



Harmonization By Doing (HBD) History & Global Lessons Learned

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

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Duke University Medical Center
Director, Cardiovascular Devices Unit
Duke Clinical Research Institute



Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

Global Regulatory Harmonization

December 2003

FDA U.S. Food and Drug Administration
CENTER FOR DEVICES AND RADIATION
[FDA Home Page](#)

[FDA](#) > [CDRH](#) > [International Issues](#) > Japan - U.S. "Harmonization"

Japan - U.S. "Harmonization"

"Harmonization by Doing," commonly known as HBD, is a pilot project launched in December 2003 to address regulatory barriers that may be impeding the effort to move both Japan and the U.S. toward international harmonization. The initiative includes:

- U.S. Food and Drug Administration (FDA)
- Japan's Pharmaceutical and Food Safety Agency (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 2003 to address regulatory barriers that may be impeding the effort to move both Japan and the U.S. toward international harmonization. HBD will utilize parallel development, applying device projects by FDA and MHLW-PMDA in conjunction with each other to eliminate redundancies, added costs, and time delays inherent in the current regulatory process. The goal is to create guidance and discuss policy but to develop common

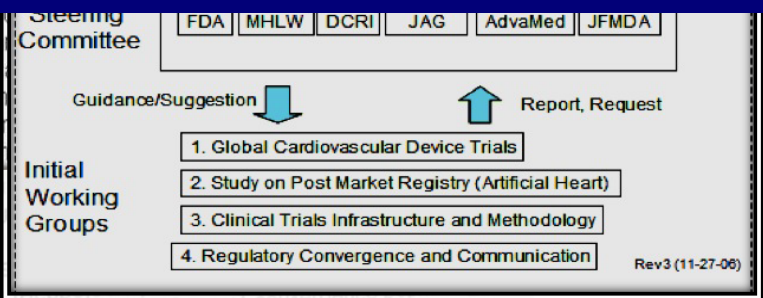


Pharmaceuticals and Medical Devices Agency, Japan

2003-2004: Japan MHLW launches PMDA



April 2004: PMDA Adopts Early Consultation





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



Duke Clinical Research Institute

FROM THOUGHT LEADERSHIP
TO CLINICAL PRACTICE

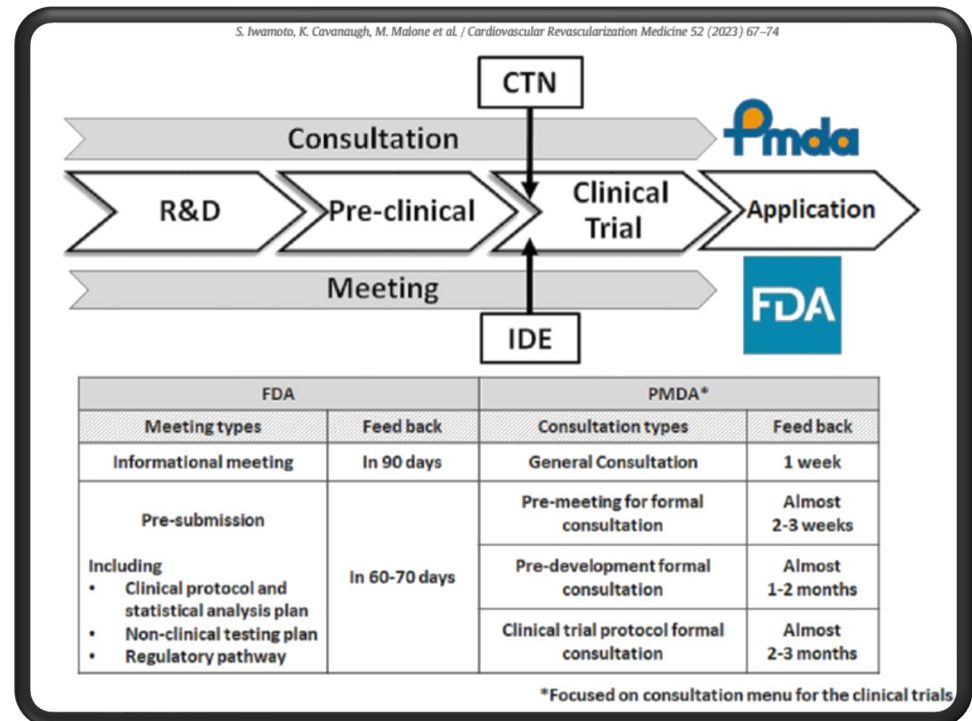


2023: Key Considerations for Global Japan-USA Trials: A 20 Year Legacy of Successful Predicates!

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 Fearnat^g,
Takahiro Uchida^h, Chie Iwaishiⁱ, Kazuhisa Senshu^j, Ryo Konishi^j,
Koji Ikeda^k, Yuka Suzuki^l, Fumiaki Ikeno^m, Atsushi Tamuraⁿ, Mami Ho^o,
Moe Ohashi^o, Hiroshi Katayama^p, Mitchell W. Krucoff^q



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

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)

Duke Clinical Research Institute, Interventional Device Trials

- 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

- 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”



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

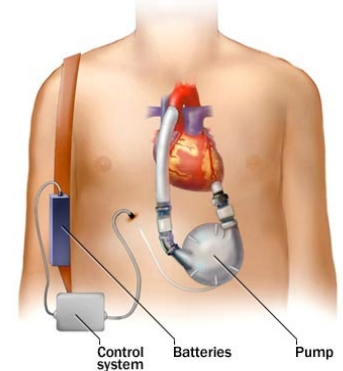


Duke Clinical Research Institute

FROM THOUGHT LEADERSHIP
TO CLINICAL PRACTICE



Linking Post-Market Surveillance: LVADS



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 **JACC**
JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY

J Am Coll Cardiol, 2010; 56:738-740, doi:10.1016/j.jacc.2010.05.021
© 2010 by the American College of Cardiology Foundation

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



Duke Clinical Research Institute



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 1936-8796/\$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 device
of their conformity to
safety and effectiveness free

THE PRESENT AND FUTURE

CLINICAL STATEMENTS

Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part I: Clinical Trial Design Principles A Consensus Document From the Mitral Valve Academic Research Consortium

Gregg W. Stone, MD,* Alec S. Vahanian, MD,† David H. Adams, MD,‡ William T. Abraham, MD,§
Jeffrey S. Borer, MD,¶ Jeroen J. Bax, MD, PhD,|| Joachim Schofer, MD,|| Donald E. Cutlip, MD,||
Mitchell W. Krucoff, MD,|| Eugene H. Blackstone, MD,|| Philippe G  n  reux, MD, PhD,||
Robert J. Siegel, MD,|| Paul A. Grayburn, MD,|| Maurice Enriquez-Sarano, MD,|| Michael J. Mack, MD,||
Patrizio Lancellotti, MD, PhD,|| Gerasimos Filippatos, MD,|| Arie Pieter Kappetein, MD, PhD,||
Mitral Valve Academic Research Consortium (MVARC)

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 Caiaeta, MD, PhD; John Eikelboom, MD, MBS; Sanjay Kaul, MD;
Stephen D. Wiviott, MD; Venu Menon, MD; Eugenia Nikolsky, MD, PhD;
Victor Serebreny, MD, PhD; Marco Valgimigli, MD, PhD; Pascal Vranckx, MD;
David Taggart, MD, PhD; Joseph F. Sabik, MD; Donald E. Cutlip, MD; Mitchell W. Krucoff, MD;
E. Magnus Ohlsson, MD; Philippe Gabriel Steg, MD; Harvey White, MB, ChB, DSc

Advances in antithrombotic therapy, along with an early
ischemic events and death in patients with acute coronary
syndrome (ACS), unstable angina, non-ST-segment-elevation
myocardial infarction (NSTEMI), and ST-segment-elevation
myocardial infarction (STEMI). However, the combination
of bleeding and thrombotic events remains a major concern.
In this report, the Bleeding Academic Research Consortium
(BARC) defines standard definitions for bleeding events
in clinical trials, and the importance of bleeding events in
the context of cardiovascular outcomes.

Editorial see p 2664

Bleeding complications have been associated with an
increased risk of subsequent adverse outcomes, including MI,
stroke, stent thrombosis, and death, in patients with ACS and
in those undergoing percutaneous coronary intervention
(PCI), as well as in the long-term antithrombotic
management of patients with ACS and in the management
of bleeding risk of antithrombotic agents and interventions.
The importance of bleeding events in the context of cardiovascular
outcomes has been emphasized in numerous clinical trials.

therapies.^{1,2} Unlike ischemic clinical events (eg, cardiac
death, MI, stent thrombosis), for which there is now general
consensus on end-point definitions,³⁻⁷ there is substantial
heterogeneity among the many bleeding definitions currently
in use. Lack of standardization makes it difficult to optimally
organize key clinical trial processes such as adjudication, and
even more difficult to interpret relative safety comparisons of
different antithrombotic agents across studies, or even within
a given trial, because results may vary according to the
definitions⁸ used for bleeding. Finally, as reflected by the
various terms used to describe bleeding (serious, severe,
catastrophic, major, life-threatening, etc), the heterogeneity
may undermine the ability of clinical trials to
meaningfully derive the balance of safety and efficacy in
vascular interventions.
In response to the need to develop, disseminate, and
ultimately adopt standardized bleeding end-point definitions
for patients receiving antithrombotic therapy, the Bleeding
Academic Research Consortium (BARC) convened in Fe-
bruary 2010 at the US Food and Drug Administration

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-ang  le 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

Background—Although most clinical trials of coronary stents have measured nominally identical safety and effectiveness
end points, differences in definitions and timing of assessment have created confusion in interpretation.
Methods and Results—The Academic Research Consortium is an informal collaboration between academic
organizations in the United States and Europe. Two meetings, in Washington, DC, in January 2006

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

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

Gregg W. Stone^{1,2*}, Alec S. Vahanian³, David H. Adams⁴, William T. Abraham⁵,
Jeffrey S. Borer⁶, Jeroen J. Bax⁷, Joachim Schofer⁸, Donald E. Cutlip⁹,
Mitchell W. Krucoff¹⁰, Eugene H. Blackstone¹¹, Philippe G  n  reux^{1,2,12},
Michael J. Mack¹³, Robert J. Siegel¹⁴, Paul A. Grayburn¹⁵, Maurice Enriquez-Sarano¹⁶,
Patrizio Lancellotti¹⁶, Gerasimos Filippatos¹⁷, and Arie Pieter Kappetein¹⁸, for the
Mitral Valve Academic Research Consortium (MVARC)

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-ang  le 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

Stanford University Medical Center, Center for Interventional Vascular Therapy, 173 Fort Washington Avenue, Heart Center, 2nd floor, New York, NY 10032, USA,
*Jan 2010; revised 30 September 2010; accepted 6 October 2010



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. Tchong, 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. Tchong, 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



IMDRF/Registry WG/N46 FINAL:2017



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*



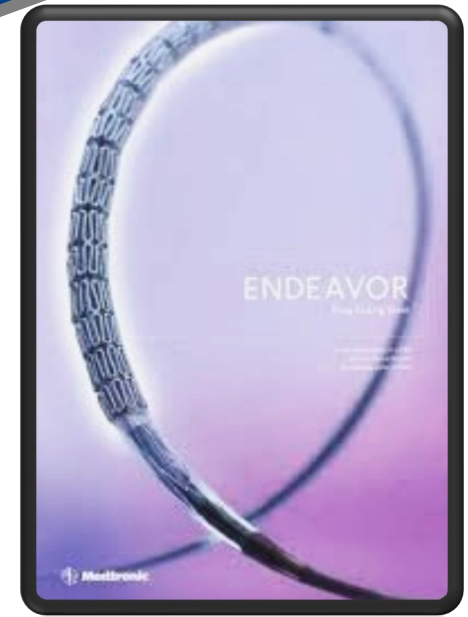
The clinical evaluation of the Endeavor zotarolimus-eluting coronary stent in Japanese patients with de novo native coronary artery lesions: primary results and 3-year follow-up of the Endeavor Japan study☆☆☆

[Shigeru Saito](#) , [Ross Pprie](#), [Jeffery J. Popma](#), [John Alexander](#), [Mitchell W. Krucoff](#), on behalf of the [Investigators](#)

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

Approved in Japan & USA

- Identical study design
- Identical patient population
- Identical core laboratories
- Enhanced poolability
- Enhanced interpretability



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



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, 09/29/12 | 9993 reads

Author(s):

Shigeru Saito, MD¹, Shigeru Nakamura, MD², Kazuaki Isshiki, MD⁵, Haruo Hirayama, MD⁶, Tadashi Nonogi, MD, PhD⁹, Kazuaki Mitsudo, MD¹⁰, Takahiko Saito, MS, MPH¹³, Alexandra J. Lange, MD¹⁵, Katsuhisa Waseda, MD, PhD¹⁶, R. S. Vir, MD, PhD¹⁶

October 2012

Approved in Japan & USA

- **Concomitant enrollment**
- **Identical inclusion/exclusion**
- **Identical endpoints**
- **Identical core laboratories**



2009: Zilver PTX (Cook Medical) for PAD

First Trans-Pacific single protocol global RCT

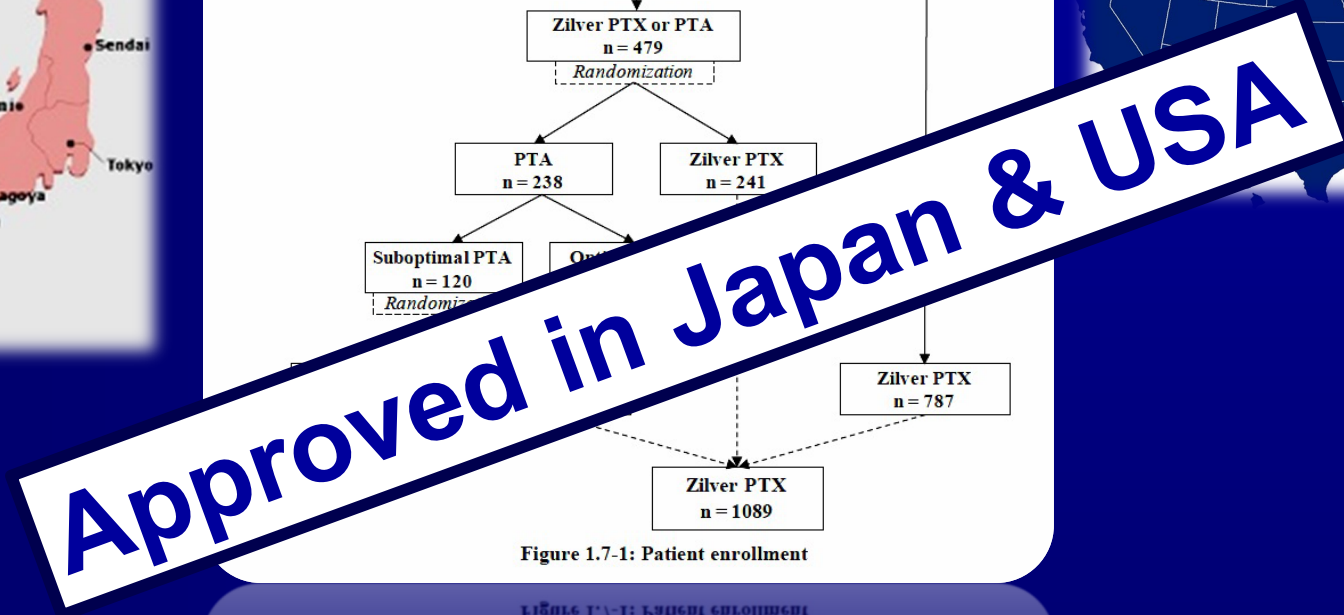


Figure 1.7-1: Patient enrollment

n = 1089
Zilver PTX



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, Naoki Shlofmitz, Robert Thatcher and Mitchell W. Krucoff

Cardiovascular Revascularization Medicine, 2022-04-01, Volume 37, Pages 112-119

Approved in Japan & USA

Diam

COAS Micro Crown



Japan-USA 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)

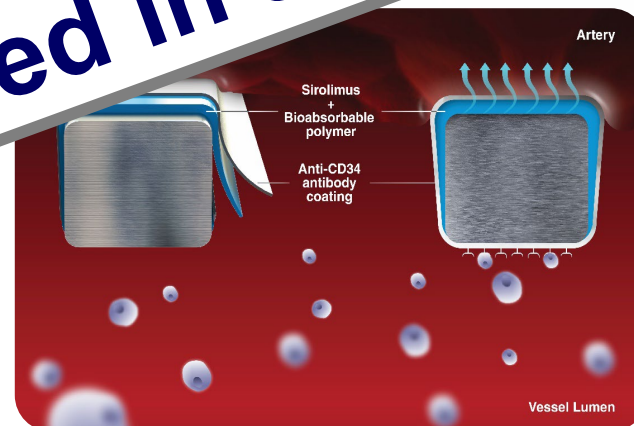
First Trans-Pacific single protocol RCT for CAD DES



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 disease and non-ST-elevation acute coronary syndrome

David F. Kong, MD, Stephen M. Rowland, PhD, Akiko Maehara, MD, Shigeru Nakamura, MD, Hussein R. Al-Khalidi, MD, Debbie Morrell, MD, Diane Joseph, MD, Yumiko Ogasawara, MD, Barry D. Bertollet, MD, Mark D. Rothenberg, MD, and Mitchell W. Krucoff, MD

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

**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>



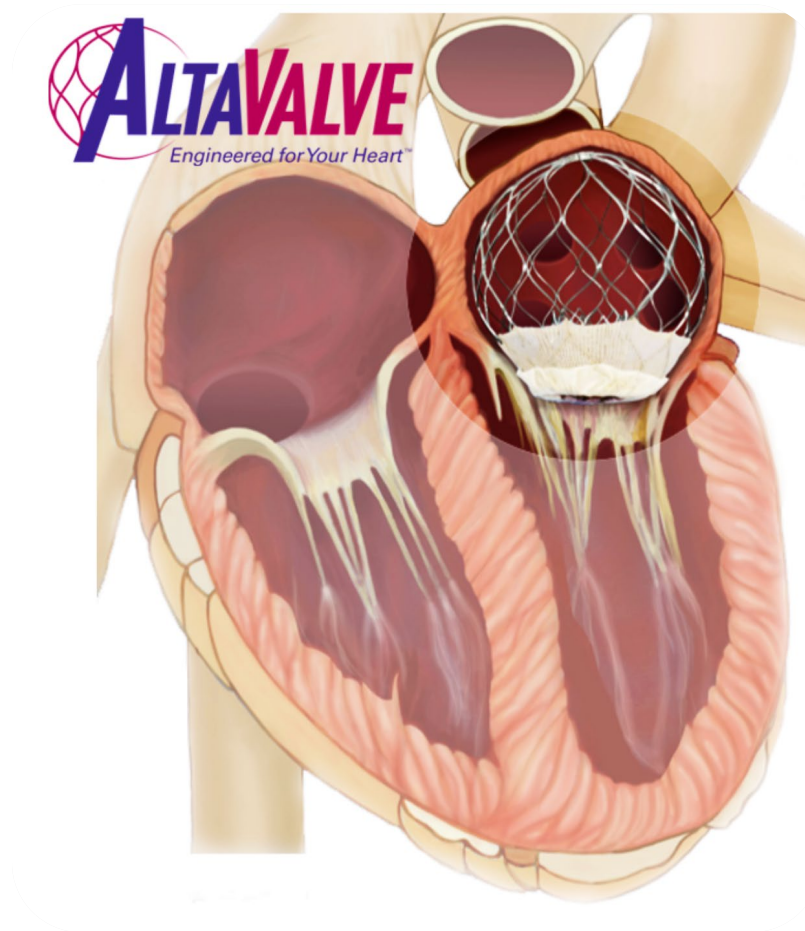
Duke Clinical Research Institute

FROM THOUGHT LEADERSHIP
TO CLINICAL PRACTICE



4C Medical Percutaneous Mitral AltaValve

First Trans-Pacific EFS POC



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

IC 2018

ICH 2018

HB Doing

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



Duke Clinical Research Institute

FROM THOUGHT LEADERSHIP
TO CLINICAL PRACTICE

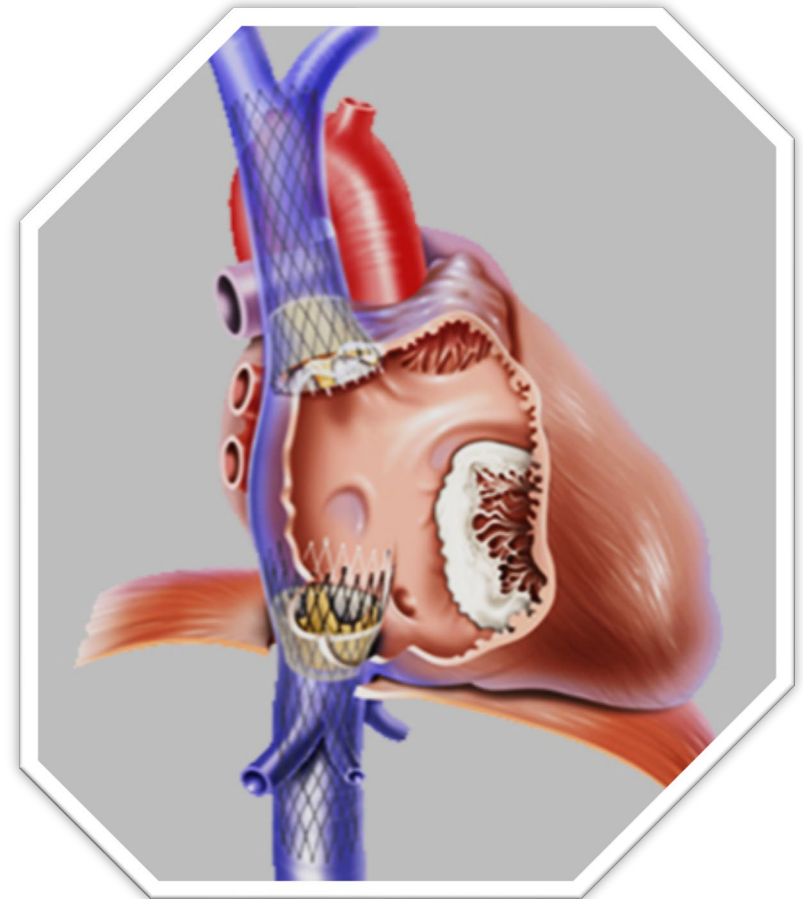


Percutaneous Bi-caval TRICVALVE (P&F/OrbusNeich) *Trans-Pacific Expedited Breakthrough Device POC*



P&F PRODUCTS & FEATURES

OrbusNeich®
Pioneers in life-changing technologies

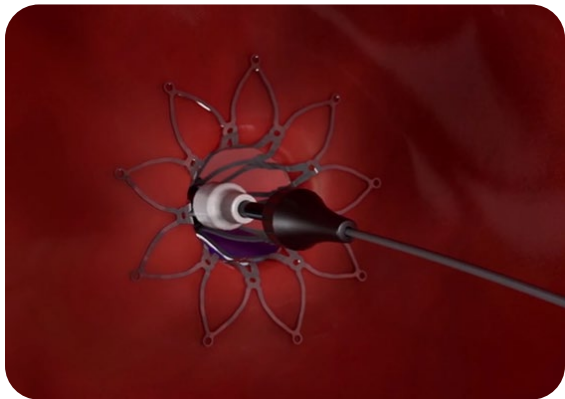
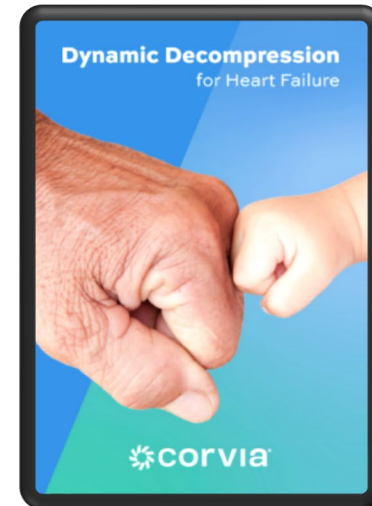


Duke Clinical Research Institute

<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*



LimFlow
Transforming CLTI

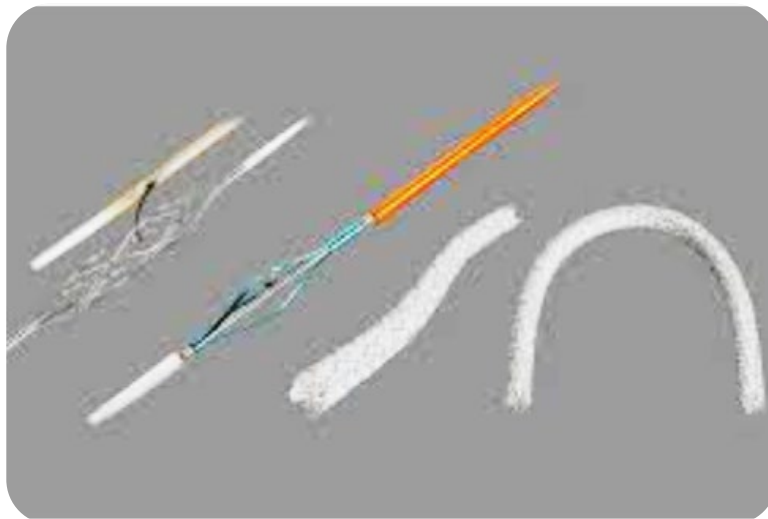


Figure 1. Overview of the authors' proposed conceptual framework for the study.

HB *Doing*

Harmonizing Device Classification POC

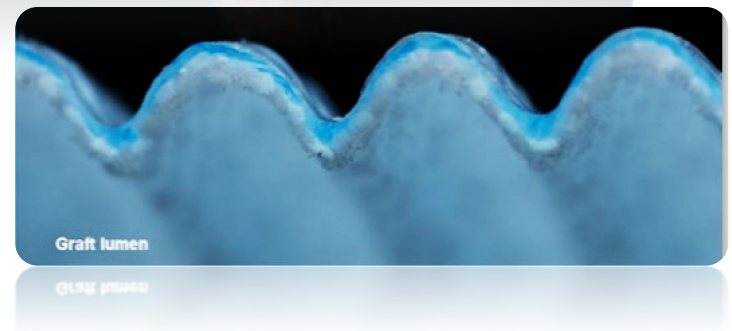
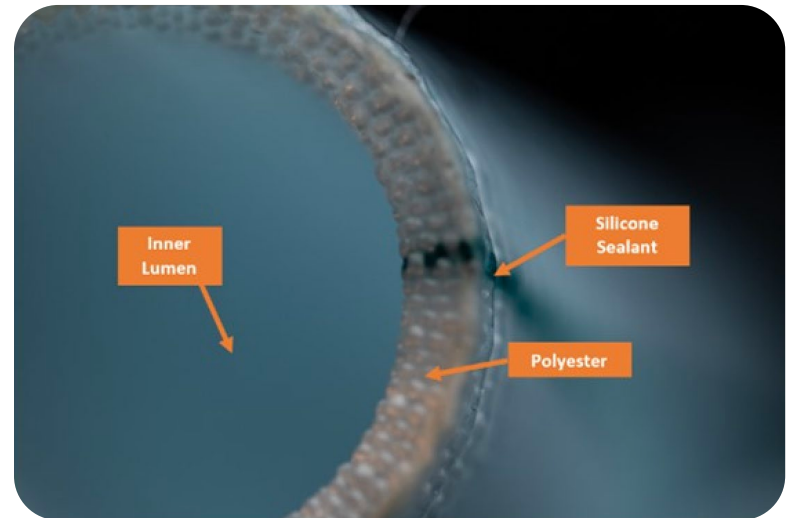


Duke Clinical Research Institute

FROM THOUGHT LEADERSHIP
TO CLINICAL PRACTICE



Diaxamed Vascular Graft POC





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)



Japan-USHBD East 2017 Think Tank Meeting



HBD-for-Children **Progress and Challenges**

Satoshi Yasukochi, MD
Nagano Children's Hospital
JSPCCS vice-president

December 7th, 2017

National Center for Global Health and Medicine (NCGM)

tct2017

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Cardiovascular
Research Foundation

tct2017

POC candidates

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



Duke Clinical Research Institute



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

Background: The Harmonization By Doing (HBD)-for-Children working group aims to foster a partnership among academia, industry and regulatory agencies to focus on streamlining medical device development and regulatory approval. Traditionally focused on development of pediatric medical devices, the “HBD-for-Children” program, with the goal of accelerating the development of pediatric medical devices for pediatric use lags behind that of adults in both countries.

Methods and Results: Activities of the program have included: (1) conducting a survey with industry to be challenges that constrain the development of pediatric medical devices; (2) categorizing pediatric medical device based on global availability and exploring concrete solutions for the early application and regulatory approval in 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 global introduction of pediatric medical devices for patients in a timely manner. Through the program, academia, industry and agencies can work together to facilitate innovative pediatric device development from a multi-stakeholder perspective and 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

Approved in Japan & USA

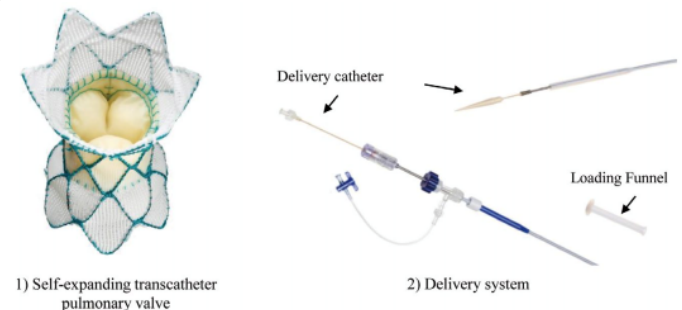


Figure 2. The Harmonization By Doing (HBD)-for-Children working group chose the Medtronic Harmony™ Transcatheter Pulmonary Valve (TPV) System as proof of concept (POC) and supports the process of its global development, including conducting a global clinical trial. The Harmony™ TPV system consists of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



HBD for Children: *Renata Medical Minima Stent POC*

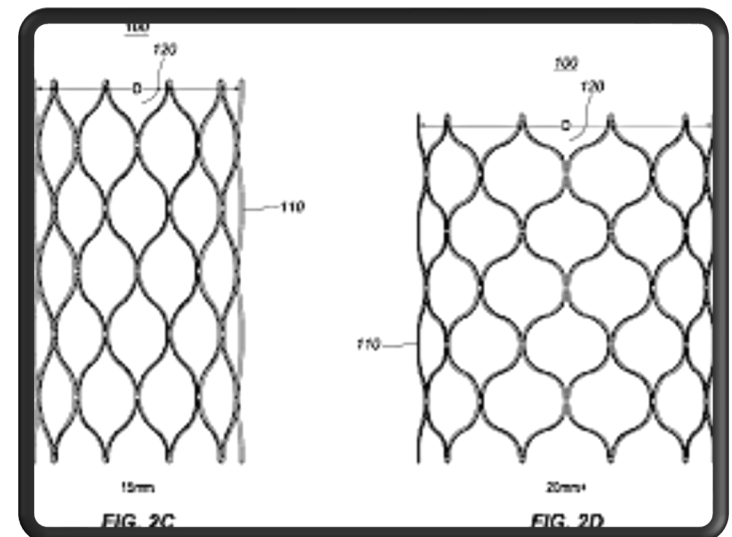
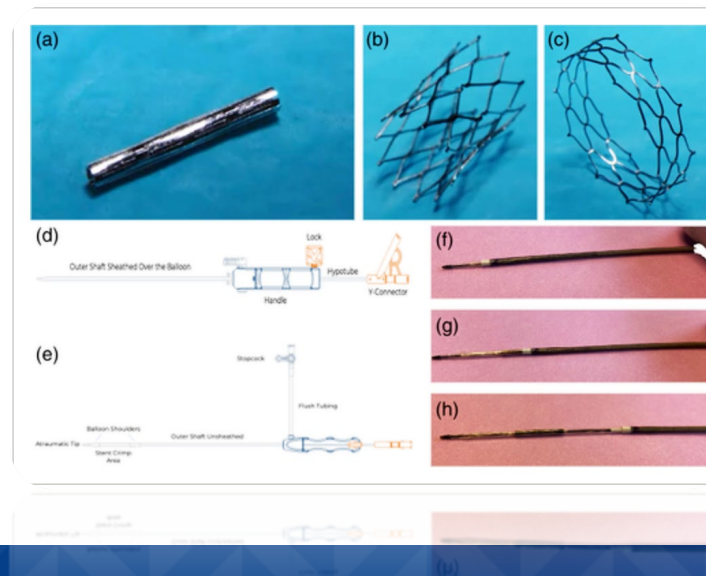


PEDIATRIC AND CONGENITAL HEART DISEASE | [Open Access](#) | CC BY-NC-ND 4.0

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

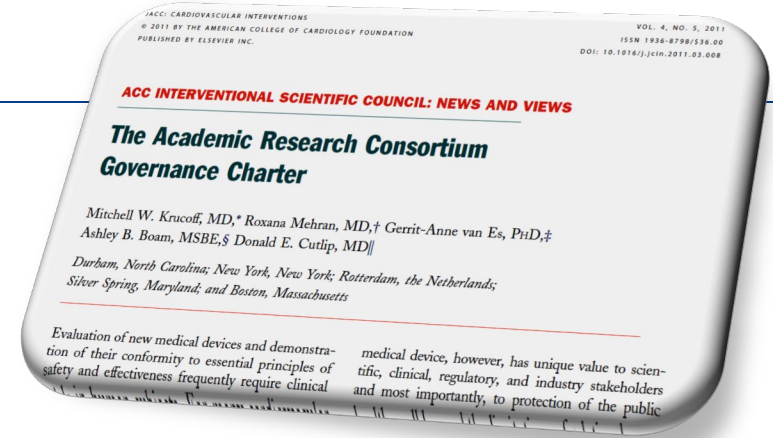
Evan M. Zahn MD, FACC, MSCAI ✉, Eason Abbott BS, Neil Tailor MD, Shyam Sathanandam MD, Dustin Armer BS

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



The Academic Research Consortium (ARC):

ARC for Children



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!*

