Voice of the Patients Their Role in Defining Outcomes

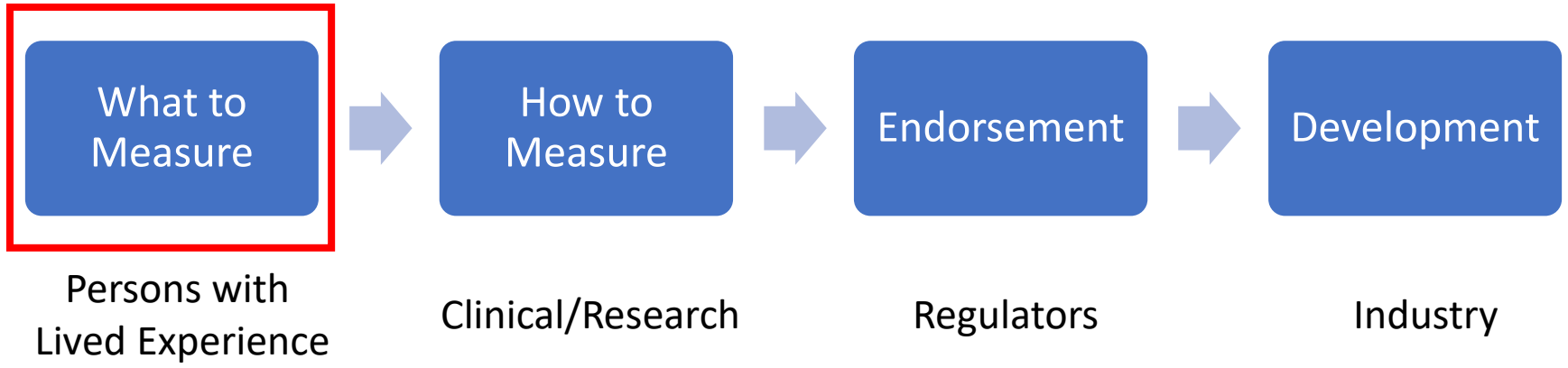
SCOPE 14th June 2022

Linda Jones & Jane Hsieh
Co-Chairs SCOPE

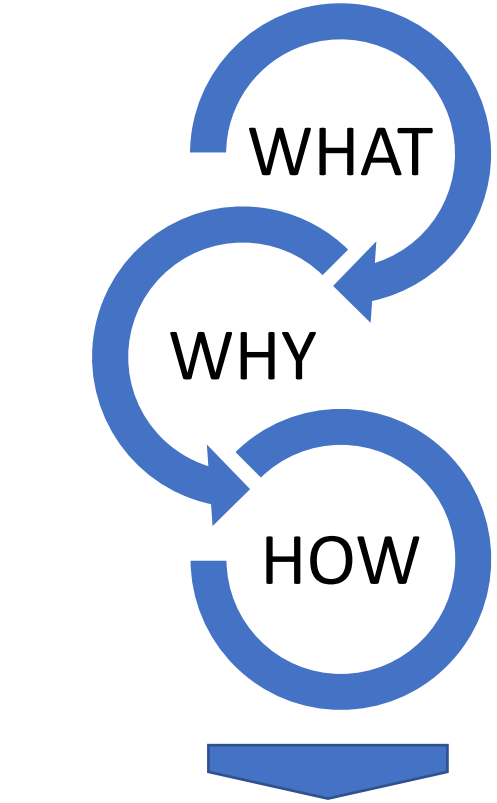
Spinal Cord Injury Community Opportunity, Need and Goal

Our Objective

Gain regulatory authority and other stakeholder acceptance on key scales, measures and end points (focus on primary) to clinically assess treatments aimed at providing functional improvement in persons living with SCI



The Value of PFDD for the SCI Research Community



is Patient Focused Drug Development?

Jonathan Stokes
Senior Director Patient-Centered Outcomes Research, AbbVie

is Patient Focused Drug Development so Important?

Jane Hsieh
SCOPE Co-Chair

Megan Moynahan
Executive Director, Institute for Functional Restoration, Case Western Reserve University

does Patient Focused Drug Development work?

Brian M. Culley
Chief Executive Officer
Lineage Cell Therapeutics

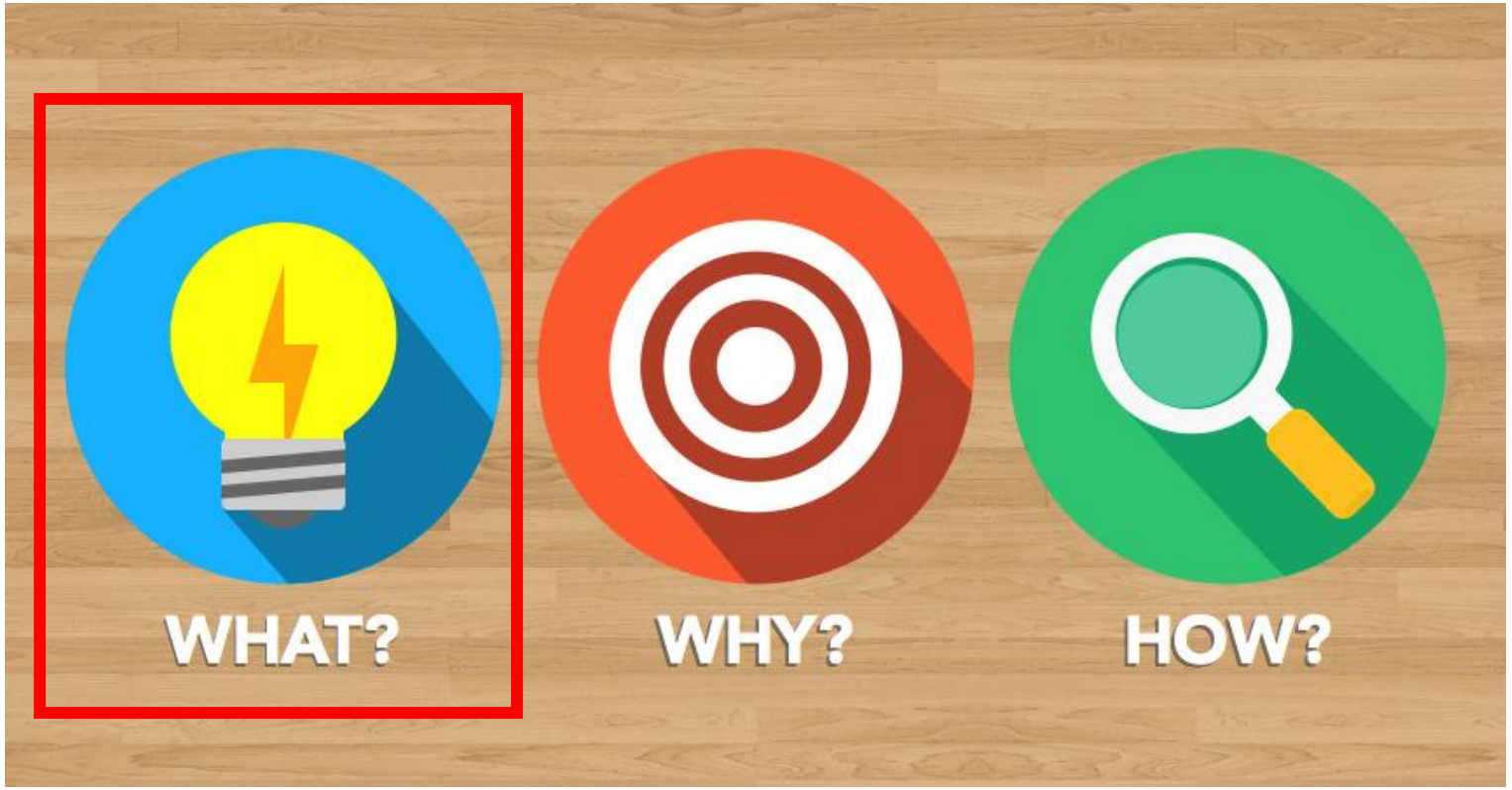
for the SCI Community?

Linda Jones
SCOPE Co-Chair

Jerod Neider

WHAT
is Patient Focused Drug Development?

Jonathan Stokes
Senior Director Patient-Centered Outcomes Research,
AbbVie

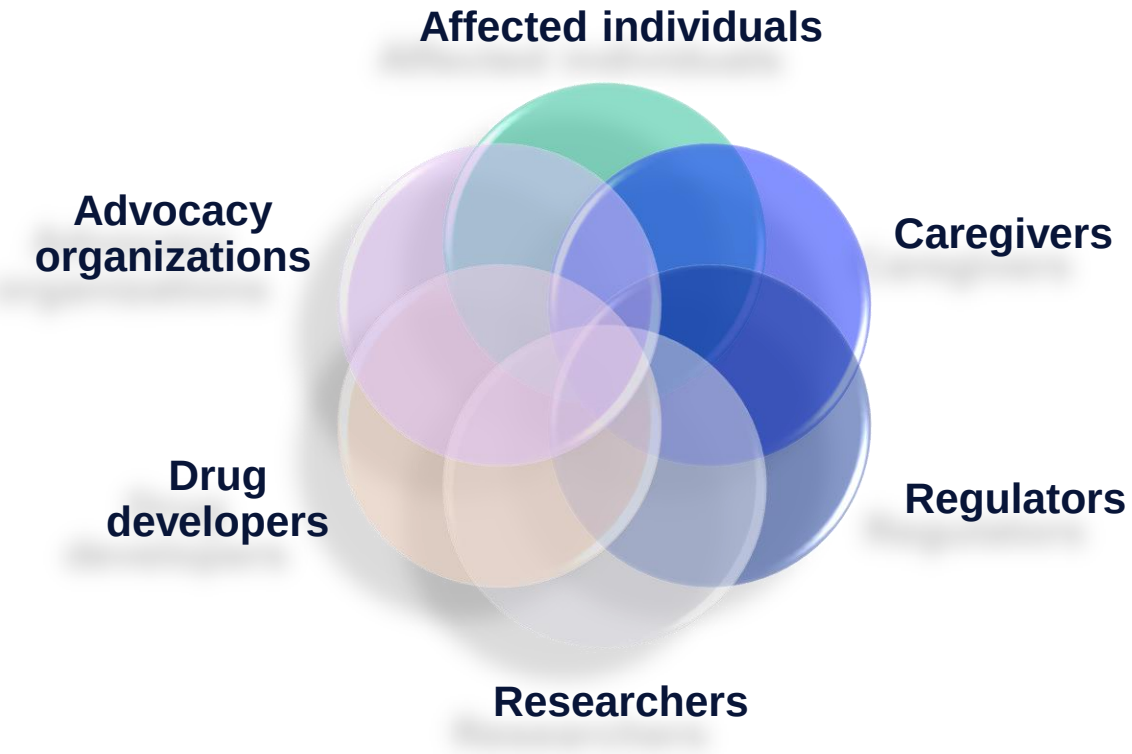


Patient Focused Drug Development (PFDD)

Patient-focused drug development (PFDD) **is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation.**

As experts in what it is like to live with their condition, patients are uniquely positioned to inform the understanding of the therapeutic context for drug development and evaluation.

Multi-stakeholder engagement and alignment



Patient Experience Data (PED)

What are Patient Experience Data (PED)*?

Data that are **collected by any persons** and are intended to provide information about **patients' experiences with a disease or condition**

Includes the experiences, perspectives, needs and priorities of patients related to (but not limited to)

1. Symptoms of their condition and its natural history	2. Input on which outcomes are important to them
3. Experience with treatments	4. Input on which outcomes are important to them
5. Patient preferences for outcomes and treatments	6. Relative importance of any issue as defined by patients

Value of PED and Clinical Outcomes Assessments (COAs)

Regulators are frequently requiring evidence of treatment efficacy from the patient's perspective

Patients, providers and payers are increasingly seeking patient-relevant endpoints and evidence when making medical care and reimbursement decisions

By generating such evidence, the true benefit of new therapies can be demonstrated to the ultimate consumer, the patient

Source: https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development

* Defined in Title III, section 3001 of the 21st Century Cures Act, as amended by section 605 of the FDA Reauthorization Act of 2017 (FDARA)1

PFDD Meetings

FDA-led Patient-Focused Drug Development (PFDD) Public Meetings

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People living with a condition are uniquely positioned to inform the understanding of the therapeutic context for drug development and evaluation. In 2012, the U.S. Food and Drug Administration (FDA) established the Patient-Focused Drug Development (PFDD) initiative to more systematically obtain the patient perspective on specific diseases and their currently available treatments. PFDD meetings are unique among FDA public meetings, with a format designed to engage patients and elicit their perspectives on two topic areas: (1) the most significant symptoms of their condition and the impact of the condition on daily life; and, (2) their current approaches to treatment.

- **Premise:** Patients are uniquely positioned to inform FDA understanding of the clinical context for drug review and regulatory decision making
- **Design:** **Public meetings**, each on a specific disease/condition, to systematically obtain patients' perspectives on severity of a condition, its impact on daily life, and their assessments of available treatment options
- **Potential Outcomes**: Help FDA, drug developers and others understand the patient experience & can inform:
  - **Clinical trial endpoints and relevant COA-related concepts to assess**
  - What patients consider **unmet needs for therapies** and what **risks they would potentially be willing to tolerate** with a therapy
  - What patients consider a **meaningful treatment benefit**, etc.

- Alopecia Areata
- Alpha-1 Antitrypsin
- Autism
- Breast Cancer
- Chagas Disease
- Chronic Fatigue Syndrome/Myalgic Encephalomyelitis
- Chronic Pain
- Female Sexual Dysfunction
- Fibromyalgia
- Functional Gastrointestinal Disorders
- Hemophilia A, B, and Other Heritable Bleeding Disorders
- Hereditary Angioedema
- Human Immunodeficiency Virus (HIV)
- Huntington's disease
- Idiopathic Pulmonary Fibrosis
- Inborn Errors of Metabolism
- Lung Cancer
- Narcolepsy
- Neuropathic Pain Associated with Peripheral Neuropathy
- Non-tuberculous Mycobacterial Lung Infections
- Opioid Use Disorder
- Patients Who Have Received an Organ Transplant
- Parkinson's Disease
- Psoriasis
- Pulmonary Arterial Hypertension
- Sarcopenia
- Sickle Cell Disease
- Stimulant Use Disorder
- Systemic Sclerosis
- Vitiligo

Note: An increasing number of PFDD Meetings currently externally-led using FDA meetings as a model

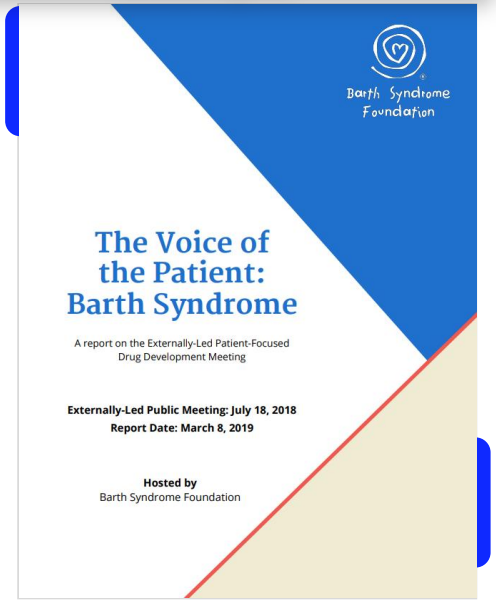
Externally-led PFDD Meetings

Key Considerations

- **Request Process:** Letter of Intent (LOI)
  - Importance of the meeting in the context of the disease
  - Details regarding the meeting plan
  - LOIs reviewed quarterly; expect meeting to occur ~ 1 year from request
- **Meeting**:
  - 1-day meeting, with FDA attendance (in-person depending)
  - Cost is variable and incurred by organizer
  - Speakers include: affected individuals, caregivers, clinicians, researchers
  - In-meeting exercises to collect real-time data characterizing lived experience
- **Outcome:** Voice of the Patient (VoP) report
  - Documents output of the meeting and understanding of the condition
  - Drafted by FDA stakeholders have opportunity to review / revise
  - Useful as input into evidentiary basis for concepts to be evaluated in trials

https://www.fda.gov/industry/prescription-drug-user-fee-amendments/externally-led-patient-focused-drug-development-meetings

Example



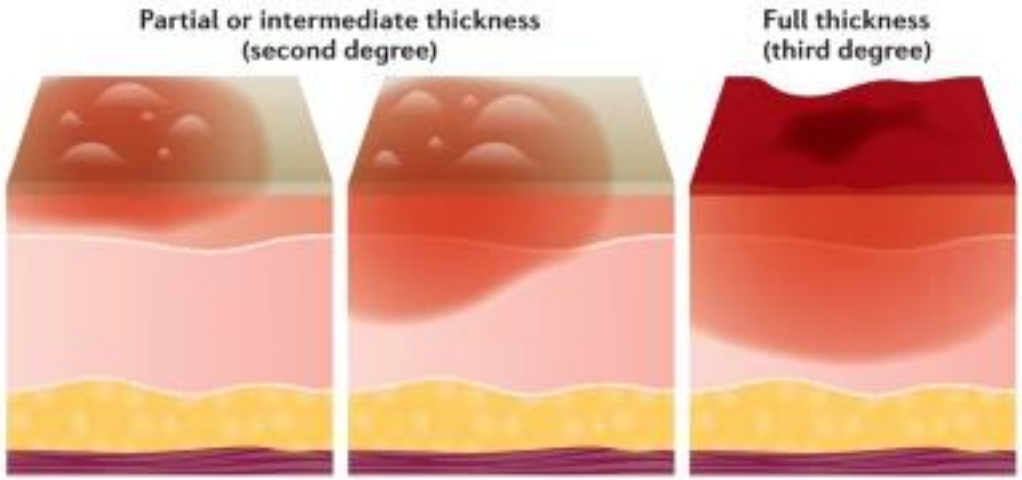
WHY
is Patient Focused Drug Development so Important?

Jane Hsieh
Co-Chairs SCOPE

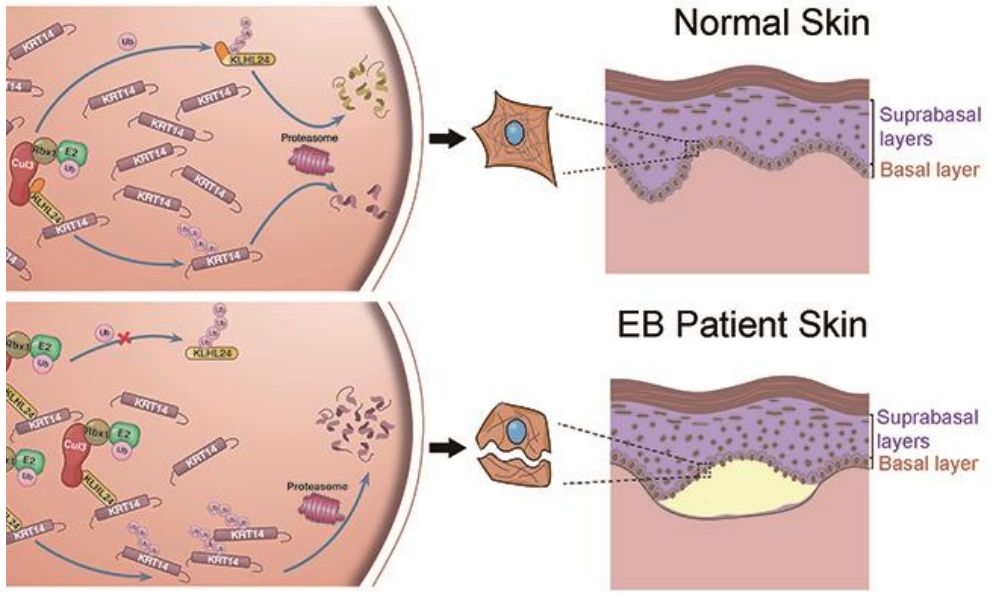
Megan Moynahan
Executive Director, Institute for Functional Restoration,
Case Western Reserve University

PFDD – Why?

Pre 2018: Epiderolysis Bullosa (EB) trials were directed by FDA to follow outcomes per FDA burn wound guidelines, despite different mechanism of EB wound injury and healing.



Burn wounds characterized by cause of burn and by depth



EB is a genetic skin fragility disorder due to defective structural proteins in the skin. Wounds are caused by trivial trauma and friction. EB wounds rarely heal significantly.

PFDD – Why?

2018 04 06 EL-PFDD meeting for Epidermolysis Bullosa).

- Complete wound healing not expected for EB due to ever-present genetic defect in skin cells.
- Yet, FDA required EB trials to yield "clinically meaningful" treatment effect based on FDA burn wound guidelines.
- EB PFDD highlighted that even slight shrinkage of wounds would prevent pain even if 100% healing was not achievable.
- As a result of the 2018 EB PFDD, FDA immediately released a disease specific guidance (2019) that allowed for disease specific endpoints (incremental healing and analgesic effects).

Guidance for Industry

Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment

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

debra
Care, Research, Cure

Epidermolysis Bullosa: Developing Drugs for Treatment of Cutaneous Manifestations

Guidance for Industry

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)

June 2019
Clinical/Medical

* Dystrophic Epiderolysis Bullosa Research Association of America

Other examples of demonstrated impact of PFDD

Oxalosis & Hyperoxaluria Foundation

STEPPING STONES TO A CURE

EL-PFDD meeting for primary hyperoxaluria was held virtually on 2020 10 05 and resulted in:

- Orphan drug designation for Oxlumo
- Breakthrough therapy designation granted for Oxlumo
- Alnylam was granted pediatric disease priority review

The 2021 11 23 approval of Oxlumo represents the input from patients, treating physicians, experts and sponsors at a patient-focused drug development meeting and through other collaborative efforts.

https://www.thefdalawblog.com/2020/12/fda-credits-recent-drug-approval-to-patient-community-engagement-we-applaud-the-agency-for-the-recognition-and-its-legacy-of-pfdd/

Other examples of demonstrated impact of PFDD

2017 04 18 EL-PFDD meeting for Spinal Muscular Atrophy (sponsored by CureSMA) identified the risks that this patient population would accept in exchange for identified treatment benefits and led to the approval of

- first ever-systemic gene therapy (Luxturna (2017 12) and
- Zolgensma (2019 05) by AveXis) for SMA.

https://www.thefdalawblog.com/2019/05/a-historic-day-in-drug-development-avexis-gene-therapy-for-sma-approved/

Other examples of demonstrated impact of PFDD

2015 11 16 EL-PFDD meeting for amyloidosis (sponsored by Amyloidosis Research Consortium) impacted

- 2018 approval of Onpattro (Alnylam Pharmaceuticals),
- Tegsedi (Ionis/Akcea Therapeutics), and
- Vyndaqel (Pfizer).

https://amyloidosis.org/fda-approves-two-treatments-for-hattr-amyloidosis-in-2018/

FDA's Center for Devices Approach

- Called "Patient Preferences" <– search term for program, guidance documents.
- For devices, the approach is to have companies perform well designed surveys to collect evidence that FDA will need to make its regulatory decision.
  - Require an actual application with risk and benefit estimates; patient population; and effectiveness claims.
- FDA works with companies to make sure the conduct of the survey will be rigorous and unbiased.
  - Companies engage with FDA through its existing presubmission process.
  - Similar to PFDD: attention to survey design, study rigor, addressing sources of bias.

FDA Guidance (2016)

Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and *De Novo* Requests, and Inclusion in Decision Summaries and Device Labeling

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Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

Document issued on August 24, 2016.
This document will be in effect as of October 23, 2016.

The draft of this document was issued on May 18, 2015.

For questions about this document regarding CDRH-regulated devices, contact the Office of the Center Director (CDRH) at 301-796-5900 or Anindita Saha at 301-796-2537 (Anindita.Saha@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.

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Publication (2016)

A Framework for Incorporating Patient Preferences Regarding Benefits and Risks into Regulatory Assessment of Medical Technologies.

Martin Ho, et al., International Society for Pharmacoeconomics and Outcomes Research (ISPOR). 2016:746-750.

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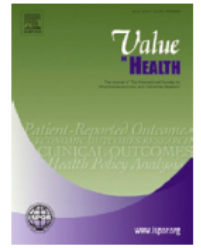


A Framework for Incorporating Patient Preferences Regarding Benefits and Risks into Regulatory Assessment of Medical Technologies

Martin Ho, MSc[1], Anindita Saha, BSE[1], K. Kimberly McCleary, BA[2], Bennett Levitan, MD, PhD[3], Stephanie Christopher, MA[4,], Kristen Zandlo, MBA[4], R. Scott Braithwaite, MD, MSc, FACP[5], A. Brett Hauber, PhD[6], on behalf of the Medical Device Innovation Consortium's Patient Centered Benefit-Risk Steering Committee*

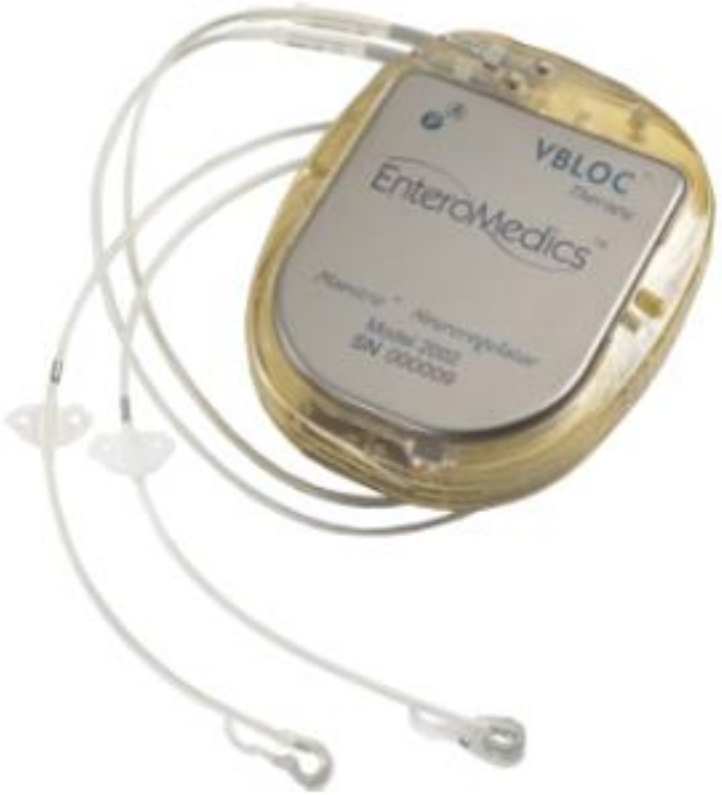
[1]*Center for Devices and Radiological Health, Food and Drug Administration, Silver Spring, MD, USA;* [2]*FasterCures, Milken Institute, Washington, DC, USA;* [3]*Janssen Research and Development, LLC, Titusville, NJ, USA;* [4]*Medical Device Innovation Consortium, Minneapolis, MN, USA;* [5]*Department of Population Health, NYU School of Medicine, New York, NY, USA;* [6]*RTI Health Solutions, Research Triangle Park, NC, USA*

ABSTRACT

Background: In response to 2012 guidance in which the US Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) stated the importance of patient-centric measures in regulatory benefit-risk assessments, the Medical Device Innovation Consortium (MDIC) initiated a project. The project was used to develop a framework to help the Food and Drug Administration (FDA) and industry sponsors understand how patient preferences regarding benefit and risk might be integrated into the review of innovative medical devices. **Methods:** A public-private partnership of experts from medical device industry, government, academia and non-profits collaborated on development of the MDIC patient centered benefit-risk framework. **Results:** The MDIC Framework examines what patient preference information is and the potential use and value of patient preference information in the regulatory process and across the product development life cycle. The MDIC Framework also includes a catalog of patient preference assessment methods and an agenda for future research to advance the field. **Conclusions:** This article discusses key concepts in patient preference assessment of particular importance for regulators and researchers that are addressed in the MDIC Framework for patient centered benefit-risk assessment as well as the unique public-private collaboration that led its development.

Keywords: patient-derived preferences, preference-based measures, preferences, regulatory.

Sentinel Case Example: Vagal Nerve Block for Obesity



<u>VBLOC Maestro® ReCharge – *FDA Approved.*</u>
Study did not meet its original endpoint.
<u>FDA sponsored</u> a survey of patients that established patients' willingness to accept risks associate with the clinical outcomes observed in the study.

Case Example 2: Home Dialysis

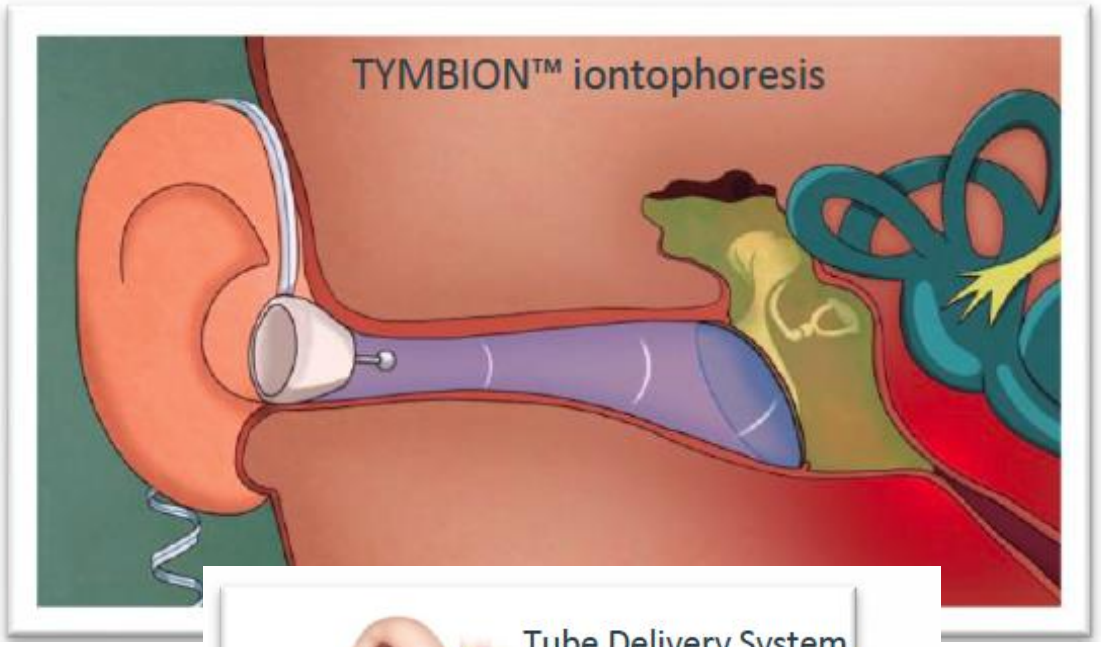
<u>NxStage Home Dialysis – *FDA Approved*</u>

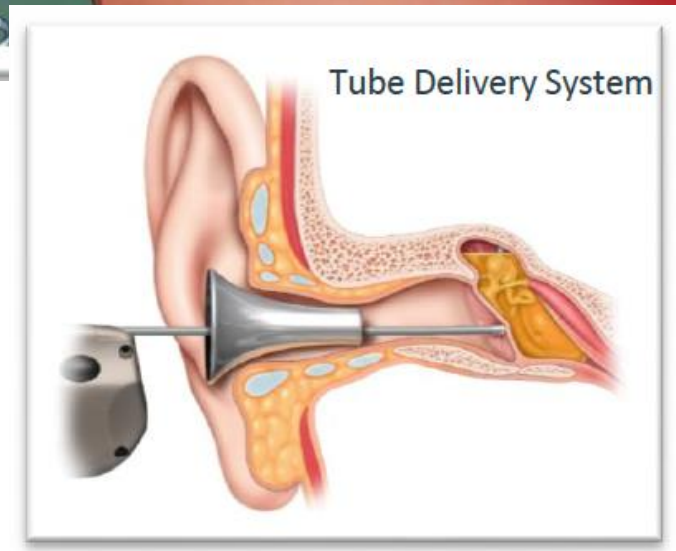
Patient survey quantified the level of risk that patients would accept in exchange for doing hemodialysis in the home alone.

Case Example 3: Pediatric insulin pump

<u>Animas VIBE– *FDA Approved.*</u>
Continuous glucose monitor with insulin pump for pediatric use. Family and caregiver surveys, usability and human-factors testing, and risk analysis conducted to support approval.

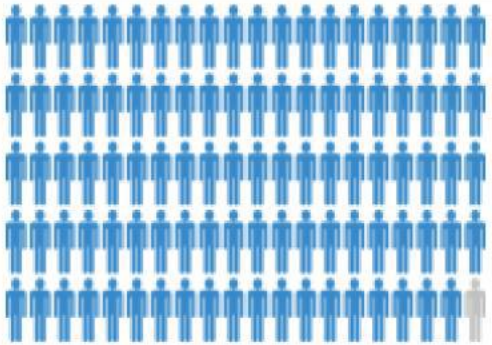
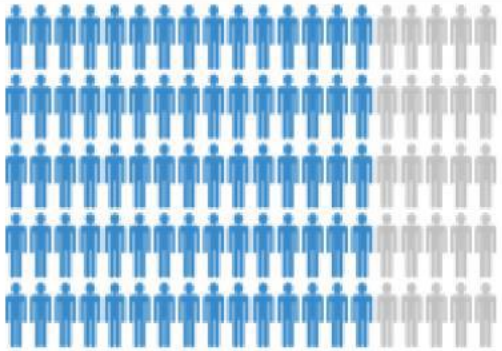
Case Example 4: Outpatient Ear Tube System





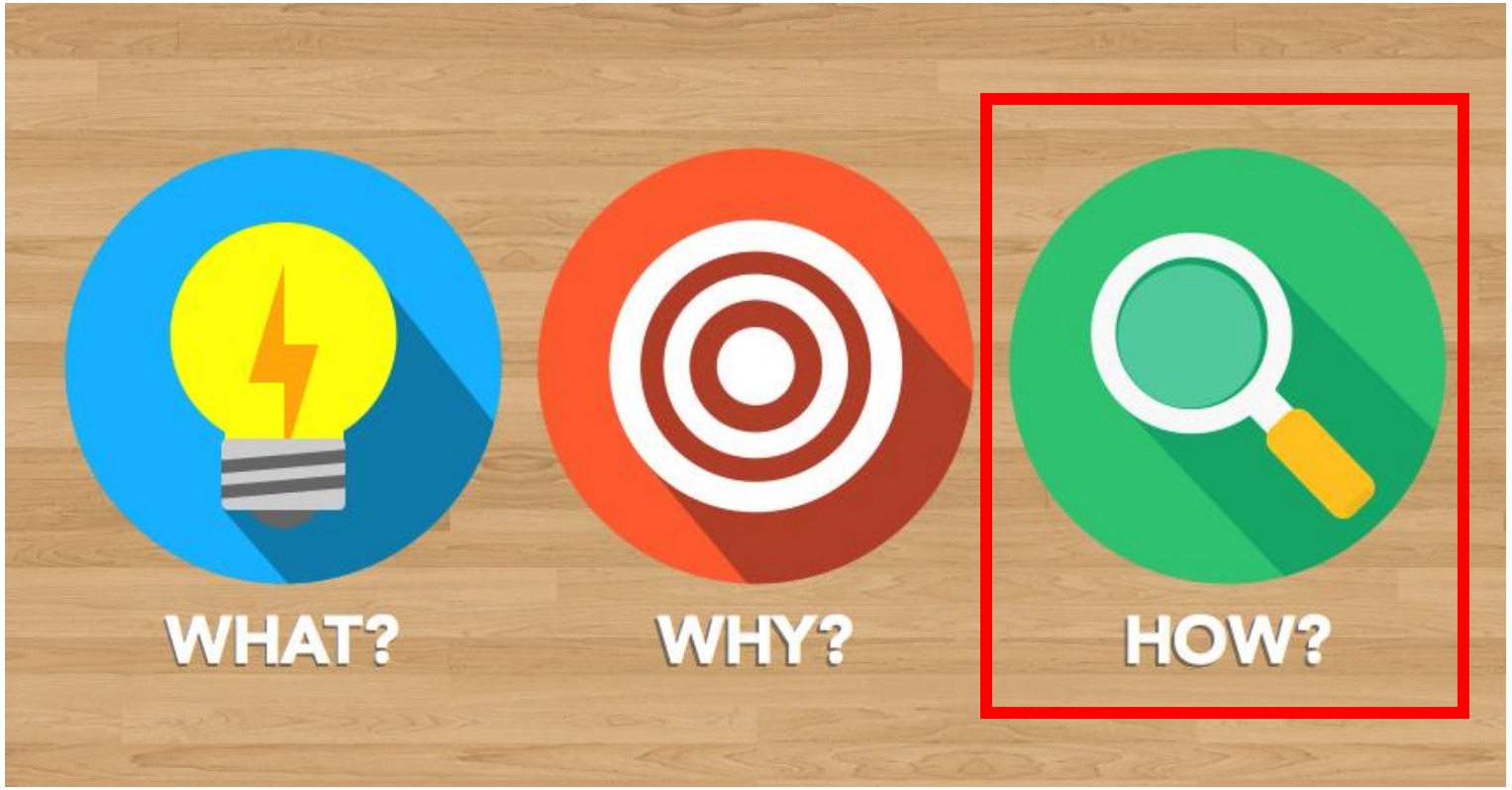
The product can be inserted in an outpatient procedure in the doctor's office rather than in the operating room.

Example of Forced Choice Survey Question

	Operating Room	Doctor's Office
Chance of success	 More than 99 out of 100 children (more than 99%) will leave the operating room with ear tubes	 75 out of 100 children (75%) will leave the doctor's office with ear tubes 25 out of 100 children (25%) will not be able to get ear tubes inserted in the doctor's office and will need to go to the operating room to get the tubes inserted on a different day
Which location would you choose?	☐	☐

HOW
does Patient Focused Drug Development work?

Brian M. Culley
Chief Executive Officer
Lineage Cell Therapeutics



A Collaborative Approach to a Successful PFDD

1. Requires genuine cooperation among patients, caregivers, academia, and industry stakeholders

2. Alignment on content/goals/message - preparation
   - What are (and what are *not*) the key messages?
   - How obvious are the gaps?
   - How much consensus is there on the issues?

3. Use of the PFDD as an opportunity to learn
   - Understanding what is important to patients and caregivers (ex: tradeoffs)
   - Understanding the limits and process of developing an experimental therapy

4. Leadership by an external third party and endorsed by multiple stakeholders
   - Supports authenticity and broad buy-in
   - Drives neutrality and minimizes conflict (patient-focused)

PFDD Success Story – Sickle Cell Disease (SCD)

Background (2014)

- For decades, SCD had one approved agent – a repurposed cancer drug
- 30% of SCD clinical trials failed to complete enrollment
- A focus on pain as the primary symptom led to excessive corporate and regulator attention on: pain medication options, dosing schedules, pain scores, opioid stigma, etc.
- A 30X prevalence-weighted imbalance in funding for SCD versus CF

PFDD Success Story – Sickle Cell Disease (SCD)

Specific Steps

- High industry collaboration and participation among “competing” sponsors
- Involved with selection and organization of patients
  - Identified and engaged with potential spokespersons
  - Assisted with obstacles to patient participation
  - Aligned on key messages and worked to help patients prepare
  - Delivered key messages repeatedly and in a thoughtful, authentic, and credible way
    - Not the time to be a hero
- Invited additional, targeted FDA staff to participate
- Influenced content at the meeting through focus on key topics
  - Maintained contact with key stakeholders before and after

PFDD Success Story – Sickle Cell Disease (SCD)

Results

- **The Voice of the Patient in Sickle Cell Disease (Feb 2014)**
  https://www.fda.gov/industry/prescription-drug-user-fee-amendments/public-meeting-sickle-cell-disease-patient-focused-drug-development

- Greater acceptance of alternate outcome measures: PROs, crisis rate, TCD/stroke, etc.

  - *Emmaus – L-glutamine (2017)*
    - *Reduction in frequency of crisis and days hospitalization due to acute chest syndrome*
  - *Novartis – Adakevo (2019)*
    - *Reduced frequency and duration of vaso-occlusive crises*
  - *Global Blood Therapeutics (2019) – Oxbryta*
    - *Percentage increase in hemoglobin, reduction in VOCs*

- New entrants into SCD product development (irony -> new enrollment issues!)

- In 5 years, from nothing to 3 SCD-specific FDA-approved agents (and a similar effort got SCD added to the PRV program!)

- Next up: a functional, lifetime cure (gene therapy)

The OPPORTUNITY

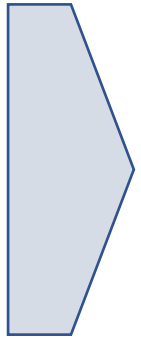
Linda Jones
SCOPE Co-Chair

Jerod Neider

Jerod Nieder

- My name is Jerod Nieder.
- I am a 39-year-old C5/6 Quadriplegic who currently resides in Louisville, KY.
- I am a full-time research participant for spinal cord injury starting my journey with small testosterone studies to being the first individual tested with transcutaneous stimulation and most recently being implanted with the epidural stimulator.
- I am a strong advocate for balancing social and mental well-being along with my passion for continued growth in physical health.
- I serve as a peer mentor for the Christopher & Dana Reeve Foundation and have a outreach blog to motivate those that may be in a similar situation to mine in addition to educating others about the day-to-day nuances of living life with a disability.

The CHALLENGE



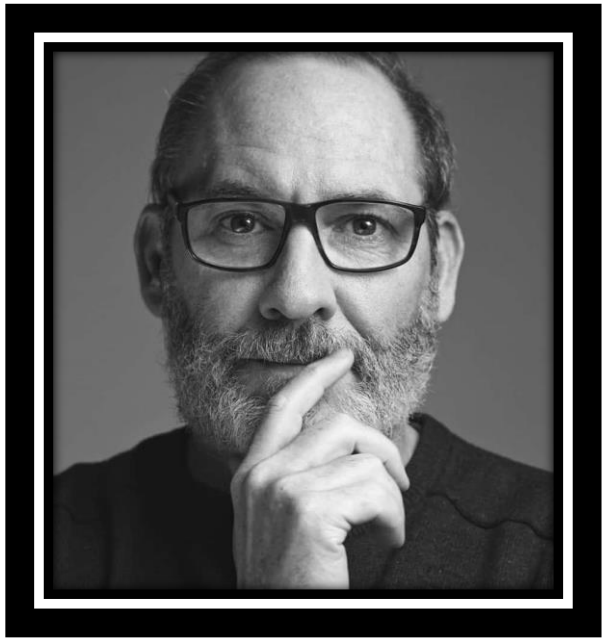
PRONEURON BIOTECHNOLOGIES

AIS impairment scale

Targeting Recovery: Priorities of the Spinal Cord-Injured Population

KIM D. ANDERSON

The OPPORTUNITY



PRONEURON BIOTECHNOLOGIES

AIS impairment scale

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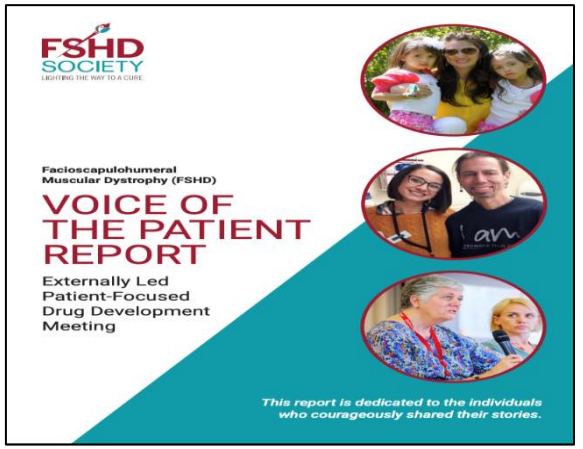
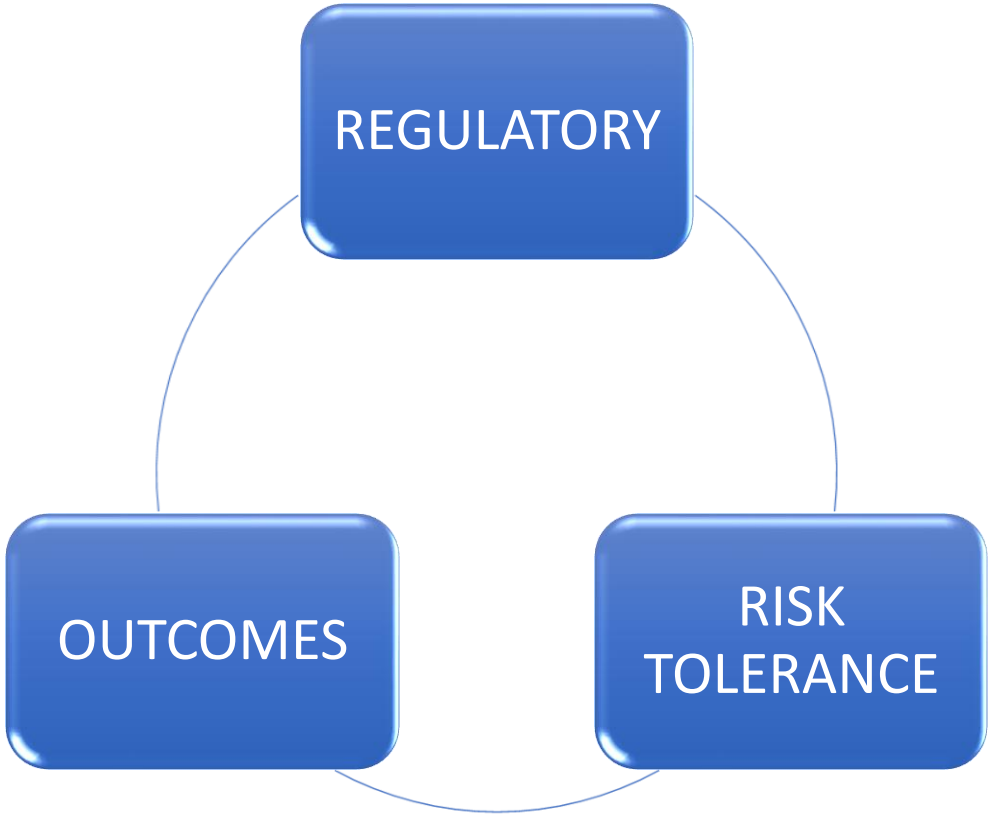
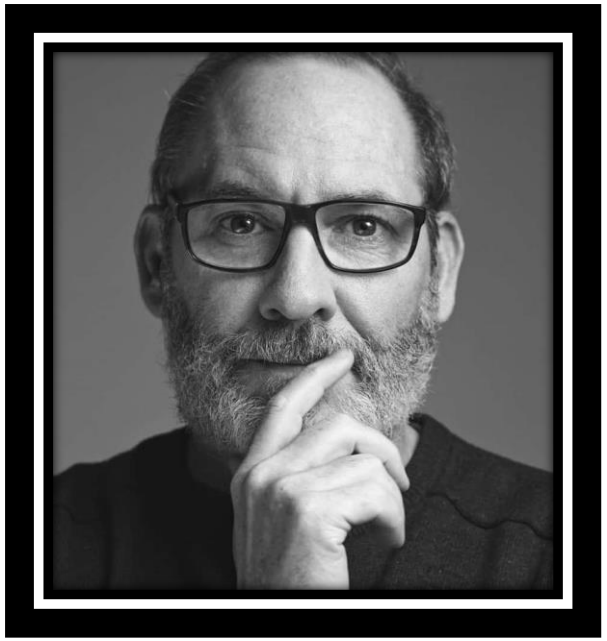


The OPPORTUNITY

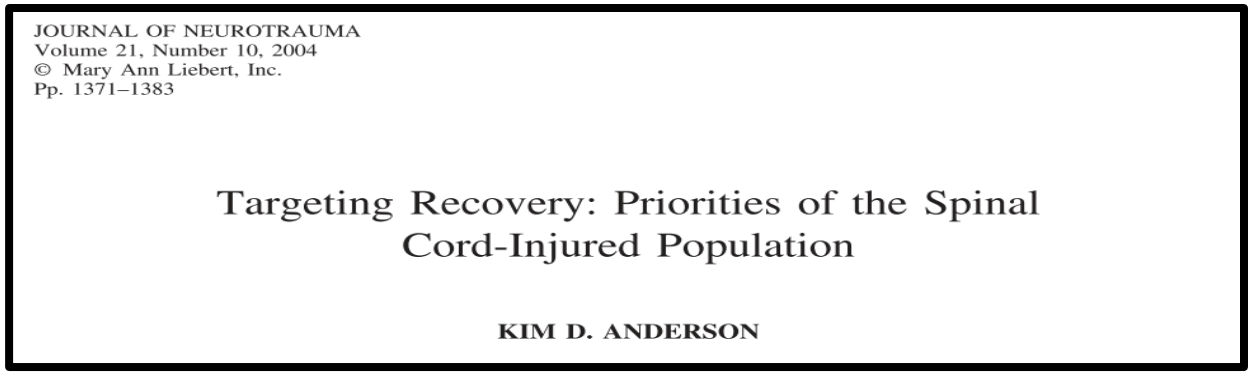




The OPPORTUNITY

OUTCOMES

Function **not** outcomes to assess function



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Pp. 1371–1383

Targeting Recovery: Priorities of the Spinal Cord-Injured Population

KIM D. ANDERSON

Impairment based measures

Neurological level of injury in complete SCI

Motor scores

Functional Outcomes

General

SCIM III

Neuromuscular Recovery Scale

Task Specific

GRASSP

CUE- T

10 Meter Walk Test

6 Minute Walk Test

SCI-Functional Ambulation Index

A Closing Thought- The Ideal Outcome……

Our Objective

Gain regulatory authority and other stakeholder acceptance on key concepts, measures, and endpoints to clinically assess treatments aimed at providing functional improvement in persons living with SCI

Desired Outcome

Define what is meaningful for the persons living with SCI (patient & care provider)

Desired Outcome

Validated and endorsed measures to construct endpoint(s) for functional improvement in SCI

Desired Outcome

FDA accepted endpoint(s) to measure functional improvement in SCI

Strategic Imperative 1

Identify and gain support and endorsement with optimal **stakeholder** set

Strategic Imperative 2

Secure input and **drive alignment** from stakeholder groups

Strategic Imperative 3

Secure **regulatory alignment** and **endorsement** of endpoint strategy

Thank You