Joint Approval Programmes For Innovative Devices Between Japan-USA

Harmonization By Doing (HBD) 2003-2024

Mitchell W. Krucoff, MD, FACC, FAHA, FSCAI

Professor, Medicine/Cardiology

Duke University Medical Center

Director, Cardiovascular Devices Unit

Founding Co-Chair, HBD Public Private Partnership

Duke Clinical Research Institute

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

HBD Constructs: 10 Year Perspective

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Global Cardiovascular Device Innovation: Japan-USA Synergies

– Harmonization by Doing (HBD) Program, a Consortium of Regulatory Agencies, Medical Device Industry, and Academic Institutions –

Takahiro Uchida, MD; Fumiaki Ikeno, MD; Koji Ikeda, PhD; Yuka Suzuki, PhD; Koji Todaka, MD; Hiroyoshi Yokoi, MD; Gary Thompson, BSc; Mitchel Krucoff, MD; Shigeru Saito, MD
on behalf of the Harmonization by Doing Program Working Group

Background: Global medical devices have become more popular, but investment money for medical device development is not easily available in the market. Worldwide health-care budget constraints mean that efficient medical device development has become essential. To achieve efficient development, globalization is a key to success. Spending large amounts of money in different regions for medical device development is no longer feasible.

Methods and Results: In order to streamline processes of global medical device development, an academic, governmental, and industrial consortium, called the Harmonization by Doing program, has been set up. The program has been operating between Japan and the USA since 2003. The program has 4 working groups: (1) Global Cardiovascular Device Trials; (2) Study on Post-Market Registry; (3) Clinical Trials; and (4) Infrastructure and Methodology Regulatory Convergence and Communication. Each working group has as its goals the achievement of speedy and efficient medical device development in Japan and the USA. The program has held multiple international meetings to deal with obstacles against efficient medical device development.

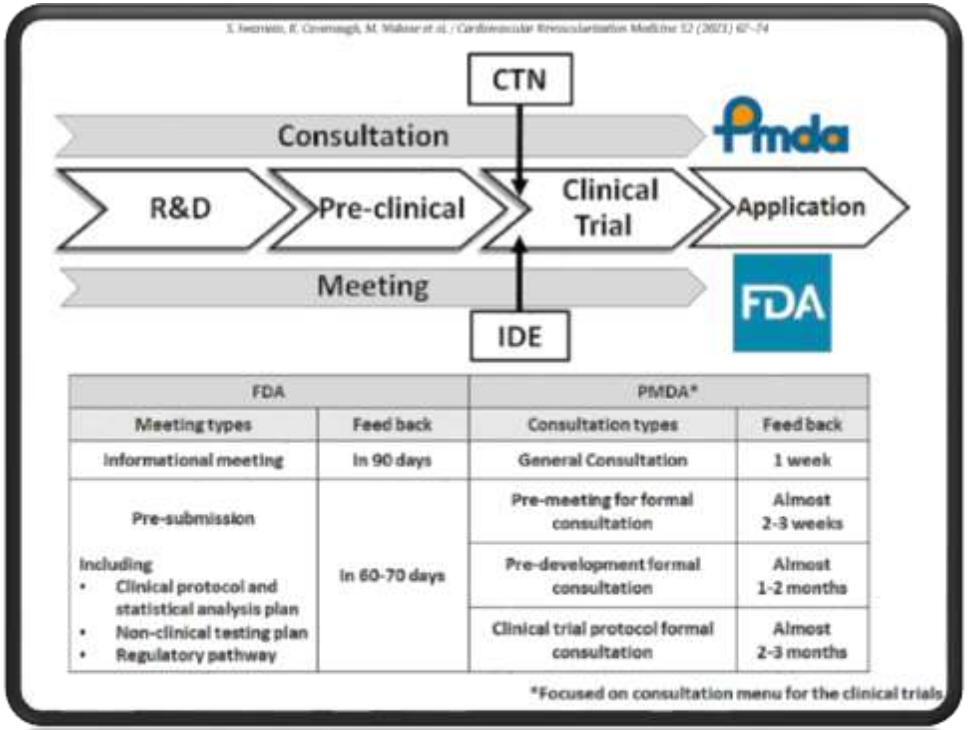
Uchida T et al, Circulation Journal 2013

2023: Key Considerations for Global Japan-USA Trials:
A 20 Year Legacy of Successful Predicates!

Clinical

Global Medical Device Clinical Trials Involving Both the United States and Japan: Key Considerations for Development, Regulatory Approval, and Conduct

Shin Iwamoto [a], Kenneth Cavanaugh [b], Misti Malone [b], Aaron Lattes [c], Robert Thatcher [d], Katherine Kumar [e], Steve Rowland [f], Neal Fearnot [g], Takahiro Uchida [h], Chie Iwaishi [i], Kazuhisa Senshu [j], Ryo Konishi [j], Koji Ikeda [k], Yuka Suzuki [l], Fumiaki Ikeno [m], Atsushi Tamura [n], Mami Ho [o], Moe Ohashi [o], Hiroshi Katayama [p], Mitchell W. Krucoff [q]



FDA		PMDA*	
Meeting types	Feed back	Consultation types	Feed back
Informational meeting	In 90 days	General Consultation	1 week
Pre-submission Including • Clinical protocol and statistical analysis plan • Non-clinical testing plan • Regulatory pathway	In 60-70 days	Pre-meeting for formal consultation	Almost 2-3 weeks
		Pre-development formal consultation	Almost 1-2 months
		Clinical trial protocol formal consultation	Almost 2-3 months

*Focused on consultation menu for the clinical trials

Iwamoto S, Cavanaugh K et al. Card Revasc Med 52(2023) p.67-74

HBD

Program History

Global Regulatory Harmonization

Duke-FDA Memo of Understanding
December 2003

FDA U.S. Food and Drug Administration

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

Department of Health and Human Services

FDA Home Page | CDRH Home Page | Search | A-Z Index

FDA > CDRH > International Issues > Japan - U.S. "Harmonization By Doing" HBD Pilot Program Initiative

Questions?

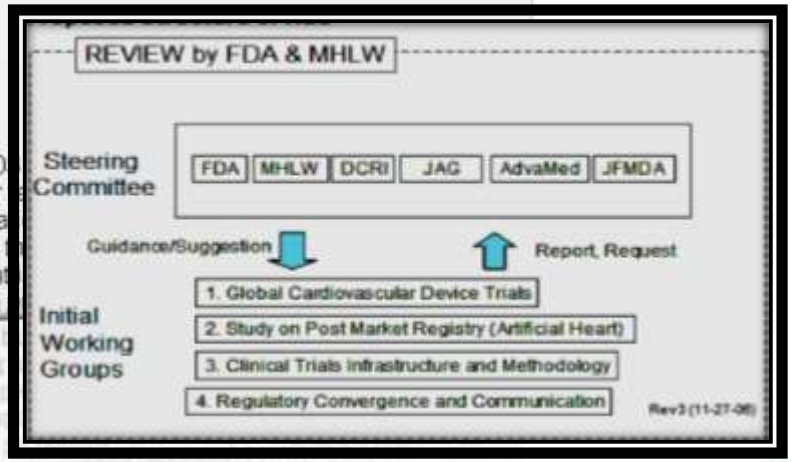
Japan - U.S. "Harmonization By Doing" HBD Pilot Program Initiative

"Harmonization by Doing," commonly known as HBD, is an international effort to develop global clinical trials and address regulatory barriers that may be impediments to timely device approvals. This process is a cooperative effort to move both Japan and the U.S. toward international regulatory harmonization. Participants in this process include:

- U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH),
- Japan 's Pharmaceutical and Food Safety Bureau (PFSB) of the Ministry of Health, Labour, and Welfare (MHLW) and its review agency, the Pharmaceutical and Medical Devices Agency (PMDA),
- Duke Clinical Research Institute (DCRI),
- Japanese academic community, and
- Japanese and U.S. medical device industry.

What is the HBD initiative?

The HBD initiative is a pilot project launched in December 200
and MHLW-PMDA premarket review of device cardiovascular
to harmonization, HBD will utilize parallel development, applica
device projects by FDA and MHLW-PMDA in conjunction with
eliminate redundancies, added costs, and time delays inherent
to create guidance and discuss policy but to develop common



http://www.fda.gov/cdrh/international.html

HBD Foundational Principles for Advancing Global CV Health

- ***HBD MISSION***: Facilitate better, safer CV devices reaching patients faster in the world's two biggest device markets
- ***Trans-Pacific METHODS***:
  - Inclusive pre-competitive collaboration: academics, regulators and industry
  - Aligning global principles of benefit/risk medical device evaluation
  - Identify barriers to implementation and promote novel solutions
- **HBD *SPIRIT:***
  - Unique culture: honest communication, good faith and trust
  - Creativity: working together far more productive than working in silos (including during a pandemic!)
- ***PRAGMATISM "101":***
  - Small steps to big changes
  - "DOING": proof of concept (POC) demonstration projects

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  - "DOING": proof of concept (POC) demonstration projects

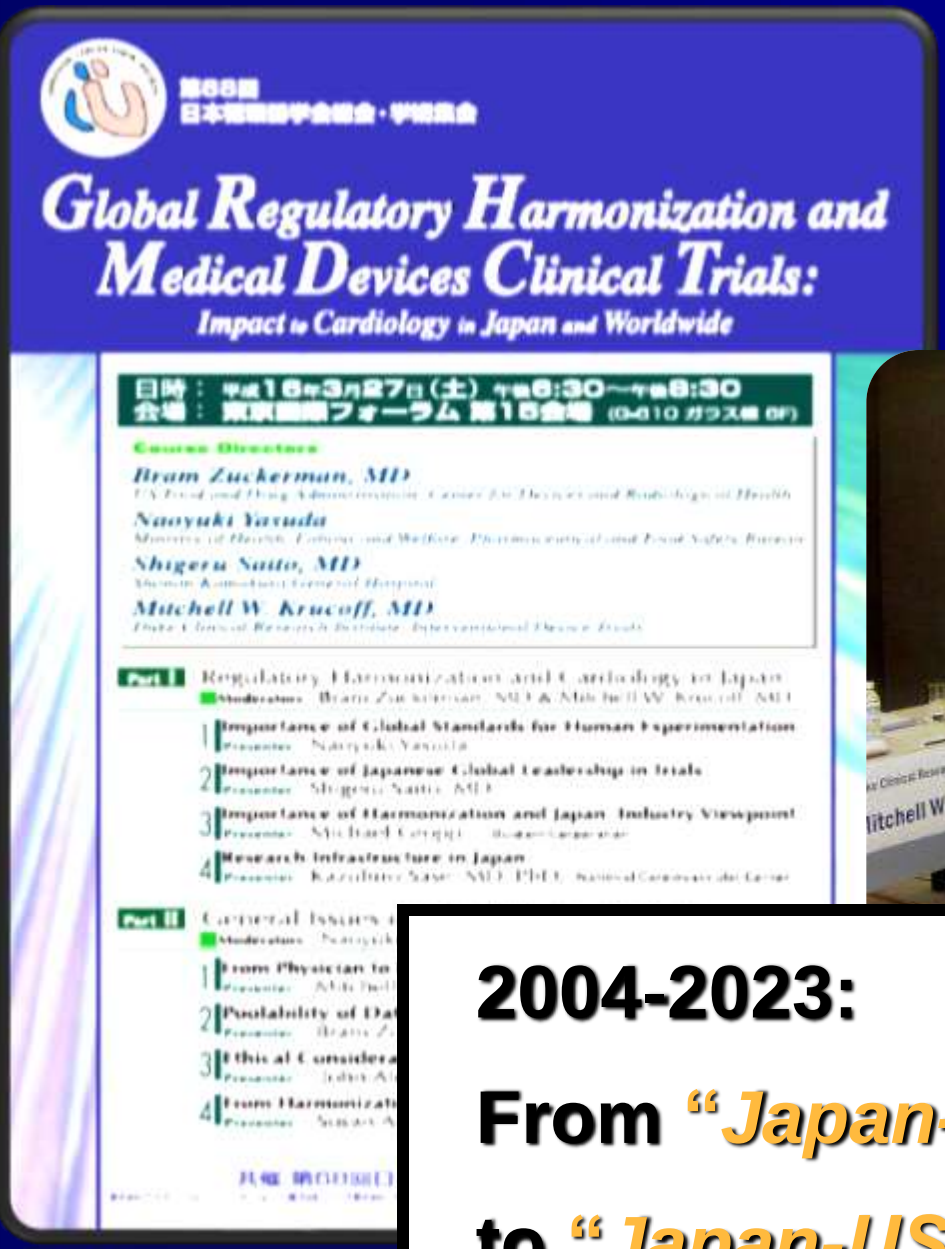
“HBD”

Harmonization By Dialogue

Thinktank Programs
Educational Symposia

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Japan Circulatory Society
March 2004
Tokyo, Japan



2004-2023:

From *"Japan-USA Barriers"*

to *"Japan-USA Synergies"*

, CIT, PS, ned, CR

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

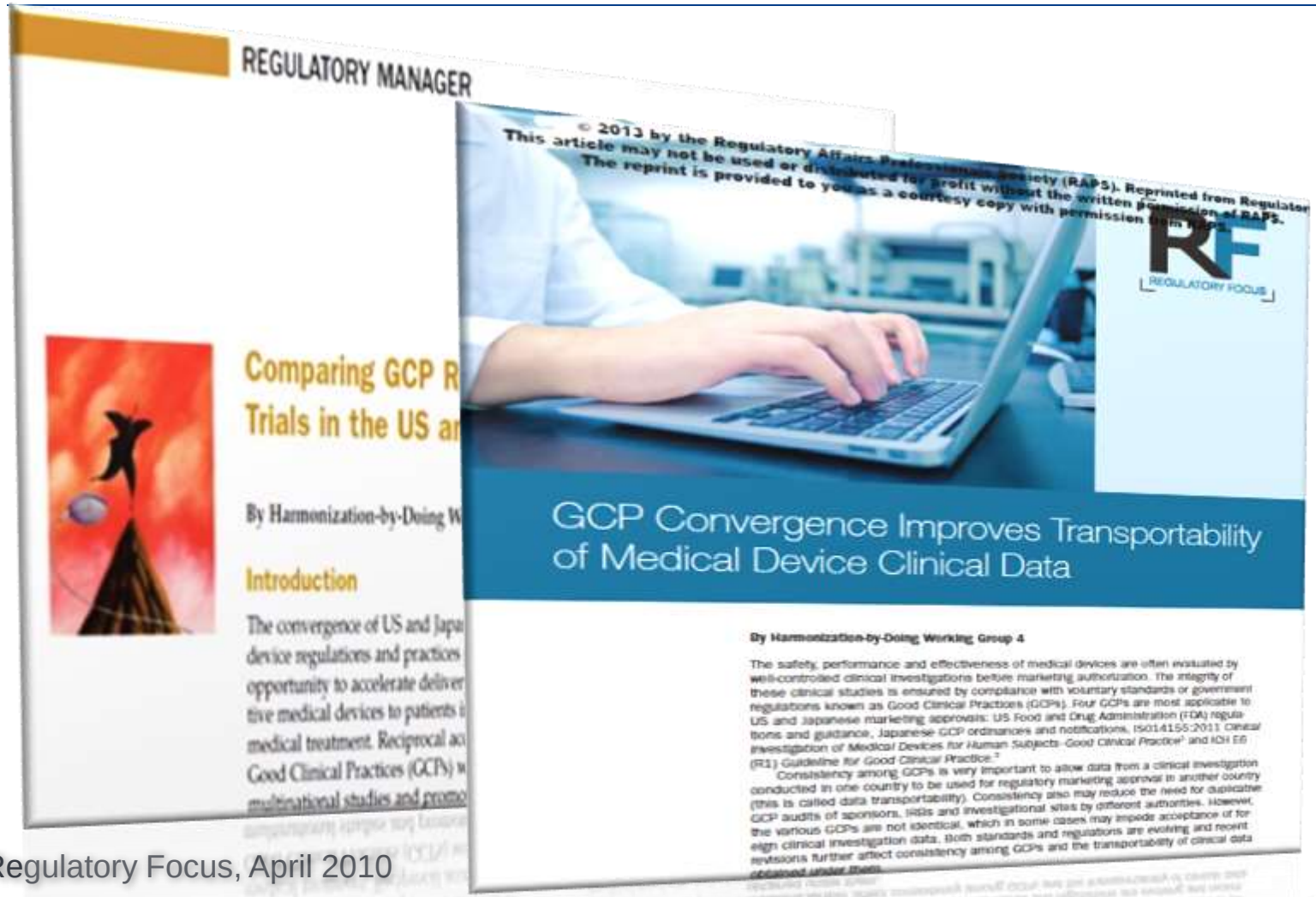
“HBD”

Harmonization By Documentation

Good Clinical Practice Standards

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Regulatory Convergence:
Ethics, Methods and Science of Human Studies



Regulatory Focus, April 2010

Regulatory Focus, January 2013

“HBD”

Harmonization By Data

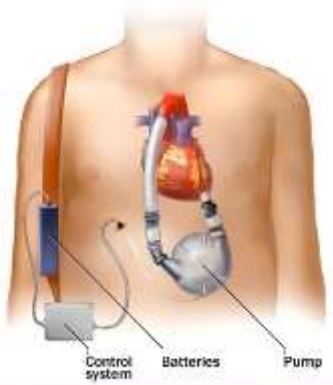
Real World Evidence POCs:

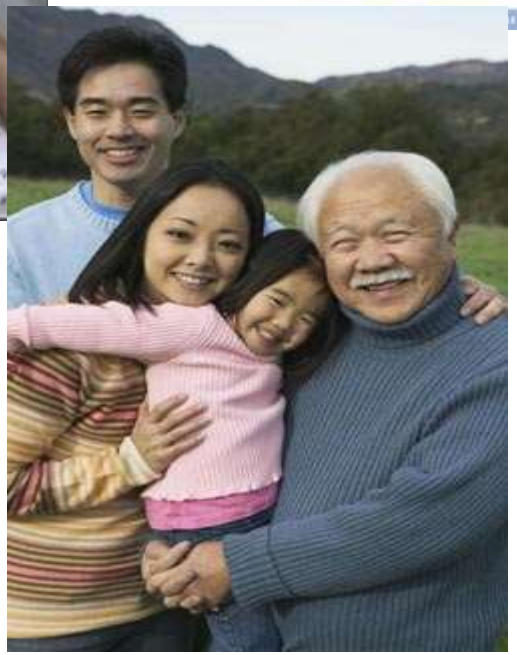
RWE Infrastructure (Device Registries)

Consistent & Re-usable Data Structure

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Linking Post-Market Surveillance: LVADS





JACC
JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY

J Am Coll Cardiol, 2010; 56:738-740, doi:10.1016/j.jacc.2010.05.021

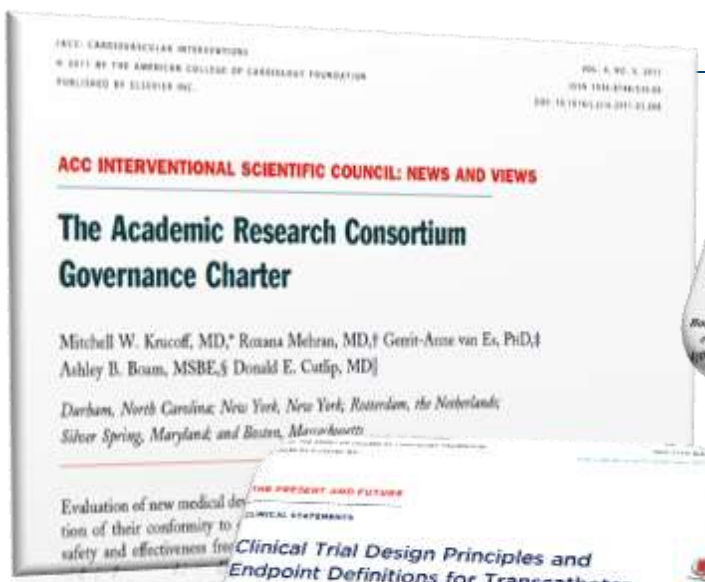
INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support): A New Paradigm for Translating Registry Data Into Clinical Practice

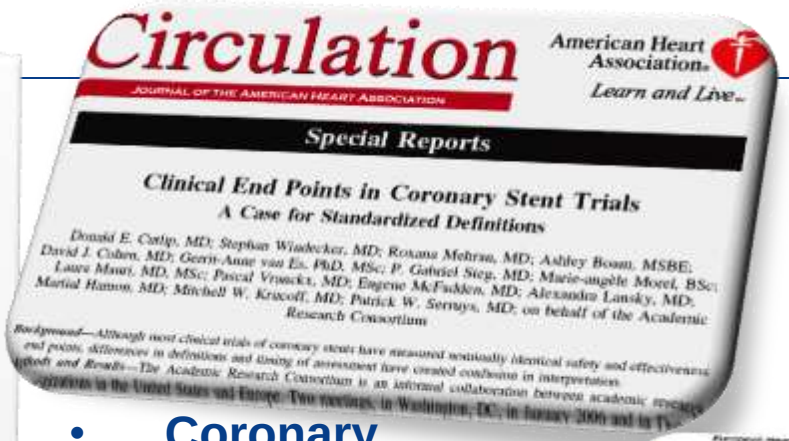
Marissa A. Miller, Karen Ulisney, and J. Timothy Baldwin

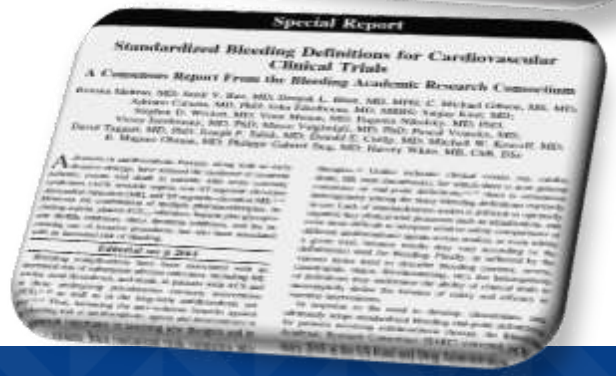
2006 JMACS

The Academic Research Consortium (ARC): 2007-2024

Pragmatic consistent definitions for device evaluation







- Coronary
- Bleeding
- Aortic valve
- Mitral valve
- Neurologic
- Denervation for hypertension
- MCS for shock
- PAD
- DEB
- HBR CAD
- HBR TAVR
- Cardiogenic Shock
- DAPT modulation

Peripheral ARC (PARC)

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Evaluation and Treatment of Patients With Lower Extremity Peripheral Artery Disease

Consensus Definitions From Peripheral Academic Research Consortium (PARC)

Manesh R. Patel, MD,* Michael S. Conte, MD,† Donald E. Cutlip, MD,‡§ Nabil Dib, MD,‖ Patrick Geraghty, MD,¶ William Gray, MD,#** William R. Hiatt, MD,†† Mami Ho, MD, PhD,‡‡ Koji Ikeda, PhD,§§ Fumiaki Ikeno, MD,‖‖ Michael R. Jaff, DO,¶¶ W. Schuyler Jones, MD,‡ Masayuki Kawahara, MD,‡‡ Robert A. Lookstein, MD,## Roxana Mehran, MD,# ## Sanjay Misra, MD,*** Lars Norgren, MD,††† Jeffrey W. Olin, MD,## Thomas J. Povsic, MD, PhD,* Kenneth Rosenfield, MD,††† John Rundback, MD,§§§ Fadi Shamoun, MD,‖‖‖ James Tcheng, MD,* Thomas T. Tsai, MD,¶¶¶ Yuka Suzuki, PhD,### Pascal Vranckx, MD,**** Bret N. Wiechmann, MD,†††† Christopher J. White, MD,‡‡‡‡ Hiroyoshi Yokoi, MD,§§§§ Mitchell W. Krucoff, MD*

ABSTRACT

The lack of consistent definitions and nomenclature across clinical trials of novel devices, drugs, or biologics poses a significant barrier to accrual of knowledge in and across peripheral artery disease therapies and technologies. Recognizing this problem, the Peripheral Academic Research Consortium, together with the U.S. Food and Drug Administration

Patel MR et al, JACC 2015: 65:931-41

TAVR Re-usable Minimum Core Data Structure

Enhanced quality & interoperability, reducing redundancy

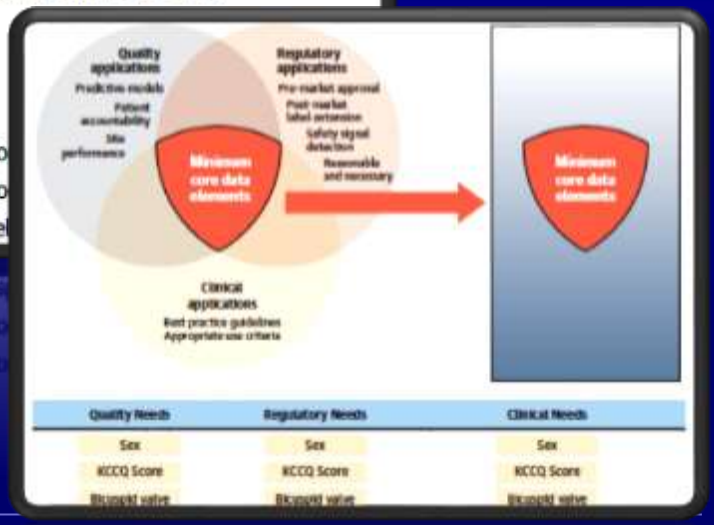
Minimum Core Data Elements for Evaluation of TAVR

A Scientific Statement by PASSION CV, HVC, and TVT Registry

Matheus Simonato, MD,[a,*] Sreekanth Vemulapalli, MD,[b,*] Ori Ben-Yehuda, MD,[c,d] Changfu Wu, PhD,[e] Larry Wood, MBA,[f] Jeff Popma, MD,[g] Ted Feldman, MD,[f] Carole Krohn, MPH,[h] Karen M. Hardy, BS, RHIA,[i] Kimberly Guibone, DNP,[j] Barbara Christensen, MSHA, RN,[k] Maria C. Alu, MS,[d] Shmuel Chen, MD,[l] Vivian G. Ng, MD,[l] Katherine H. Chau, MD,[l] Bahira Shahim, MD, PhD,[d] Flavien Vincent, MD,[d] John MacMahon, MSE,[m] Stefan James, MD,[n] Michael Mack, MD,[o] Martin B. Leon, MD,[l] Vinod H. Thourani, MD,[p] John Carroll, MD,[q] Mitchell Krucoff, MD[b]

ABSTRACT

Transcatheter aortic valve replacement (TAVR) is the standard of care for severe, symptomatic ao
TAVR data collection contributes to benefit/risk assessment and safety evidence for the U.S. Fo
tration, quality evaluation for the Centers for Medicare and Medicaid Services and hospitals, as we



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DUKE UNIVERSITY MEDICAL CENTER

Simonato M et al, JACC CV Interventions: 15 (7), 2022

IMDRF Essential Principles for Device Evidence: Registry Infrastructure and Analytic Methodologies 2017-2018

IMDRF/Registry WG/N46 FINAL:20

IMDRF International Medical Device Regulators Forum

Final Document

Title: Tools for Assessing the Usability of Registries in Support of Regulatory Decision-Making

Authoring Group: Patient Registries Working Group

Date: 27 March 2018

Yuan Lin, IMDRF Chair

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IMDRF/Registry WG/N42FINAL:20

IMDRF International Medical Device Regulators Forum

FINAL DOCUMENT

Title: Methodological Principles in the Use of International Medical Device Registry Data

Authoring Group: IMDRF Patient Registries Working Group

Date: 16 March 2017

Kimby Barton, IMDRF Chair

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http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170316-methodological-principles.pdf

HBD

Harmonization By Doing

Global device evidence & clinical trial POCs

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

2005: Endeavor Japan (Medtronic): *First Trans-Pacific HBD POC*

The clinical evaluation of the Endeavor zotarolimus-eluting coronary stent in Japanese patients with de novo native coronary artery lesions: primary results and 3-year follow-up of the Endeavor Japan study☆☆☆

Shigeru Saito, Ross Prpic, Jeffery J. Popma, John Alexander, Mitchell W. Krucoff, on behalf of the Endeavor Japan Investigators

Cardiovascular Revascularization Medicine
Volume 12, Issue 5, Pages 273–279, September–October, 2011

Approved in Japan & USA

- Identical [illegible]xclusion
- Id[illegible]points
- Id[illegible]ical core laboratories
- Enhanced poolability
- Enhanced interpretability

2007: SPIRIT III Japan (Abbott Vascular): *First Trans-Pacific Concomitant Enrollment CAD*

JIC JOURNAL OF INVASIVE CARDIOLOGY

Mid-Term Results of Everolimus-Eluting Stent in a Japanese Population Compared With a US Randomized Cohort: SPIRIT III Japan Registry With Harmonization by Doing

Wednesday, 08/29/12 | 9993 reads

Author(s):

Shigeru Saito, MD[1], Shigeru Nakamura, MD[2]
MD[5], Haruo Hirayama, MD[6], Tadashi
Kazuaki Mitsudo, MD[10], To
Alexandra J. Lan
PhD[16], R

aaki Isshiki,
Nonogi, MD, PhD[9],
iko Saito, MS, MPH[13],
a, MD[15], Katsuhisa Waseda, MD,
hir, MD, PhD[16]

er 2012

Approved in Japan & USA

- C *enrollment*
- Id ical inclusion/exclusion
- Identical endpoints
- Identical core laboratories

2017 HARMONEE Study (OrbusNeich)

First Trans-Pacific single protocol RCT for CAD DES

ESC European Society of Cardiology

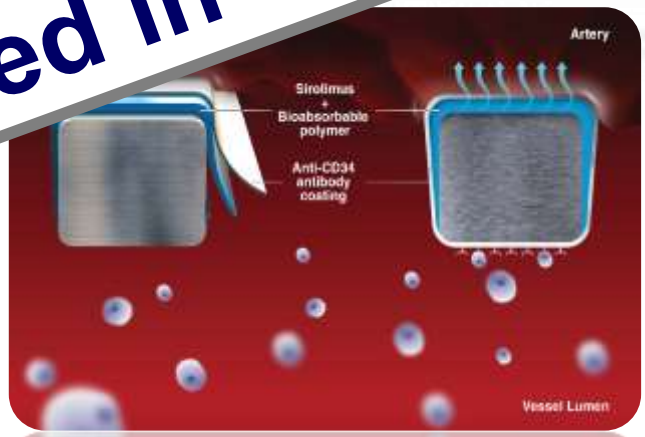
CLINICAL RESEARCH
Interventional cardiology

Japan-United States of America Harmonized Assessment by Randomized Multicentre Study of OrbusNEich's Combo StEnt (Japan-USA HARMONEE) study: primary results of the pivotal registration study of combined endothelial progenitor cell capture and drug-eluting stent in patients with ischaemic coronary disease and non-ST-elevation acute coronary syndrome

Shigeru Saito[1], Mitchell W. Krucoff[2]*, Shigeru Nakamura[3], Akiko Maehara[5], Hussein R. Al-Khalidi[2], Debbie Morrell[6], Diane Joseph[2], Barry D. Bertolet[9], Mark D. Rothenbe and David F. Kong[2]

Rationale and design of the Japan-USA harmonized assessment by randomized, multicenter study of OrbusNEich's combo StEnt (Japan-USA HARMONEE): Assessment of a novel DES platform for percutaneous coronary revascularization in patients with ischemic coronary dise and non–ST-elevation syndrome

Approved in Japan



The COMBO-Plus Dual Therapy Stent

Kong DF et al Am Heart J 2017;187:112-121

Saito S, Krucoff MW et al. European Heart Journal (2018) 0, 1–9 doi:10.1093/eurheartj/ehy275

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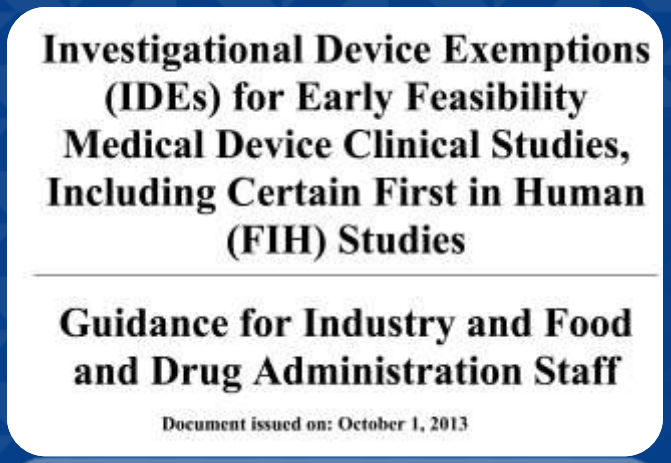
From Thought Leadership to Clinical Practice

HARMONEE



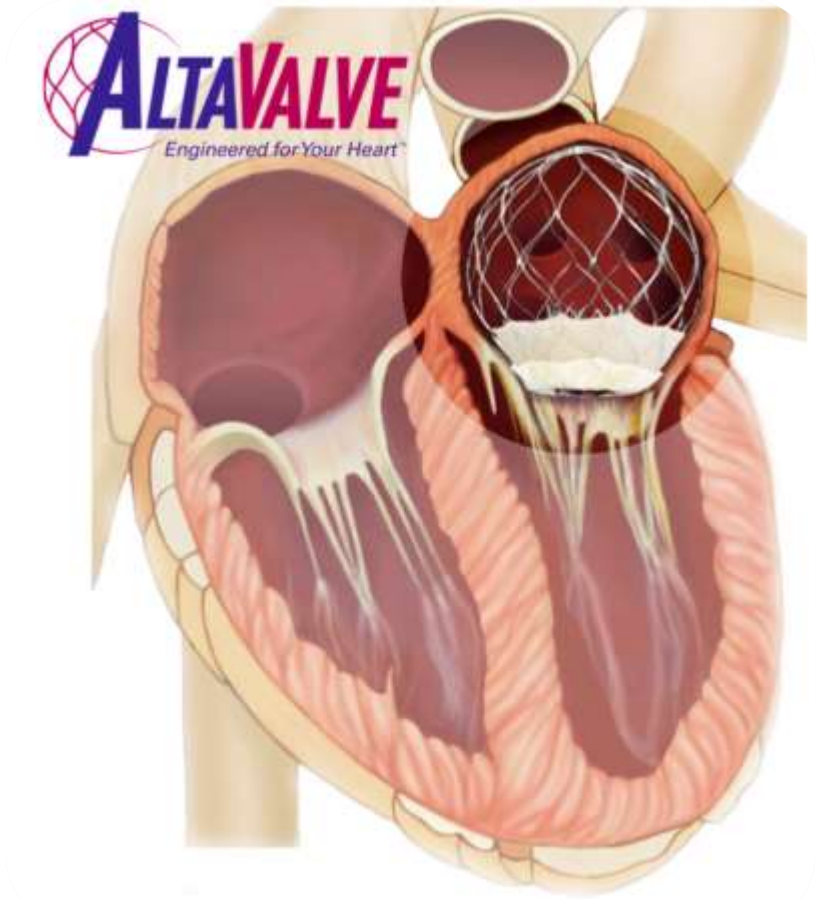
HB *Doing*

Trans-Pacific Early Feasibility Studies (EFS) POCs 2013-2023

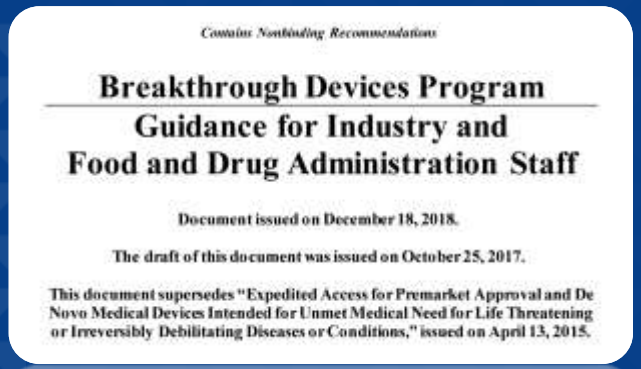
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm279103.pdf

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

4C Medical Percutaneous Mitral AltaValve
First Trans-Pacific EFS POC



https://www.4cmed.com/technology


Contains Nonbinding Recommendations

Breakthrough Devices Program
Guidance for Industry and Food and Drug Administration Staff

Document issued on December 18, 2018.

The draft of this document was issued on October 25, 2017.

This document supersedes "Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions," issued on April 13, 2015.


Rolling Reviews in SAKIGAKE and Breakthrough Therapy Designation

Toshiyoshi TOMINAGA, Ph.D.
Associate Executive Director
Pharmaceuticals and Medical Devices Agency

A GATHERING OF GLOBAL PERSPECTIVES


New Horizons for Innovation: Japanese Regulatory Initiatives with HBD

Takanashi, Fumihito, MPH
Ministry of Health, Labour and Welfare, Japan (MHLW)

tct2019

HB *Doing*

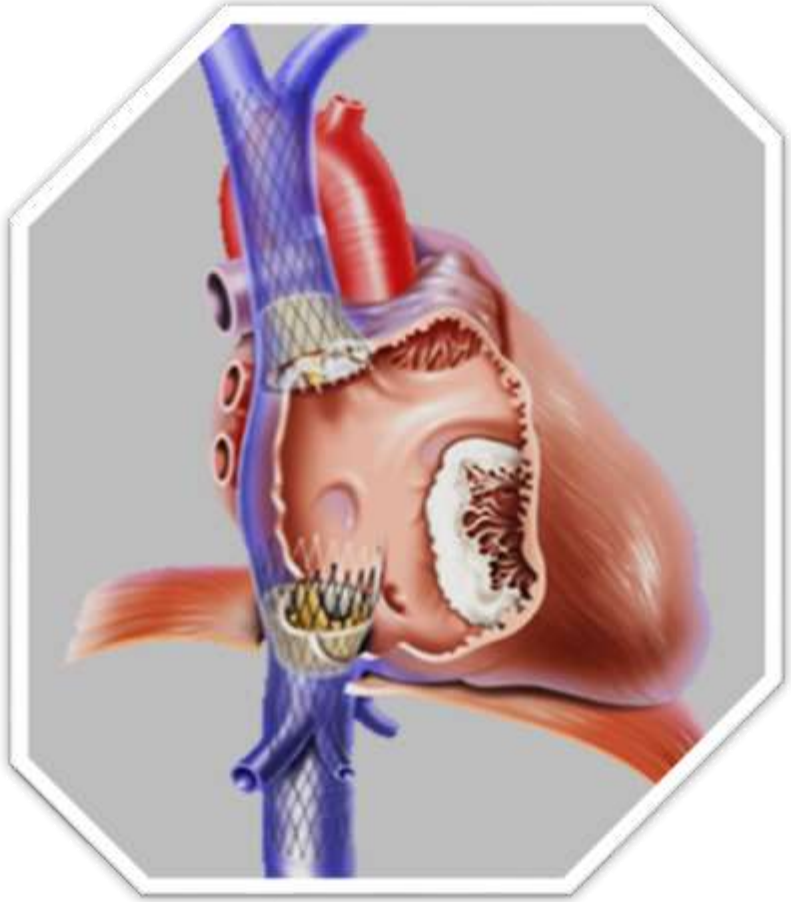
Breakthrough Devices & Fast-track Review Program POCs 2018-2023

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Percutaneous Bi-caval TRICVALVE (P&F/OrbusNeich)
Trans-Pacific Expedited Breakthrough Device POC

P&F PRODUCTS & FEATURES

OrbusNeich®
Pioneers in life-changing technologies



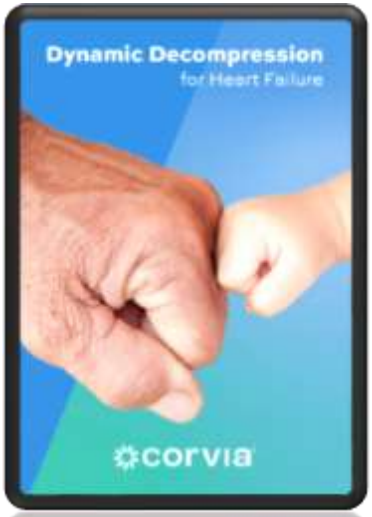
https://productsandfeatures.com/patients-and-care-workers/information-of-disease-and-possible-treatments/treatment-methods/tricvalve-transcatheter-bicaval-valves/

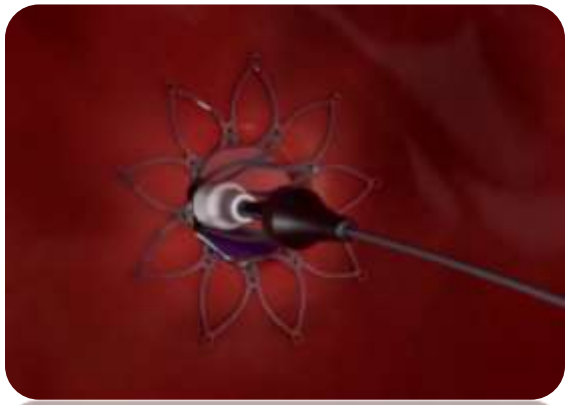
https://orbusneich.com/us/

The Intra-Atrial Shunt System IASD® (Corvia)

Trans-Pacific Breakthrough Device POC

corvia





HBD for Children:
2016-2024

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

HARMONY POC (Medtronic):
First Trans-Pacific Pediatric Pulmonic Valve

Advance Publication

Circulation Journal
doi:10.1253/circj.CJ-19-1092

ORIGINAL ARTICLE
Pediatric Cardiology and Adult Congenital Heart Disease

Partnership Between Japan and the United States for Early Development of Pediatric Medical Devices
— Harmonization By Doing for Children —

Sara Takahashi; Nicole Ibrahim, PhD; Satoshi Yasukochi, MD; Richard Ringel, MD; Frank Ing, MD; Hideshi Tomita, MD; Hisashi Sugiyama, MD; Masaaki Yamagishi; Thomas J. Forbes, MD; Sung-Hae Kim, MD; Mami Ho, MD; Nicol… Yasuko Nakamura; Koji Mineta; Neal Fearnot, PhD; D… Eric Vang, PhD; Russel Haskin; Lisa A. M. Becker, Ph… Kisaburo Sakamoto, MD; Carl… on behalf of the Harmonization b…

Background: The Harmonization By Doi… …ership am… academia, industry and regulator… …ocus on streamlining medical device develop… …traditionally focused on dev… intended to treat condit… …d the "HBD-for-Children" program, w… development of pediatric… …devices for pediatric use lags behind that of adults in both countries.

Methods and Results: Act… …program have included: (1) conducting a survey with industry to be… challenges that constrain the …elopment of pediatric medical devices; (2) categorizing pediatric medical device… based on global availability and exploring concrete solutions for the early application and regulatory approval i… and (3) facilitating global clinical trials of pediatric medical devices in both countries.

Conclusions: The establishment of the HBD-for-Children program is significant because it represents a gl… introduction of pediatric medical devices for patients in a timely manner. Through the program, academia, ind… agencies can work together to facilitate innovative pediatric device development from a multi-stakeholder pers… could also encourage industry partners to pursue the development of pediatric medical devices.

Key Words: Global clinical trial; Global harmonization; Harmonization By Doing for Children; Pediatric medical device

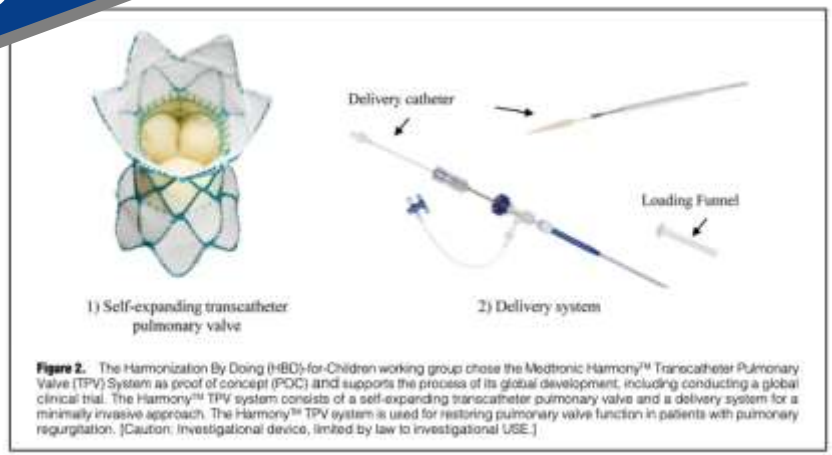


Figure 2. The Harmonization By Doing (HBD)-for-Children working group chose the Medtronic Harmony™ Transcatheter Pulmonary Valve (TPV) System as proof of concept (POC) and supports the process of its global development, including conducting a global clinical trial. The Harmony™ TPV system consists of a self-expanding transcatheter pulmonary valve and a delivery system for a minimally invasive approach. The Harmony™ TPV system is used for restoring pulmonary valve function in patients with pulmonary regurgitation. [Caution: Investigational device, limited by law to investigational USE.]

Approved in Japan & USA

HBD for Children:
Renata Medical Minima Stent POC

Catheterization & Cardiovascular Interventions

PEDIATRIC AND CONGENITAL HEART DISEASE | Open Access

Preliminary testing and evaluation of the renata minima stent, an infant stent capable of achieving adult dimensions

Evan M. Zahn MD, FACC, MSCAI, Eason Abbott BS, Neil Tailor MD, Shyam Sathanandam MD, Dustin Armer BS

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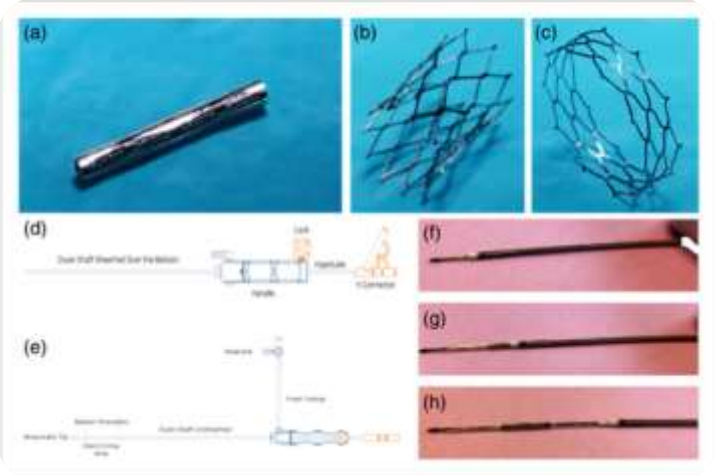

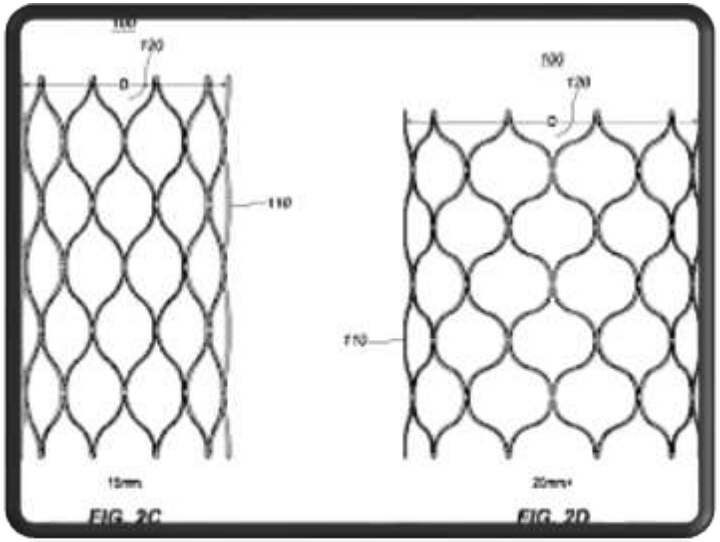

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