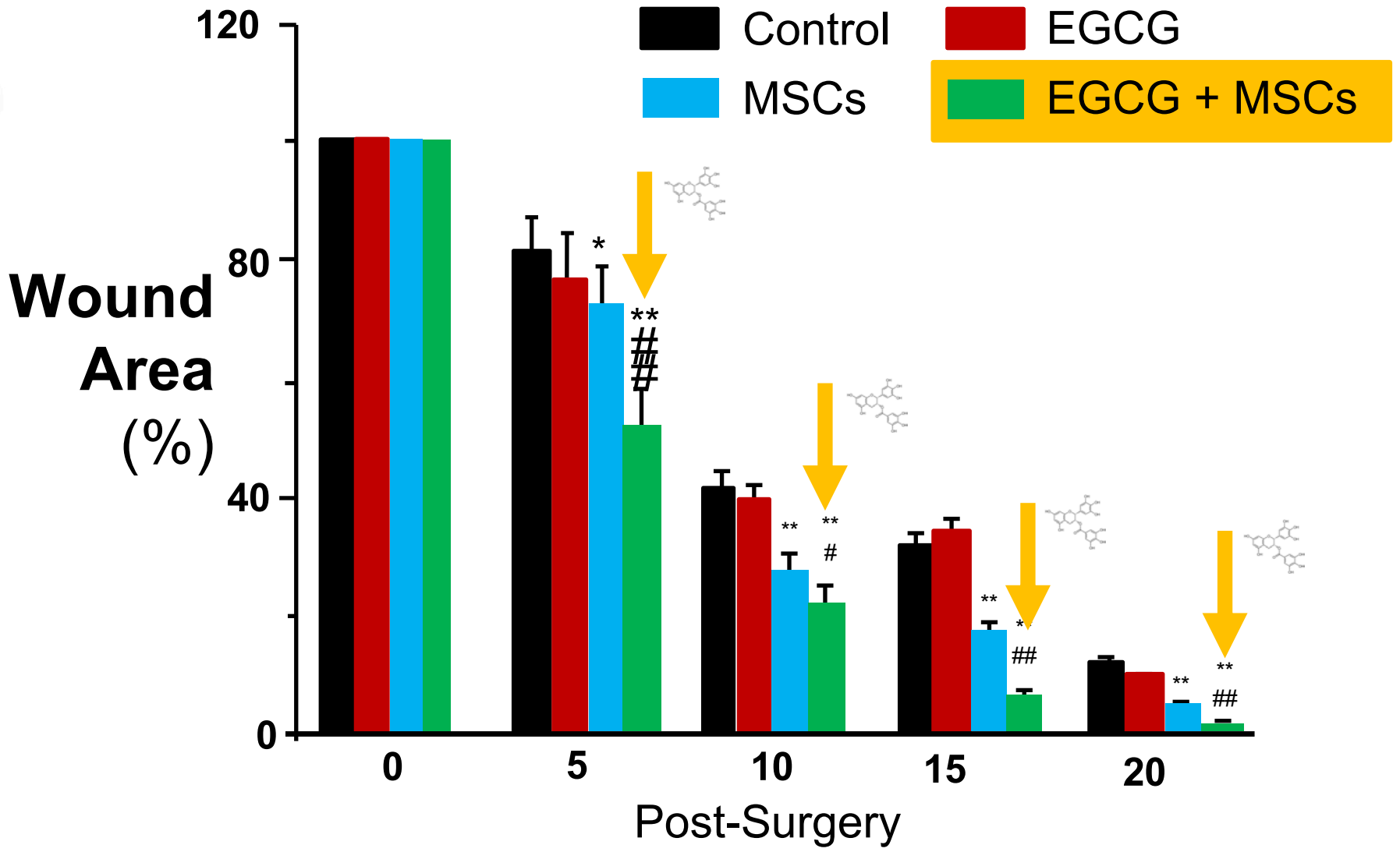
In non-healing wounds, mesenchymal stem cell (MSC)-based therapies have the potential to activate a series of coordinated cellular processes, including angiogenesis, inflammation, cell migration, proliferation and epidermal terminal differentiation. As pro-inflammatory reactions play indispensable roles in initiating wound repair, sustained and prolonged inflammation exhibit detrimental effects on skin wound closure. We investigated the feasibility of using an antioxidant agent epigallocatechin-3-gallate (EGCG), along with MSCs, to improve wound repair through their immunomodulatory actions. In a rat model of wound healing, a single dose of EGCG at 10 mg/kg increased the efficiency of MSC-induced skin wound closure. Twenty days after the wound induction, MSC treatment significantly enhanced the epidermal thickness, which was further increased by EGCG administration. Consistently, the highest extent of growth factors upregulation for neovascularization induction was seen in the animals treated by both MSCs and EGCG, associated with a potent anti-scarring effect throughout the healing process. Finally, expression levels of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6, in the wound area were reduced by MSCs, and this reduction was further potentiated by EGCG co-administration. EGCG, together with MSCs, can promote skin wound healing likely through their combinational effects in modulating chronic inflammation.

KEYWORDS

angiogenesis, EGCG, immunomodulation, mesenchymal stem cells, wound healing

GREEN TEA EGCG Amplifies Mesenchymal Stem Cell Effects For Wound Closure





Clin Exp Pharmacol Physiol 2016;43:1115

Foods that Stimulate Wound Healing

Bamboo shoots
Black chokeberry
Black raspberries
Black tea
Blueberries
Cranberries
Chinese celery
Sea bass
Cacao
Collard greens
Eggplant
Green beans
Green tea
Kale
Mango
Oats
Mustard greens
Omega 3 PUFA
Peaches
Pistachios
Plums
Spinach
Swiss chard
Watercress

SOME FUTURE INNOVATIONS

- Electroceuticals
- Dietary therapies
- Microbiome therapy

Cell Host & Microbe

Article

Bacteria induce skin regeneration

Gaofeng Wang,[1,2] Evan Sweren,[1] Haiyun Liu,[1] Eric Wier,[1] Martin P. Alphon
Yingchao Xue,[1] Junjie Chen,[3] Seungman Park,[3] Yun Chen,[3] Sam Lee,[1] Yu
William Andrews,[4] Maureen A. Kane,[4] Erika Dare,[1] Sashank K. Reddy,[1,5] Z
and Luis A. Garza[1,7,9,*]
[1]Department of Dermatology, Johns Hopkins University Schoo of Medicine, Baltimo
[2]Department of Plastic and Aesthetic Surgery, Nanfang Hosp Medic
510515, China
[3]Department of Mechanical Engineering, Johns Hopkins Uni
[4]Department of Pharmaceutical Sciences, School of Pharm
[5]Department of Plastic and Reconstructive Surgery, Johns
[6]Department of Dermatology and Microbiology, Perelman
[7]Department of Cell Biology, Johns Hopkins University Sc
[8]Present address: Immunology, Janssen Research and D
[9]Lead contact
*Correspondence: lag@jhmi.edu
https://doi.org/10.1016/j.chom.2021.03.003

SUMMARY

Environmental factors that enhance rege
are attributed roles in repairing and rege
sessed the function of skin bacteria in
rare adult organogenesis model. WIH
lowest in germ-free (GF), intermediat
type mice, even those infected with
cage changes or topical antibiotics d
dent IL-1R-MyD88 signaling are nec
small trial, a topical broad-spectrum
sults demonstrate a role for IL-1β t
plications of topical prophylactic a

International Journal of
Molecular Sciences

MDPI

Review

Wound Microbiota and It

Małgorzata Zielińska [1], Agnieszka Pawłows
Arkadiusz Baran [1], Dagmara Filipecka-Tyc
Joanna Bogusławska [4] and Anna Scholz [1,*]

1 Ist Department
02-097 Warsaw,
2 Students Resea
01-004 Warsaw
3 Students Scien
20-093 Lublin,
4 Department of
02-097 Warsaw
* Correspondenc

nature communications

Article

Dermal injury drives a skin to gut axis that disrupts the intestinal microbiome and intestinal immune homeostasis in mice

hen[1,2], Kellen J. Cavagnero [1], Gibraan Rahman[2],
inton[1], Hana Schwarz [1], Elizabeth A. Brown[1],
amura[1], Fengwu Li[1], Nita H. Salzman [3],
. Gallo [1]

crobial community in the intestine may influence
ans such as the brain, lung, and skin. These
ase or have beneficial functions, leading to the
the gut explain the co-occurrence of intestinal and
that the reverse can occur, and that skin directly
isruption of the dermis by skin wounding or the
an results in increased expression in the colon of
and *Muc2*, and skin wounding changes the com-
stinal bacteria. Enhanced expression *Reg3* and
xposure to hyaluronan released by these skin
the colon microbiome after skin wounding is
se bacteria penetrate the intestinal epithelium
an sodium sulfate (DSS) as seen by the ability to
litis with oral antibiotics, in germ-free mice, and
ion to unwounded mice from mice with skin
rovide direct evidence of a skin-gut axis by
the skin disrupts homeostasis in intestinal host
robiome.

Advanced Drug Delivery Reviews 192 (2023) 114671

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/adr

ELSEVIER

Role of wound microbiome, strategies of microbiota delivery system and clinical management

Qinghan Tang [a,1], Nannan Xue [a,b,1], Xiaofeng Ding [c,d], Kevin H.-Y. Tsai [e], Jonathan J. Hew [f], Ruihan Jiang [a], Rizhong Huang [a], Xuxi Cheng [a], Xiaotong Ding [a], Yuen Yee Cheng [g], Jun Chen [a,b,*], Yiwei Wang [a,b,e,*]

[a] Jiangsu Provincial Engineering Research Center of TCM External Medication Development and Application, Nanjing University of Chinese Medicine, Nanjing 210023, PR China
[b] Jiangsu Collaborative Innovation Center of Chinese Medicinal Resources Industrialization, Nanjing University of Chinese Medicine, Nanjing 210023, PR China
[c] Department of Burns and Plastic Surgery, Nanjing Drum Tower Hospital Clinical College of Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing 210023, PR China
[d] Department of Plastic Surgery, Shanghai Fourth People's Hospital, School of Medicine, Tongji University, Shanghai 200434, PR China
[e] Burns and Reconstructive Surgery Group, ANZAC Research Institute, Concord Hospital, The University of Sydney, Concord West, NSW 2137, Australia
[f] General Surgery, Lesimore Hospital, NSW 2480, Australia
[g] Institute for Biomedical Materials and Devices, School of Mathematical and Physical Sciences, University of Technology Sydney, NSW 2007 Australia

‘GLASS CEILING’ CHALLENGES

- Trial Design
- Patient Selection
- Clinical Endpoints
- Biomarkers & Imaging
- Quality of Healing
- Recurrence
- Personalized Therapy
- Cost Effectiveness

“Invest in generating the evidence!”

“Knowing is not enough; we must apply. Being willing is not enough; we must do.”

— Leonardo da Vinci

Driving Innovation in Wound Care Summit

SAWC Spring WHS | WCCC Wound Care Collaborative Community | WOUNDS A Compendium of Clinical Research and Practice

Disrupting the Barriers to Innovation: With Evidence and Collaborations

Vickie R Driver, DPM, MS
Professor, Washington State Univ.
School of Medicine Chair,
Wound Care Collaborative Community

www.woundcarecc.org

WCCC Wound Care Collaborative Community

Supporters

Premier

ORGANOGENESIS

Supporters

BIOLAB SCIENCES

convatec

essity

kerecis

MediWound

MIMEDX

MIMOSA

MolecuLight

Mölnlycke

Noxy HEALTH PRODUCTS

Reapplix

Contributors

AROA

aranzmedical

BioGenCell
Unique Therapy for Unique People

GR CONSULTING

Reprise Biomedical

medaxis

Imbed BIOSCIENCES

ONENESS
Oneness Biotech Co., Ltd.

SolasCure

URGO MEDICAL
Healing people®

Driving Innovation in Wound Care Summit

Wound Care Collaborative Community (WCCC): In the Beginning

- Years of successfully working with the Food and Drug Administration (FDA) and the wound care community on defining meaningful & patient-centric endpoints (WEF-CEP initiative)~ 7 years

- Following this extensive research effort, three publications,1,2,3 and a community outreach program, the FDA asked us to consider developing a Wound Care Collaborative Community

1. Driver VR, et al. *Wound Rep Regen* 2017;25 (3):454–465. 2. Driver VR, et al. *Wound Rep Regen.* 2019;27(1):80-89. 3. Gould LJ, et al. *Wound Rep Regen* 2020;1-10.

WHAT IS A COLLABORATIVE COMMUNITY?

A community of continuing forums, including the private and public sectors to achieve common objectives.

Developed when:

- Challenges are ill-defined or there is no consensus
- Incremental or unilateral efforts to address the challenge have been ineffective
- Partners seek to optimize efforts, including preventing duplication of efforts

Collaborative Communities

MDIC MEDICAL DEVICE INNOVATION CONSORTIUM

NEST Coordinating Center An initiative of MDIC

STRIPE STANDARDIZING LABORATORY PRACTICES IN PHARMACOGENOMICS

RESCUE Collaborative Community

WCCC WOUND CARE COLLABORATIVE COMMUNITY

CCOI

Collaborative Community on Ophthalmic Imaging

Pathology Innovation Collaborative Community Plcc
The Alliance for Digital Pathology

MedTechColor

FNIH 25 Foundation for the

Heart Valve COLLABORATORY

DATAcc

Digital Health Measurement Collaborative Community

Xavier Artificial Intelligence (AI) World Consortium

International Liquid Biopsy Standardization Alliance (ILSA)


A Bridge to Unknown Waters

United Effort to Confront Barriers

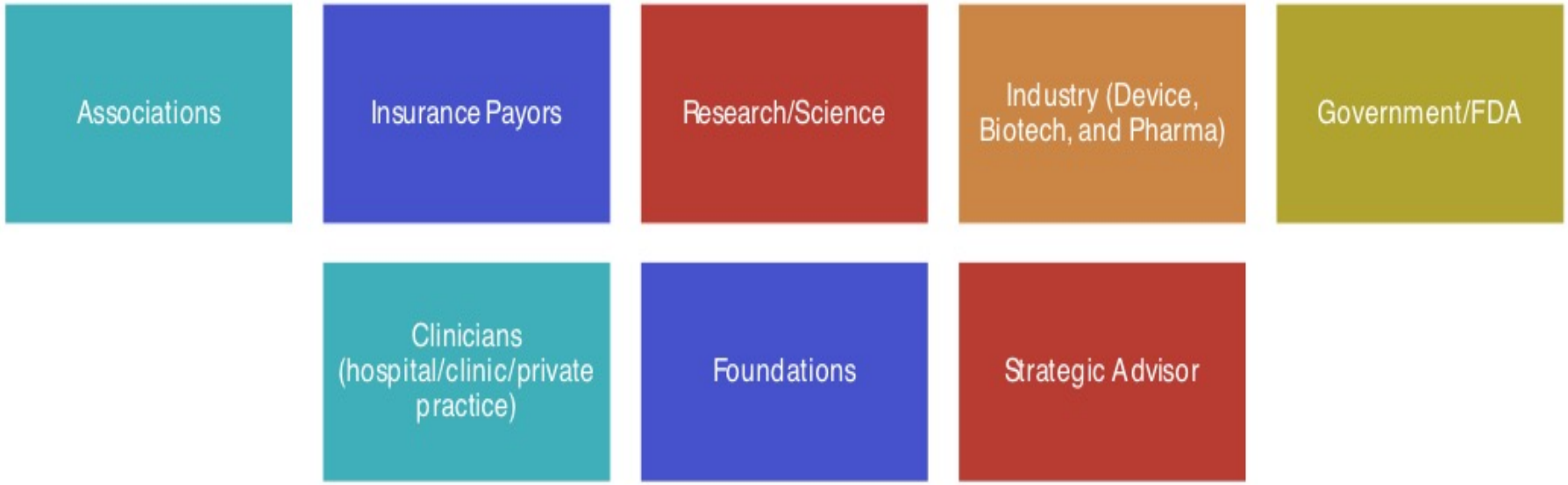
- At the request of the FDA started a Collaborative Community in 2021
- Investigated what a collaborative community should be
- Agreed that new diagnostics and treatments were severely lacking at the bedside
- Developed Work Groups to explore the most critical inhibiting factors of innovation in wound care
- Recruited top-notch content experts
- Focused on improving research methods and processes, then clinical practice
- Constant strength, weakness, opportunities, and threats (SWOT) analysis

FDA = Food and Drug Administration.

Wound Care Collaborative Community

- The **W Triple C** (WCCC)
  - Non-profit 501c with a board of directors and work group leaders
  - Volunteer work groups with content experts
  - Structured platform and timelines to gain results
  - Closely partnered with the FDA, Centers for Medicare & Medicaid Services (CMS), and the National Institutes of Health (NIH)
  - Dedicated to developing and publishing the evidence

FDA = Food and Drug Administration.



NIH National Institute of Diabetes and Digestive and Kidney Diseases

Strategic Solutions, Inc. Helping Medical Researchers Make Headlines

INOVA HEALTH SYSTEM

AAWC Association for the Advancement of Wound Care

CRS Chisholm Clinical Research Services

WASHINGTON STATE UNIVERSITY

FDA

WHS WOUND HEALING SOCIETY

CLI GLOBAL SOCIETY #CLIFighters

THE UNIVERSITY OF ARIZONA COLLEGE OF MEDICINE TUCSON Surgery

UNIVERSITY of VIRGINIA SCHOOL OF MEDICINE

APWCA AMERICAN PROFESSIONAL WOUND CARE ASSOCIATION

U.S. WOUND REGISTRY™

BOSTON UNIVERSITY SCHOOL OF MEDICINE

Intellicure™

Officers and Board of Directors

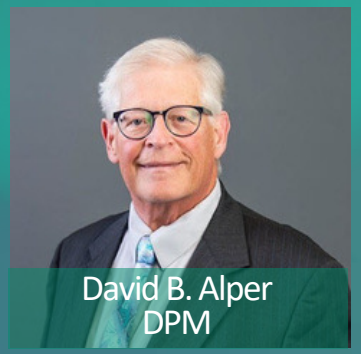
Driving Innovation in Wound Care Summit

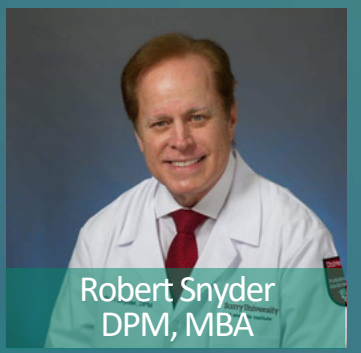
SAWC Spring WHS | WCCC | WOUNDS

Chair

Vice-Chair

Treasurer/Secretary



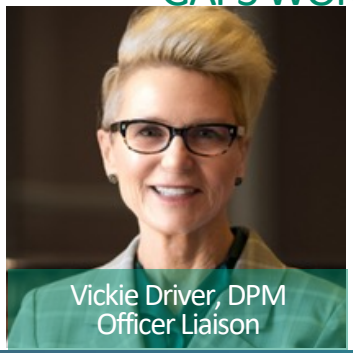


Work Group Leaders

GAPS WORK GROUP


Howard Walthall, JD
Chair


Randy Schwartz, BA
Co-Chair


Vickie Driver, DPM
Officer Liaison

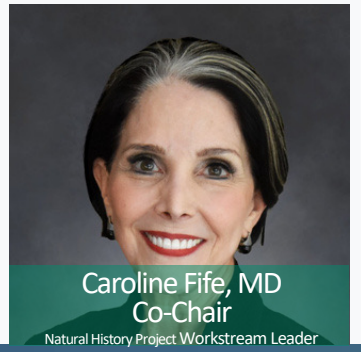

Marissa Carter, PhD
Clinical Trial Standards and Reporting Workstream Leader


Marjana Tomic-Canic, PhD
Pre-Clinical Trial Standards and Reporting Workstream Leader

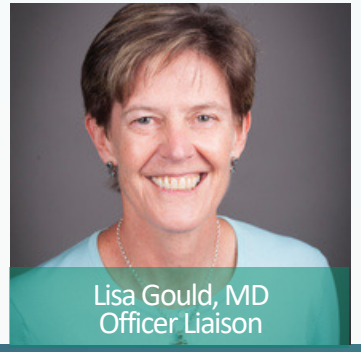

Sarah Griffiths, PhD
Dressing Standards Workstream Leader

REAL WORLD EVIDENCE WORK GROUP


Joseph Rolley, MS
Chair

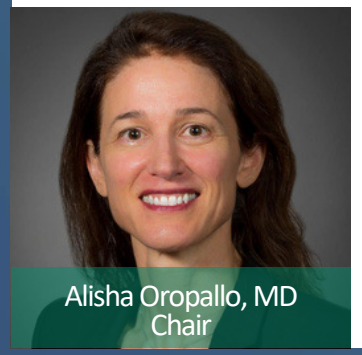

Caroline Fife, MD
Co-Chair
Natural History Project Workstream Leader

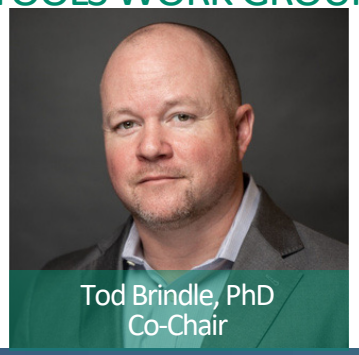

John Lantis, MD
Co-Chair

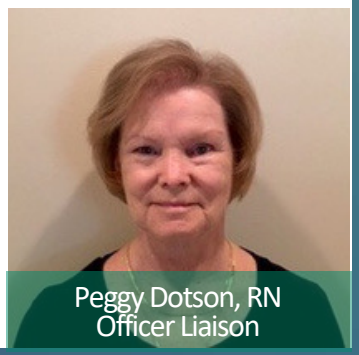

Lisa Gould, MD
Officer Liaison


Maribel Henao, DPM
Standard of Care for Clinical Research and Clinical Practice Workstream Leader

TOOLS WORK GROUP


Alisha Oropallo, MD
Chair


Tod Brindle, PhD
Co-Chair


Peggy Dotson, RN
Officer Liaison

WCCC
WOUND CARE
COLLABORATIVE
COMMUNITY

Driving Innovation in Wound Care Summit

SAWC Spring WHS | WCCC | WOUNDS

Supporters

AliraHealth

Mölnlycke®

tidesmedical®

Dr. Robert Snyder

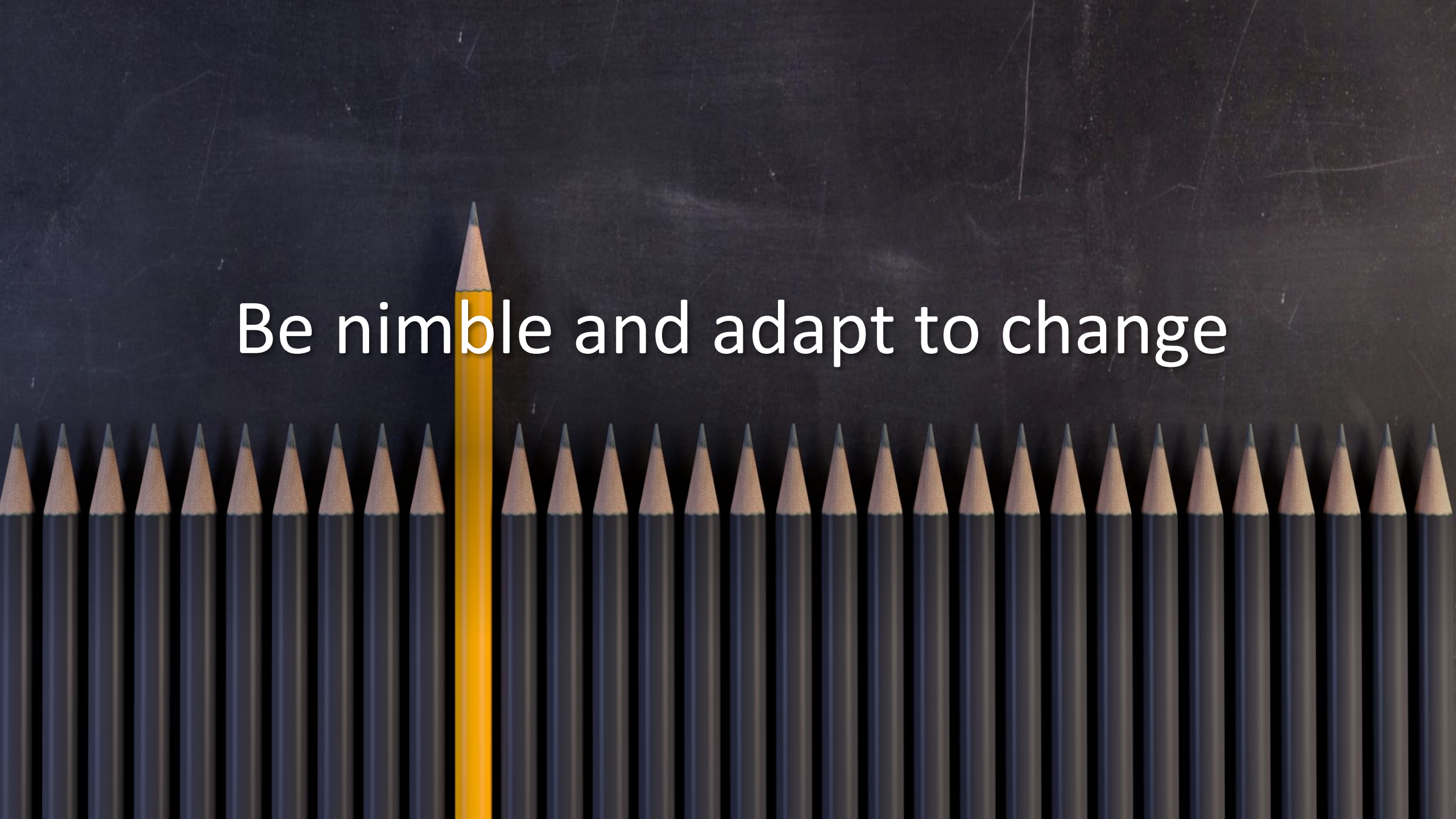
Organogenesis inc.
Empowering Healing

solventum

Disrupting the Barriers to Allow for Innovation

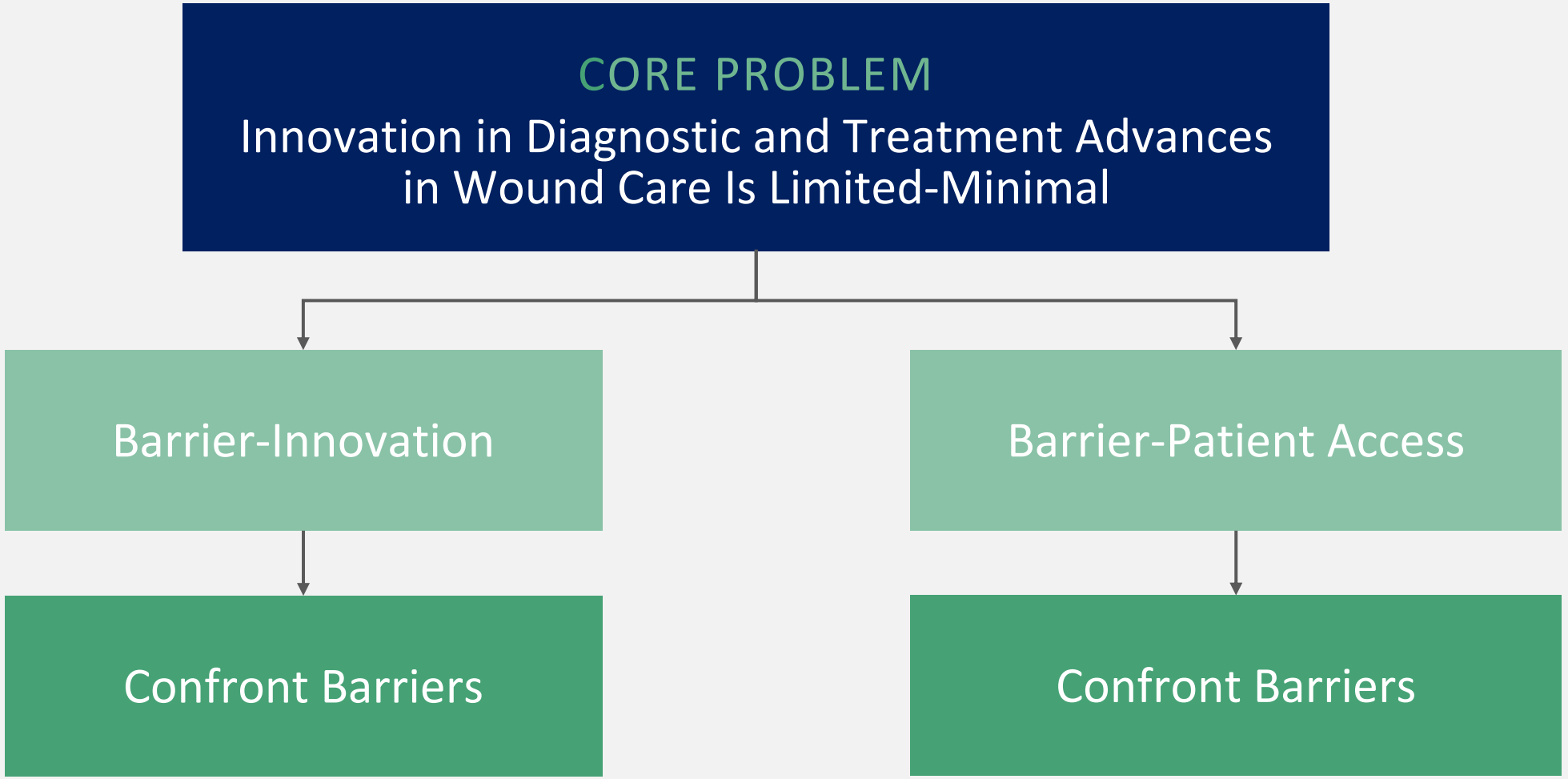
Inhibiting Barriers Requires Evidence Intended to Move the Needle

- Build a bridge toward the ultimate vision of driving innovation
- Understand key barriers
- Work groups focused on inhibiting barriers
- Find the gaps and work to close them:
  - Improve the quality of research, the quality-of-care standards, and innovations for our patients
- Work as a community for productive outputs
- Be nimble and adapt to change


Be nimble and adapt to change

If We Can Break Down the Barriers to Allow for Innovation

We Can Help Drive Innovation


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

Barriers to Innovation in Wound Care

Complaining is a neutral word that expresses legitimate dissatisfaction with the goal of finding a solution.

ROOT CAUSE #1
Barriers to Innovation and Patient Access

PRIMARY CAUSE #1
Investor hesitancies in commercial investment and research and development

PRIMARY CAUSE #2
Lack of understanding the natural history of disease

PRIMARY CAUSE #3
Clinical trial development and execution

Barriers to Innovation: Primary Cause # 1

Significant Investor Hesitancies in Commercial Investment

- High risk: Low probabilities-reliability of clinical trials
  - High rate of trial failure: Trial design, standard of care (SOC), multidisciplinary, endpoints (EPs) not reachable, lack validated tools for EPs, 2006 FDA guidance not updated
- Commercial viability: reimbursement landscape changes
- Real-world data (RWD): not properly collected/utilized to define population
- The regulatory and reimbursement system penalizes innovation and rewards me-too products.
  - Innovators that navigate the complexity and barriers face me-too copies that leverage the innovator products as 510(k) predicates with the same reimbursement as the innovator.
- Industry has low self-esteem; unwilling to step up to novel

FDA = Food and Drug Administration

Barriers To Innovation: Primary Cause # 2
Understanding The Natural History Of Disease

- Lack of standards and translation of pre-clinical models to human clinical trials.
- Much of the scientific and clinical data is focused on low-complexity patients with superficial wounds.
- There is no standardized approach to using RWD in wound research. Used alone or in conjunction with data gathered from randomized clinical trials (RCTs). RWD can help researchers gain insights into how diagnostics and therapies perform in the real world.
- Most current therapies do not understand target pathways and the mechanism of the product.

RWD = Real-world data.

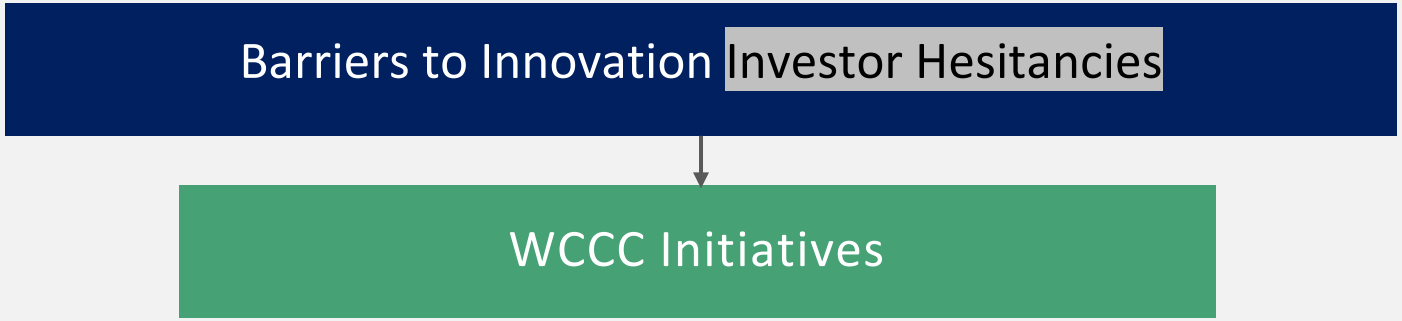
Barriers to Innovation Cause #3
Failure-Clinical Trial Development and Execution

- No agreed-upon clinical trial standards across sites and trial
  - Need prescriptive measures and protocol violations
- Lack of meaningful clinical endpoints
- Standardized and validated measurement and diagnostic tools not understood or agreed upon for support of EPs
- Enrollment based on limited parameters and patient population
  - Slow enrollment and not real world.
- Lack of trained clinical trial sites and SOC practice standards
- No agreement on reasonable comparator

EPs = Endpoints; SOC = Standard of care.

In a Nutshell

- Owning the problems
- Discussing the solutions in play
- Making it matter and stick
- What is missing?



- Research and publications defining meaningful & patient-centric endpoints
  - Wound-Care Experts/FDA-Clinical Endpoints Project (WEF-CEP)
- Initiatives to modernize systems and streamline processes to reduce the burden of confusion and ineffectiveness of clinical research in wound care that drives investors away
- Develop a standardized approach to RWD in wound research and the role it plays in FDA approvals and public and commercial payer coverage decisions
- Identify a minimal set of treatment standards for use in comparative clinical trials, higher quality evidence for regulatory decision-making

FDA = Food and Drug Administration; RWD = Real-world data; WCCC = Wound Care Collaborative Community.

Barriers to Innovation: The Natural History Of Disease

WCCC Initiatives

- Develop a Natural History Project focused on harnessing real-world data to differentiate real-world patients with chronic wounds vs those studied in RCTs.
- Develop a Fit For Purpose Project to best meet FDA real-world evidence (RWE) guidelines for expanded labeling, ensuring RWD meets FDA's criteria of fit-for-purpose, high quality, relevance, and reliability

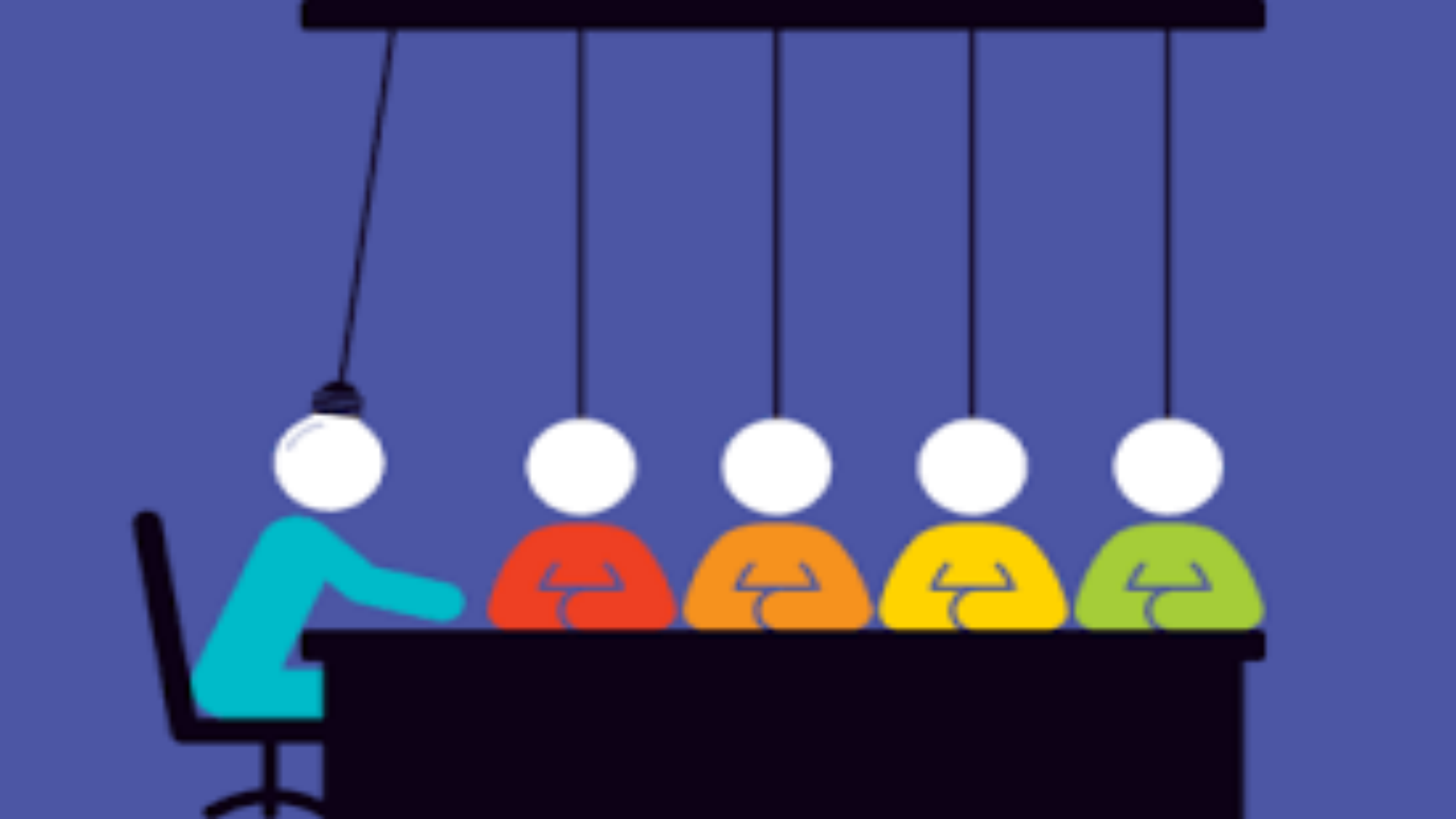
WCCC = Wound Care Collaborative Community; FDA = Food and Drug Administration; RCTs = Randomized clinical trials; RWD = Real-world data.

Barriers to Innovation- Clinical Trial Development And Execution

WCCC Initiatives

- Develop pre-clinical and clinical trial reporting guidance/min-core dataset
- Develop clinical trial development standards/guidelines
- Develop clinical SOC best practices for clinical trial development
- Identify barriers to the utilization of new EPs
- Identify valid tools that accurately and reproducibly support new primary and secondary EPs, validated through the WEF-CEP Initiative, and publish findings
- Identify a minimal set of treatment standards for use in comparative clinical trials

WCCC = Wound Care Collaborative Community; SOC = Standard of care; EPs = Endpoints;
WEF-CEP = Wound-Care Experts/FDA-Clinical Endpoints Project.



Join Us:

www.woundcarecc.org

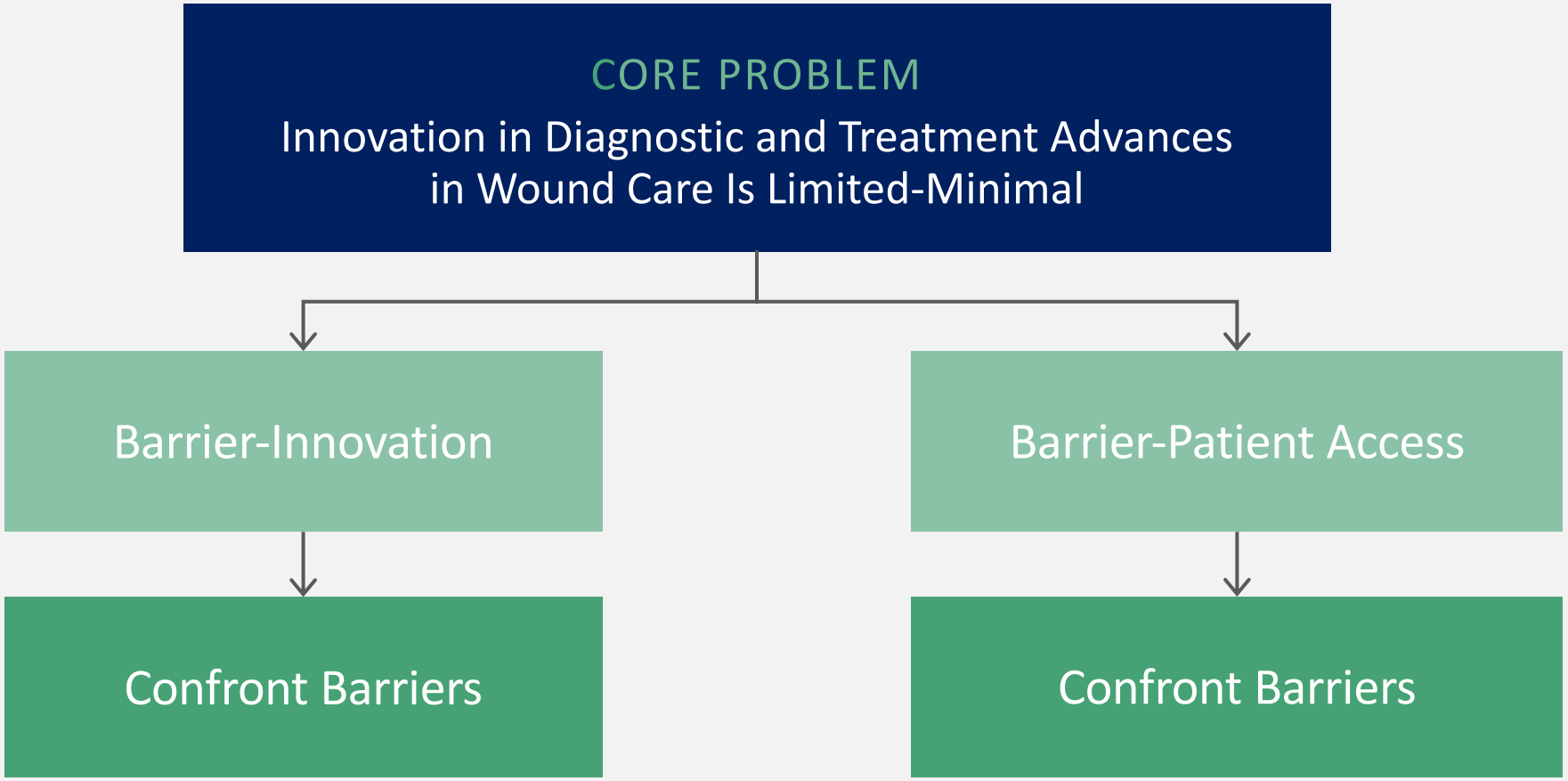
Panel 1:

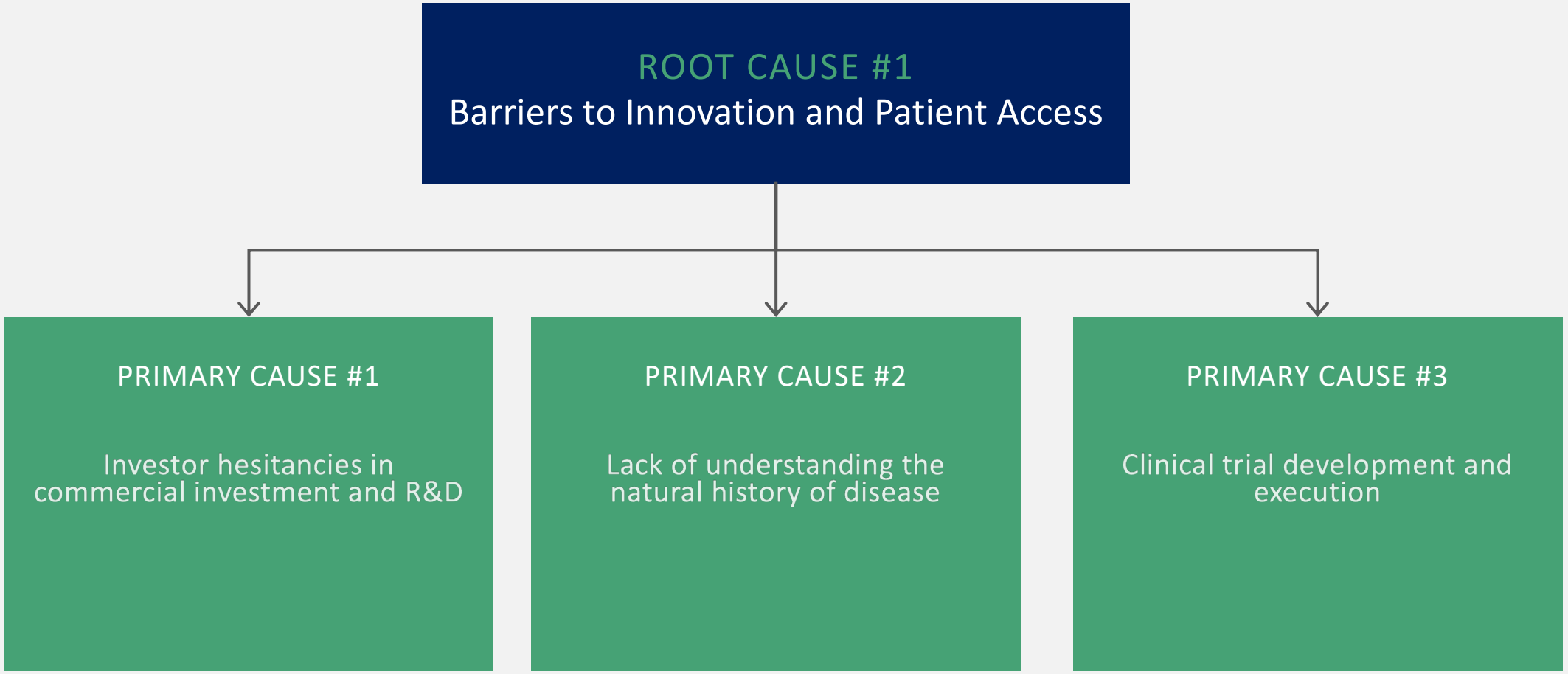
Drilling Down on Disrupting Barriers in Wound Care Innovation–Buy-in and Collaboration

Panel 1:
Drilling Down on Disrupting Barriers in Wound Care Innovation – Buy-in and Collaboration

Panel Chair:
Howard Walthall, CEO, ProgenaCare; WCCC Gaps Work Group Chair

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


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



R&D = Research and Development

Discussion Points

4 discussion topics - 10 minutes each	Panelist
FDA Perspectives What barriers has the FDA identified to innovation in wound care? How can the wound care community and the WCCC best collaborate with FDA to overcome the barriers identified by the FDA and the WCCC?	CC DV
Clinician and Research Perspectives How do the barriers to innovation that the WCCC has identified impact patients and patient care? How should clinicians and researchers leverage the work being done by the WCCC, the FDA and others to help overcome these barriers?	AO BE
Industry Perspectives How do the barriers that the WCCC has identified impact innovation projects within your organizations? How should industry participants leverage the work being done by the WCCC, the FDA and others to help overcome these barriers?	EW MS JH KM
Closing thoughts: How can FDA and the Wound Care Community best collaborate to remove or mitigate the identified barriers and accelerate innovation in wound care?	All

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

Driving Innovation in Wound Care Summit

SAWC Spring WHS | WCCC Wound Care Collaborative Community | WOUNDS A Compendium of Clinical Research and Practice

BREAK

10:35AM – 10:45AM

Driving Innovation in Wound Care Summit

SAWC Spring WHS | WCCC Wound Care Collaborative Community | WOUNDS A Compendium of Clinical Research and Practice

Panel 2:
Alternative Primary and Co-primary Endpoints

Panel 2: Alternative Primary and Co-primary Endpoints

Panel Chair:
Vickie R Driver, DPM, MS
Professor, Washington State Univ. School of Medicine
Chair, WCCC

Organization	Name & Title
FDA CDRH	Cynthia Chang, PhD, Director, Division of Infection Control and Plastic Surgery Devices
FDA CDER	Dev Verma, MD Medical Officer
WCCC	Alisha Oropallo, MD, Chair TWG, Director Dept. Vascular Surgery, Northwell Health
WCCC	Lisa Gould, MD, PhD, Vice-Chair WCCC
WCCC	Peggy Dotson, RN, BS, Secretary/ Treasure
WCCC	Marissa Carter, PhD, Work Stream Chair
ProgenaCare	Howard Walthall, JD, CEO
ConvaTec	Cristin Taylor PA-C, DPT Senior Director Medical Affairs

How We Got Here - Outgrowth

- Years of successfully working with the FDA and the wound care community on defining meaningful & patient-centric EPs (WEF-CEP initiative)
- Following this extensive research effort, three publications,[1,2,3] and a community outreach program… the FDA asked us to consider developing a WCCC
- Charter developed and accepted Dec 2020 by the FDA

1. Driver VR, et al. *Wound Rep Regen* 2017;25 (3):454–465. 2. Driver VR, et al. *Wound Rep Regen* 2019;27(1):80-89. 3. Gould LJ, et al. *Wound Rep Regen* 2020;1-10.
FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community; EPs = Endpoints; WEF-CEP = Wound-Care Experts/FDA-Clinical Endpoints Project.

How We Got Here

WEF-CEP → WCCC

2014 - 2015

Engaged with FDA
- Primary EPs - key problem

Launched WEF-CEP
- 28 relevant EPs
- Developed Clinician Survey

2016 - 2017

Completed Cl. Survey
- Presented to FDA
- Published results - 2017

Completed Evidence Research for 15 Endpoints
- Presented to FDA
- Published - 2019

2018 – 2020

Completed Patient Survey
- Published Results
- Submitted Final EPs

Presented Evidence FDA-Critical Path Innovation Meetings (CPIM)

2021 - WCCC Charter developed/submitted to FDA

1. Driver VR, et al. *Wound Rep Regen* 2017;25 (3):454–465. 2. Driver VR, et al. *Wound Rep Regen* 2019;27(1):80-89. 3. Gould LJ, et al. *Wound Rep Regen* 2020;1-10.
FDA = Food and Drug Administration; WCCC = Wound Care Collaborative Community; EPs = Endpoints; WEF-CEP = Wound-Care Experts/FDA-Clinical Endpoints Project.

Content Validated CVI 0.85 or >

15 Evidence-Based EPs:

- Time to heal
- Percent area reduction
- Reduced infection
- Reduced pain
- Reduced recurrence
- Increased physical function/ ambulation
- Amputation reduction
- Reduced analgesia use
- Reduced depression
- Reduced social isolation
- Percent volume reduced
- Reduced odor
- Cost effectiveness
- Reduced cost of treatment
- Reduced bioburden

6 Primary EPs Recommended
(with a validated measurement tool)

1. Percent area reduction (PAR)
2. Reduced infection
3. Reduced pain/analgesia use
4. Increased physical function and ambulation
5. Quality of life
6. Cost-effectiveness

EPs = Endpoints

WCCC Tools Work Group (TWG)

Project Goal

- Identify barriers to utilization of new endpoints
- Identify valid tools that accurately and reproducibly support new primary and secondary endpoints, validated through the WEF-CEP initiative

Project Focus: Improve Clinical Studies to Encourage Innovation in Wound Care

- Evaluate information on methods /devices to measure new EPs
- Engage with industry, researchers, and patient-reported outcomes (PRO) developers
- Summarize findings and provide feedback to FDA and wound care community,
- Publish findings

WCCC = Wound Care Collaborative Community; EPs = Endpoints; WEF-CEP = Wound-Care Experts/FDA-Clinical Endpoints Project.

Tools Work Group

- Initial Priority Barrier:
  - Identify valid tools to support using Percent Area Reduction (PAR) and/or Percent Volume Reduction (PVR) as a primary endpoint.
    - Improve clinical trials
    - Improve FDA approval process
    - Facilitate clinical care
- Bring awareness to wound care community
  - The importance of new endpoints in wound care

1. Rennie M, et al. *Wounds*. 2023;35(9):8-9. 2. Oropallo A, et al. *Wounds*. 2024;36(2):A3-A6. doi:10.25270/wnds/360224-2.
FDA = Food and Drug Administration; EPs = Endpoints.

TWG Sub-Group Review PAR/PVR Devices

- Initiated a sub-group to consolidate collective data by full TWG, develop a working list of devices and features to measure PAR/PVR, and develop a survey for wound care companies to capture further data.

Team Members

- Holly Korzendorfer, PT, PhD
- Windy Cole, DPT
- Scott LaRaus, DPT
- Francis James, Industry
- Alisha Oropallo, MD
- Peggy Dotson, RN, BS

TWG = Tools Work Group; PAR = Percent area reduction; PVR = Percent volume reduction.

Process: TWG Sub-Group

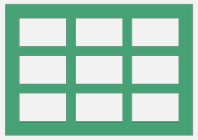
Identified Issues:

(L × W) method overestimates the area of the wound by over 44%

Digital imaging can:

- Reduce variability
- Record progress over time
- Automate process

Digital imaging tools (DITs) have the potential to measure wound physiology



Assessed:

Current tools that measure PAR and PVR (primary or secondary function)

Compared features, specs and published data

Created:

Working list of tools with features/ capabilities to measure PAR/ PVR to include in Survey to industry

TWG = Tools Work Group; PAR = Percent area reduction; PVR = Percent volume reduction.

Process: TWG Sub-Group

Developed a letter to engage the industry's involvement in the survey

Developed the survey questionnaire

The survey was distributed amongst FDA-registered device manufacturers with devices that capture wound images/ photography (13)

TWG = Tools Work Group; FDA = Food and Drug Administration.

Survey Questionnaire Highlights

Device tracking	PAR/PVR; Area, depth, volume calculation, circumferential, concave, convex wounds
Measurement method	Laser, 3D, Digital photo
Pixel to centimeter scale	Reference marker identification
Skew correction	Identification type
Segmentation of color	Identification, quality measurement, calibration
Clarity focus	Identification
Features guiding user for consistent photos	Availability
Editing feature	Measurement adjustment of actual wound
Trajectory graph	Treatment outcomes
Historical photo visualization	Maintain consistency and reproducibility of the measurement
Primary device function	Purpose, portable, electronic medical record (EMR) integration

TWG = Tools Work Group; PAR = Percent area reduction; PVR = Percent volume reduction.

Upcoming Projects to Address Barriers

Projects	Work Plan Deadline
PAR/PVR Tools Survey completion	Q2
Publication PAR/PVR Tools - Part II submission Develop summary /recommendations for FDA	Q2
Color Effects in Wound Photography (manuscript submission	Q2
Wound photography using Infrared (survey completion)	Q3
Wound photography using Infrared (manuscript submission)	Q3
Wound photography using fluorescence (survey submission)	Q4
Wound photography using fluorescence (manuscript submission)	Q4

PAR = Percent area reduction; PVR = Percent volume reduction; FDA = Food and Drug Administration.

Panel Discussion Points:

4 Discussion Points - 10 Minutes Each	Panelist
1. How endpoints other than complete wound healing will encourage innovation.	DV CT AO
2. Difference between multiple, co-primary and co-composite EPs b) expected implications on study size and cost of using co-primary or composite endpoints.	MC HW
3. How and when single verses multiple endpoints are needed. b) FDA guidance availability to support decision making in crafting a clinical trial. Include the point that meaningful EPs are few, especially those that are validated.	CC DV CT MC
4. The patient's perspective regarding the need for additional primary endpoints.	LG PD
Closing: WCCC and the FDA need to work closely together utilizing the research completed by WEF-CEP and the WCCC tools WG to guide the process for broader usage of additional primary endpoints. WCCC recommends: WCCC work with the FDA to draft an updated 2006 wound healing guidance document or an amendment to existing draft guidance.	VRD DV CC PD LG

WCCC = Wound Care Collaborative Community; EPs = Endpoints; WEF-CEP = Wound-Care Experts/FDA-Clinical Endpoints Project.

Endpoints: Multiple, Primary

- Known as MPEs, these EPs are considered independent and may or may not be correlated in some way
- Hypothesis testing: Union-intersection principle
- No type 2 error to be controlled, but type 1 error will need adjustment
- Adjustment can be done using hierarchical, closed loop, simultaneous methods, or a combination of both
- Example might be landmark complete wound healing at time X and amputation rate
- Does the intervention influence at least **one** of the primary endpoints?
- Must reject **at least one** of the null hypotheses.

EPs = Endpoints.

Endpoints: Co-Primaries (CPEs)

- A subset of MPEs, CPEs are usually considered related and so are likely to be correlated in some way
- Hypothesis testing: intersection-union principle
- No type 1 error control needed but a serious type 2 error exists (proportional loss of power as number of endpoints increases); for example, n=2 power might drop from 80% to 70% assuming r=0.5
- To compensate for type 2 error, sample size must be substantially **increased**
- Requires **conjoint** analysis for accuracy, which can be challenging.
- Does the intervention have an effect on at least **one** of the primary endpoints?
- Must reject **all** of the null hypotheses.
- Not recommended generally for wound care trials unless endpoints have some relationship (e.g., PRO families).

EPs = Endpoints.

Endpoints: Composites

- A composite endpoint (CEP) is an outcome that combines two or more endpoints of interest within a single variable
- Examples include:
  - Multiple different types of events
  - Incidence of multiple complications
- Components **must** be of **similar clinical importance** to patients
- **Frequency of occurrence** of components must be similar over the same time period (i.e., no predominance)
- **Treatment effect** must be similar for each component
- Global ranking or composite endpoint weighting techniques may be helpful.

EPs = Endpoints.

Panel Discussion Points:

4 Discussion Points- 10 minutes each	Panelist
1. How EPs other than complete wound healing will encourage innovation.	**DV CT AO**
2. Difference between multiple, co-primary and co-composite EPs- **b**) expected implications on study size and cost of using co-primary or composite endpoints.	**MC HW**
3. How and when single verses multiple endpoints are needed. **b)** FDA guidance availability to support decision making in crafting a clinical trial. Include the point that meaningful EPs are few, especially those that are validated.	**CC DV CT MC**
4. The patient's perspective regarding the need for additional primary endpoints.	**LG PD**
Closing: WCCC and the FDA need to continue to work closely together utilizing the research completed by WEF-CEP and the WCCC tools WG to guide the process for broader usage of additional primary endpoints. WCCC recommends: WCCC work with the FDA to draft an updated 2006 wound healing guidance document or an amendment to existing draft guidance.	**VRD DV CC PD L G**

WCCC = Wound Care Collaborative Community; SOC = Standard of care; EPs = Endpoints; WEF-CEP = Wound-Care Experts/FDA-Clinical Endpoints Project.

LUNCH

Crystal Ballroom DEF

11:50AM – 12:35PM

Driving Innovation in Wound Care Summit

SAWC Spring WHS | WCCC Wound Care Collaborative Community | WOUNDS A Compendium of Clinical Research and Practice

Q&A with Program Chair: Vickie R Driver, DPM, MS and Session Chairs

Participate n the Audience Q&A by scanning the QR Code below:

https://meet.ps/WCCC

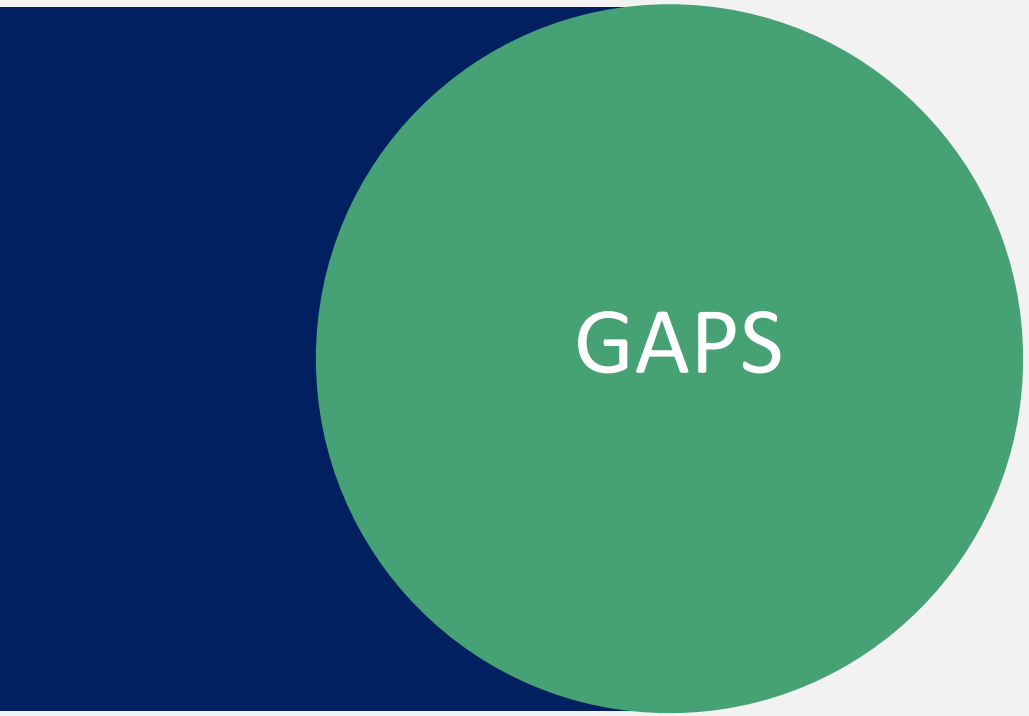
Panel 3:
Generating and Reporting Evidence

Panel 3:
Generating and Reporting Evidence

Panel Chairs:
Marissa Carter PhD and
Marjana Tomic-Canic PhD

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

WORK GROUPS



Identification of gaps in wound care trials (human and animal) and clinical practice

WCCC-GAPS Work Group

Project Goals

- Develop reporting standards (guidelines) for clinical trials in wound care
- Develop pre-clinical testing standards and reporting guidelines in wound care

Project

1. Reporting standards/guidelines for clinical trials
    a. Identify variables that affect wound healing from literature searches of prognostic models
    b. Create guidelines for reporting like CONSORT
2. Pre-clinical testing standards and reporting guidelines
    a. Select pre-clinical testing models and develop rationale/short summary of the models
    b. Develop checklists for reporting – general (applies to all) and model-specific

WCCC-GAPS Work Group (GWG)

- Initial Priorities Project 1:
  - Literature search: systematic reviews of prognostic models
  - Extract data from the systematic reviews and individual studies
  - Reach a consensus on those patient/wound/other variables that need to be reported as a minimum
  - Develop CONSORT-like guidelines for these variables

- Initial Priorities Project 2 :
  - Select most relevant pre-clinical models
  - Develop a reporting list for each of the models
  - Create a written document to obtain feedback and input from stake holders

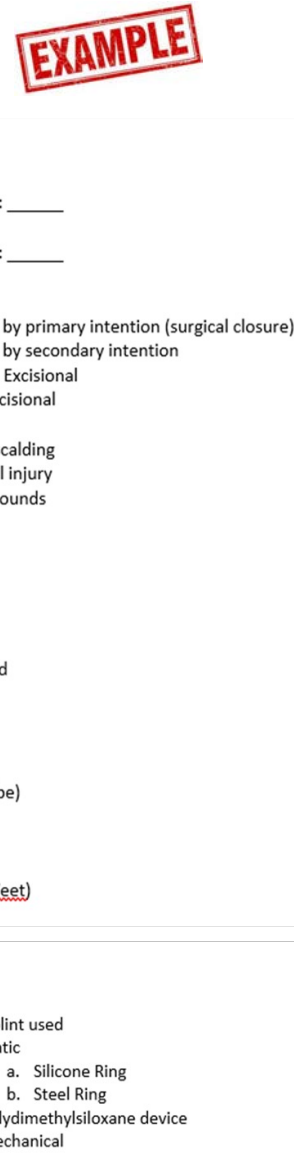
Schulz KF, Altman DG, Moher D; CONSORT Group. BMC Med 2010;8:18.
Weaver C, Ahles S, Murphy KJ, Shyam S, et al; Adv Nutr 2024;15(1):100154. [Example of similar project in nutrition]

PROCESS (Project 1) - GWG

- Assessed:
  - Variables that affect wound healing, amputation rates, or wound recurrence
- Created:
  - Protocol for literature search (prognostic models); to be registered with Open Science Framework
  - Data extraction template
- Identified Issues:
  - Authors of clinical trials frequently do not report variables that affect wound outcomes
  - Creates problems for end-users of trials in identifying relevant population(s)
- Developing recommendations:
  - CONSORT-like criteria that should be the **standard method** for reporting in wound care clinical trials

PROCESS (Project 2) - GWG

- Assessed:
  - Published literature and pre-INDs to review information being reported regarding pre-clinical testing to identify most frequent models and experimental variables
- Created:
  - Models, uses and limitations and supporting literature
  - Reporting lists capturing checklist of experimental variables for each of the models: Rodent (24 items); Porcine (25 items); Rabbit (21 items)
- Identified Issues:
  - Structuring reporting checklists for each model creates a lot of redundancy; needs to be better organized/consolidated
  - Human ex vivo model should also be included (frequently used; reliable model for testing)
  - Justifications/rationale of specific reporting requirements is missing
- Developing recommendations:
  - Reporting document with checklists includes summary for each model (including uses and limitations and justification for requirements of specific reporting), checklist for reporting experimental variables for pre-clinical models



GAPS Work Group

- Work Progress [Project 1]:
  - Literature search (systematic reviews of prognostic models) in progress
  - Data extraction from systematic reviews and individual studies in progress

- Work Progress [Project 2]:
  - Document created and checklists consolidated working title *Wound Reporting in Animal and Human Preclinical Studies (WRAHPS)*
  - Draft document sent for input/review to WCCC, FDA, WHS
  - Final editing in progress

WCCC- GAPS Work Group

Future focus:

- Develop clinical trial reporting guidelines for wound care
  - Variables that affect key wound outcomes
  - Format and rationale for reporting
  - Discussion with FDA and other interested parties
  - Publish in Wounds
  - Discussion with editors of key wound care journals for mandatory reporting

- Finalize pre-clinical reporting guidelines for wound care
  - Finalize the reporting guidelines document
  - Create a drop-down fillable reporting forms
  - Contact editors of major wound journals to obtain agreement for simultaneous publication in WRR, JWC and Wounds and finalize publication
  - Reach out to scientific journal editors (other than wound-specialized journals) and educate them
  - Monitor reporting and identify challenges and implementation of mandatory reporting

WCCC-GAPS Work Group (Discussion Questions)

Focus	Questions	Panelists
Barriers (human clinical)	Methodology of the process for developing wound care human clinical trial reporting guidelines	MJC: JA/RS/DV
Acceptance	Assuming that the guidelines can be published, how will industry and clinical trial investigators implement them?	MJC: CF/AL/MR
Buy-in (pre-clinical)	Reporting guidelines in multiple wound journals. Challenges to adoption/ implementation standardized reporting among stake-holders	MTC: JA/LV/RS
Immediate/ long-term steps (pre-clinical)	Best approaches and concrete steps Implement pre-clinical testing guidelines for reporting.	MTC: SV/AL/MR

WCCC-GAPS Work Group (Discussion Questions)

Focus	Questions	Panelists
Closing Discussion	WCCC, industry, FDA working more closely together on reporting guidelines and standards for pre-clinical and clinical trial areas Same groups should help incorporate standards and guidelines into an updated draft of the 2006 wound healing guidance document or amendment to such document.	MJC/MTC: DV/RS/AL/CF

Closing/Call to Action Items

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

Panel 4:
Real-World Evidence in FDA and Payer Decision-Making

Panel 4:
Real-World Evidence in FDA and Payer Decision-Making Panel

Panel Chair:
Joe Rolley, Principal, JTR Business Consulting, LLC & Co-Chair RWE Group, WCCC

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

WORK GROUPS

REAL-WORLD EVIDENCE

Develop a standardized approach to real world data in wound research and the role it plays in FDA approvals and public and commercial payer coverage decisions.

RWE Use by FDA or CMS in Decision Making is Minimal

- FDA (CDRH):
  - Post-market surveillance and indication expansion requests
  - Examples include registries and claims data as a source of RWD
  - Vast majority are PMAs; few 510(k)s
  - Number of wound technology RWE examples: Zero
- CMS:
  - Since 2005, only 27 medical devices or procedures have been provided Coverage with Evidence Development (CED) pathway
  - Only four had their evidence development programs retired and their national coverage retained.
  - CMS ceded coverage of an additional two devices or procedures to the discretion of Medicare's regional administrative contractors
  - Number of wound technology CED examples: One (PRP)
- MACs:
  - There is no CED-type program for the use of RWE in LCD decisions

Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions, Selected examples with file summaries, details on real-world data source, populations, and descriptions of use, Center for Devices and Radiological Health
Coverage With Evidence Development: Where Are We Now? (ajmc.com)
Coverage with Evidence Development | CMS

Improving the Quality of RCTs and Utilization of RWE in Decision Making

WCCC RWE Priorities

Establish an RWE Knowledge Base	Definition of Real-World Evidence (COMPLETED)	Real-World Database Landscape (COMPLETED & SUBMIITED FOR PUBLICATION
Build the Case for Using Risk Stratification in RCTs	Inclusion, Exclusion Criteria in RCTs for Regulatory & Coverage Decisions (COMPLETED)	Standard of Care for Wounds in Clinical Research
Reset Expectations of 'Safety and Effectiveness' and 'Reasonable and Necessary' Criteria for Chronic wounds	Natural History of People with Wounds Based on Real-World Data	Fit-for-Purpose Project

Only ~10% of Real-World Wound Databases are Ready, Willing and Available for 3rd Party Research

Northwell Health®

Intellicure™

STATinMED
The Authority in Real-World Evidence

komodo

Natural History Project

Project Goals

- To describe the treatment and outcome of patients with diabetic foot ulcers (DFUs) and venous leg ulcers (VLU)
- To identify the difference between real world patients and subjects enrolled in most prospective clinical trials.
- To identify real world practice standards for accepted care to help define the current standard of practice and the gaps that exist between actual practice and ideal care.

Key Questions

- How generalizable are most prospective diabetic foot ulcer studies when compared to real world patients and real world DFUs?
- What do real world patients with DFUs look like in terms of level of comorbid disease, time in service, and adverse events
- What does the patient journey look like in terms of time to access expert care, time in service and quality of care in DFU patients?
- What do real world patients with VLUs look like in terms of level of comorbid disease, time in service, and adverse events
- What does the patient journey look like in terms of time to access expert care, time in service and quality of care for patients with VLUs?
- What is the gap between “ideal” care and the care generally provided to VLUs?

First Look at Natural History Data

- Data range: 1/1/2021 – 12/31/2022
- Summary:
  - Patients: 51,708
  - "Wounds": 160,341
  - Visits: 616,496
  - Age (median): 66 years
- Source:
  - US States: 29
  - Clinics/practices: 149
  - Practitioners: 527
- DFU Data:
  - DFUs: 26,042 (16.2%)
  - DFU Patients: 10,955
  - DFUs per pt: 2 (median)
  - Ulcers/pt: 4 (median)
  - New DFUs: 41.2% (new DFU while in Tx)
- VLU Data:
  - VLUs: 34,236 (21.4%)
  - VLU Patients: 12,065
  - VLUs per pt: 2 (median)
  - Ulcers/pt: 5 (median)
  - Size of VLU: 6 cm^2 (median); 21.2 cm^2 (mean)

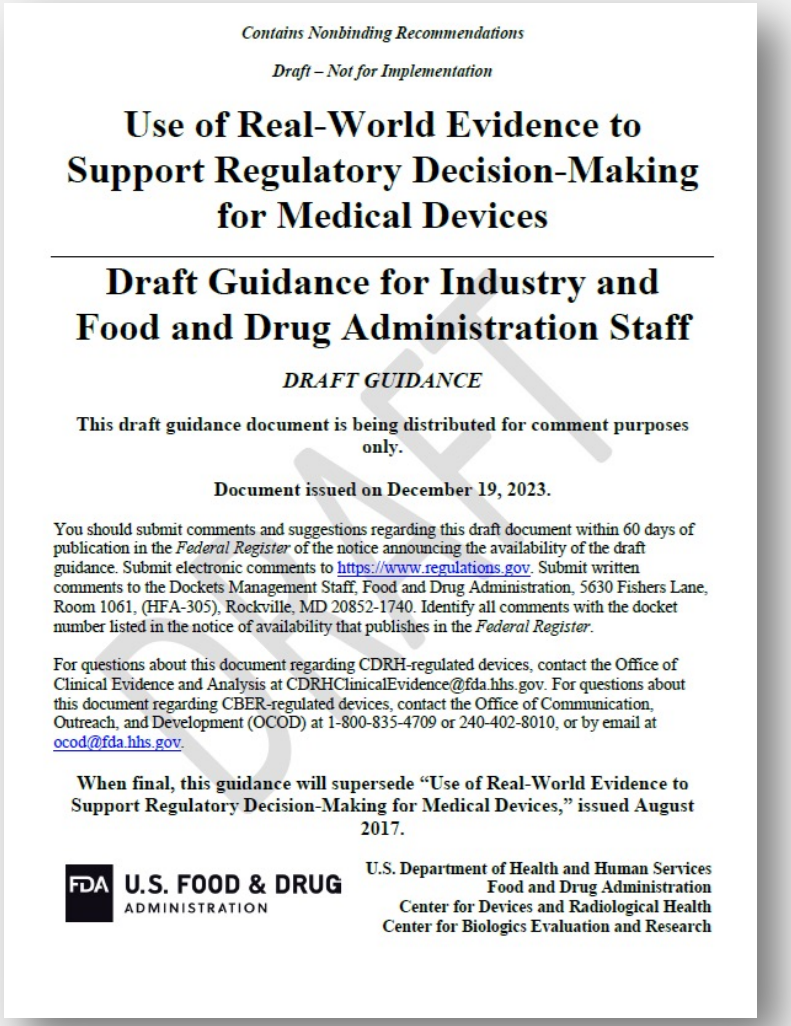
DFU comorbidity	Count (%)
Hypertension (HTN)	5,094 (46.45)
Obesity	3,874 (35.33)
Peripheral Arterial Disease (PAD)	3,112 (28.38)
Hyperlipidemia	2,266 (20.66)
Autoimmune Disease	1,762 (16.07)
Congestive Heart Failure (CHF)	1,208 (11.02)
Chronic Kidney Disease (CKD)	1,093 (9.97)

Wagner	Count (%)
Grade 1	7,133 (27.4)
Grade 2	10,105 (38.8)
Grade 3	5,379 (20.7)
Grade 4	1,278 (4.9)
Grade 5	46 (0.2)

VLU Comorbidity	Count (%)
Hypertension (HTN)	5,047 (41.8)
Obesity	4,792 (39.7)
Peripheral Arterial Disease (PAD)	2,182 (18.0)
Hyperlipidemia	1,883 (15.6)
Autoimmune Disease	1,654 (13.7)
Congestive Heart Failure (CHF)	1,608 (13.3)
Atrial Fibrillation (AFib)	893 (7.4)
Chronic Kidney Disease (CKD)	795 (6.5)

These data are still undergoing analysis and confirmation, and values may change.

FDA RWE Draft Guidance Document



Contains Nonbinding Recommendations

Draft – Not for Implementation

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on December 19, 2023.

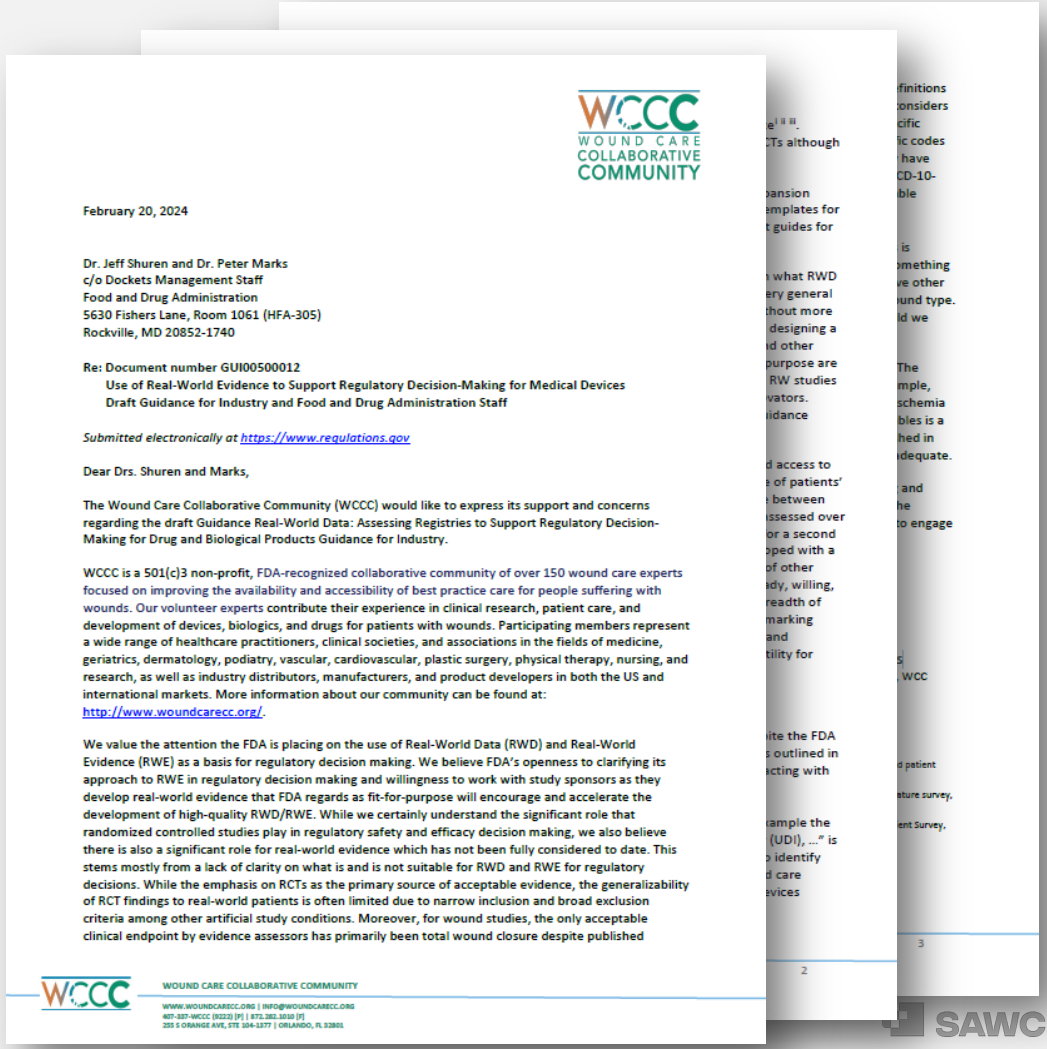
You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852-1740. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document regarding CDRH-regulated devices, contact the Office of Clinical Evidence and Analysis at CDRHClinicalEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010, or by email at ocod@fda.hhs.gov.

When final, this guidance will supersede "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," issued August 2017.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research



WCCC WOUND CARE COLLABORATIVE COMMUNITY

February 20, 2024

Dr. Jeff Shuren and Dr. Peter Marks
c/o Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852-1740

Re: Document number GUI00500012
Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
Draft Guidance for Industry and Food and Drug Administration Staff

Submitted electronically at https://www.regulations.gov

Dear Drs. Shuren and Marks,

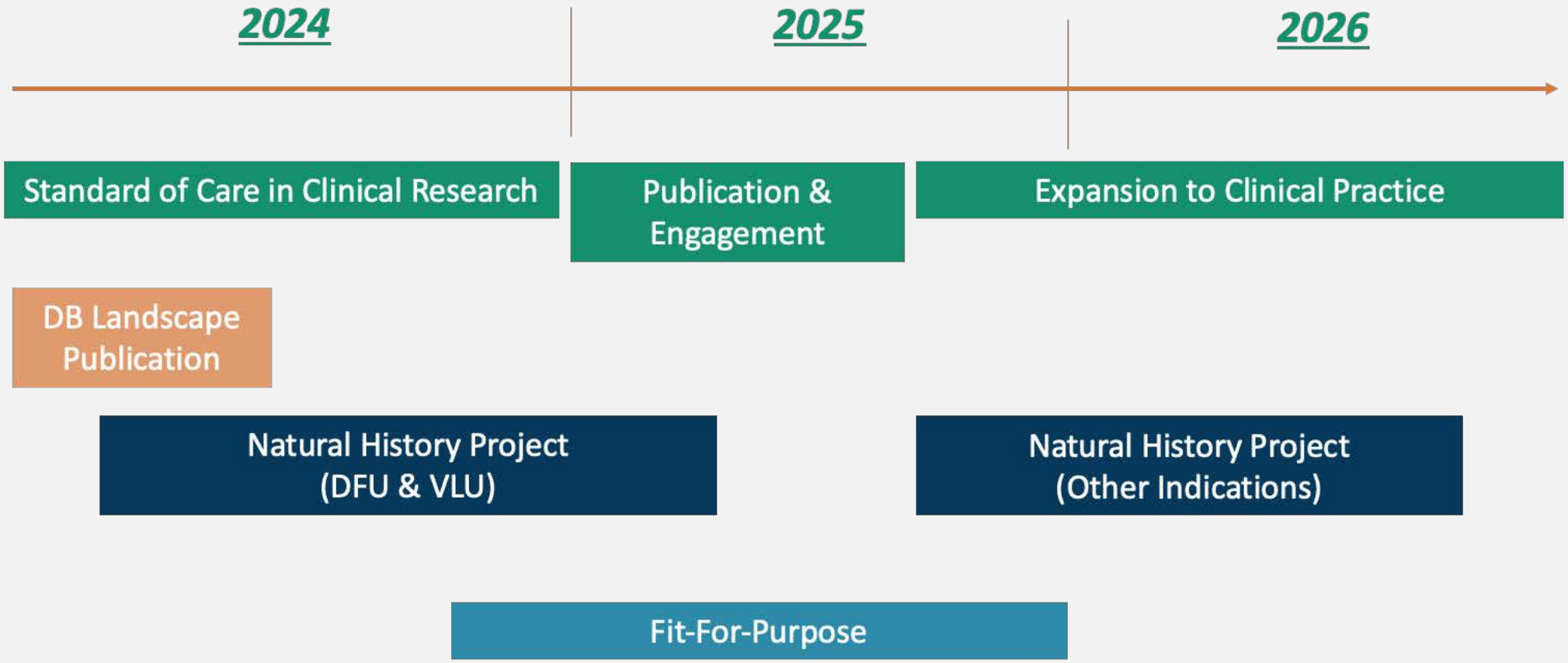
The Wound Care Collaborative Community (WCCC) would like to express its support and concerns regarding the draft Guidance Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry.

WCCC is a 501(c)3 non-profit, FDA-recognized collaborative community of over 150 wound care experts focused on improving the availability and accessibility of best practice care for people suffering with wounds. Our volunteer experts contribute their experience in clinical research, patient care, and development of devices, biologics, and drugs for patients with wounds. Participating members represent a wide range of healthcare practitioners, clinical societies, and associations in the fields of medicine, geriatrics, dermatology, podiatry, vascular, cardiovascular, plastic surgery, physical therapy, nursing, and research, as well as industry distributors, manufacturers, and product developers in both the US and international markets. More information about our community can be found at: http://www.woundcarecc.org/.

We value the attention the FDA is placing on the use of Real-World Data (RWD) and Real-World Evidence (RWE) as a basis for regulatory decision making. We believe FDA's openness to clarifying its approach to RWE in regulatory decision making and willingness to work with study sponsors as they develop real-world evidence that FDA regards as fit-for-purpose will encourage and accelerate the development of high-quality RWD/RWE. While we certainly understand the significant role that randomized controlled studies play in regulatory safety and efficacy decision making, we also believe there is also a significant role for real-world evidence which has not been fully considered to date. This stems mostly from a lack of clarity on what is and is not suitable for RWD and RWE for regulatory decisions. While the emphasis on RCTs as the primary source of acceptable evidence, the generalizability of RCT findings to real-world patients is often limited due to narrow inclusion and broad exclusion criteria among other artificial study conditions. Moreover, for wound studies, the only acceptable clinical endpoint by evidence assessors has primarily been total wound closure despite published

WCCC WOUND CARE COLLABORATIVE COMMUNITY

RWE Projects Timeline



Question 1: Barriers

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

Question 2: RCTs vs. RWE

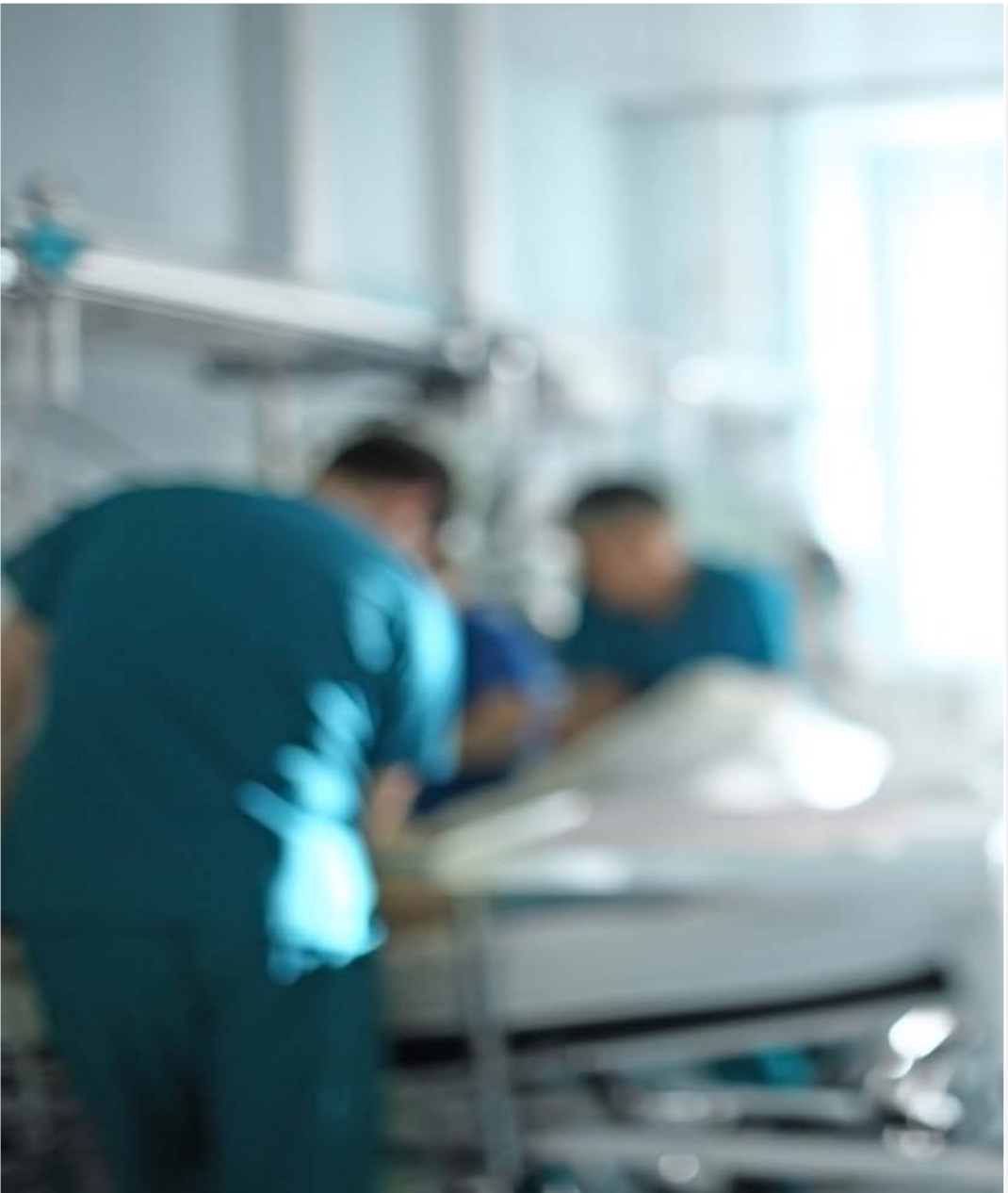
Question	Panelists
▪ The Natural History Project will leverage real-world data to characterize the real-world chronic wound patient versus those commonly studied in RCTs today. We understand why FDA and payers wants to understand efficacy in an environment where there are few confounding variables, but that fact virtually necessitates non-generalizable trials. ▪ Are you concerned about that reality? ▪ Can RW databases facilitate comparative effectiveness research better than RCTs given that many patients have multiple wounds and wounds of mixed etiology? ▪ How do you foresee the outputs from the Natural History Project impacting your decision-making for DFUs and VLUs and what actions will you take to incorporate the findings of this project into your decision making?	C. Chang (D. Verma) D. Kommala W. Ennis W. Tettelbach

Question 3: FDA RWE Guidance

Question	Panelists
The recent proposed guidance for RWE describes a process for RW studies that is perhaps even more challenging and expensive than RCTs. Further, concerns regarding the use of RWD center on the potential for statistical bias, variabilities in delivering the standard of care, and access to real-world data. ▪ Why would a sponsor choose to conduct an RW study instead of an RCT which is traditionally more acceptable by both FDA and payers? ▪ What role can/should the WCCC play in assisting wound researchers navigate FDA's RWE processes?	C. Chang (D. Verma) D. Kommala W. Tettelbach C. Fife

Question 4: The Future

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



Closing and Call-to-Action Items From Discussion Points

Panel 5:

Defining Standard of Care in Wound Care

Panel 5:
Defining Standard of Care in Wound Care

Panel Chair:
Maribel Henao DPM, MSPT
Chair WCCC SOC WS

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

Standard of Care (SOC) Project

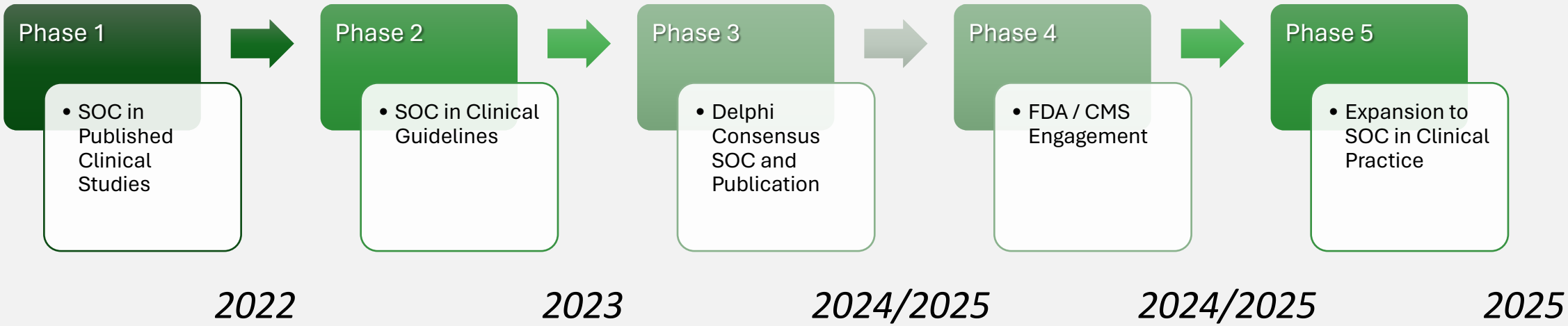
Rationale

- In clinical trials, standardization reduces bias, ensures validity, and allows for generalization to a larger real-world population.
- Findings from an analysis of the published studies submitted to FDA and payers for decision making on skin substitutes revealed variations and lack of transparency in what constituted SOC.
- SOC has been described and published by different societies and organizations through practice guidelines, consensus documents, or compendiums.
- There is no unified recommendation on what constitutes “standard of care” for adoption in clinical research and practice.

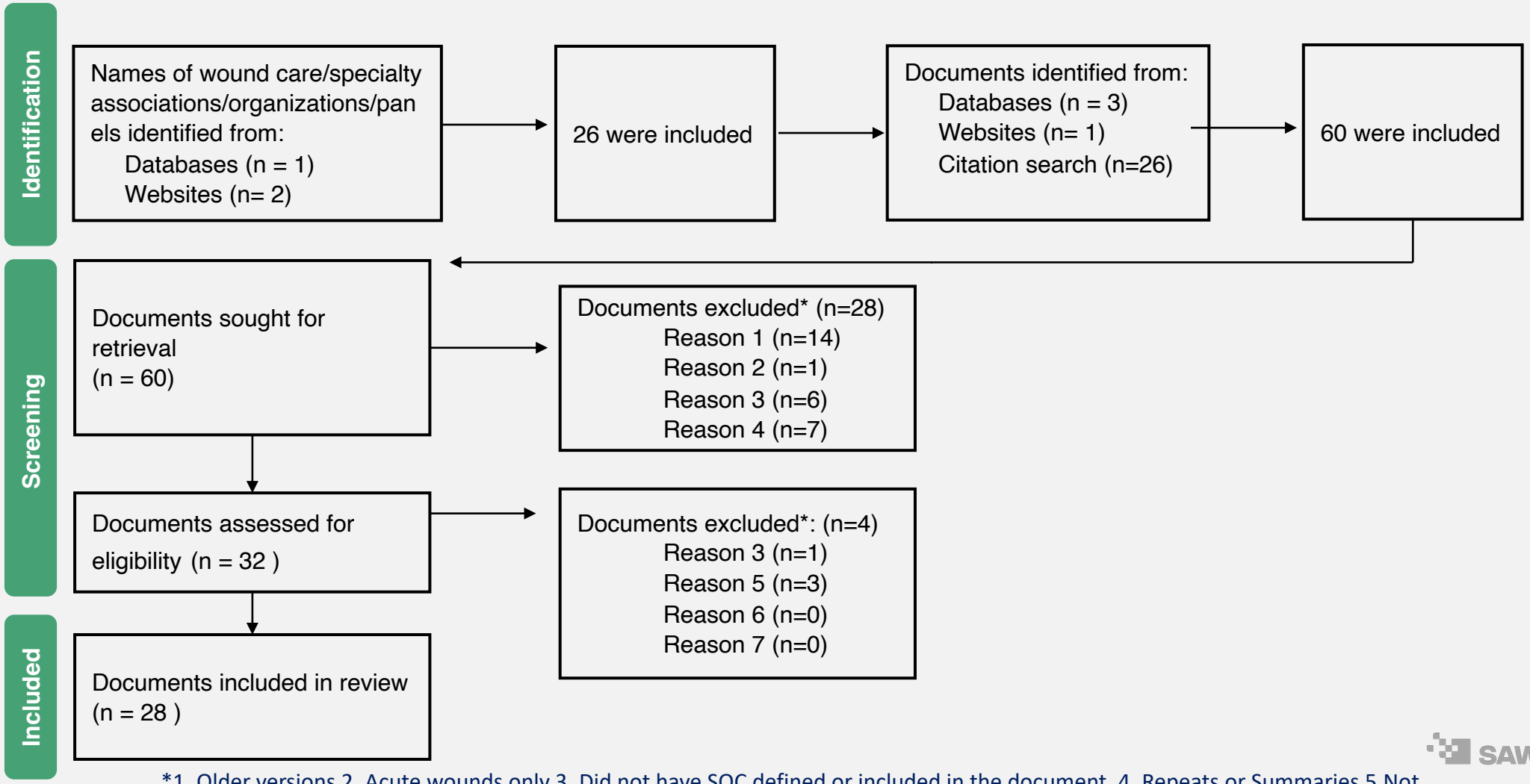
Standard of Care (SOC) Project

Project Goal:

- The aim of this project is to identify a minimal set of treatment standards for use in comparative clinical trials for innovative wound technologies.
- Build consensus of what constitutes "standard of care" across chronic wound indications for adoption in clinical research.
- Focus is to improve and refine future clinical trial design- Not to invalidate or denounce current published RCTs



Identification of Studies via Databases, Websites, and Other Methods



*1. Older versions 2. Acute wounds only 3. Did not have SOC defined or included in the document. 4. Repeats or Summaries 5.Not peer-reviewed 6. Industry sponsored by one company only. 7. Did not use a standardized method to determine quality of evidence.

Standard of Care (SOC) Project Progress to Date

- Completed systematic review of 32 wound care SOC guidelines published by professional societies, regulatory bodies, payers, and other organizations to identify consistencies and gaps and selected 28 for analysis based on internally developed eligibility criteria
- Excluded:
  - Non-peer reviewed
  - Industry supported by one company only
  - Did not use a standardized method to determine quality of evidence
  - Did not have SOC defined or included in the document
- Engaged Solventum research experts to validate the methodology utilized to date and assist with collating the first level analysis.
  - Currently underway.

Current Results–High Level

- Wound Assessment
  - Proper wound assessment- including accurate diagnosis
  - Evaluate arterial perfusion
  - Evaluate deep tissue infection and/or osteomyelitis
  - Soft tissue biopsy followed by bone and soft tissue
- Patient Assessment
  - Nutritional evaluation
  - Referral to specialists
- Patient Management
  - Addressing tobacco cessation, weight management, or other psychosocial/patient related factors
- Wound Treatment
  - Measures to prevent or treat wound infection/bioburden/biofilm
  - Wound bed preparation
  - Debridement recommended to remove necrotic/nonviable tissue/slough and excessive bacterial burden and to maintain the readiness of the wound bed for healing
  - Surgical debridement as the type of debridement
  - Selecting a proper wound dressing to control exudate and maintain moisture balance
  - When applicable, offloading DFUs was listed
  - Compression for VLUs
  - Surgery Recommended
  - Change to advanced therapies when reaching a certain timeframe and/or objectives during clinical assessment

Current Results

- Tied
- Recommendations for diabetes management, when applicable
- Minority
- Evaluation for venous disease
- Edema management
- Pain management

Discussion Point Q1: Barriers

Question	Panelists
As discussed in the beginning of the presentation, SOC in clinical trials has been poorly defined and variations to what constitutes SOC has been observed. In addition, SOC has been defined differently in guidelines. ▪ At the completion of this project, when a unified consensus for SOC has been established and published, how would you incorporate the results of this project when reviewing or designing/completing clinical trials in the future?	C. Chang R. Snyder Y. Arnold D. Kommala

Discussion Point Q2: Current Results of SOC Project

Question	Panelists
▪ Looking at the initial results of the SOC project so far, do you foresee any issues with these recommendations as compared to what you are currently designing as SOC in clinical trials?	J. Lantis Y. Arnold T. Jacobson

Current Results–High Level

- Wound Assessment
  - Proper wound assessment- including accurate diagnosis
  - Evaluate arterial perfusion
  - Evaluate deep tissue infection and/or osteomyelitis
  - Soft tissue biopsy followed by bone and soft tissue
- Patient Assessment
  - Nutritional evaluation
  - Referral to specialists
- Patient Management
  - Addressing tobacco cessation, weight management, or other psychosocial/patient related factors
- Wound Treatment
  - Measures to prevent or treat wound infection/bioburden/biofilm
  - Wound bed preparation
  - Debridement recommended to remove necrotic/nonviable tissue/slough and excessive bacterial burden and to maintain the readiness of the wound bed for healing
  - Surgical debridement as the type of debridement
  - Selecting a proper wound dressing to control exudate and maintain moisture balance
  - When applicable, offloading DFUs was listed
  - Compression for VLUs
  - Surgery Recommended
  - Change to advanced therapies when reaching a certain timeframe and/or objectives during clinical assessment

Current Results

- Tied
- Recommendations for diabetes management, when applicable
- Minority
- Evaluation for venous disease
- Edema management
- Pain management

Discussion Point Q3: Outputs

Question	Panelists
There have been discussions to update the FDA Guidance document Guidance for Industry Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment) that was published in 2006. ▪ What types of outputs do you need to see from our group that would facilitate adoption by the FDA into the Guidance Document? For payors? (e.g. published practice guideline, consensus document etc).	C. Chang D. Kommala

Guidance for Industry

Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment

Additional copies are available from:

Office of Training and Communications
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication, Training, and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800
http://www.fda.gov/cber/guidelines.htm
or
Office of Communication, Education, and Radiation Programs
Division of Small Manufacturers, International and Consumer Assistance, HFZ-220
Center for Devices and Radiological Health
1350 Piccard Drive
Rockville, MD 20850-4307
DSMICA E-mail: dsmica@cdrh.fda.gov
DSMICA Fax: 301-443-8818
(Tel) Manufacturers Assistance: 800-638-2041 or 301-443-6597
(Tel) International Staff: 301-827-3993
http://www.fda.gov/cdrh/ggpmain.html

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

June 2006
Clinical/Medical

Received: 21 June 2023 | Revised: 17 October 2023 | Accepted: 27 November 2023
DOI: 10.1111/wrr.13133

Check for updates

GUIDELINES

Wound Repair and Regeneration — WILEY

WHS (Wound Healing Society) guidelines update: Diabetic foot ulcer treatment guidelines

Lawrence A. Lavery DPM, MPH[1] | Mehmet A. Suludere MD[1] | Chris E. Attinger MD[2] | Matthew Malone DPM, PhD[3] | Gu Eon Kang PhD[4] | Peter A. Crisologo DPM[1] | Edgar J. Peters MD, PhD[5,6] | Lee C. Rogers DPM[7]

[1]Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, Texas, USA
[2]Department of Plastic Surgery MedStar Hospital System, Washington, DC, USA
[3]Infectious Diseases and Microbiology, School of Medicine, Western Sydney University, Sydney, New South Wales, Australia
[4]Department of Bioengineering, University of Texas at Dallas, Richardson, Texas, USA
[5]Department of Internal Medicine, Section of Infectious Diseases, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
[6]Amsterdam Institute for Infection and Immunity and Amsterdam Movement Sciences, Amsterdam, The Netherlands
[7]Department of Orthopaedic Surgery, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

Correspondence
Lawrence A. Lavery, Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA.
Email: larry.lavery@utsouthwestern.edu

BACKGROUND

ally, it is estimated that at least 536.6 million people are diag- d with diabetes globally, and it is projected that by 2045, the nt of people with diabetes will increase by 49.6% to a total of million individuals.[1] Diabetic foot ulcers (DFUs) are a growing problem. DFUs are a leading cause of infection, amputation, spitalisation in patients with diabetes mellitus.

delines for the treatment of DFUs were published by the Healing Society (WHS) in 2006 and 2016. However, in ew years new evidence has emerged that has improved our ding of previous recommendations. The objectives of the guidelines are to systematically evaluate the medical litera- t clinicians in making health care decisions, identify areas dditional research, and to clarify controversial diagnosis nt strategies. An advisory panel comprised of academi- ns, and researchers was chosen to update the 2016

HODS

, we published guidelines to improve the informa- with our goal to improve patient care. Even in the ality human data, the WHS developed guidelines proach to evidence citations and past approaches to evidence-based guidelines. There is a growing number of randomised clinical trials (RCTs), meta-analysis, and society directed practice guidelines that evaluate diagnoses, treatments, and prevention strategies for patients with DFUs. There is better evidence to support recommendations. The strength of evidence supporting a guideline is listed as Level I, Level II, or Level III.

The strength of evidence used in the previous guidelines has been retained:

Level I: Meta-analysis or at least two RCTs supporting the intervention of the guideline. Another route would be multiple laboratory or animal experiments with at least two clinical series supporting the laboratory results.
Level II: Less than Level I, but at least one RCT and at least two significant clinical series or expert opinion papers with literature reviews supporting the intervention. Experimental evidence that is quite convincing, but not yet supported by adequate human experience.
Level III: Suggestive data of proof of principle, but lacking sufficient data such as meta-analysis, RCT, or multiple clinical series.

3 | DATA SOURCES AND SEARCHES

Since the 2006 and 2016 guidelines, we sought to capture the highest quality of literature available regarding DFU diagnosis using a key

JWC International Consensus Document

Implementing TIMERS: the race against hard-to-heal wounds

Inflammation/infection
Moisture
Edge
Regeneration
Social factors

Discussion Point Q4: Future Phases

Question	Panelists
Our project will be divided into phases, with the first phase establishing the fundamentals of SOC. ▪ What levels of detail should be included in the next phase of the project? (e.g. offloading- what type? Frequency of debridement?)	C. Chang R. Snyder Y. Arnold D. Kommala

Discussion Point Q5: Future Phases

Question	Panelists
▪ We are planning on using an eDelphi method to complete consensus on the first phase of this project. Do you agree with this method or are there better alternatives? ▪ Do you anticipate us facing any obstacles using the eDelphi method?	J. Lantis T. Jacobson D. Kommala

Key Takeaways

- In clinical trials, standardization reduces bias, ensures validity, and allows for generalization to a larger real-world population.
- A unified consensus on what constitutes SOC is important and necessary for clinical research (including RCTs and RWE) and clinical practice.
- Results from this project will be utilized and adopted for clinical research trials, with future plans to expand to clinical practice. Initial phases will consist of establishing a minimal set of treatment standards, and future phases will establish specifics to the set of treatment standards.
- Focus is to improve and refine future clinical trial design- Not to invalidate or denounce current published RCTs

Driving Innovation in Wound Care Summit

SAWC Spring WHS | WCCC Wound Care Collaborative Community | WOUNDS A Compendium of Clinical Research and Practice

Q&A and Closing remarks

Participate n the Audience Q&A by scanning the QR Code below:

https://meet.ps/WCCC

Driving Innovation in Wound Care Summit

SAWC Spring WHS | WCCC Wound Care Collaborative Community | WOUNDS A Compendium of Clinical Research and Practice

Join us:

www.woundcarecc.org

WCCC WOUND CARE COLLABORATIVE COMMUNITY

Invitation-Only Reception for Panelists and Sponsors

Crystal Ballroom DEF

5:00PM