Introduction of Harmonization By Doing (HBD) 2003-2017

Mitchell W. Krucoff MD, FACC, FSCAI, FAHA
Professor of Medicine / Cardiology
Duke University Medical Center
Director, Cardiovascular Devices Unit
Director, MDEpiNet Coordinating Center
Duke Clinical Research Institute
mitchell.krucoff@duke.edu
September 2003

TCT 2003: 15th Annual Transcatheter Cardiovascular Therapeutics
September 15 - 19, 2003; Washington, DC

The Maureen and Mike Mansfield Foundation
Promoting Understanding and Cooperation in U.S.-Asia Relations since 1983

Program Overview

The Mansfield Fellowship Program—named after Mike Mansfield, former U.S. Ambassador to Japan, Senate Majority Leader, U.S. Senator and U.S. Congressman from Montana—is a first-of-its-kind program for both the United States and Japan. The two-year Fellowships enable U.S. federal government employees to develop an in-depth understanding of Japan, learn how its government works, and establish relationships with their counterparts in the government of Japan as well as in the business, professional and academic communities.
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, Labor, and Welfare (MHLW) and its review agency, the Pharmaceutical and Medical Devices Agency (PMDA)
- Duke Clinical Research Institute (DCRI)
- Japanese academic community
- Japanese and U.S. medical device industry

What is the HBD initiative?

The HBD initiative is a pilot project launched in December 2003 that seeks to harmonize the U.S. FDA and MHLW-PMDA premarket review of device cardiovascular technology. In order for HBD to harmonize, FDA will utilize parallel development, application submission, and joint review of device projects by FDA and MHLW-PMDA in conjunction with the above-named initial working groups to create guidance and discuss policy but to develop common protocols for additional guidance and discussion.
2003-2004: Japan MHLW launches PMDA
April 2004: PMDA Adopts Early Consultation

- Early discussion of clinical trial science & strategy
- Potential to coordinate with pre-IDE discussions in USA
June 2009: The “Collaborative Scheme” for parallel medical device development

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

ANNOUNCEMENT (June 23, 2009): U.S. – Japan Pilot Program Regarding Medical Device Collaborative Consultation and Review of Premarketing Applications

Japan MHLW/PMDA and U.S. FDA announced this week the launch of a bilateral pilot program on collaborative consultation and review of new cardiovascular devices. The goal of the pilot program is to advance both the speed and quality of clinical/statistical consultations and the regulatory review process for potential earlier market access and improved public health benefit. This collaboration would permit the scientific review staff of both MHLW/PMDA and FDA to discuss the contents of an individual submission in order to gain valuable regulatory information pertaining to device development and clinical trial design.

The Collaborative Scheme is one of several focused topics that will be discussed at the upcoming Japan-US Harmonization By Doing (HBD) West 2009 Meeting, July 16-17 at the FDA White Oak Campus.

- FDA announcement (English)
- MHLW announcement (tsuchi) (Japanese)
HBD: 15 Years & Beyond
Identifying & Transforming Barriers to Device Innovation

- Pre-competitive collaboration, trust & good will
- International regulatory convergence
- Research infrastructure efficiencies
- Structured data elements & definitions
- Stakeholder education & engagement
- Pilot “POC” projects

Medical Device Innovation: Prospective Solutions for an Ecosystem in Crisis
Adding a Professional Society Perspective

Mitchell W. Krucoff, MD,* Ralph G. Brindis, MD, MPH,† Patricia K. Hodgson, BA,* Michael J. Mack, MD,‡ David R. Holmes, Jr, MD§

Durham, North Carolina; San Francisco, California; Dallas, Texas; and Rochester, Minnesota

Krucoff MW et al, J Am Coll Cardiol Intv 2012;5:790–6
Uchida T et al, Circulation Journal 2013
HBD

Global regulatory convergence
Regulatory Convergence: Ethics, Methods and Science of Human Studies

Comparing GCP Regulations and Practices: Trials in the US and Japan
By Harmonization-by-Doing Working Group

GCP Convergence Improves Transportability of Medical Device Clinical Data
By Harmonization-by-Doing Working Group

Regulatory Focus, April 2010
Regulatory Focus, January 2013
HBD

Research infrastructure efficiencies
Advancing Research Infrastructure:
Study processes – time lines

- Protocol development
- Study design
- Site selection

- Steering Committee
  - DSMC
  - Safety Desk
  - CEC

- Site start-up
- Training
- Investigator and Coordinator Meeting

- Site Queries
- Monitoring

- Operations Team
  - Study Documents

- Contracting

- First Patient in
  - Randomization
  - CEC
  - Safety Reporting

- Last Patient in

Database lock
HBD Site Visits  March 2004: Shonan Kamakura
HBD

Stakeholder education & engagement
2004-2017: From “Japan-USA Barriers” to “Japan-USA Synergies”
December 2004: Kamakura Public Forum

Attention to the Patient’s Perspective
October 2007

11th Conference of the Global Harmonization Task Force
October 3-4, 2007

Tomiko Tawaragi
MHLW
About IMDRF

The International Medical Device Regulators Forum (IMDRF) was conceived in February 2011, as a forum to discuss future directions in medical device regulatory harmonization. It is a voluntary group of medical device regulators from around the world who have come together to build on the strong foundational work of the Global Harmonization Task Force on Medical Devices (GHTF). The Forum will accelerate international medical device regulatory harmonization and convergence.

In October 2011, representatives from the medical device regulatory authorities of Australia, Brazil, Canada, China, European Union, Japan and the United States, as well as the World Health Organization (WHO) met in Ottawa to address the establishment and operation of this new Forum.

A copy of the outcome statement from this meeting is available on the Therapeutic Goods Administration website.

IMDRF contacts

Chair:
Dr Larry Kelly
Group Coordinator
Monitoring and Compliance Group
Therapeutic Goods Administration
Australia
Email: imdrafchair@tga.gov.au

Secretariat:
Email: imdrafsecretariat@tga.gov.au
HB Doing

Pilot “POC” Projects:
Novel Informative Data-structure
“Harmonization By Data”
INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support): A New Paradigm for Translating Registry Data Into Clinical Practice

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

J Am Coll Cardiol. 2010; 56:738-740. doi:10.1016/j.jacc.2010.05.021
© 2010 by the American College of Cardiology Foundation
Peripheral Academic Research Consortium (PARC)

Face to Face Workshops
FDA Headquarters, White Oak, Maryland
February 2012 & 2013
Evaluation and Treatment of Patients With Lower Extremity Peripheral Artery Disease 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,‖ W. Schuyler Jones, MD,‖‖ Michael R. Jaff, DO,¶¶ W. Schuyler Jones, MD,¶¶ Roxana Mehran, MD,# ## Sanjay Misra, MD,*** Lars Norgren, MD,††† Jeffrey W. Olin, MD,## Thomas J. Powsic, MD, Ph.D,*, Kenneth Rosenfield, MD,††† John Runyan, 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, †††† Mitchell W. Krucoff, MD,* Mami Ho, MD, PhD, Koji Ikeda, PhD,¶ Fumiaki Ikomo, MD, Masayuki Kawahara, MD, Robert A. Lookstein, MD,# Roxana Mehran, MD,# ## Sanjay Misra, MD,*** Lars Norgren, MD,††† Jeffrey W. Olin, MD,## Thomas J. Powsic, MD, Ph.D,*, Kenneth Rosenfield, MD,††† John Runyan, 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, †††† 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 and other stakeholders, has collaborated to develop a set of consensus definitions to facilitate research and clinical practice.

Integrated Definitions & Registries: Harmonization By Data

Tracking Real-World Outcomes

The TVT Registry™ is a new benchmarking tool developed to track patient safety and introduced transcatheter aortic valve replacement (TAVR) procedure. Created by The American College of Cardiology (ACC), the TVT Registry is designed to monitor the treatment of aortic stenosis.

Employing a first-of-its-kind transcatheter heart valve technology, TAVR provides a consideration to be impossible for conventional aortic valve replacement surgery.

Through the capture and reporting of patient demographics, procedure details, and Registry provides a data repository capable of delivering insight into clinical practice.

For Participating Hospitals, the TVT Registry Offers:

- Quarterly reports containing practice patterns, demographics and outcomes of patient performance with that of the national experience
- Standardized, evidence-based data elements and definitions
- A web-based data collection tool
- A wide range of other quality improvement tools to advance quality improvement

The TVT Registry Measures:

- Patient demographics, provider and facility characteristics
- History/risk factors, cardiac status and detailed health status
- Well-defined indications for the procedure
- Pre, intra and post procedure data points and adverse event rates
- Outcomes at 30 days and one year

Providing an Invaluable Data Source

August 24, 2015
NEST: The Vision
Real World Evidence of Device Benefit/Risk, Safety

- More real world
- Less unique effort & cost
- More value across ecosystem:
  - Regulatory decisions
  - Best practice guidelines
  - Payer decisions
  - Patient information

Learning model:
- Use/re-use structure solutions
- Linked architecture

International application

JAMA Published online July 11, 2016
MDEpiNet PPP PASSION CV Registries
Program Launch
October 2014

Predictable And SuStainable Implementation Of National CardioVascular Registries:

- Coronary
- Valves
- ICD/CRT
- Peripheral/Endo
Registry Assessment of Peripheral Interventional Devices (RAPID)

Jack L. Cronenwett, M.D.
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
RAPID Partners

• **3 Major U.S. Societies / Registries**
  • American College of Cardiology (ACC)
    • National Cardiovascular Disease Registry (NCDR)
  • Society of Interventional Radiology (SIR)
    • National Interventional Radiology Quality Registry (NIRQR)
  • Society for Vascular Surgery (SVS)
    • Vascular Quality Initiative (VQI)

• **5 International Partners**
  • Japan’s Pharmaceuticals and Medical Devices Agency (PMDA)
  • Global Medical Device Nomenclature Agency (GMDNA)
  • Australian Vascular Audit
  • German Vascular Society
  • Northern German Association for Vascular Medicine
RAPID Partners

- 7 U.S. Agencies
  - FDA (CDRH pre- and post-market, and CDER)
  - Agency for Healthcare Research and Quality (AHRQ)
  - Centers for Medicare and Medicaid Services (CMS)
  - Department of Defense (DOD) Healthcare Resources
  - Office of the National Coordinator (ONC)
  - National Heart, Lung and Blood Institute (NHLBI)
  - National Library of Medicine (NLM)

- 6 EHR / Registry / Clinical Research Companies
  - Epic
  - M2S
  - MedStreaming
  - Healthjump
  - Boston Biomedical Assoc.
  - Novella Clinical, Quintiles
RAPID Partners

• 12 Device Manufacturers
  • Abbott
  • Aortic Medical Inc.
  • Avinger
  • Boston Scientific
  • Cardiovascular Systems Inc
  • Cook Medical
  • CR Bard
  • Medtronic
  • Spectranetics Corp
  • Terumo
  • Volcano Corp/Phillips Health Technology
  • WL Gore
<table>
<thead>
<tr>
<th>Data Element Label</th>
<th>Data Element Definition</th>
<th>Value set</th>
<th>Definitions of the elements of the value set</th>
<th>Reference source</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONDITION - MODIFIED RUTHERFORD CLASSIFICATION</td>
<td>Categorical description of the symptoms associated with the obstruction of the lumen of the peripheral arteries (NCI C78533).</td>
<td>0</td>
<td>Asymptomatic: documented peripheral arterial disease, without symptoms of claudication or ischemic pain</td>
<td>Adapted from VQI PVI registry, Rutherford J Vasc Surg 1997;26:517-38, ACC/AHA PAD Data Standards Circulation 2012;125:395-467, and PARC J Am Coll Cardiol 2015.</td>
</tr>
<tr>
<td>Modified Rutherford Category</td>
<td></td>
<td>1</td>
<td>Mild claudication: ischemic limb muscle pain that does not limit walking, or limits walking only after &gt;2 blocks (&gt;600 feet, or 2 football fields)</td>
<td></td>
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<tr>
<td></td>
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<td>2</td>
<td>Moderate claudication: ischemic limb muscle pain that limits walking to 1-2 blocks (300-600 feet, or 1-2 football fields)</td>
<td></td>
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<td></td>
<td></td>
<td>3</td>
<td>Severe claudication: ischemic limb muscle pain that limits walking to &lt;1 block (&lt;300 feet, or 1 football field)</td>
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<td></td>
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<td>4</td>
<td>Ischemic rest pain: pain in the distal foot at rest felt to be due to limited arterial perfusion</td>
<td></td>
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<td></td>
<td>5</td>
<td>Minor tissue loss: nonhealing ischemic ulcer(s) on distal leg, or focal gangrene with diffuse pedal ischemia</td>
<td></td>
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<td></td>
<td>6</td>
<td>Major tissue loss: ischemic gangrene extending above TM level, functional foot no longer salvageable without extensive revascularization efforts</td>
<td></td>
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</tbody>
</table>
HB Doing

Pilot “POC” Projects:
Clinical Trials
2005: Endeavor Japan (Medtronic)

- Identical inclusion/exclusion
- Identical endpoints
- Identical core laboratories
- Enhanced poolability
- Enhanced interpretability

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, Jeffrey J. Popma, John Alexander, Mitchell W. Krucoff, on behalf of the ENDEAVOR Japan Investigators

Cardiovascular Revascularization Medicine
Enhanced poolability & interpretability

- Concomitant enrollment
- Identical inclusion/exclusion
- Identical endpoints
- Identical core laboratories
2009: Zilver PTX (Cook Medical)

Single protocol global RCT

Randomized Study (IDE G030251)  
Zilver PTX or PTA  
n = 479  
Randomization

PTA  
n = 238  
Suboptimal PTA  
n = 120  
Randomization

Optimal PTA  
n = 118

Zilver PTX  
n = 241

Single Arm Study

Zilver® PTX® Drug-Eluting Peripheral Stent - P100022

This is a brief overview of information related to FDA’s approval to market this product. See the links below to the Summary of Safety and Effectiveness Data (SSED) and product labeling for more complete information on this product, its indications for use, and the basis for FDA’s approval.

**Product Name:** Zilver® PTX Drug-Eluting Peripheral Stent  
**PMA Applicant:** Cook, Inc.  
**Address:** 750 Daniels Way, P.O. Box 489, Bloomington, IN 47402-0489  
**Approval Date:** November 14, 2012  
To evaluate the performance of the Coronary OAS Micro Crown in treating *de novo*, severely calcified coronary lesions

- Prospective, single-arm, multi-center Investigational Device Exemption (IDE) study conducted in Japan and the USA
- Harmonization by Doing (regulatory collaboration between Japan and the USA)

100 patients enrolled

<table>
<thead>
<tr>
<th></th>
<th>USA</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>74</td>
<td>26</td>
</tr>
<tr>
<td>Sites</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

1-year follow-up completed* (93/100)

*6 subjects died and 1 subject lost to follow-up
Harmonized Assessment by Randomized Multicenter Study of OrbusNEich’s COMBO StEnt

Japan-USA *HARMONEE: Primary Report*
Of A Randomized Trial of a Bioabsorbable Polymer-Based DES With A Luminal CD34+ Antibody Coating vs A Durable Polymer-Based DES in Patients With Coronary Artery Disease

The COMBO Plus Dual Therapy Stent
Enrollment & Follow-Up: ITT population

33 sites
439 pts (77%)

572 patients randomized

17 sites
133 pts (23%)

287 COMBO

285 EES

3 (1.0%) non-protocol stent

2 (0.7%) withdrew or lost to FU

285 (99.3%) 1 year clinical FU

271 (95.1%) 1 year angio FU

261 (91.6%) 1 year FFR

Cohort A&B 1 year OCT FU
(n=70)
65 (92.9%)

279 (97.9%) 1 year clinical FU

262 (93.9%) 1 year angio FU

256 (91.8%) 1 year FFR

Cohort A&B 1 year OCT FU
(n=70)
63 (90.0%)
HB Doing

Pilot “POC” Projects:
New Directions
Early Feasibility Studies: Can We Do Together?

Investigational Devices (IDEs) for Early Medical Device Clinical Including Certain First In Human (FIH) Studies

Guidance for Industry and Drug Administrators

Document issued on: October


Based on our experiences of EFS in Japan and discussions in HBD activity, we’d like to build up the successful framework of EFS and make the environment to perform it better in Japan.

EFS in Japan: PMDA View

Sara Takahashi
Reviewer
Office of Medical Devices III
Pharmaceuticals and Medical Devices Agency (PMDA), Japan
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)
Investigator-oriented clinical trial
Collaborative clinical trial
Enlighten and education
Promote Certification system
Promote approval process & regulation
Simplified of clinical trial
Adjusting regulation between US and Japan

HBD for children

Industry

Public grant

Academia

Research & development of new device

Cost of approval process
Market scale
Contribution to society

Investigator-oriented clinical trial
Collaborative clinical trial
Enlighten and education
Promote Certification system
HBD-Children Work Report & schedule

- **2016**
  - Kick-Off Meeting At PMDA

- **2017**
  - Session of HBD-C At CRT 2017
    In Washington
    On 2/20/2017
  - Session of HBD-C At TCT2017
    In Denver
    On 10/30/2017
  - Dec 8
    HBD East 2017
    Think Tank Meeting
  - Chaired by Yasukochi S (JSPCCS) and Ibrahim N (FDA)
    Ing F, Ringel R, (US)
    Sugiyama H (JSPCCS)

- **2018**
  - Mar 3-6
    CRT 2018
    In Washington DC
  - Jul 5-7
    JSPCCS 2018
    in Yokohama, Japan
  - Sep 5-8
    PICS 2018
    in Las Vegas
    Or
    Sep 23-25
    TCT2017
    In San Diego
  - Tentative nominee
    - HBD session for HBD-for-children
    - Nicole Ibrahim (FDA)
    - Frank Ing (US academia)
    - Richard Ringel (US academia)
    - Tom Forbes (US academia)
Introduction and achievement of HBD-for-Children

Yasuko Nakamura
Reviewer, Office of Medical Devices III
Pharmaceuticals and Medical Devices Agency (PMDA)
An established scheme ↔ HBD

- Development of pediatric medical device tends to delay in the U.S. and Japan but there are **high needs** in clinical institutions.
- Regulatory authorities have to resolve problems in the U.S. and Japan.

**HBD has made a great contribution to promote innovative medical device development for ADULT!**

We will find problems of development of pediatric medical devices in the U.S. and Japan and propose solutions *by Doing.*
<table>
<thead>
<tr>
<th>POC candidate</th>
<th>Covered CP Stent</th>
<th>Medtronic Melody Transcatheter Pulmonary Valve</th>
<th>AMPLATZER muscular VSD occluder</th>
</tr>
</thead>
<tbody>
<tr>
<td>industry</td>
<td>NuMED</td>
<td>Medtronic</td>
<td>ST.JUDE MEDICAL</td>
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</tbody>
</table>

![Covered CP Stent Image](image1.png)
![Medtronic Melody Transcatheter Pulmonary Valve Image](image2.png)
![AMPLATZER muscular VSD occluder Image](image3.png)
Remember, Luke Skywalker:

“Don’t try... Do!”

Harmonization By Doing

Thank you!
Introduction of Harmonization By Doing (HBD) 2003-2017

Mitchell W. Krucoff MD, FACC, FSCAI, FAHA
Professor of Medicine / Cardiology
Duke University Medical Center
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mitchell.krucoff@duke.edu
Flow to the approval

IDE application approval

U.S.

Pre-IDE consultation consultation
meeting

Clinical trial

Japan

consultation consultation

application approval
Clinical Evaluation of New Medical Devices

United States
Canada
Mexico
Guatemala
El Salvador
Panama
Dominica
Venezuela
Columbia
Brazil
Paraguay
Argentina
Chile
Uruguay

U.K.
Ireland
France
Spain
Portugal
Netherlands
Belgium
Germany
Denmark
Norway
Iceland
Finland
Poland
Czech Rep.
Switz.
Austria
Slovenia
Italy
Hungary
Romania
Bulgaria
Greece
Ukraine
Turkey
Israel
Estonia
Latvia
Lithuania
Georgia

United Arab Emirates
India
China
Thailand
Malaysia
Singapore
Indonesia
Hong Kong
Australia
New Zealand
South Africa
Taiwan
Japan

Redundancy
Added Cost
Time Delay
Limited knowledge
...to develop and maintain national and international scientific infrastructure and...methodological approaches...to overcome and eliminate discontinuities in evaluation and surveillance that currently exist within the TPLC...