Japan-USD HBD East 2017 Think Tank Meeting
December 7, 2017
National Center for Global Health and Medicine (NCGM)
Session 2: Real World Evidence

View from Japanese Academia
- Lessons Learned from the J-MACS -

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COI Disclosure

I have no financial conflict of interest with this presentation.

ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Japanese registry for Mechanically Assisted Circulatory Support: First report

J-MACS
Japanese registry for Mechanically Assisted Circulatory Support

Takeshi Nakatani, MD, PhD,[a] Kazuhiro Sase, MD, PhD,[b] Hiroaki Oshiyama,[b] Masatoshi Akiyama, MD, PhD,[c] Masao Horie,[c] Kan Nawata, MD, PhD,[c] Tomohiro Nishinaka, MD, PhD,[c] Yoshihisa Tanoue, MD, PhD,[c] Koichi Toda, MD, PhD,[c] Masao Tozawa,[c] Shunichi Yamazaki,[c] Masanobu Yanase, MD,[c] Hiroshi Ohtsu, MS,[d] Michiko Ishida, PhD,[e] Ayaka Hiramatsu, MPharm,[e] Kensuke Ishii, PhD,[e] Soichiro Kitamura, MD, PhD[f] and on behalf of the J-MACS investigators

From the [a]Principal investigator, Chair, J-MACS Operating Committee, Maki Hospital, Osaka, Japan; [b]Co-principal investigator, J-MACS Operating Committee, Juntendo University, Tokyo, Japan; [c]Investigator, J-MACS Operating Committee, Nipro Corporation, Osaka, Japan; [d]National Center for Global Health and Medicine, Tokyo, Japan; [e]Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; and the [f]Chair, J-MACS Steering Committee, National Cerebral and Cardiovascular Center, Osaka, Japan.

The Journal of Heart and Lung Transplantation 2017 36, 1087-1096

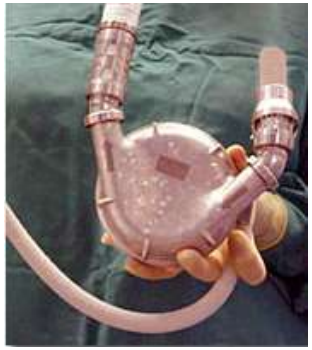
How Do You Measure An Innovation?

Left Ventricular Assist Device (LVAD)

2009/11/18	HeartMateXVE
2010/12/08	EVAHEART
2010/12/08	DuraHeart
(under review)	Jarvic 2000
2012/11/29	HeartMateII

Pre-implant Device Strategy

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



The Artificial Heart: Prototypes Policies and Patients; Institute of Medicine Report, 1991.

"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."

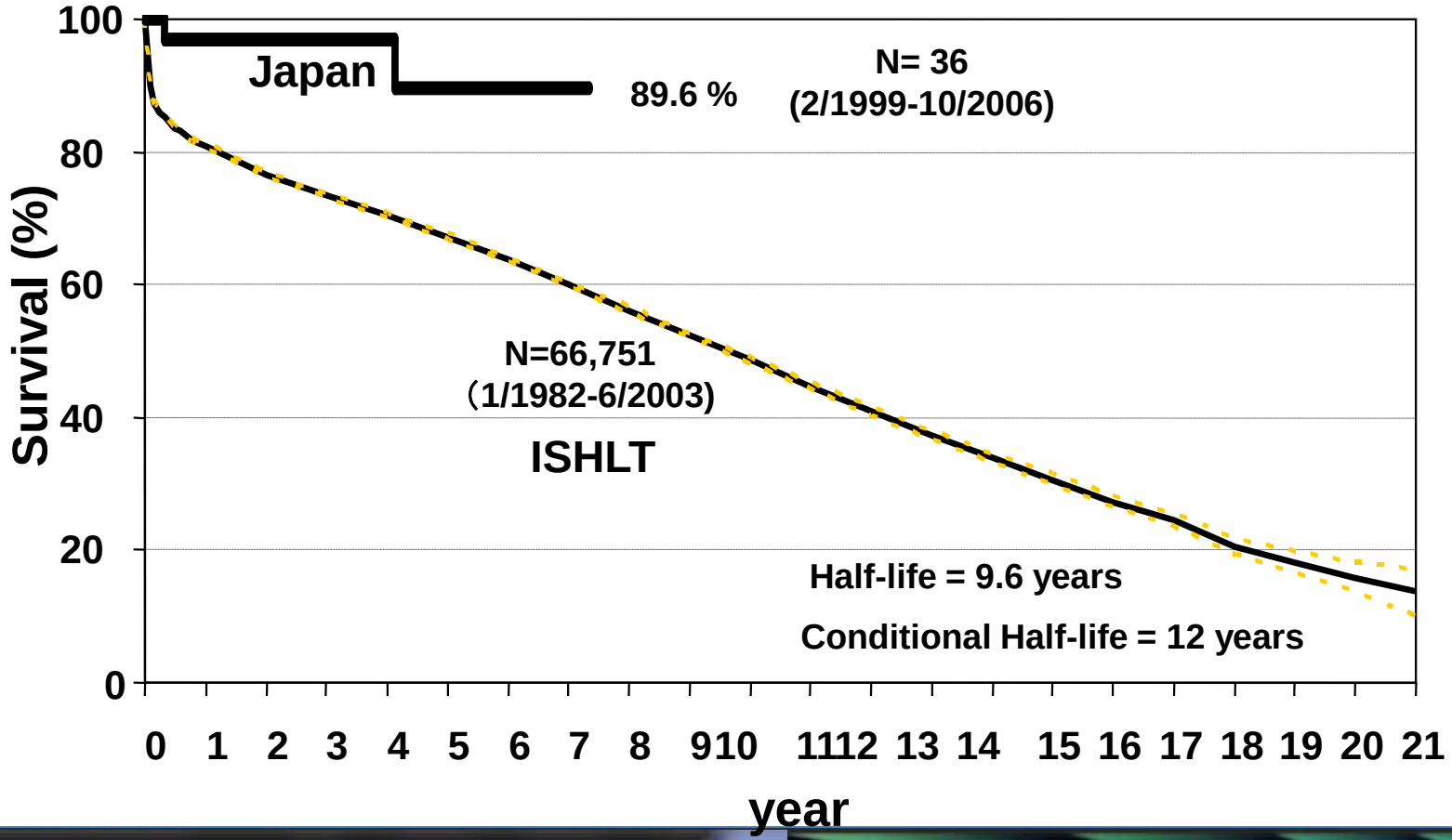
HBD Program Launch

Japan Circulatory Society
March 2004
Tokyo, Japan

DUKE UNIVERSITY MEDICAL CENTER

CRI
Duke Clinical Research Institute

Excellent Survival Rate after Heart Transplantation in Japan



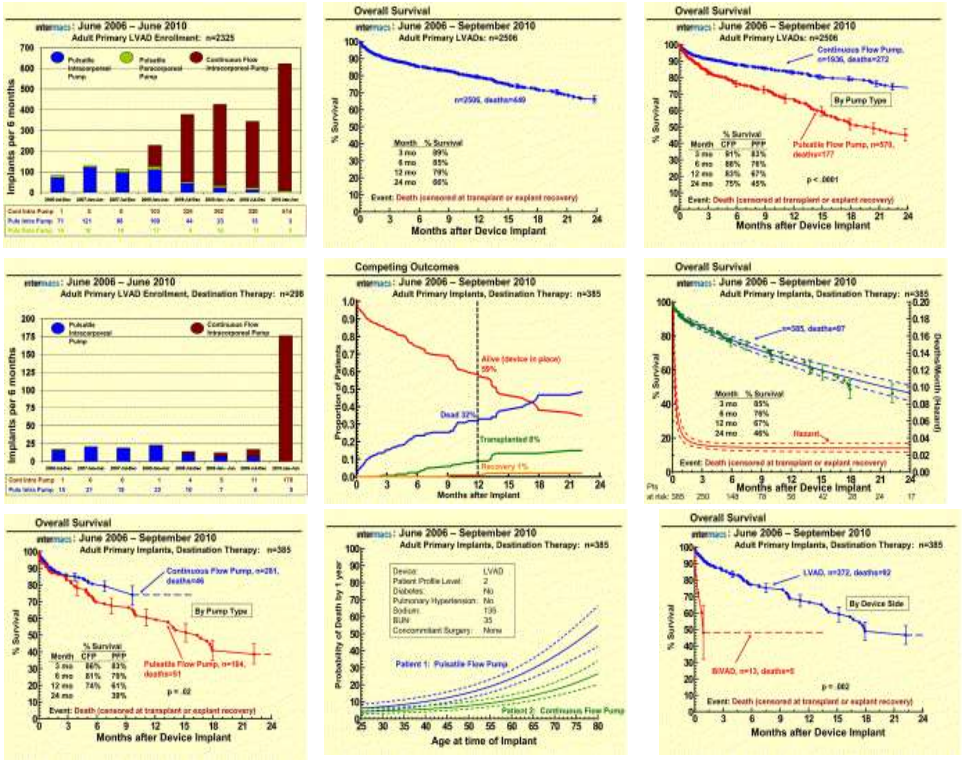
INTERMACS

Interagency Registry for Mechanically Assisted Circulatory Support

NHLBI Contract #HHSN268200548198C www.intermacs.org

- 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

June 2006 – July 15,2013
149 Hospitals
10,148 Patients

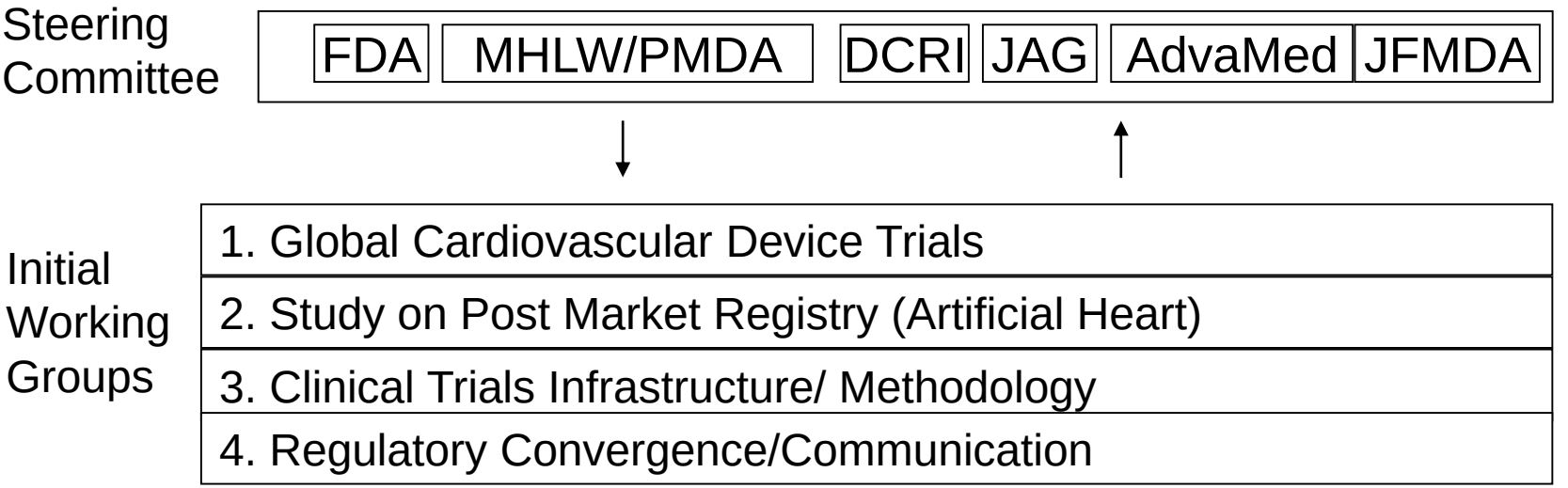


Third INTERMACS Annual Report:

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.

Harmonization by Doing (HBD)

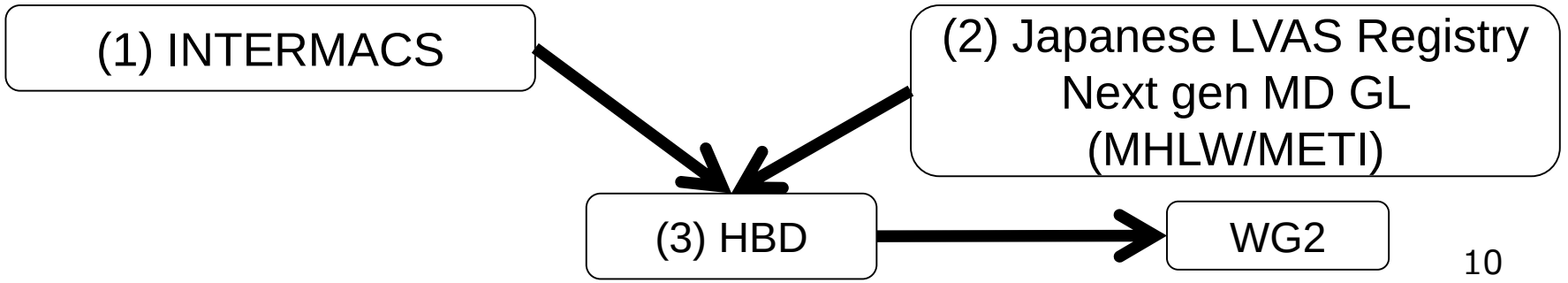
- Japanese Circulation Society - April 2004
- Japanese Coronary Association - December 2005
- Think Tank in Tokyo - December 2005
- FDA, MHLW, Japanese academia discuss scientific concerns and regulatory issues – July 2006
- HBD-West meeting in Durham, NC– January 2007
- HBD-East meeting in Tokyo – July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



HBD Harmonization By Doing

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)



Initial Report of Japanese registry for Mechanically Assisted Circulatory Support (J-MACS)

Takeshi Nakatani, MD,PhD[1], Kazuhiro Sase, MD, PhD[2], Hiroaki Oshiyama[3], and J-MACS Study Group
Dept. of Transplantation, National Cerebral and Cardiovascular Center[1], Clinical Pharmacology, Juntendo University[2], Japan Medical Devices Manufacturers Association[3]

J-MACS
Japanese registry for Mechanically Assisted Circulatory Support

Background

Clinical application of ventricular assist device (VAD) in Japan began in 1980 and 1343 cases were reported to Japanese Association for Clinical Ventricular Assist Systems, up to September 2011. Of those, 610 received various types of VAD (extracorporeal, n=460: implantable, n=150) as a bridge to transplantation. The mean support time was 383 days and 137 cases later underwent transplantation. Establishment of a database of mechanical circulatory support device (MCSD) cases is needed for development and promotion of clinical applications of new devices. For this purpose, INTERMACS was organized in USA and began data collection in 2006.

Methods

Japanese government has launched a Japanese database - Japanese registry for Mechanically Assisted Circulatory Support (J-MACS) - as an enterprise based on the Pharmaceuticals and Medical Devices Agency (PMDA)

Data Candidates for J-MACS

- Nipro-Toyobo
- EVAHEART (March 2011)
- DuraHeart (March 2011)
- Jarvik 2000
- Heartmate II

Nipro-Toyobo
Extracorporeal type
Intended long-term use as BTT

J-MACS: Registry Design

Prospective design

J-MACS is a prospective registry and post-marketing observational research, that will collect clinical data, including follow up, essentially as it happens.

Eligibility: inclusion criteria

1. Patients who receive a durable VAS (Ventricular Assist Systems) which is approved.
2. Patients who receive a VAS after hospital activated.
3. Patients who have signed informed consent for the registry.

Data collections

J-MACS basically collect data in the same way (in Japanese) as INTERMACS.

- Data items, Timing for data collection, Definitions of adverse event, QOL (EuroQOL ED-5D), Neuro-congnitive data (Trail making test Part B) , etc.
- Add or alter the item/definitions which need for Japanese data
- Post implant follow up data will be collected at 1 week, 1 month, 3 months, 6 months and every 6 months after that.
- Major outcomes after implant, e.g. transplant, death, explant, rehospitalization, and adverse

Second Mid-term Plan (FY2009 to 2013)

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

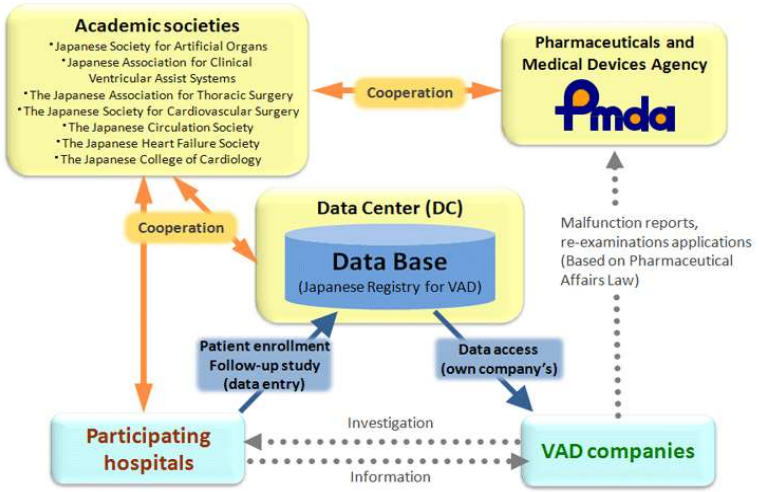
Strengthening and Improvement of Safety Measures Services

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

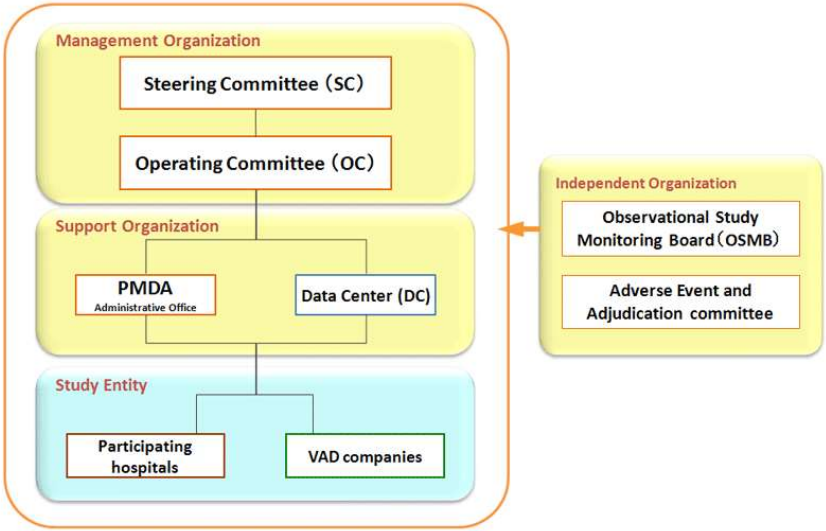
The Agency shall:

- 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.

The framework of J-MACS



Organization of J-MACS



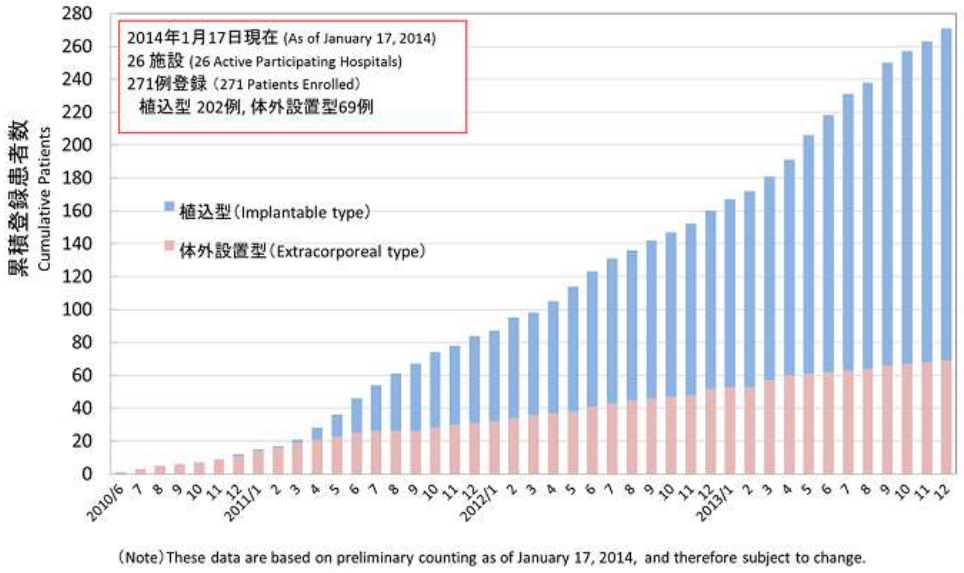
「植込型補助人工心臓実施基準管理委員会」認定による植込型補助人工心臓実施施設

日本における補助人工心臓に関連した市販後のデータ収集
Japanese registry for Mechanically Assisted Circulatory Support

J-MACS Statistical Report

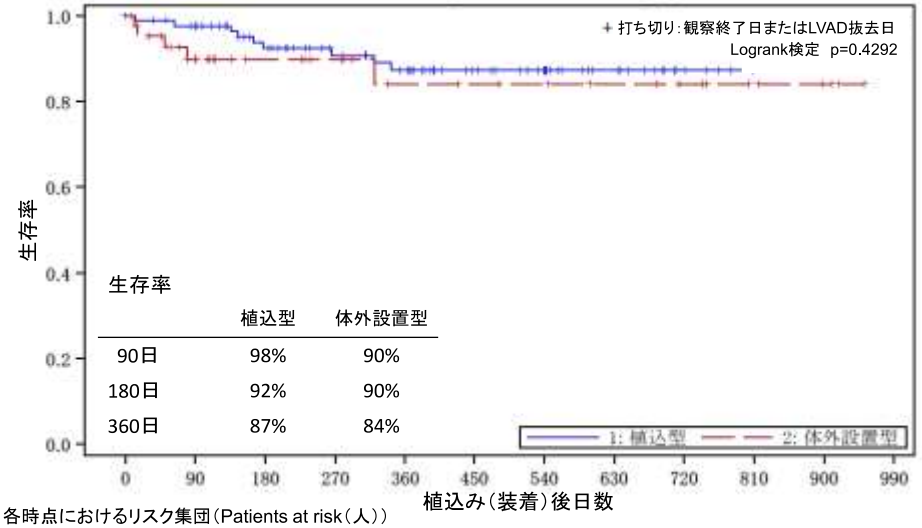
独立行政法人医薬品医療機器総合機構
安全第一部調査分析課
2013年9月

J-MACS 登録患者数の推移
The number of Patient Enrollment
Jun. 2010 - Dec. 2013



(Note) These data are based on preliminary counting as of January 17, 2014, and therefore subject to change.

生存率曲線
Primary LVAD（植込型/体外設置型）
Kaplan-Meier Plot



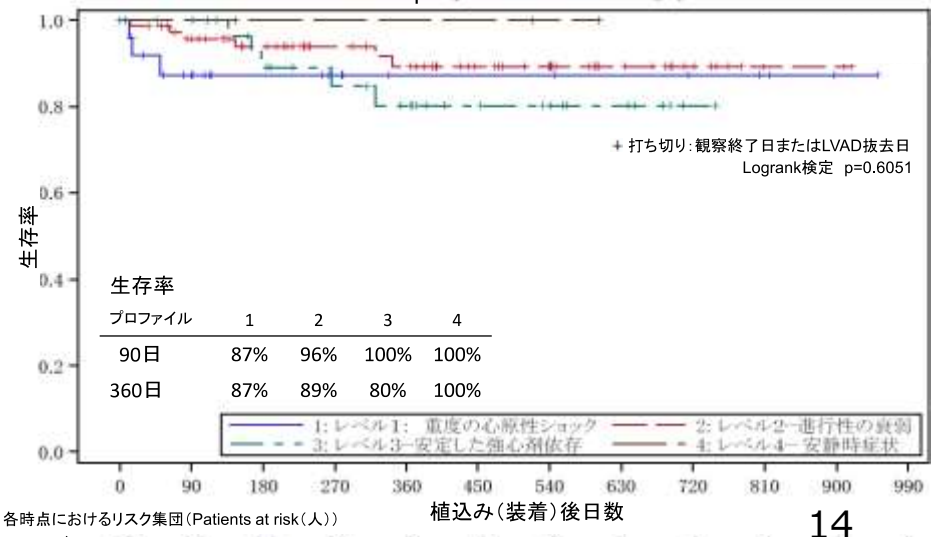
生存率

	植込型	体外設置型
90日	98%	90%
180日	92%	90%
360日	87%	84%

各時点におけるリスク集団(Patients at risk(人))

植込型	91	83	69	55	49	35	29	15	5	0	
体外設置型	44	30	22	19	14	13	12	10	8	5	3	0

生存率曲線
Primary LVAD（患者プロファイル別）
Kaplan-Meier Plot



生存率

プロファイル	1	2	3	4
90日	87%	96%	100%	100%
360日	87%	89%	80%	100%

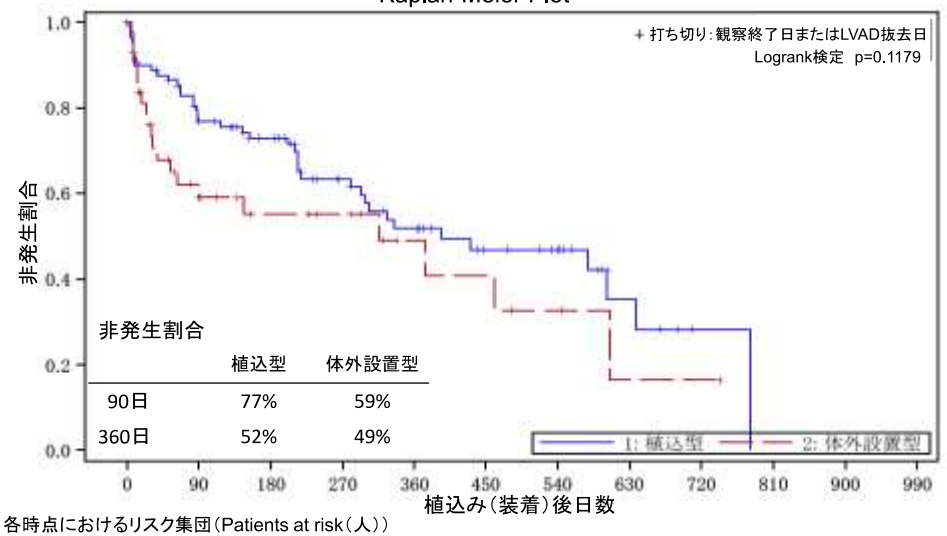
各時点におけるリスク集団(Patients at risk(人))

レベル1	26	17	12	10	6	6	6	5	4	3	1	0
レベル2	73	62	53	42	38	29	25	14	8	2	2	0
レベル3	33	31	24	20	17	11	9	6	1	0		
レベル4	3	3	2	2	2	2	1	0				

装置の不具合

Primary LVAD（植込型/体外設置型）

Kaplan-Meier Plot



非発生割合

	植込型	体外設置型
90日	77%	59%
360日	52%	49%

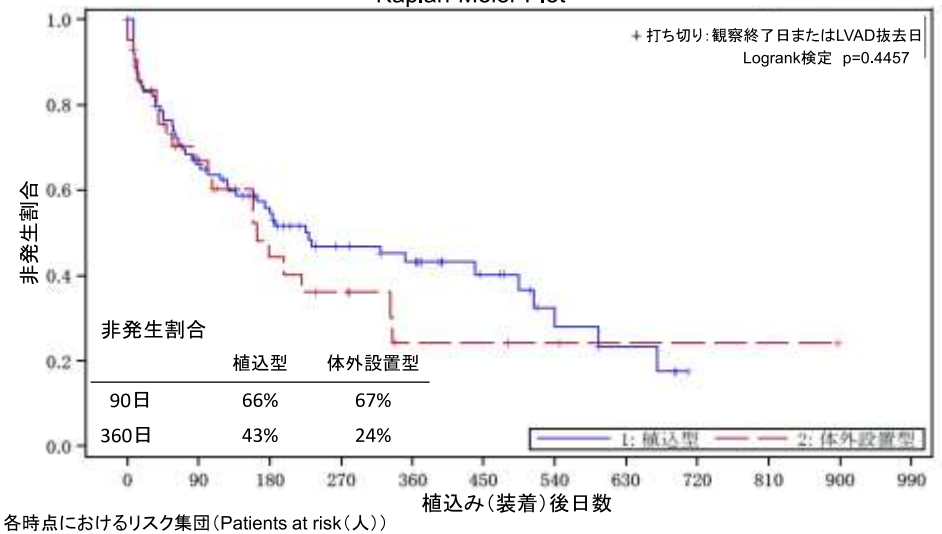
各時点におけるリスク集団（Patients at risk（人））

植込型	91	63	52	34	26	17	14	5	1	0
体外設置型	44	20	13	11	6	5	3	1	1	0

主要な感染

Primary LVAD（植込型/体外設置型）

Kaplan-Meier Plot



非発生割合

	植込型	体外設置型
90日	66%	67%
360日	43%	24%

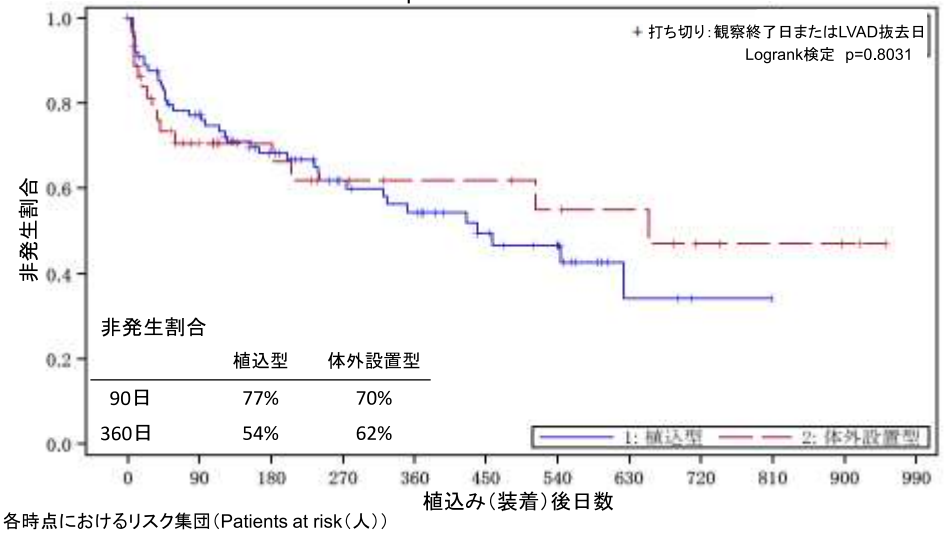
各時点におけるリスク集団（Patients at risk（人））

植込型	91	56	40	27	23	13	7	4	0	
体外設置型	43	21	11	8	3	3	2	1	1	1	0

神経機能障害

Primary LVAD（植込型/体外設置型）

Kaplan-Meier Plot



非発生割合

	植込型	体外設置型
90日	77%	70%
360日	54%	62%

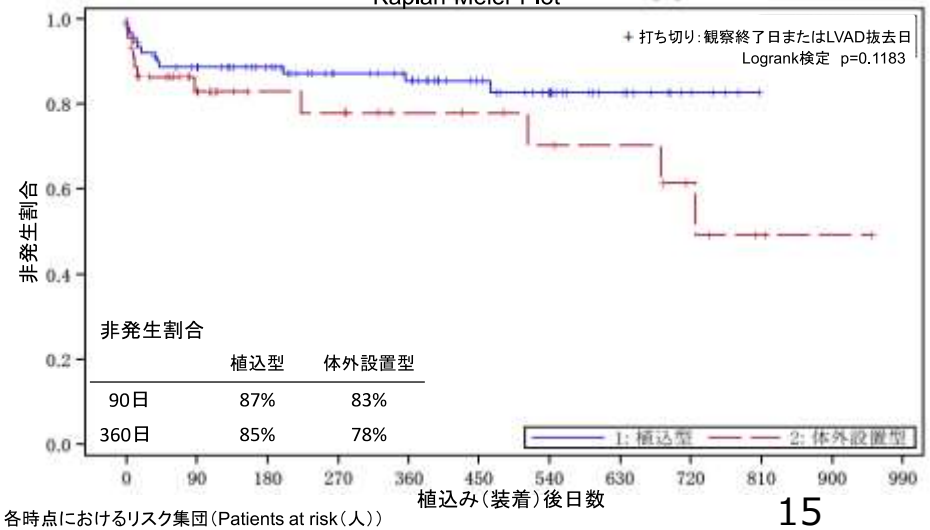
各時点におけるリスク集団（Patients at risk（人））

植込型	91	64	49	34	29	19	15	4	1	0
体外設置型	44	23	16	12	10	10	8	7	4	3	2	0

大量出血

Primary LVAD（植込型/体外設置型）

Kaplan-Meier Plot



非発生割合

	植込型	体外設置型
90日	87%	83%
360日	85%	78%

各時点におけるリスク集団（Patients at risk（人））

植込型	91	74	64	51	46	33	26	13	5	0
体外設置型	44	25	17	16	12	11	9	8	5	2	1	0

ELSEVIER

J-MACS Japanese registry for Mechanically Assisted Circulatory Support

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Japanese registry for Mechanically Assisted Circulatory Support: First report

Takeshi Nakatani, MD, PhD,[a] Kazuhiro Sase, MD, PhD,[b] Hiroaki Oshiyama,[b] Masatoshi Akiyama, MD, PhD,[c] Masao Horie,[c] Kan Nawata, MD, PhD,[c] Tomohiro Nishinaka, MD, PhD,[c] Yoshihisa Tanoue, MD, PhD,[c] Koichi Toda, MD, PhD,[c] Masao Tozawa,[c] Shunichi Yamazaki,[c] Masanobu Yanase, MD,[c] Hiroshi Ohtsu, MS,[d] Michiko Ishida, PhD,[e] Ayaka Hiramatsu, MPharm,[e] Kensuke Ishii, PhD,[e] Soichiro Kitamura, MD, PhD[f] and on behalf of the J-MACS investigators

From the [a]Principal investigator, Chair, J-MACS Operating Committee, Maki Hospital, Osaka, Japan; [b]Co-principal investigator, J-MACS Operating Committee, Juntendo University, Tokyo, Japan; [c]Investigator, J-MACS Operating Committee, Nipro Corporation, Osaka, Japan; [d]National Center for Global Health and Medicine, Tokyo, Japan; [e]Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; and the [f]Chair, J-MACS Steering Committee, National Cerebral and Cardiovascular Center, Osaka, Japan.

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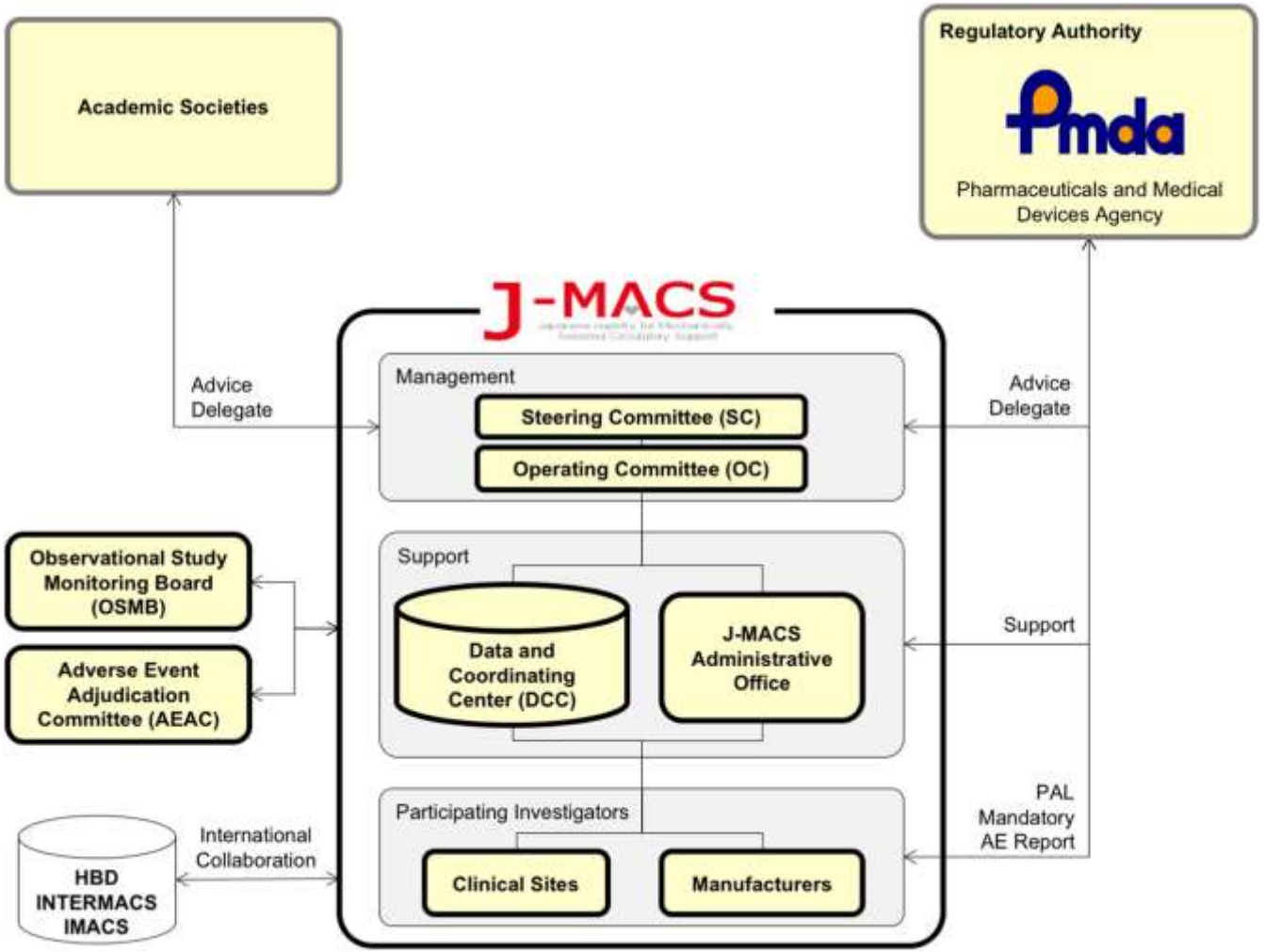
The present study design, including data elements, follow-up schedule and adverse event definitions, was implemented so as to harmonize with INTERMACS[7] through the United States–Japan Medical Device Harmonization by Doing (HBD) program.[8–10]

J-MACS
Japanese registry for Mechanically Assisted Circulatory Support



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J-MACS
Japanese registry for Mechanically Assisted Circulatory Support

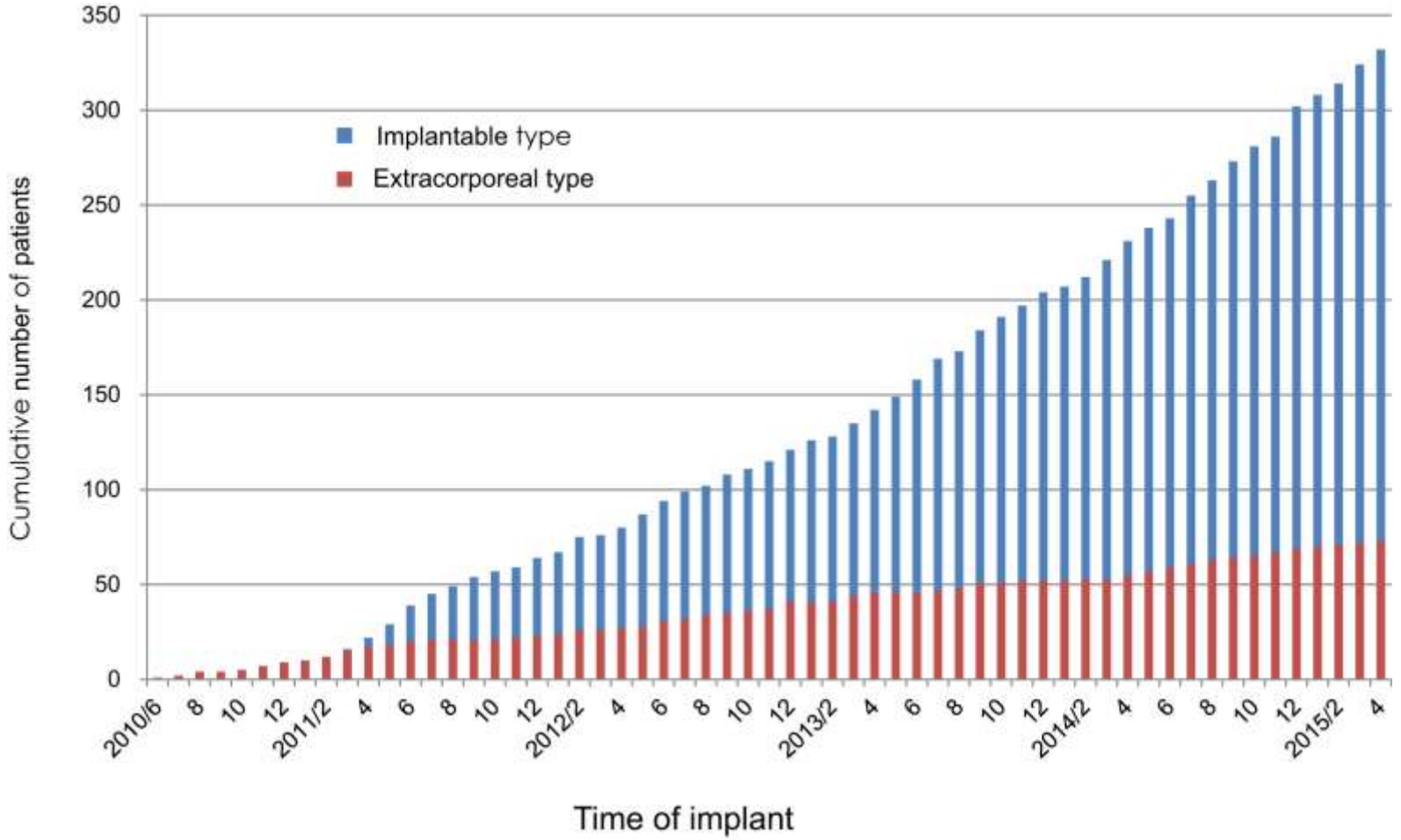

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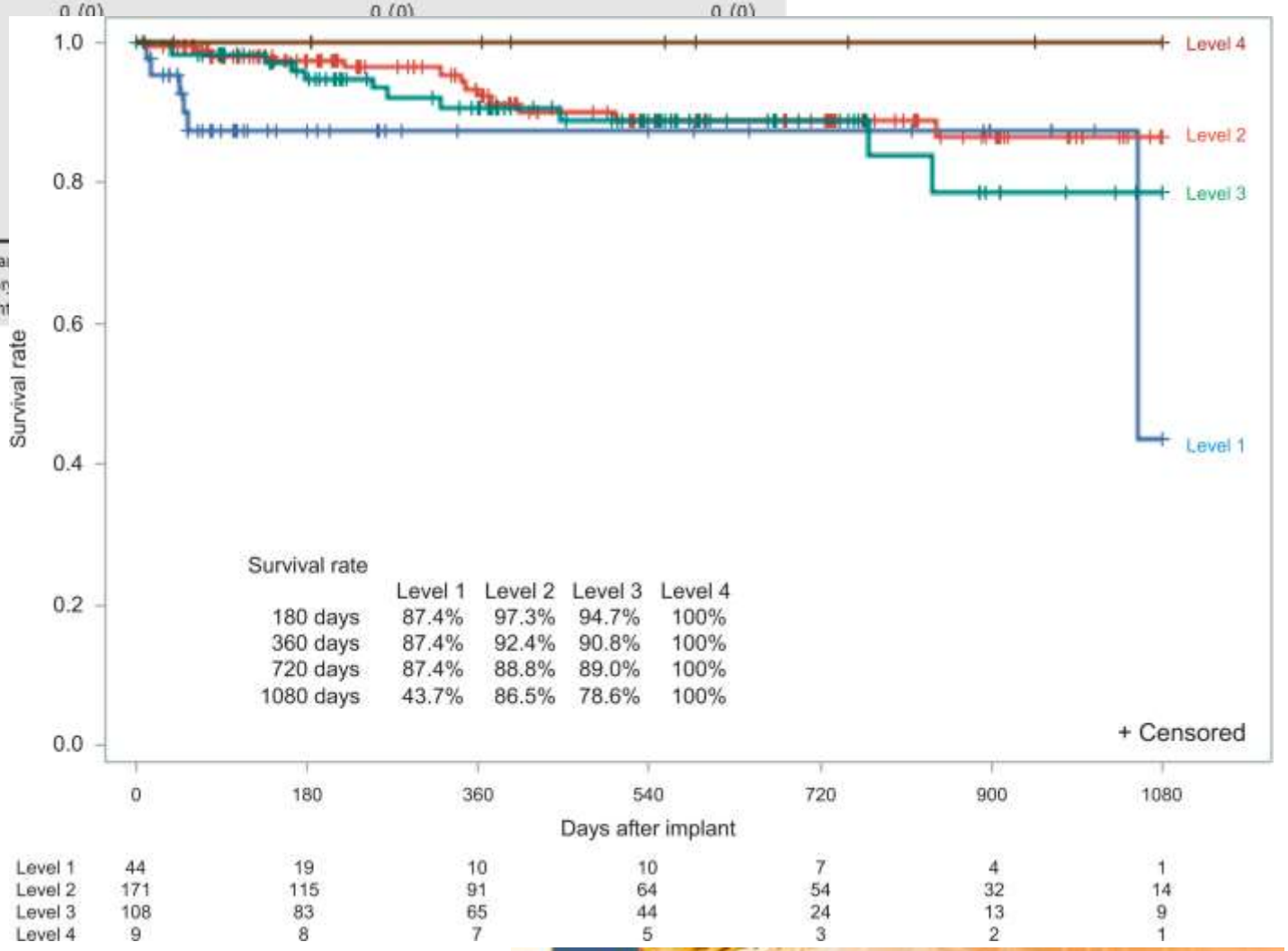
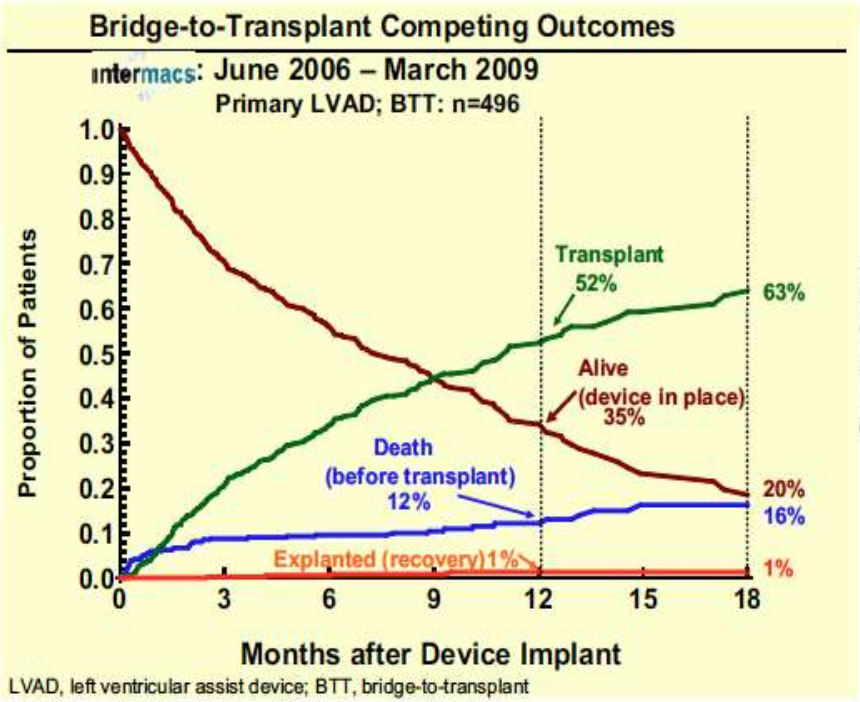
Table 3 Pre-implant Patient Profiles and Device Atrategies (J-MACS: June 2010 to April 2015)

	Implantable (%) (n = 259)	Extracorporeal (%) (n = 73)	Total (%)
Pre-implant INTERMACS patient profile			
Level 1: Critical cardiogenic shock	8 (3)	36 (49)	44 (13)
Level 2: Progressive decline	136 (53)	35 (48)	171 (52)
Level 3: Stable but inotrope-dependent	106 (41)	2 (3)	108 (33)
Level 4: Recurrent advanced HF	9 (4)	0 (0)	9 (3)
Level 5: Exertion intolerant	0 (0)	0 (0)	0 (0)
Level 6: Exertion limited	0 (0)	0 (0)	0 (0)
Level 7: Advanced NYHA Class III	0 (0)	0 (0)	0 (0)
Pre-implant device strategy			
Bridge to transplant, listed			
Bridge to transplant, applied			
Bridge to transplant, pre-application			
Long-term support without transplant			
Post-ADHF[a]			
Pre-ADHF			
Others			

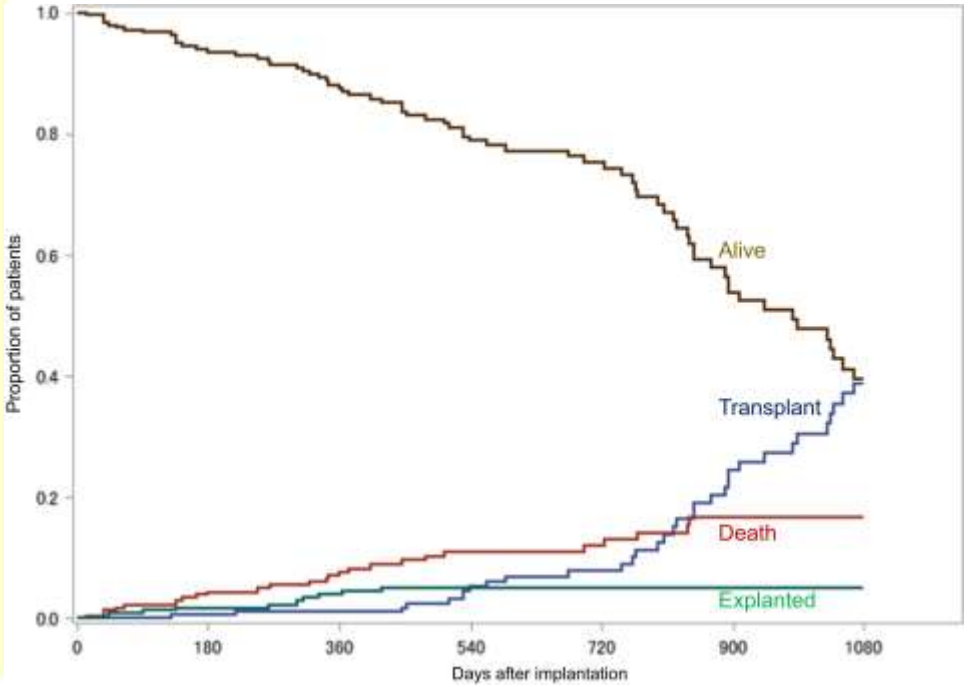
ADHF, acute decompensated heart failure; HF, hea
Japanese registry for Mechanically Assisted Circulator
[a]ADHF requiring VAD support as INTERMACS patient

J-MACS
Japanese registry for Mechanically Assisted Circulatory Support



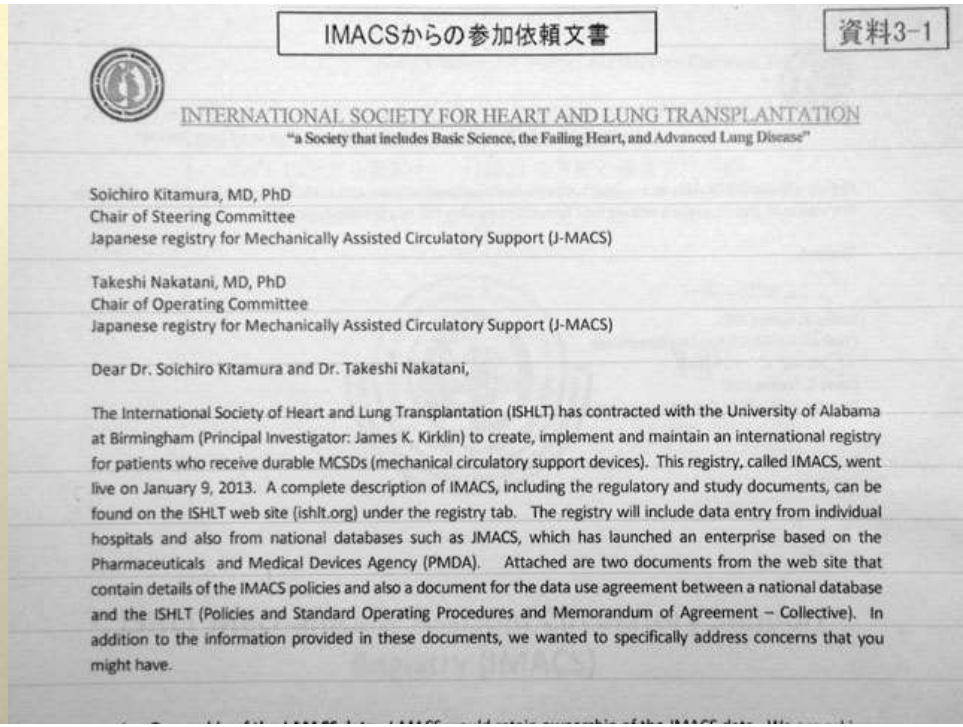


Kirklin, et al. Third INTERMACS Annual Report:
J Heart Lung Transplant. 2011 Feb;30(2):115-23.



Nakatani et al. J-Macs First Report.
J Heart Lung Transplant. 2017 Oct; 36(10):1087-1096.

International Society for Heart and Lung Transplantation (ISHLT) Helps Global Collaboration to Establish “IMACS”



IMACSからの参加依頼文書

資料3-1

INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

"a Society that includes Basic Science, the Failing Heart, and Advanced Lung Disease"

Soichiro Kitamura, MD, PhD
Chair of Steering Committee
Japanese registry for Mechanically Assisted Circulatory Support (J-MACS)

Takeshi Nakatani, MD, PhD
Chair of Operating Committee
Japanese registry for Mechanically Assisted Circulatory Support (J-MACS)

Dear Dr. Soichiro Kitamura and Dr. Takeshi Nakatani,

The International Society of Heart and Lung Transplantation (ISHLT) has contracted with the University of Alabama at Birmingham (Principal Investigator: James K. Kirklin) to create, implement and maintain an international registry for patients who receive durable MCSDs (mechanical circulatory support devices). This registry, called IMACS, went live on January 9, 2013. A complete description of IMACS, including the regulatory and study documents, can be found on the ISHLT web site (ishlt.org) under the registry tab. The registry will include data entry from individual hospitals and also from national databases such as JMACS, which has launched an enterprise based on the Pharmaceuticals and Medical Devices Agency (PMDA). Attached are two documents from the web site that contain details of the IMACS policies and also a document for the data use agreement between a national database and the ISHLT (Policies and Standard Operating Procedures and Memorandum of Agreement – Collective). In addition to the information provided in these documents, we wanted to specifically address concerns that you might have.

1. IMDRF/REGISTRY WG/N33FINAL:2016 (30 Septemer 2016) Principles of International System of Registries Linked to Other Data Sources and Tools.
2. IMDRF/REGISTRY WG/N42FINAL:2017 (16 March 2017) Methodological Principles in the Use of International Medical Devide Registry Data.

Definition of medical device registry

Organized system with a primary aim to improve the quality of patient care that continuously collects relevant data, evaluates meaningful outcomes and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale (e.g. international, national, regional, and health system)'

Qualifiers to define the impact, value and sustainability of the medical device registry:

1. DEVICE: Has sufficient device information (unique device identification)
2. QUALITY SYSTEM: Is part of continual quality assurance system as device technologies get adopted (including outlier identification).
3. BENEFICIAL CHANGE: Has established mechanisms to bring beneficial change in health care delivery through stakeholder participation.
4. EFFICIENCY: Data collection is embedded in the health care delivery system and integrated with work flow of clinical teams. (Not overly burdensome. Not highly complicated. Not overly costly, etc.)
5. ACTIONABLE DATA: Provides actionable information in a relevant and timely manner to decision makers.
6. TRANPARENCY: the governance structure, data access and analytic processes are transparent.
7. LINKABILITY: Can be linked with other data sources for enhancement including adequate follow up achievement.
8. TOTAL DEVICE LIFE-CYCLE: Can serve as infrastructure for seamless integration of evidence throughout the device life cycle.

Phase 2 - Key Concepts: Signal Detection

- Single and aggregate reports and 'root cause analyses' are useful for identifying unexpected major harms
  - By shifting the focus from individual reports towards systematic summary analyses, registries can be used to detect signals depending on the degree of similarity or exchangeability in the data
  - Use of signal detection to contribute to benefit/risk assessments

- Methodologies
  - Harmonizing terminology
  - Allowing flexibility for periodic updates of data capture
  - Providing different considerations for new vs. mature devices
  - Pre-specifying threshold values
  - Establishing criteria to distinguish between provider vs. device effect

Phase 2 - Key Concepts: Between-Country Variation

Several characteristics contribute to differences among countries in both the use of medical devices as well as their associated outcomes which can impact methodologies, including:

- **Market Environment**
  - Device availability, length of market experience, etc.
- **Intrinsic and Extrinsic Ethnic Factors**
  - Characteristics of the patient population
- **Registry Characteristics**
  - Variation in granularity of data, attrition rates, etc.
- **Medical Device Regulatory Requirements**
  - Requirements for assessment of clinical data varies globally
- **Health Care Delivery Systems**
  - Differences in health care delivery systems

Contains Nonbinding Recommendations

Draft – Not for Implementation

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction and Scope

FDA is issuing this draft guidance to clarify how we evaluate real-world data to determine whether it may be sufficiently relevant and reliable to generate the types of real-world evidence that can be used in FDA regulatory decision-making for medical devices.

- **Real-World Data (RWD)** is data collected from sources outside of traditional clinical trials. These sources may include large simple trials, or pragmatic clinical trials, prospective observational or registry studies, retrospective database studies, case reports, administrative and healthcare claims, electronic health records, data obtained as part of a public health investigation or routine public health surveillance, and registries (e.g., device, procedural, or disease registries). The data is typically derived from electronic systems used in health care delivery, data contained within medical devices, and/or in tracking patient experience during care, including in home-use settings.

- **Real-World Evidence (RWE)** is the evidence derived from aggregation and analysis of RWD elements.

RWD and associated RWE could constitute valid scientific evidence, depending on the characteristics of the data. This guidance should not be interpreted to convey that FDA is changing the evidentiary standards used in regulatory decision-making; rather, this guidance

[4] Document issued July 27, 2016

This guidance was updated September 16, 2016 to correct a missing footnote.

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Real-World Evidence — What Is It and What Can It Tell Us?

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RWE is derived from data associated with outcomes from the care of heterogenous patients as experienced in real world practice settings. Data relevant to RWE comes in multiple types and forms. For Example:

- **Claims Data** derived from insurance reimbursements.
- **Clinical Trials Data** derived from the outcomes of randomized clinical trials.
- **Clinical Setting Data** derived from patient medical records and patient care.
- **Pharmacy Data** derived from prescription orders and fulfillments.
- **Patient-powered Data** derived directly from the patient experience.

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