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.
Japanese registry for Mechanically Assisted Circulatory Support: First report

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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)
“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.”
Excellent Survival Rate after Heart Transplantation in Japan

Survival (%)

Japan

89.6 %

N = 36
(2/1999-10/2006)

ISHLT

N = 66,751

Half-life = 9.6 years
Conditional Half-life = 12 years

year
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

149 Hospitals
10,148 Patients

Third INTERMACS Annual Report:
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

**Steering Committee**

| FDA | MHLW/PMDA | DCRI | JAG | AdvaMed | JFMDA |

**Initial Working Groups**

| 1. Global Cardiovascular Device Trials |
| 2. Study on Post Market Registry (Artificial Heart) |
| 3. Clinical Trials Infrastructure/Methodology |
| 4. Regulatory Convergence/Communication |
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)

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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) Information and Commongrounds System Framework. It was constructed in December 2009 and it is now maintained and operated by J-MACS Study Group, which consists of the representatives of the Pharmaceutical and Medical Devices Association.

Data Candidates for J-MACS

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

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 collection:
J-MACS basically collect data in the same way (in Japanese) as INTERMACS.
- Data items, Timing for data collection, Definitions of adverse event, GOL (EuroQOL ED-5D), Neuro-cognitive 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 events will be entered as the worsening data as part of the defined follow up schedule.
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.
「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

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

2014年1月17日現在（As of January 17, 2014）
26施設 (26 Active Participating Hospitals)
271例登録 (271 Patients Enrolled)
植込み型 202例, 体外設置型69例

(Nota) Those data are based on preliminary counting as of January 17, 2014, and therefore subject to change.
Japanese registry for Mechanically Assisted Circulatory Support: First report

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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\textsuperscript{7} through the United States–Japan Medical Device Harmonization by Doing (HBD) program.\textsuperscript{8–10}
<table>
<thead>
<tr>
<th>Pre-implant INTERMACS patient profile</th>
<th>Implantable (%) (n = 259)</th>
<th>Extracorporeal (%) (n = 73)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1: Critical cardiogenic shock</td>
<td>8 (3)</td>
<td>36 (49)</td>
<td>44 (13)</td>
</tr>
<tr>
<td>Level 2: Progressive decline</td>
<td>136 (53)</td>
<td>35 (48)</td>
<td>171 (52)</td>
</tr>
<tr>
<td>Level 3: Stable but inotrope-dependent</td>
<td>106 (41)</td>
<td>2 (3)</td>
<td>108 (33)</td>
</tr>
<tr>
<td>Level 4: Recurrent advanced HF</td>
<td>9 (4)</td>
<td>0 (0)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Level 5: Exertion intolerant</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Level 6: Exertion limited</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Level 7: Advanced NYHA Class III</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

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, heart failure
\(^a\)ADHF requiring VAD support as INTERMACS patient

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

#### Survival rate

<table>
<thead>
<tr>
<th>Days after implant</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Level 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 days</td>
<td>87.4%</td>
<td>97.3%</td>
<td>94.7%</td>
<td>100%</td>
</tr>
<tr>
<td>360 days</td>
<td>87.4%</td>
<td>92.4%</td>
<td>90.8%</td>
<td>100%</td>
</tr>
<tr>
<td>720 days</td>
<td>87.4%</td>
<td>88.8%</td>
<td>89.0%</td>
<td>100%</td>
</tr>
<tr>
<td>1080 days</td>
<td>43.7%</td>
<td>86.5%</td>
<td>78.6%</td>
<td>100%</td>
</tr>
</tbody>
</table>

+ Censored

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

1. 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.

RWE and associated RWD 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...

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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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Robert Temple, M.D., Janet Woodcock, M.D., Lily Q. Yue, Ph.D., and Robert M. Calif, M.D.
Thank you for your attention!

Enjoy your stay. Looking forward to future collaborations.