The 17th AHWP Annual Conference
Chinese Taipei
Nov. 2-6, 2012

Elements of a successful registry in the post-market surveillance system:

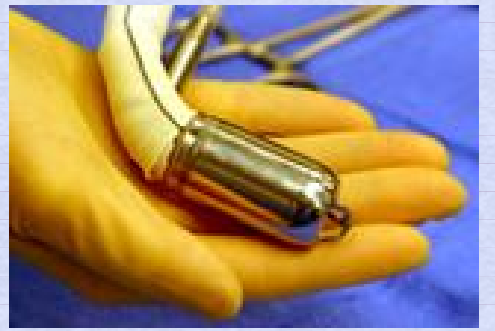
Combining Postmarket Safety Information to Support Ongoing Innovation

Atsushi TAMURA, PhD
International Coordination officer for Medical Devices,
Pharmaceuticals and Medical Devices Agency

How Do You Measure An Innovation?

Pre-implant Device Strategy

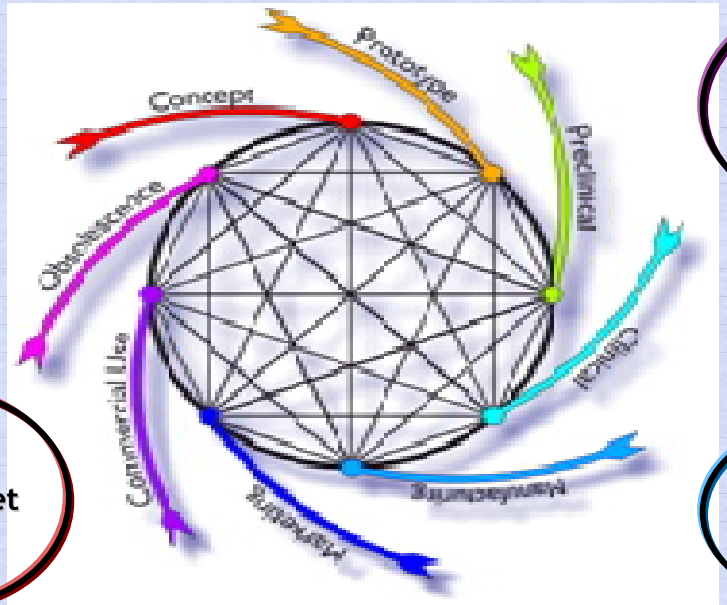
- Bridge to transplantation (BTT)
- Bridge to candidacy (BTC)
- Destination therapy (DT)
- Bridge to recovery (BTR)



Clinical Evaluation of MCSDs in Japan (EVAHEART, Jarvik2000, DuraHeart, HeartMate XVE)

From the Experience of LVAD

- *INTERMACS*
- HBD-WG2
- J-MACS



Encouraging Product Development

Ensuring Postmarket Safety

Enabling Access to Innovation

"Implantation of an MCSS is not a simple, time-limited treatment episode. Because of the patient's total dependence on the device and because problems can occur at any time, clinical trial subjects should be followed closely during the trials: they and other MCSS patients should be followed, through a *registry*, for the remainder of their lives...Maintaining a registry of MCSS recipients should be considered a routine aspect of this care…The committee recommends that *NHLBI*…support long term follow up studies of an adequate sample of MCSS patients."

The Artificial Heart: Prototypes Policies and Patients;

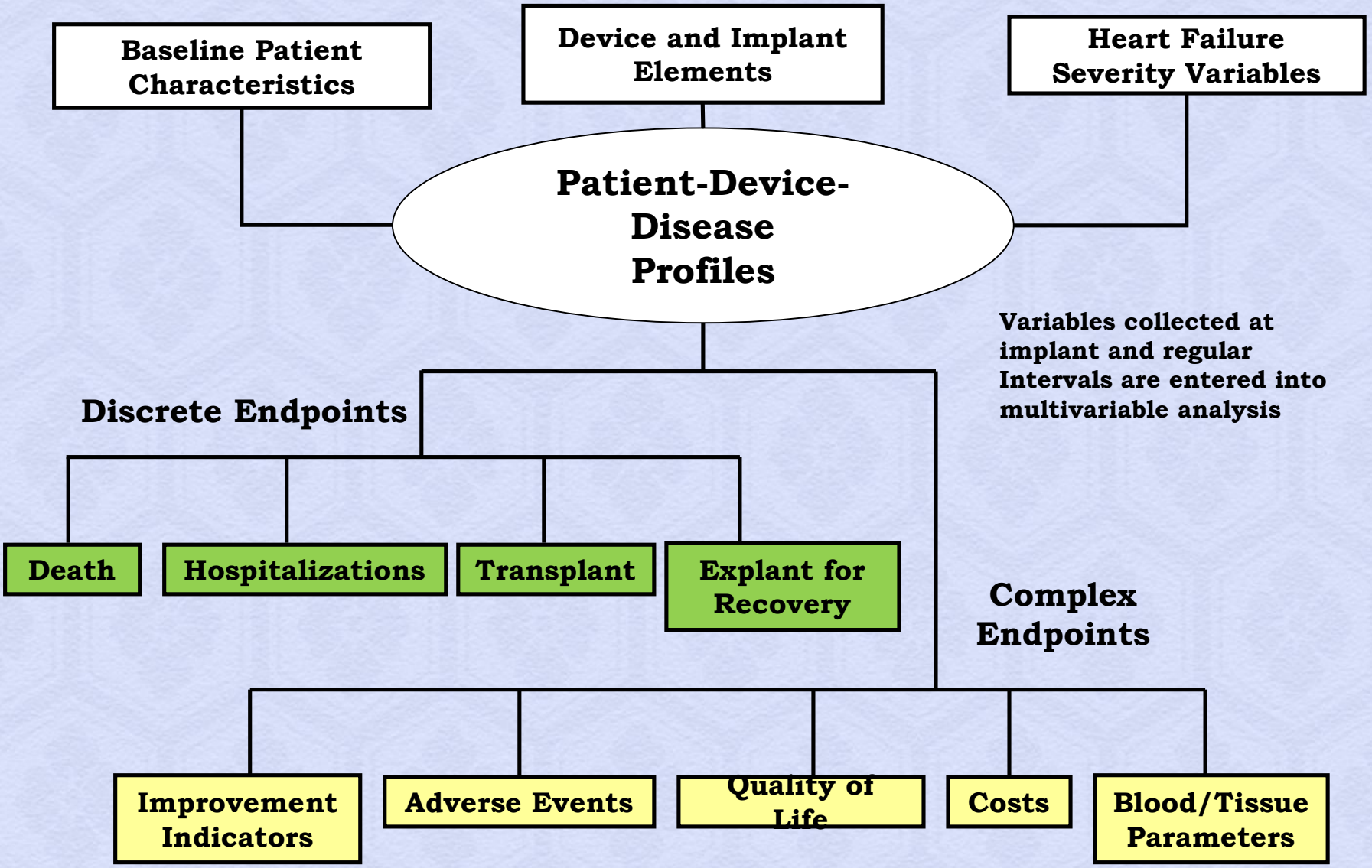
Institute of Medicine Report, 1991.

INTERMACS

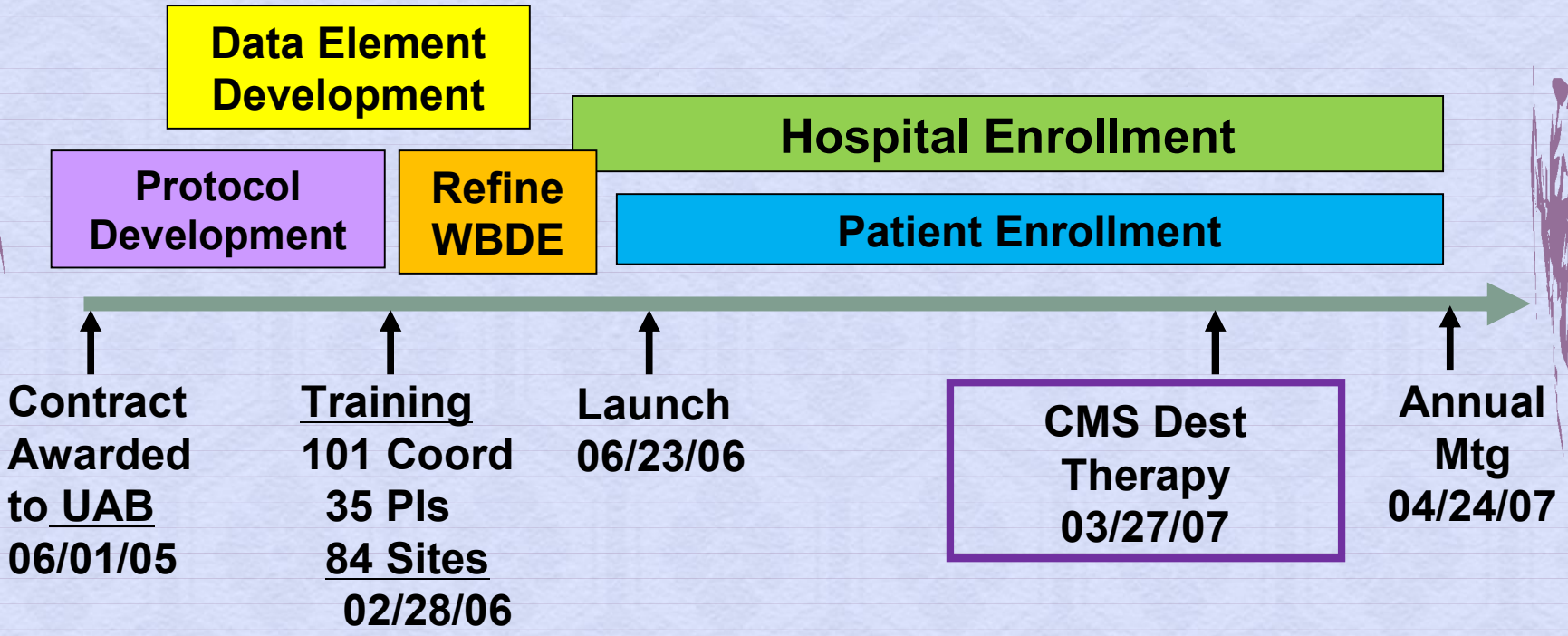
An Effective Post-Market Tool

- Prospective NIH funded registry
- Provides Enhanced Surveillance:
  - AEs, Device Malfunctions
  - QOL
  - Survival
- Develops clinical "Best Practices" (reducing complications)
- Provides means for designing & conducting post-approval studies in cost efficient way
- Allows manufacturers to obtain data from INTERMACs to fulfill post-market requirements

Baseline Variables And Endpoints



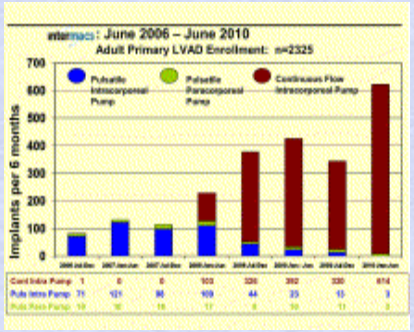
Timelines and Updates

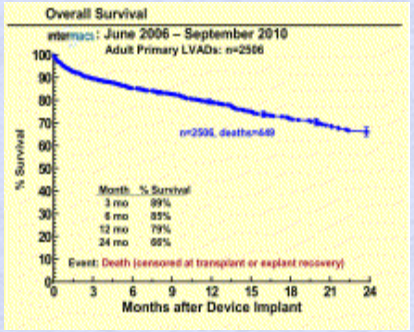


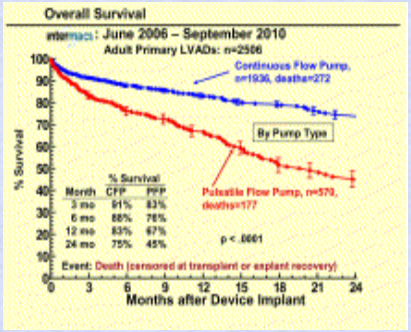
www.intermacs.org	July 2008	September 2011
Total Sites Currently Activated	100	119
Number of Patients Entered	1780	5258

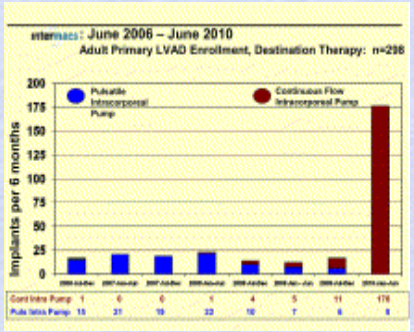
Third INTERMACS Annual Report:

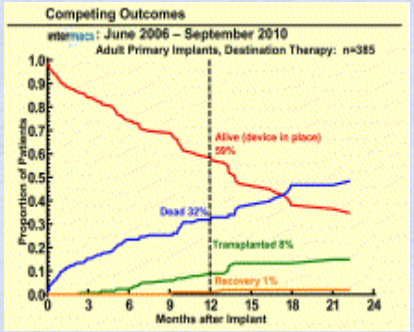
Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, Ulisney KL, Baldwin JT, Young JB. J Heart Lung Transplant. 2011 Feb;30(2):115-23.

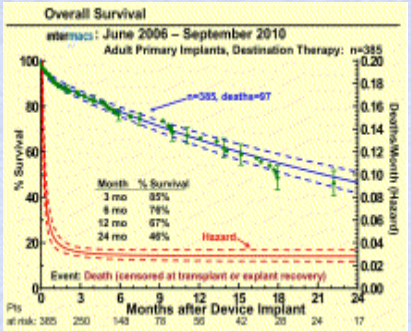


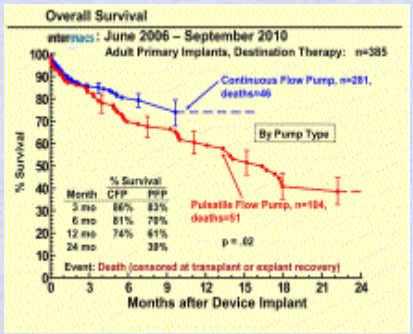


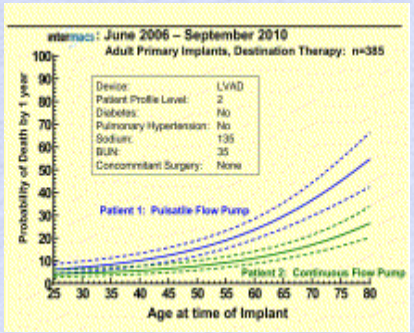


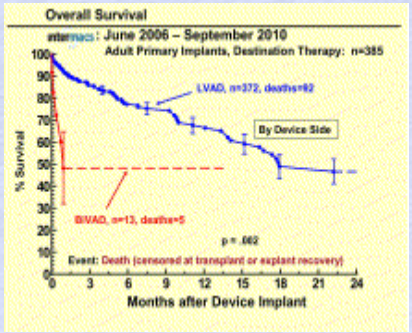








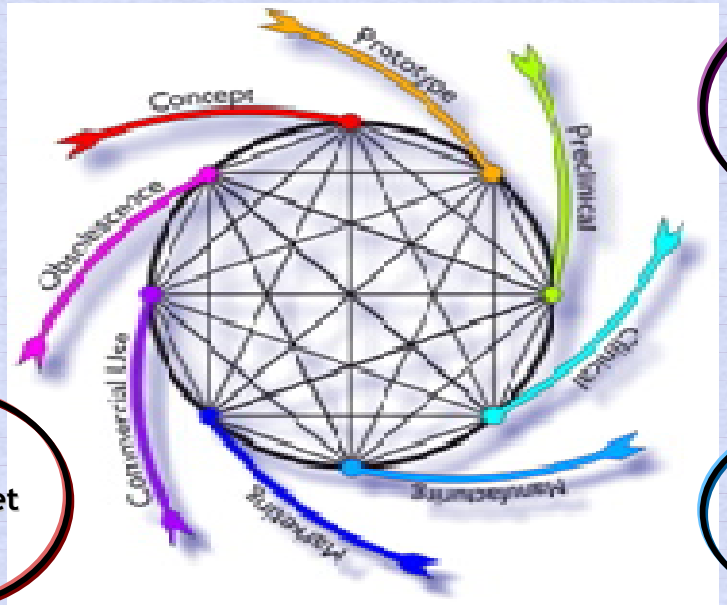




Transition from pulseatile pump to rotational pump.
Evaluation of risk/benefit/cost for BTR.

From the Experience of LVAD

- INTERMACS
- *HBD-WG2*
- J-MACS



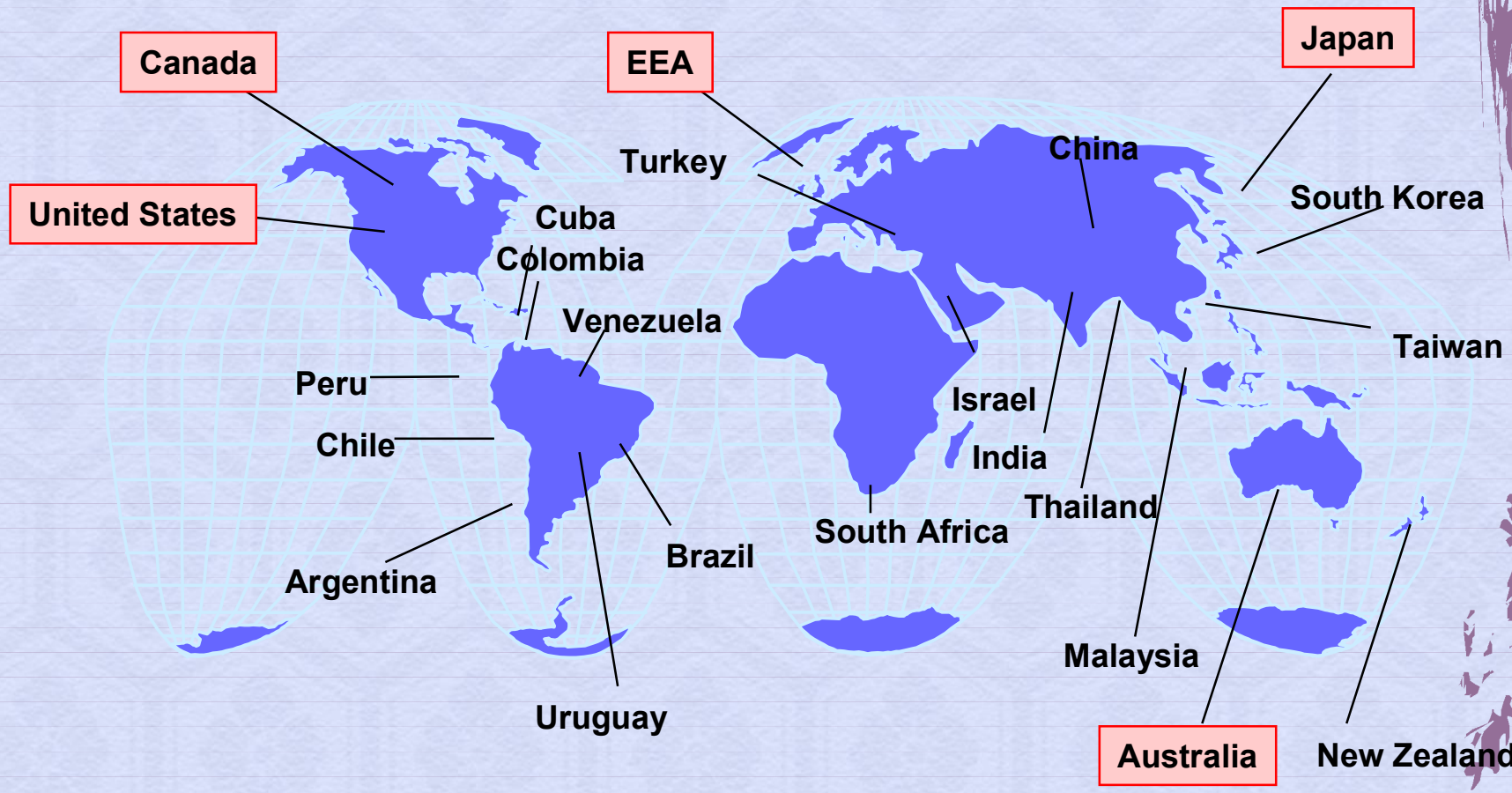
Encouraging Product Development

Ensuring Postmarket Safety

Enabling Access to Innovation

GHTF and IMDRF

Proliferation of regulatory requirements



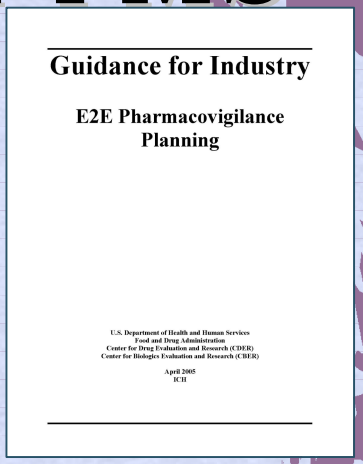
*19 → 29 Members in May 2004

Harmonized Guidances for PMS

- Pharmaceuticals
  - ICH-E2E
  - Safety Specification
  - Pharmacovigilance Plan

    http://www.fda.gov/RegulatoryInformation/Guidances/ucm129411.htm
- Medical Devices
  - GHTF-SG5/N4
  - Post Market Clinical Follow-up Studies

    http://www.ghtf.org/sg5/sg5-final.html

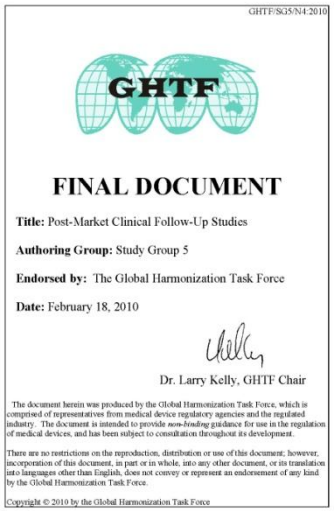


Guidance for Industry

E2E Pharmacovigilance Planning

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2005
ICH



GHTF/SG5/N4:2010

GHTF

FINAL DOCUMENT

Title: Post-Market Clinical Follow-Up Studies

Authoring Group: Study Group 5

Endorsed by: The Global Harmonization Task Force

Date: February 18, 2010

Dr. Larry Kelly, GHTF Chair

The document herein was produced by the Global Harmonization Task Force, which is comprised of representatives from medical device regulatory agencies and the regulated industry. The document is intended to provide *non-binding* guidance for use in the regulation of medical devices, and has been subject to consultation throughout its development.

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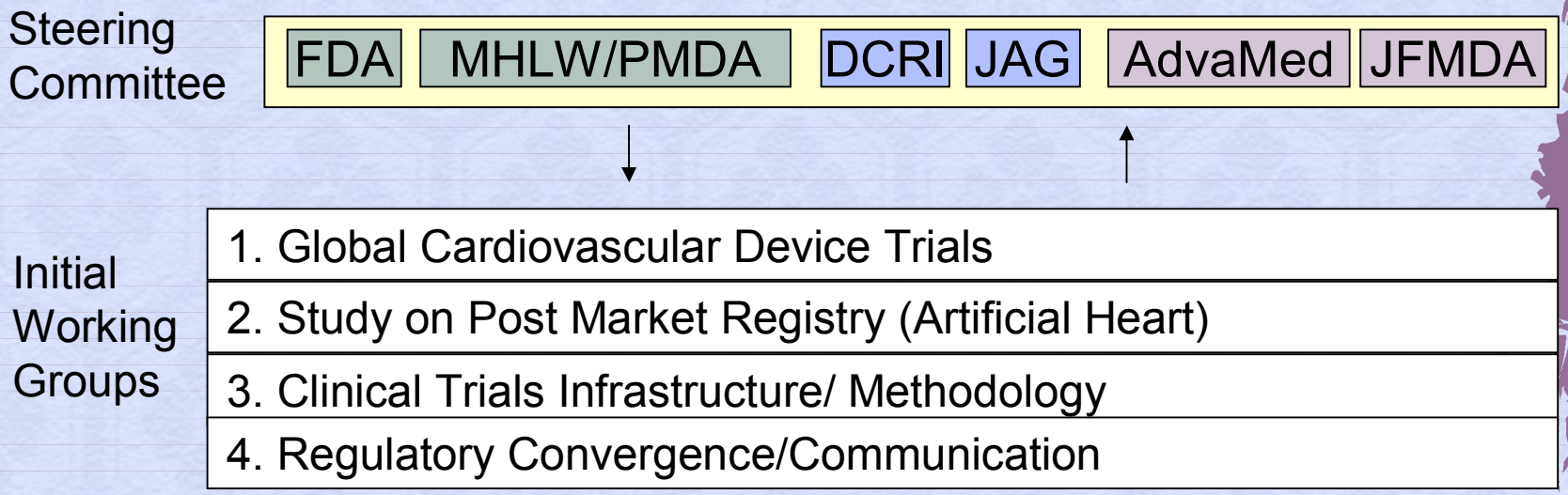
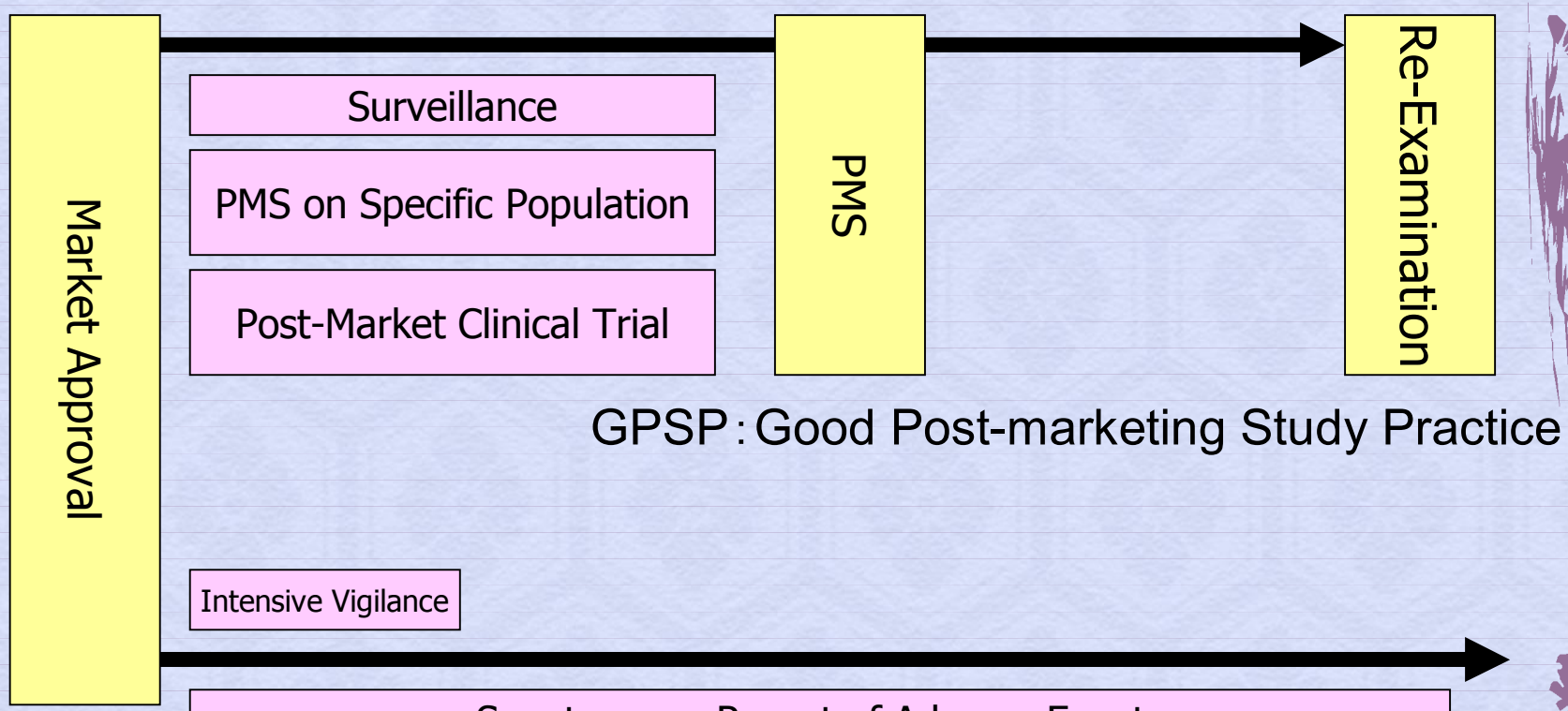
1

Harmonization by Doing (HBD)

- Japanese Circulation Society - April 2004
- Japanese Coronary Association - December 2005
- Think Tank in Tokyo - December 2005
- FDA, MHLW, Japanese academia discuss scientific concerns and regulatory issues – July 2006
- HBD-West meeting in Durham, NC– January 2007
- HBD-East meeting in Tokyo – July 2008
- HBD-West meeting in FDA White Oak – July 2009



Pharmaceuticals Affairs Law and PMS



The NEW ENGLAND JOURNAL of MEDICINE

THREE-YEAR FOLLOW-UP AFTER IMPLANTATION OF METALLIC CORONARY-ARTERY STENTS

TAKESHI KIMURA, M.D., HIROYOSHI YOKOI, M.D., YOSHIHISA NAKAGAWA, M.D., TAKASHI TAMURA, M.D., SATOSHI KABURAGI, M.D., YOSHIHIRO SAWADA, M.D., YASUKAZU SATO, M.D., HIROATSU YOKOI, M.D., NAOYA HAMASAKI, M.D., HIDEYUKI NOSAKA, M.D., AND MASAKIYO NOBUYOSHI, M.D.

Abstract *Background.* Coronary-artery stents are known to reduce rates of restenosis after coronary angioplasty, but it is uncertain how long this benefit is maintained.

Methods. We evaluated clinical and angiographic follow-up information for up to three years after the implantation of Palmaz–Schatz metallic coronary-artery stents in 143 patients with 147 lesions of native coronary arteries.

Results. The rate of survival free of myocardial infarction, bypass surgery, and repeated coronary angioplasty for stented lesions was 74.6 percent at three years. After 14 months, revascularization of the stented lesion was necessary in only three patients (2.1 percent). In contrast, coronary angioplasty for a new lesion was required in 11 patients (7.7 percent). Follow-up coronary angiography of 137 lesions at six months, 114 lesions at one year, and 72 lesions at three years revealed a decrease in minimal luminal diameter from 2.54±0.44 mm immediately after stent implantation to 1.87±0.56 mm at six months, but no further decrease in diameter at one year (in patients with paired angiograms, 1.95±0.49 mm at both six months and one year). Significant late improvement in luminal diameter was observed at three years (in patients with paired angiograms, 1.94±0.48 mm at six months and 2.09±0.48 mm at three years; $P<0.001$).

Conclusions. Clinical and angiographic outcomes up to three years after coronary-artery stenting were favorable, with a low rate of revascularization of the stented lesions. Late improvement in luminal diameter appears to occur between six months and three years. (N Engl J Med 1996;334:561-6.)

SINCE the initial report by Sigwart et al.[1] of the placement of metallic stents in coronary arteries, coronary-artery stenting has been shown to optimize

had multiple stents, 16 patients had saphenous-vein grafts as their target lesions, and 143 patients underwent the implantation of single Palmaz–Schatz stents in 147 native coronary lesions. All the patients

Kimura, T. et al. N Engl J Med 1996;334:561-567

HBD Working Group 2

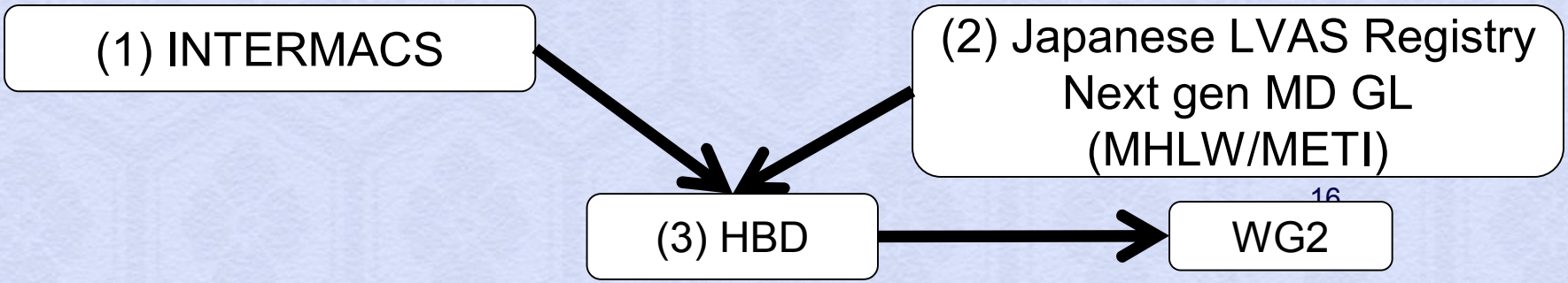
Post-Market Registries

co-chair: Eric Chen(FDA), Takeshi Nakatani(NCVC), Kazuhiro Sase(Juntendo)

- To conduct harmonized post-market studies in Japan and the United States to obtain “global” data on mechanical circulatory support devices (MCSD) usage in patients
- Continue discussions with participants regarding the interest of Japanese centers to exchange MCSD data with INTERMACS
- Japanese data can help with development of control data and management of patients

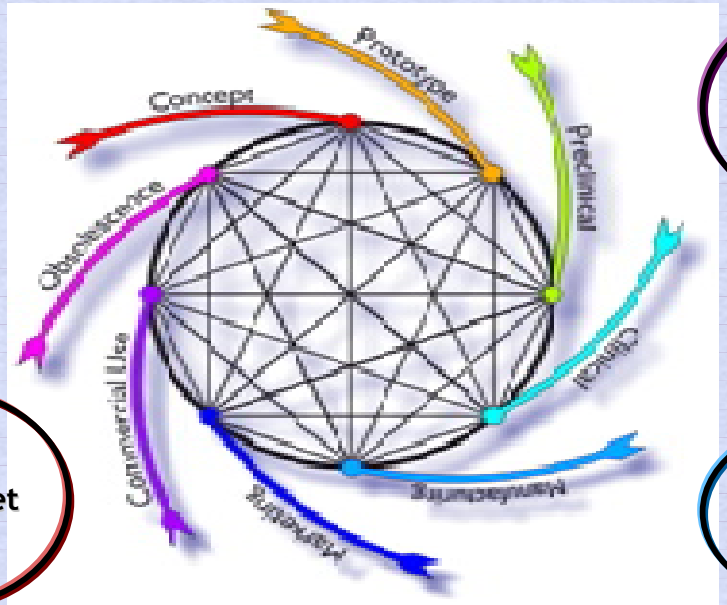
HBD-WG2 Early Discussions

- July 2006
  - FDA encourages INTERMACS to begin discussions with Japan on collecting Japanese post-market MCSD data (Rockville, MD)
- October 2006
  - MHLW and Japanese academia visit INTERMACS @ UAB
- October 2006
  - Working Group 2 meeting with INTERMACS (Rockville, MD)
- January 2007
  - HBD West Think Tank (Durham, NC)
- October 2007
  - Japanese Society of Artificial Organs (Osaka, Japan)
- July 2008
  - HBD East meeting (Tokyo, Japan)
- February 2010
  - GHTF SG5 N4 (Post-Market Clinical Follow-up Studies Document)



From the Experience of LVAD

- INTERMACS
- HBD-WG2
- *J-MACS*



Encouraging Product Development

Ensuring Postmarket Safety

Enabling Access to Innovation

Second Mid-term Plan of PMDA

(FY2009 to 2013)

http://www.pmda.go.jp/english/about/midterm.html

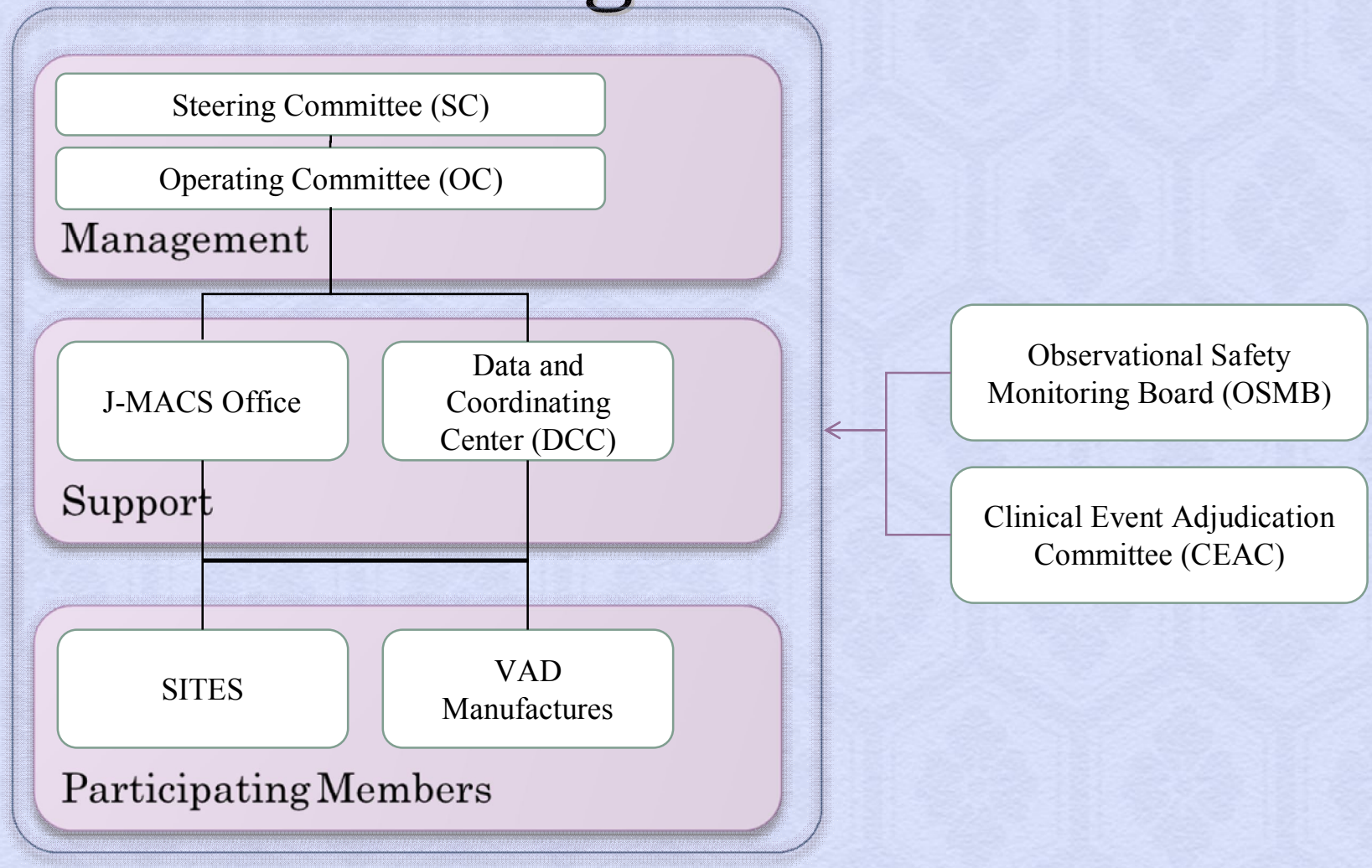
- Strengthening and Improvement of Safety Measures Services

  (b) Organization of information on adverse drug reactions and systemization of evaluation and analysis

  The Agency shall:

  - Construct a system for gathering and evaluating data on the operational status of high-risk, implantable tracking medical devices (implantable ventricular-assist devices), such as the occurrence rate of malfunctions over time, and appropriately utilize such system in the development of safety measures.

J-MACS Organizational Chart

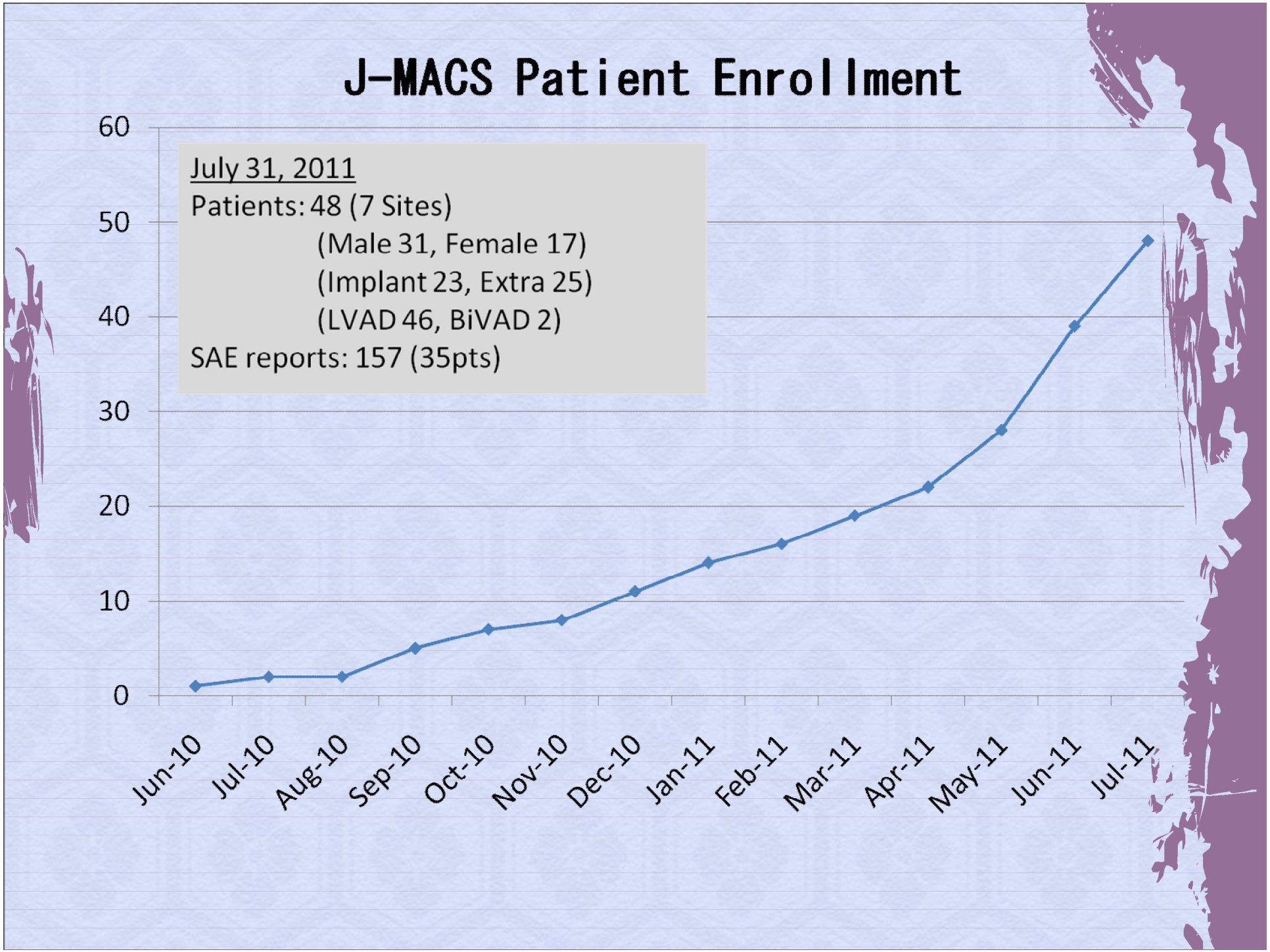


Chief Researcher: Takeshi Nakatani, MD, PhD
(Dept. of Transplantation, National Cerebral and Cardiovascular Center)
Vice-chief Researcher: Kazuhiro Sase, MD, PhD (Clinical Pharmacology, Juntendo Univ.)
Hiroaki Oshiyama (Japan Medical Devices Manufacturers Association)

Registerd Sites for J-MACS (2011/9/1)

Site	Principal Investigator	IRB	Start
Tohoku Univ	Yoshikatsu Saiki	Approved	2010/5
Tokyo Univ	Minoru Ono	Approved	2010/11
Tokyo Women's Medical U	Satoshi Saito	Approved	2010/12
National Cardiovascular Ctr	Takeshi Nakatani	Approved	2010/8
Osaka Univ	Yoshiki Sawa	Approved	2011/1
Kyushu Univ	Ryuji Tominaga	Approved	2010/7
Saitama Medical U	Hiroshi Niinami	Approved	2011/7
Hokkaido Univ	Yoshiro Matsui	Approved	2011/6
Gunma Pref Cardiovasc Ctr	Tatsuo Kaneko	Approved	2011/9
Hyogo College of Med	Yuji Miyamoto	Approved	
Sakurabashi-Watanabe HP	Takafumi Masai	Approved	
Tokyo Medical and Dental U	Hirokuni Arai	Applying	

J-MACS Patient Enrollment



Summary

- For innovative devices, well-designed post-market registries provide feedback to clinicians, manufacturers, and regulatory agencies regarding the safety, performance, and cost issues.
- Japan-US HBD helped J-MACS to be poolable with INTERMACS, to offer harmonized definitions on safety and performance as well as complementary database including long-term follow-ups.
- The experience with HBD/WG2 can be generalized to other innovative devices and therapeutic areas.

Future Direction(s)

	Focus	US resources	Japanese resources	HBD/POC
WG1	PCI PPI	ARC PARC	J-Cypher R JET	SPIRITS ENDEAVOR (?)
WG2	LVAD TAVR (?)	INTERMACS VARC NCDR/ACC	MHLW /METI (?) (?)	J-MACS (?) (?)
Other		AHA/ACC/ SCAI AdvaMed	JCS/JCC/ CCT/CVIT JFMDA	GHTF/SG5 IMDRF