# Harmonization By Doing (HBD)
# History & Global Lessons Learned


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

**Professor, Medicine/Cardiology**

***Duke University Medical Center***

**Director, Cardiovascular Devices Unit**

***Duke Clinical Research Institute***

# Global Regulatory Harmonization
# December 2003

FDA U.S. Food a

CENTER FOR DE

FDA Home Pa

FDA > CDRH > International Issues > Japan - U.S. "Harm

## Japan - U.S. "Harmonization

"Harmonization by Doing," commonly known as H
address regulatory barriers that may be impedin
effort to move both Japan and the U.S. toward in
include:

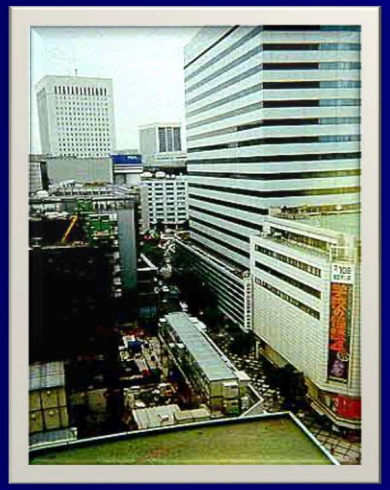
- U.S. Food and Drug Administration (FDA)
- Japan 's Pharmaceutical and Food Safety
  (MHLW) and its review agency, the Pharm
- Duke Clinical Research Institute (DCRI),
- Japanese academic community, and
- Japanese and U.S. medical device indust

**What is the HBD initiative?**

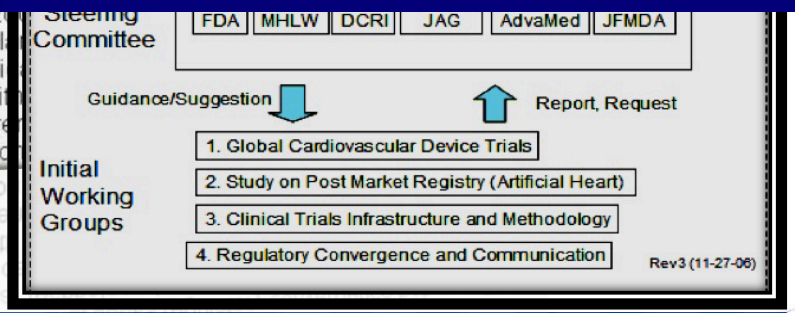
The HBD initiative is a pilot project launched in December 2
and MHLW-PMDA premarket review of device cardiovascul
to harmonization, HBD will utilize parallel development, appli
device projects by FDA and MHLW-PMDA in conjunction wi
eliminate redundancies, added costs, and time delays inhere
to create guidance and discuss policy but to develop commo

Pharmaceuticals and Medical Devices Agency, Japan

**2003-2004: Japan MHLW launches PMDA**

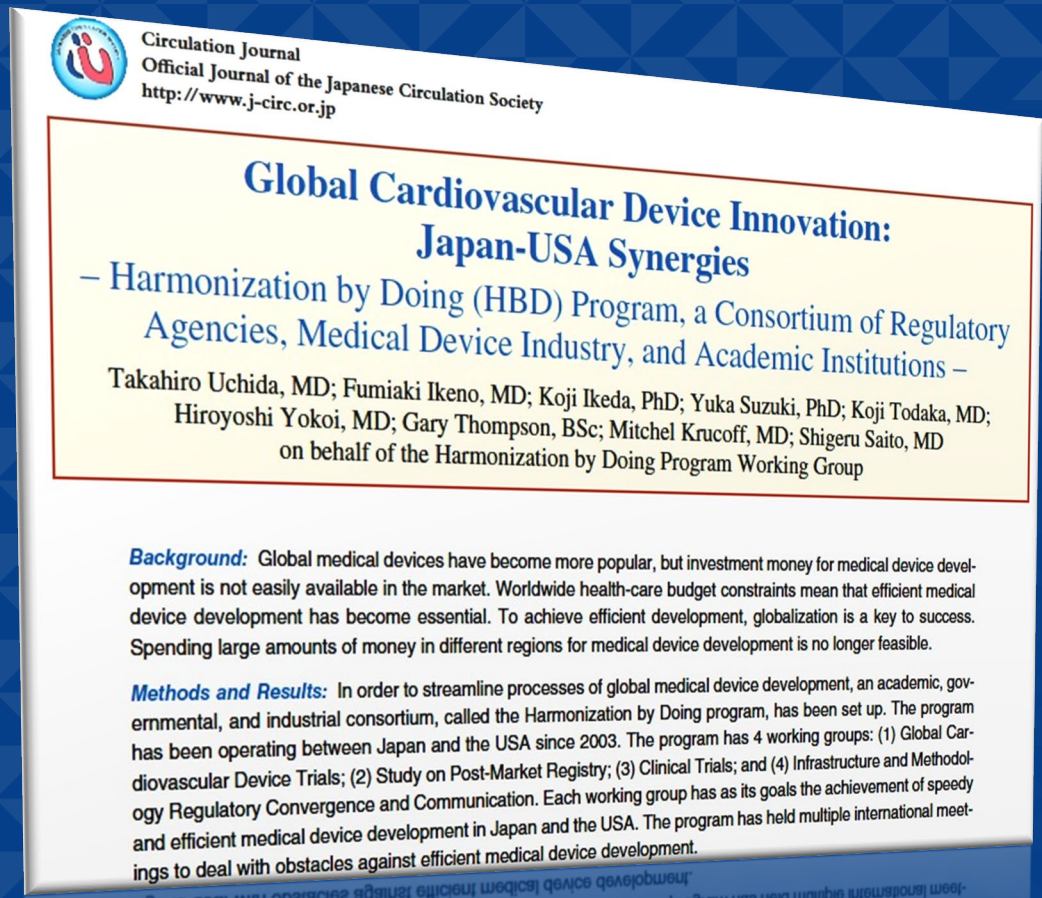


**April 2004: PMDA Adopts Early Consultation**




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





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.

# HBD

## *Program History*

**Uchida T et al, Circulation Journal 2013**

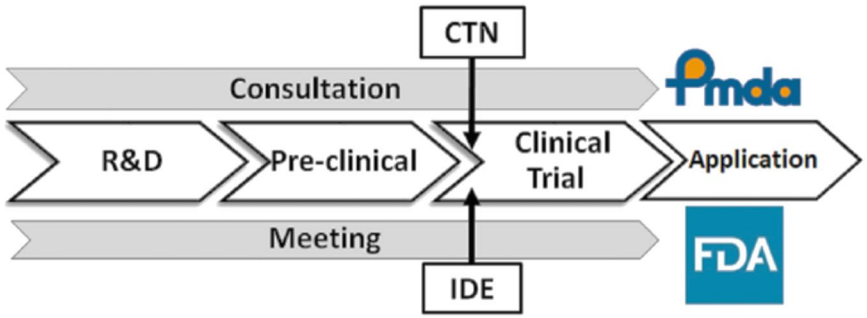
# 2023: Key Considerations for Global Japan-USA Trials:
## *A 20 Year Legacy of Successful Predicates!*

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 Lottes [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]

S. Iwamoto, K. Cavanaugh, M. Malone et al. / Cardiovascular Revascularization Medicine 52 (2023) 67–74




| FDA | | PMDA* | |
|---|---|---|---|
| Meeting types | Feed back | Consultation types | Feed back |
| Informational meeting | In 90 days | General Consultation | 1 week |
| Pre-submission<br>Including<br>• Clinical protocol and statistical analysis plan<br>• Non-clinical testing plan<br>• 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 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



# “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

第68回
日本循環器学会総会・学術集会

**Global Regulatory Harmonization and Medical Devices Clinical Trials:**
***Impact to Cardiology in Japan and Worldwide***

日時： 平成16年3月27日（土） 午後6:30～午後8:30
会場： 東京国際フォーラム 第15会場 (G-810 ガラス棟 8F)

Course Directors

*Bram Zuckerman, MD*
*US Food and Drug Administration, Center for Devices and Radiological Health*

*Naoyuki Yasuda*
*Ministry of Health, Labour and Welfare, Pharmaceutical and Food Safety Bureau*

*Shigeru Saito, MD*
*Shonan Kamakura General Hospital*

*Mitchell W. Krucoff, MD*
*Duke Clinical Research Institute, Interventional Device Trials*

Part I Regulatory Harmonization and Cardiology in Japan
Moderators: Bram Zuckerman, MD & Mitchell W. Krucoff, MD

1 Importance of Global Standards for Human Experimentation
Presenter: Naoyuki Yasuda
2 Importance of Japanese Global Leadership in Trials
Presenter: Shigeru Saito, MD
3 Importance of Harmonization and Japan: Industry Viewpoint
Presenter: Michael Gropp, Guidant Corporation
4 Research Infrastructure in Japan
Presenter: Kazuhiro Sase, MD, PhD, National Cardiovascular Center

Part II General Issues
Moderators: Naoyuk
1 From Physician to
Presenter: Mitchell
2 Poolability of Da
Presenter: Bram Z
3 Ethical Considera
Presenter: John A
4 From Harmonizati
Presenter: Susan A

共催：第68回日


**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 Data*

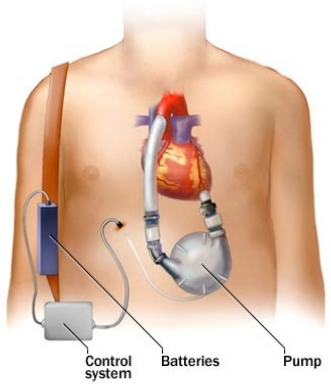
## *Real World Evidence POCs:*

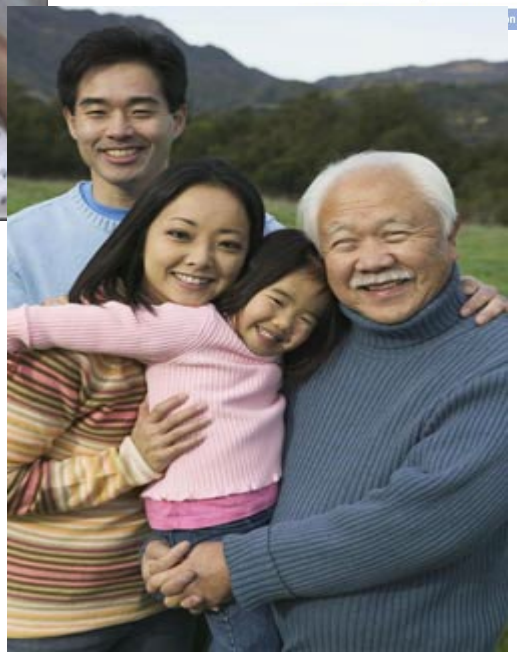
### *RWE Infrastructure (Device Registries)*

### *Consistent & Re-usable Data Structure*



# 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

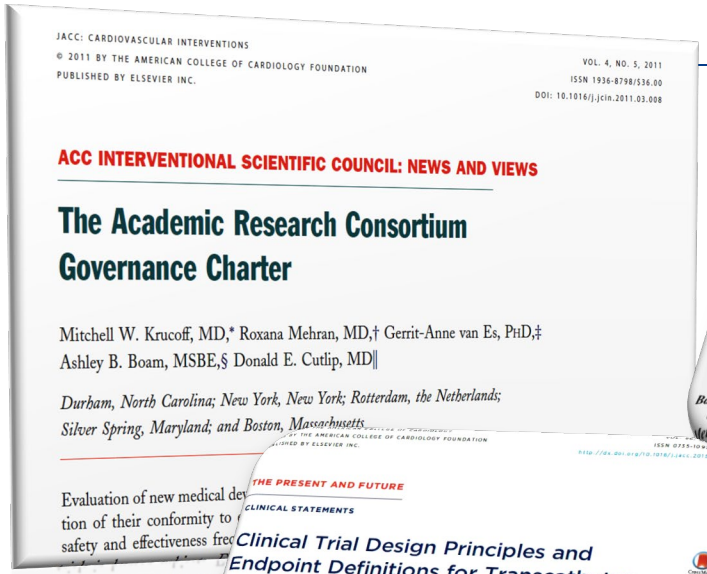

**INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support): A New Paradigm for Translating Registry Data Into Clinical Practice**

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

2006 JMACS

# The Academic Research Consortium (ARC): 2007

## *Pragmatic consistent definitions for device evaluation*

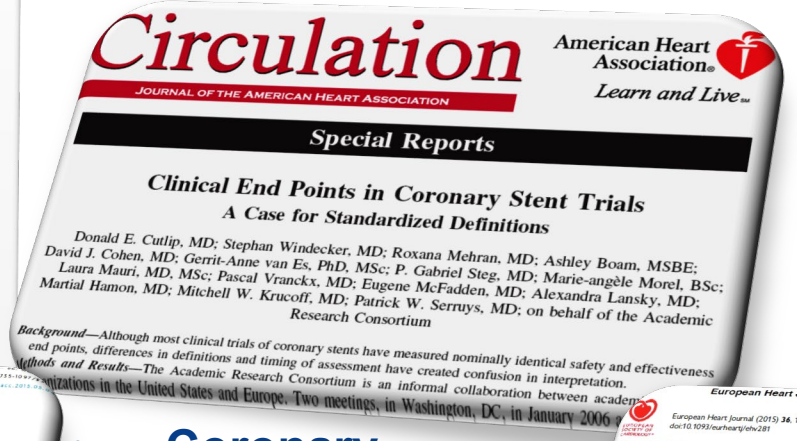

JACC: CARDIOVASCULAR INTERVENTIONS
© 2011 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.
VOL. 4, NO. 5, 2011
ISSN 1936-8798/$36.00
DOI: 10.1016/j.jcin.2011.03.008

ACC INTERVENTIONAL SCIENTIFIC COUNCIL: NEWS AND VIEWS

The Academic Research Consortium Governance Charter

Mitchell W. Krucoff, MD,* Roxana Mehran, MD,† Gerrit-Anne van Es, PhD,‡ Ashley B. Boam, MSBE,§ Donald E. Cutlip, MD‖

*Durham, North Carolina; New York, New York; Rotterdam, the Netherlands; Silver Spring, Maryland; and Boston, Massachusetts*


Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association. Learn and Live.

Special Reports

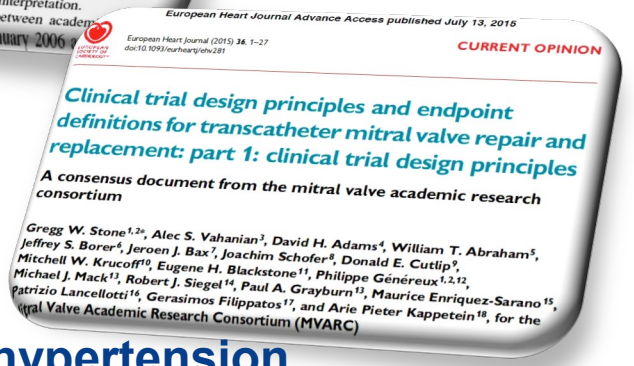
Clinical End Points in Coronary Stent Trials
A Case for Standardized Definitions

Donald E. Cutlip, MD; Stephan Windecker, MD; Roxana Mehran, MD; Ashley Boam, MSBE; David J. Cohen, MD; Gerrit-Anne van Es, PhD, MSc; P. Gabriel Steg, MD; Marie-angèle Morel, BSc; Laura Mauri, MD, MSc; Pascal Vranckx, MD; Eugene McFadden, MD; Alexandra Lansky, MD; Martial Hamon, MD; Mitchell W. Krucoff, MD; Patrick W. Serruys, MD; on behalf of the Academic Research Consortium


THE PRESENT AND FUTURE
CLINICAL STATEMENTS

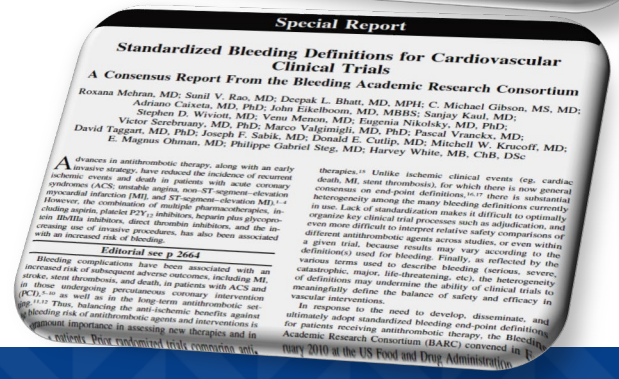
Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 1: Clinical Trial Design Principles

A Consensus Document From the Mitral Valve Academic Research Consortium


European Heart Journal Advance Access published July 13, 2016
European Heart Journal (2015) 36, 1–27
doi:10.1093/eurheartj/ehv281
CURRENT OPINION

Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 1: clinical trial design principles

A consensus document from the mitral valve academic research consortium


Special Report

Standardized Bleeding Definitions for Cardiovascular Clinical Trials

A Consensus Report From the Bleeding Academic Research Consortium

Roxana Mehran, MD; Sunil V. Rao, MD; Deepak L. Bhatt, MD, MPH; C. Michael Gibson, MS, MD; Adriano Caixeta, MD, PhD; John Eikelboom, MD, MBBS; Sanjay Kaul, MD; Stephen D. Wiviott, MD; Venu Menon, MD; Eugenia Nikolsky, MD, PhD; Victor Serebruany, MD, PhD; Marco Valgimigli, MD, PhD; David Taggart, MD, PhD; Joseph F. Sabik, MD; Donald E. Cutlip, MD; Mitchell W. Krucoff, MD; E. Magnus Ohman, MD; Philippe Gabriel Steg, MD; Harvey White, MB, ChB, DSc


European Heart Journal (2011) 32, 205–217
doi:10.1093/eurheartj/ehq406
CLINICAL RESEARCH
Valvular medicine

Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium†

Martin B. Leon*, Nicolo Piazza, Eugenia Nikolsky, Eugene H. Blackstone, Donald E. Cutlip, Arie Pieter Kappetein, Mitchell W. Krucoff, Michael Mack, Roxana Mehran, Craig Miller, Marie-angèle Morel, John Petersen, Jeffrey J. Popma, Johanna J.M. Takkenberg, Alec Vahanian, Gerrit-Anne van Es, Pascal Vranckx, John G. Webb, Stephan Windecker, and Patrick W. Serruys

- Coronary
- Bleeding
- Aortic valve
- Mitral valve
- Neurologic
- Denervation for hypertension
- MCS for shock
- PAD
- HBR
- 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

# Reusable "Minimum Core" Data Structure for Procedural Registries


Circ J 2018; 82: 316–322
doi:10.1253/circj.CJ-17-1156

REVIEW

## Registry Assessment of Peripheral Interventional Devices (RAPID)

— Registry Assessment of Peripheral Interventional Devices Core Data Elements —

W. Schuyler Jones, MD; Mitchell W. Krucoff, MD; Pablo Morales, MD; Rebecca W. Wilgus, RN, MSN; Anne H. Heath, BA; Mary F. Williams, BS; James E. Tcheng, MD; J. Danica Marinac-Dabic, MD, PhD; Misti L. Malone, PhD; Terrie L. Reed, MS; Rie Fukaya, MMedSc; Robert Lookstein, MD; Nobuhiro Handa, MD; Herbert D. Aronow, MD, MPH; Daniel J. Bertges, MD; Michael R. Jaff, DO; Thomas T. Tsai, MD, MSc; Joshua A. Smale, BS; Margo J. Zaugg, BSN; Robert J. Thatcher, MBA; Jack L. Cronenwett, MD; Durham, NC; Silver Spring, Md; Tokyo, Japan; New York, NY; Providence, RI; Burlington, Vt; Newton, Mass; Denver, Colo; Tempe, Ariz; Santa Clara, Calif; Minneapolis, Minn; Lebanon, NH

***Background:*** The current state of evaluating patients with peripheral artery disease and more specifically of evaluating medical devices used for peripheral vascular intervention (PVI) remains challenging because of the heterogeneity of the disease process, the multiple physician specialties that perform PVI, the multitude of devices available to treat peripheral artery disease, and the lack of consensus about the best treatment approaches. Because PVI core data elements are not standardized across clinical care, clinical trials, and registries, aggregation of data across different data sources and physician specialties is currently not feasible.

Jones WS, Krucoff MW et al, Circ J 2018: 82:316-22

SPECIAL COMMUNICATIONS

## Registry Assessment of Peripheral Interventional Devices (RAPID): Registry assessment of peripheral interventional devices core data elements

W. Schuyler Jones, MD,[a] Mitchell W. Krucoff, MD,[a] Pablo Morales, MD,[b] Rebecca W. Wilgus, RN, MSN,[a] Anne H. Heath, BA,[a] Mary F. Williams, BS,[a] James E. Tcheng, MD,[a] J. Danica Marinac-Dabic, MD, PhD,[b] Misti L. Malone, PhD,[b] Terrie L. Reed, MS,[b] Rie Fukaya, MMedSc,[c] Robert A. Lookstein, MD,[d] Nobuhiro Handa, MD,[c] Herbert D. Aronow, MD, MPH,[e] Daniel J. Bertges, MD,[f] Michael R. Jaff, DO,[g] Thomas T. Tsai, MD, MSc,[h] Joshua A. Smale, BS,[i] Margo J. Zaugg, BSN,[j] Robert J. Thatcher, MBA,[k] *and* Jack L. Cronenwett, MD,[l] *Durham, NC; Silver Spring, Md; Tokyo, Japan; New York, NY; Providence, RI; Burlington, Vt; Newton, Mass; Denver, Colo; Tempe, Ariz; Santa Clara, Calif; Minneapolis, Minn; and Lebanon, NH*

**ABSTRACT**

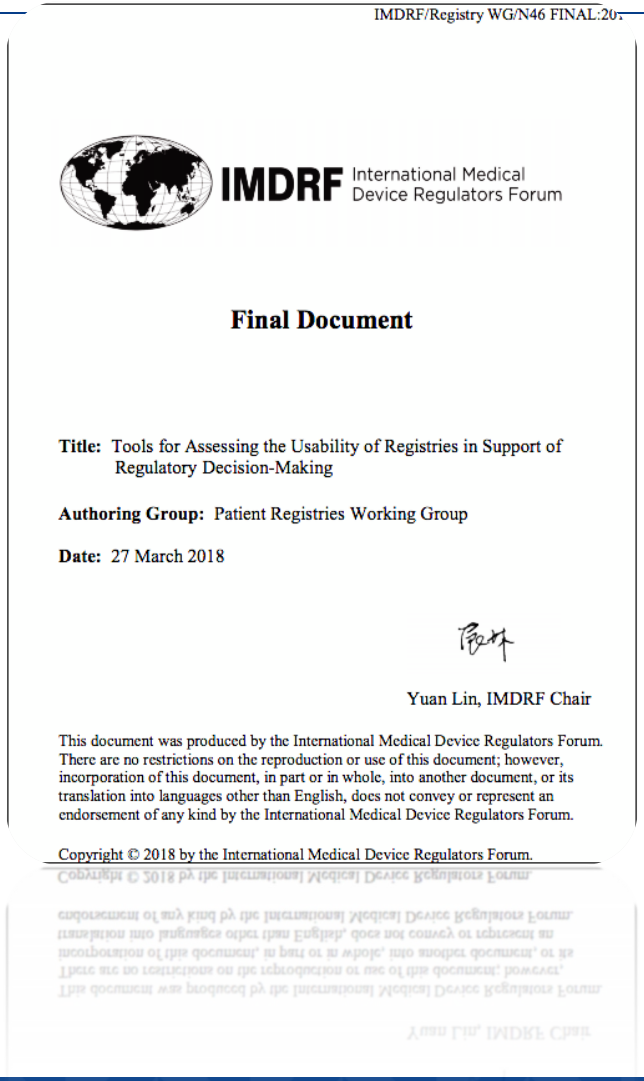
**Objective:** The current state of evaluating patients with peripheral artery disease and more specifically of evaluating medical devices used for peripheral vascular intervention (PVI) remains challenging because of the heterogeneity of the disease process, the multiple physician specialties that perform PVI, the multitude of devices available to treat peripheral artery disease, and the lack of consensus about the best treatment approaches. Because PVI core data elements are not standardized across clinical care, clinical trials, and registries, aggregation of data across different data sources and physician specialties is currently not feasible.

Jones WS, Krucoff MW et al, J Vasc Surg 2018: 67:637-45

DUKE UNIVERSITY MEDICAL CENTER

Duke Clinical Research Institute

# 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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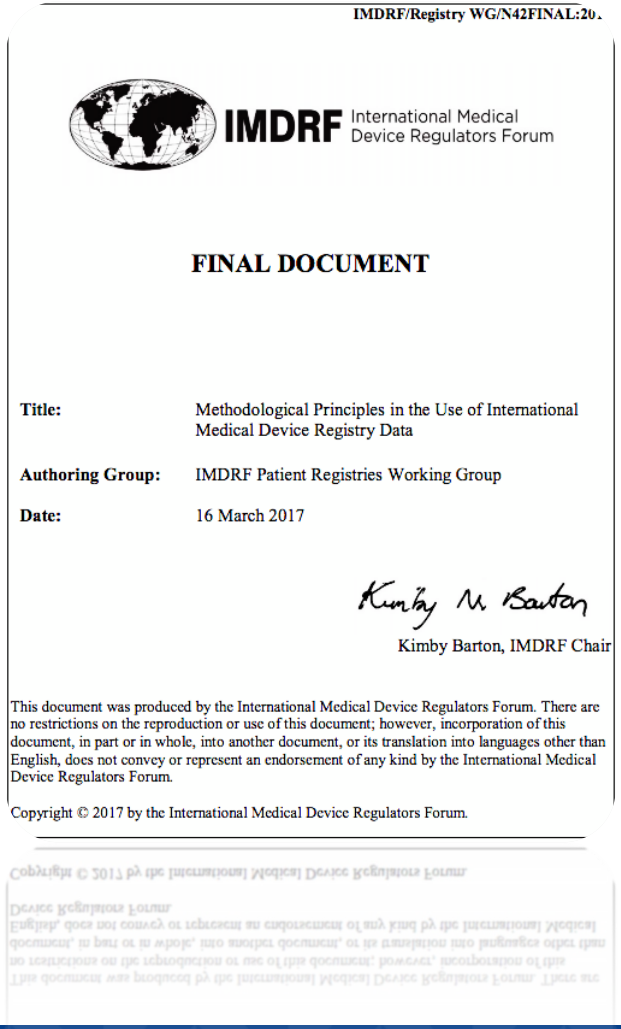

IMDRF/Registry WG/N42FINAL:20

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*

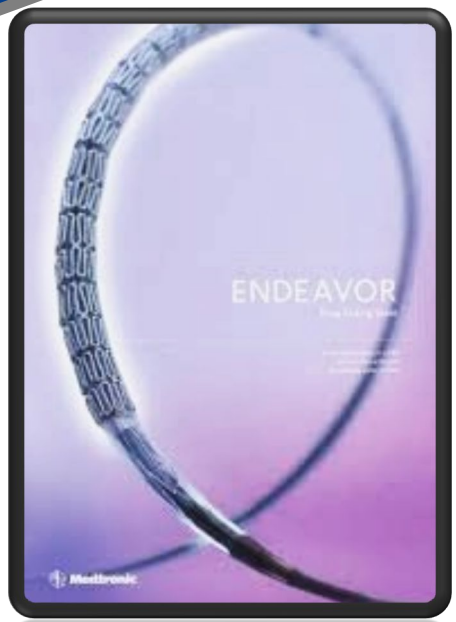

The clinical evaluation of the Endeavor zotarolimus-eluting coronary stent in Japanese patients with de novo native coronary artery lesions: primary results and 3-year follow-up of the Endeavor Japan study☆☆☆

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], Tadash
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]

ber 2012

**Approved in Japan & USA**

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


# 2009: Zilver PTX (Cook Medical) for PAD

## *First Trans-Pacific single protocol global RCT*

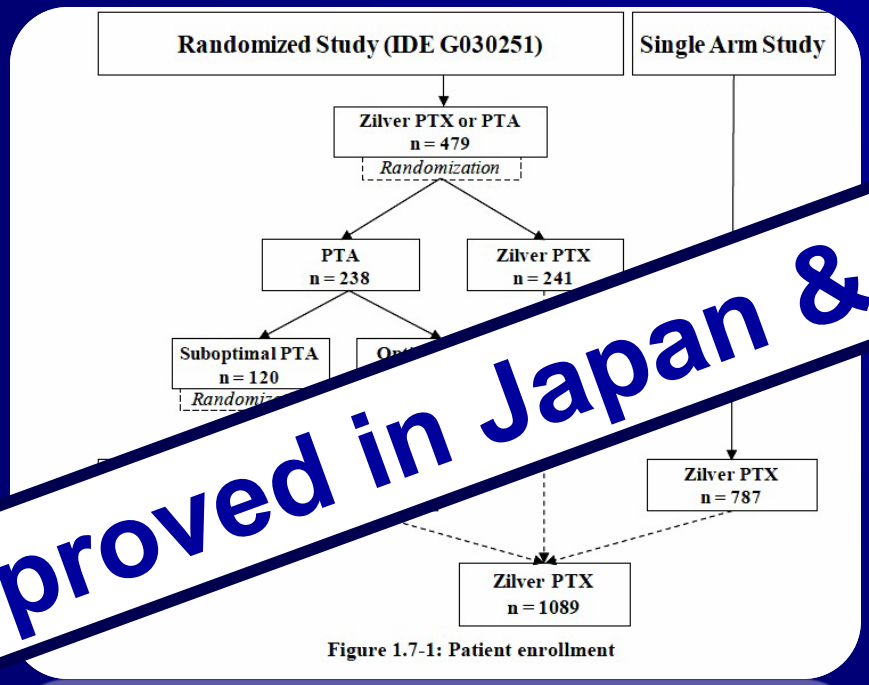
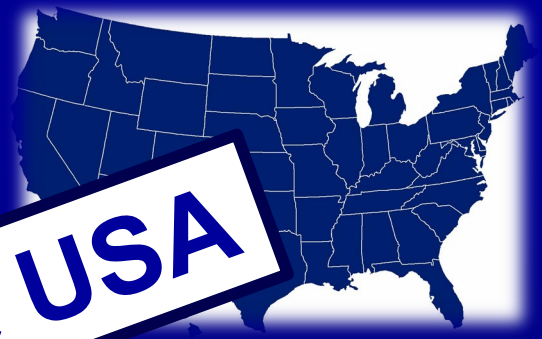




Figure 1.7-1: Patient enrollment



**Approved in Japan & USA**

DUKE UNIVERSITY MEDICAL CENTER

# 2012 COAST STUDY (CSI/Abbott Vascular):
## *First Trans-Pacific Atherectomy of Calcific Lesions*

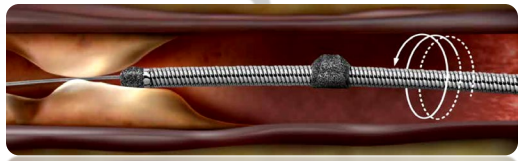
Japan-USA Orbital Atherectomy for Calcific Coronary Lesions: COAST Study, Harmonization by Doing Proof-of-Concept

Brad J. Martinsen, Katherine Kumar, Shigeru Saito, Samin K. Sharma, Fumiaki Ikeno, Ne
Shlofmitz, Robert Thatcher and Mitchell W. Krucoff

Cardiovascular Revascularization Medicine, 2022-04-01, Volume 37, Pages 112

**Approved in Japan & USA**

Diam OAS Micro Crown



Ja OA Orbital Atherectomy for Calcific Coronary Lesions: COAST Study, a Harmonization by Doing Proof-of-Concept: The Japanese and US Regulatory Perspective

Shin Iwamoto, Moe Ohashi, Haruki Shirato, Mami Ho, Misti Malone and Kenneth Cavanaugh

Cardiovascular Revascularization Medicine, 2022-04-01, Volume 37, Pages 118-119, Copyright © 2021

# 2017 HARMONEE Study (OrbusNeich)

## *First Trans-Pacific single protocol RCT for CAD DES*

ESC European Society of Cardiology

European Heart Journal (2018) 0, 1–9
doi:10.1093/eurheartj/ehy275

CLINICAL RESEARCH
*Interventional cardiology*

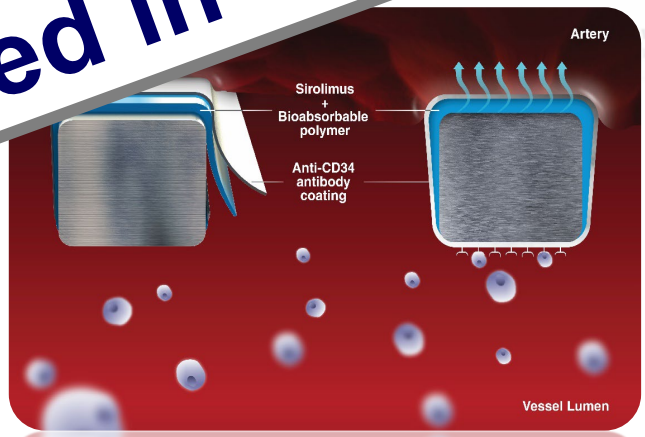
**Japan-United States of America Harmonized Assessment by Randomized Multicentre Study of OrbusNEich's Combo StEnt (Japan-USA HARMONEE) study: primary results of the pivotal registration study of combined endothelial progenitor cell capture and drug-eluting stent in patients with ischaemic coronary disease 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], Stephen ...
Debbie Morrell[6], Diane Joseph[2], Yumiko ...
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**

David F. Kong, MD, Sh...
Allison Hand... ...a Mehran, MD, Stephen M. Rowland, PhD, ...coff, MD *Durham, NC; Kamakura,*

**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

Duke Clinical Research Institute
From Thought Leadership to Clinical Practice

HARMONEE

**Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies**

**Guidance for Industry and Food and Drug Administration Staff**

Document issued on: October 1, 2013

**EFS in Japan: PMDA View**

*Sara Takahashi*
*Reviewer*
*Office of Medical Devices III*
*Pharmaceuticals and Medical Devices Agency (PMDA), Japan*

tct2017 Cardiovascular Research Foundation

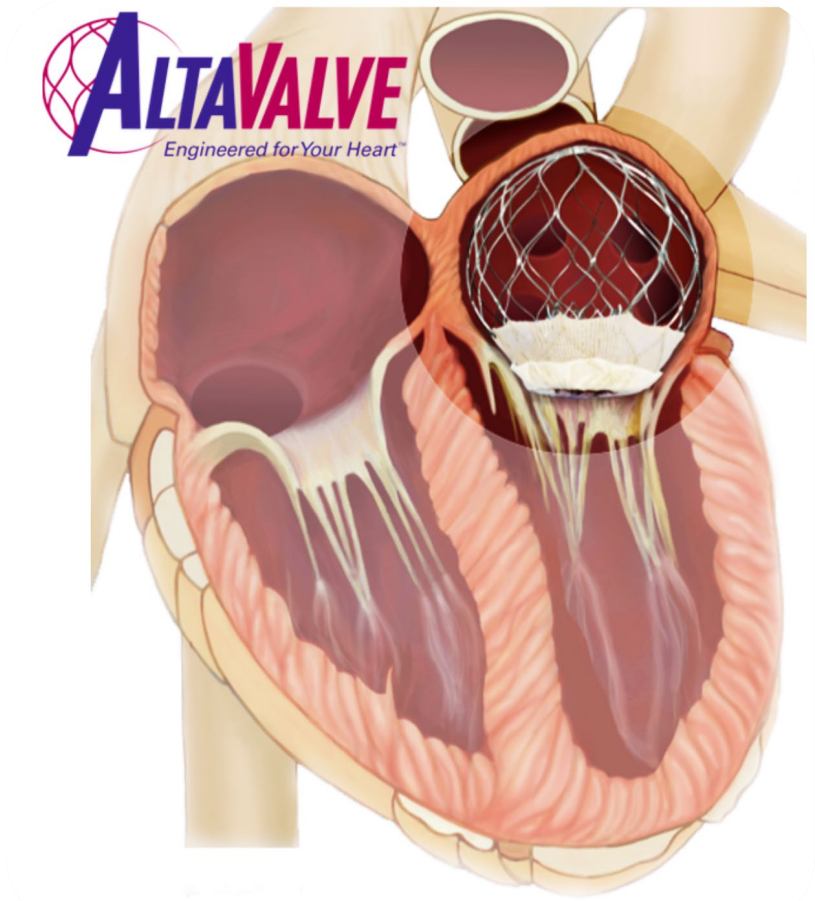
# HB *Doing*

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

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

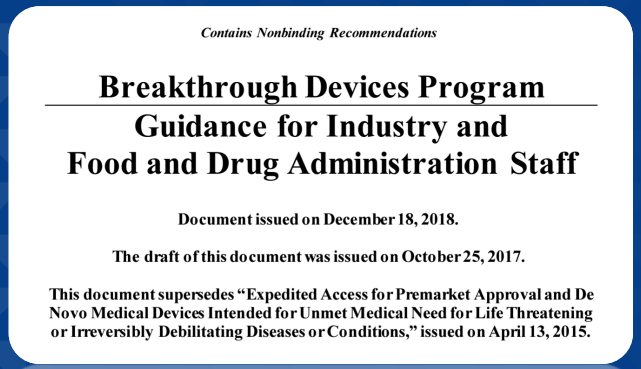
Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

# 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*

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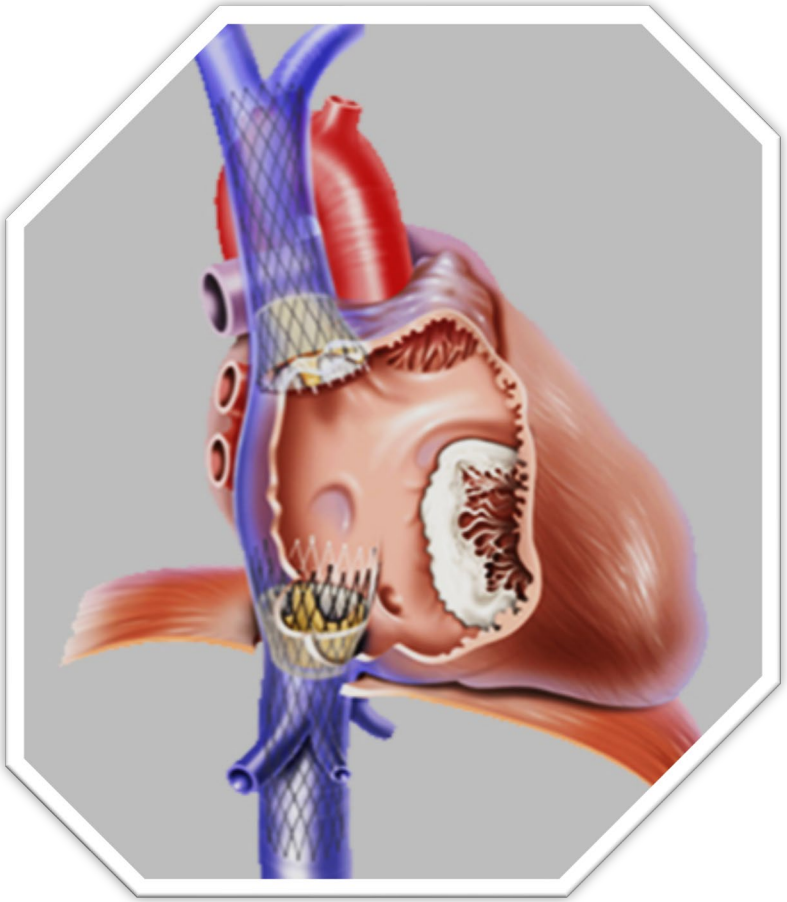
# Percutaneous Bi-caval TRICVALVE (P&F/OrbusNeich)
## *Trans-Pacific Expedited Breakthrough Device POC*

P&F PRODUCTS & FEATURES

OrbusNeich®
*Pioneers in life-changing technologies*





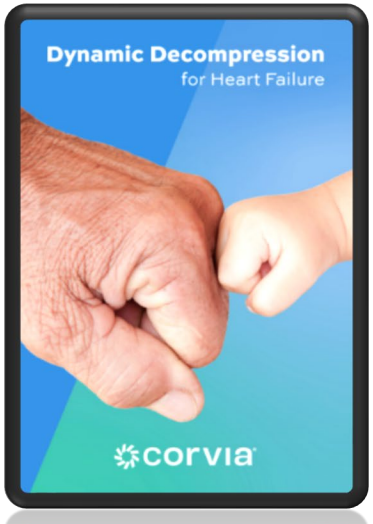
https://productsandfeatures.com/patients-and-care-workers/information-of-disease-and-possible-treatments/treatment-methods/tricvalve-transcatheter-bicaval-valves/

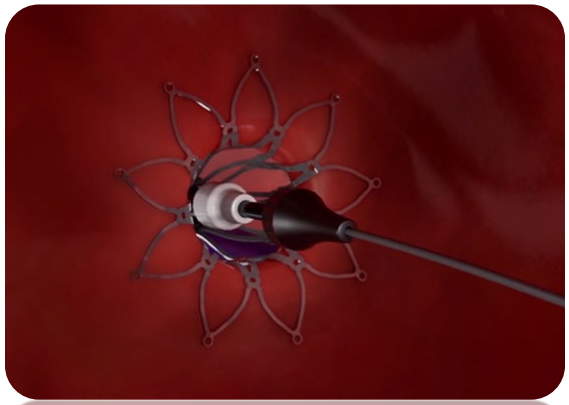
https://orbusneich.com/us/

# The Intra-Atrial Shunt System IASD® (Corvia)

## *Trans-Pacific Breakthrough Device POC*

corvia®

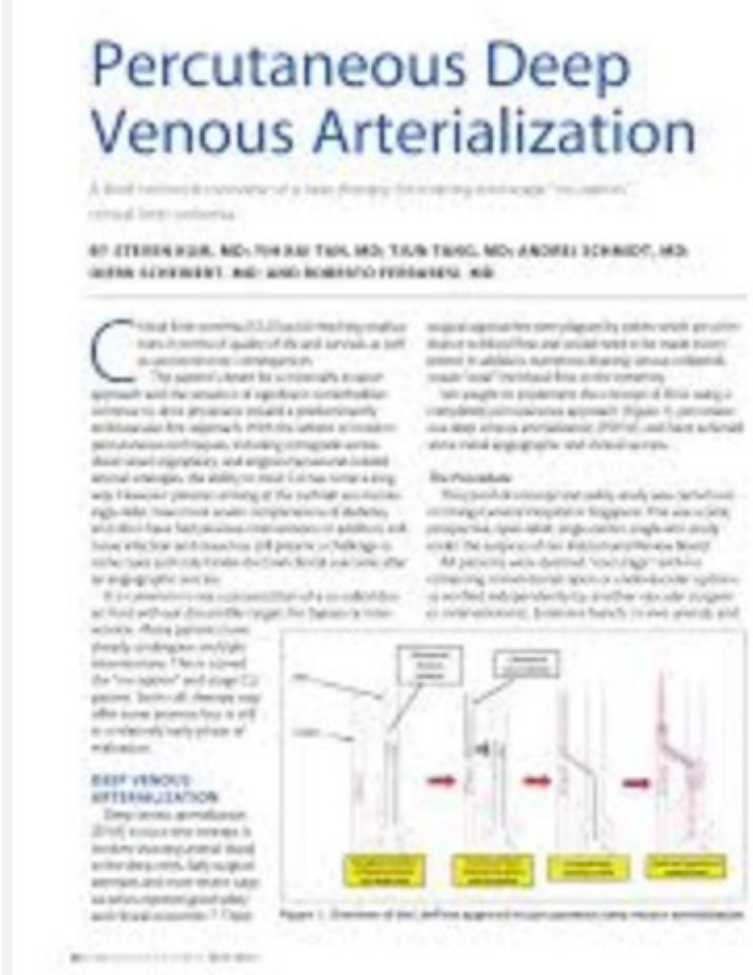





# Percutaneous Deep Venous Arterialization (LimFlow)
## *Trans-Pacific Breakthrough Device POC*

LimFlow
Transforming CLTI



Percutaneous Deep Venous Arterialization

# HB *Doing*

## *Harmonizing Device Classification POC*

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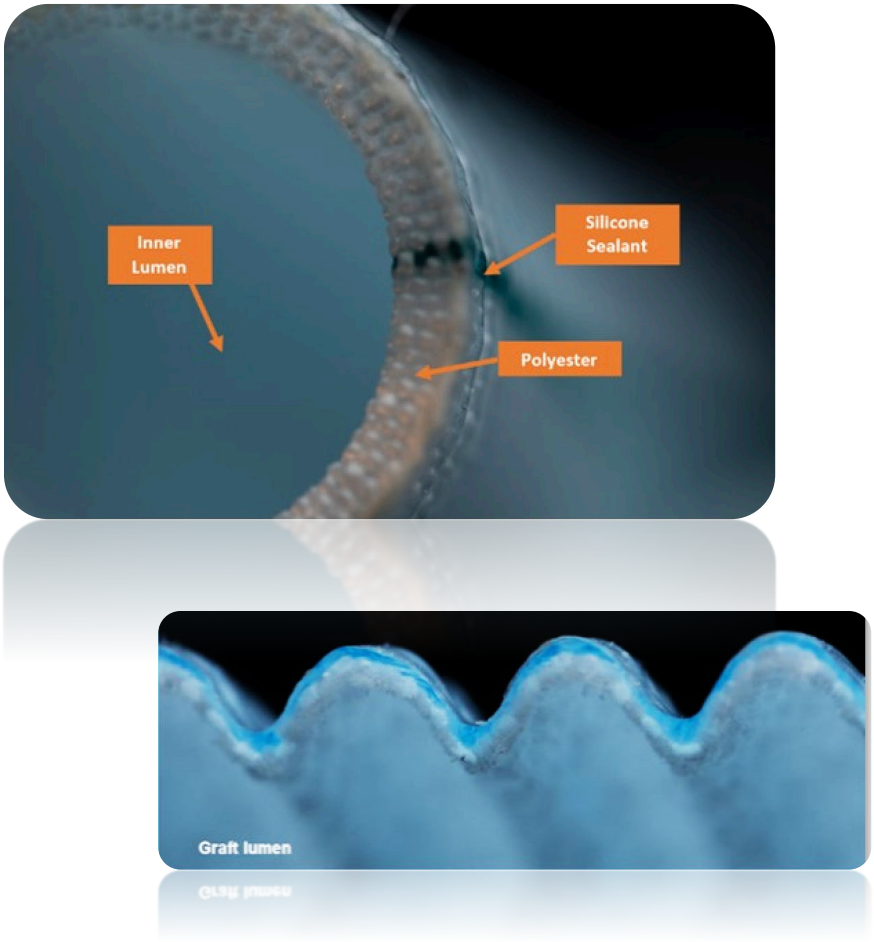
# Diaxamed Vascular Graft POC

DIAXAMED



# HBD for Children:
## *2016-2023*

Duke Clinical Research Institute | FROM **THOUGHT LEADERSHIP** TO **CLINICAL PRACTICE**

# Introduction and achievement of HBD-for-Children


***Yasuko Nakamura***

***Reviewer, Office of Medical Devices III***

***Pharmaceuticals and Medical Devices Agency (PMDA)***





# POC candidates

| | Covered CP Stent | Medtronic Melody Transcatheter Pulmonary Valve | AMPLATZER muscular VSD occluder |
|---|---|---|---|
| industry | NuMED | Medtronic | ST.JUDE MEDICAL |
| |  |  |  |



# 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 Yamagish… 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… …rship 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:*** Ac… …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

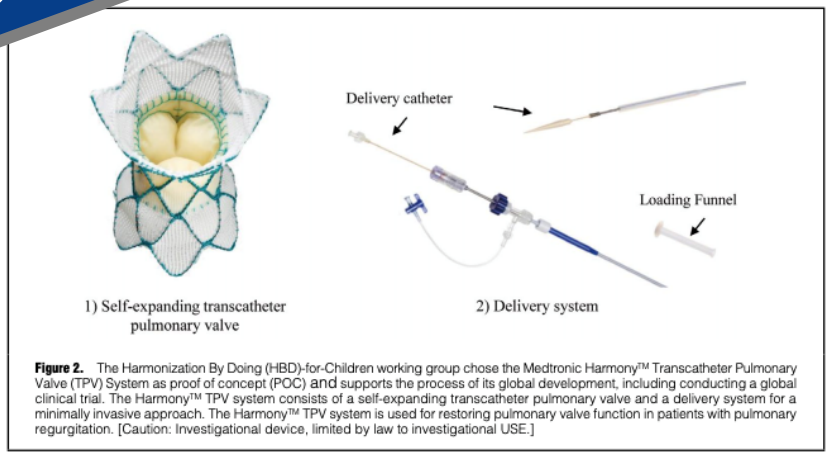



**Figure 2.** The Harmonization By Doing (HBD)-for-Children working group chose the Medtronic Harmony™ Transcatheter Pulmonary Valve (TPV) System as proof of concept (POC) and supports the process of its global development, including conducting a global clinical trial. The Harmony™ TPV system consists 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*

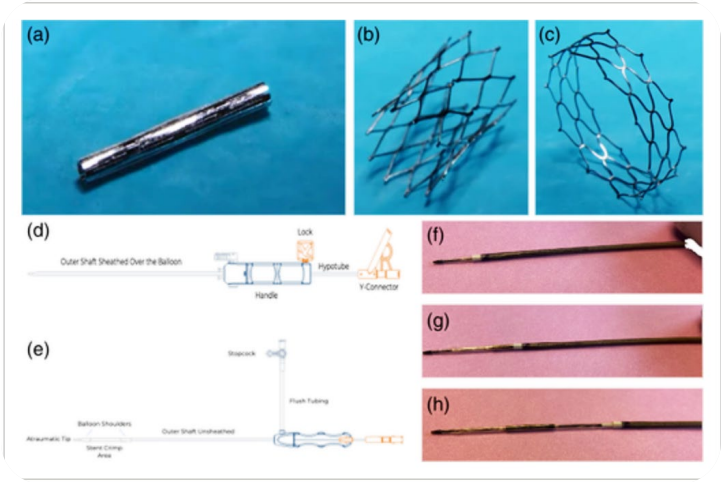
Catheterization & Cardiovascular Interventions

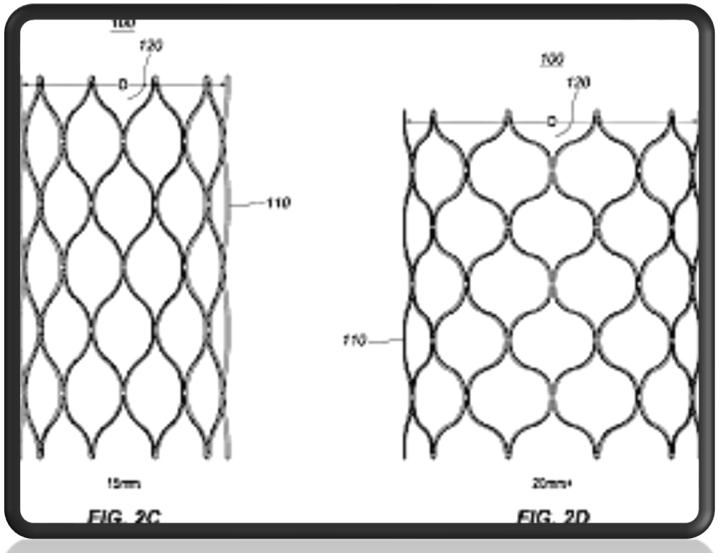
PEDIATRIC AND CONGENITAL HEART DISEASE | Open Access

## 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

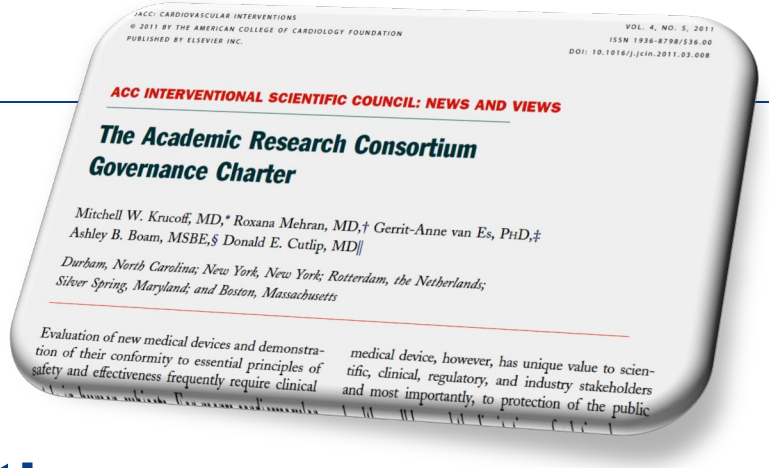
First published: 04 May 2021 | https://doi.org/10.1002/ccd.29706



# The Academic Research Consortium (ARC):

## *ARC for Children*



JACC: CARDIOVASCULAR INTERVENTIONS
© 2011 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
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VOL. 4, NO. 5, 2011
ISSN 1936-8798/$36.00
DOI: 10.1016/j.jcin.2011.03.008

ACC INTERVENTIONAL SCIENTIFIC COUNCIL: NEWS AND VIEWS

**The Academic Research Consortium Governance Charter**

Mitchell W. Krucoff, MD,* Roxana Mehran, MD,† Gerrit-Anne van Es, PhD,‡ Ashley B. Boam, MSBE,§ Donald E. Cutlip, MD‖

Durham, North Carolina; New York, New York; Rotterdam, the Netherlands; Silver Spring, Maryland; and Boston, Massachusetts

Evaluation of new medical devices and demonstration of their conformity to essential principles of safety and effectiveness frequently require clinical

medical device, however, has unique value to scientific, clinical, regulatory, and industry stakeholders and most importantly, to protection of the public

## Pragmatic consensus definitions:

## *Children are not just large adults…*

- **Pulmonary artery (vascular) stenosis**
- **Pediatric ECMO outcomes & events**
- **Etc!**

# Conclusion: Lessons Learned in 23 Years of HBD

- Most barriers to faster, more efficient R&D are PRE-competitive issues
- Stakeholders working together are much more creative and impactful than when we work separately
- Working together provides experience through shared POC projects and promotes trust and good faith across the professional people, strengthening the collaborative process
- Working together we bring better, safer devices to patient bedsides faster without device “lag” across international communities

# HBD 22th Anniversary:
## *Working Together We Have Made a Pretty Big Splash!*