PMDA Perspective: Utilization of the Disease Registry Data for Drug Development

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- Expectations for Clinical Innovation Network (CIN)
- PMDA’s challenge in CIN
- PMDA’s future plans
Expectations for disease registries

- Registries are expected to be useful for
  - Estimation of the number of patients
  - Efficient accumulation of patient data of interest
  - Recruitment of patients
  - New Drug/Medical Devices Development
  - Post-Marketing Surveillance
  etc.

- What should be done to utilize registries in clinical development?
Clinical Innovation Network (CIN)

- Background: Cost of developing a new drug or other medical products is rising
- MHLW’s measure for medical innovation
- The purpose of the CIN project is improvement of clinical studies infrastructure
  - Development of disease registries
  - Foundation of clinical trial consortium
- Expectation for the CIN project
  - Cost-effective clinical studies
  - Activation of clinical studies in Japan by entities in the world
Clinical Innovation Network (CIN)

Clinical Innovation Network (CIN)
(Improvement of Infrastructure for Clinical Study with Disease Registry)

[Background]
- Cost of developing a new drug or other medical products is rising over the world, especially in Japan compared to other countries.
- Recently, new approaches for clinical study with disease registry has been highly interesting.

[Brief overview of CIN]
- The clinical study infrastructure in Japan is improved so that cost effective clinical studies are performed with disease registries, based on Regulatory Science. The improvement will accelerate clinical studies in Japan by entities in the world, which would results in the contribution to healthy life expectancy for people.
- CIN will also support for marketing in Asia of medical products developed in Japan.

[Key Features]
- Acceleration of global clinical trials
- Asian Regulatory Training Center
- Development of registries for patients with intractable diseases
- Rare diseases drug development Gateway

[Stakeholders]
- PMDA
- AMED

[Partnership]
- National Center, Clinical Research Core Hospital
- Hospitals in networks in Japan
- Hospitals in Asia

[Objectives]
- Development of disease registries
- Foundation of a clinical trial consortium, acceleration of clinical studies
- Advancement of regenerative medicine clinical studies
- Establishment of a Clinical Trial Cooperation Office

[Supportive Measures]
- Participation in the consortium
- Industry participation
- Data provision
- Utilizes data in clinical studies
- Performs clinical studies quickly and cost-effectively

[Institutional Support]
- PMDA
- AMED

[CIN Promotion Conference]
Composed of stakeholders, including National Centers, Industries and Japanese Government; and promotes the CIN project.

http://pari.u-tokyo.ac.jp/eng/event/smp150818_mori.pdf
Clinical Innovation Network (CIN)

- **CIN Promotion Conference**
  - Suggests directions about establishment of CIN system
  - Identifies the issues for utilization of registries

- **Working Group in each National Center**
  - Since Sep, 2015
  - Discusses about making better use of existing registries and establishment of new registries in collaboration with members from industries.

- **The Study Group supported by MHLW**
  - Composed of researchers from national centers and academia
  - Research about the issues regarding the use of registries
  - The report was published
The new study groups supported by AMED

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<td>大津 敦</td>
<td>国立がん研究センター</td>
<td>産学連携全国がんゲノムスクリーニング (SCRUM-Japan) を利用したがん新薬開発に資する疾患登録システムの構築</td>
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<td>中村 治雅</td>
<td>国立精神・神経医療研究センター</td>
<td>難病、希少疾患の医薬品開発におけるクリニカルイノベーションネットワーク構想の推進を目指した疾患登録システムの構築</td>
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<td>祖父江 元</td>
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<td>林 邦彦</td>
<td>群馬大学大学院保健学研究科</td>
<td>「患者レジストリーデータを用い、臨床開発の効率化を目指すレギュラトリーサイエンス研究」</td>
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<td>武田 伸一</td>
<td>国立精神・神経医療研究センター</td>
<td>疾患登録システムの有効活用によるクリニカルイノベーションネットワーク構想の推進方策に関する研究</td>
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- PMDA’s future plans
CIN-WG at PMDA

- Projects across multi-offices at PMDA
- Established on Feb, 2016

https://www.pmda.go.jp/rs-std-jp/standards-development/cross-sectional-project/0001.html
PMDA’s contribution to CIN

- Based on the experiences on drug review
- From the perspective on regulatory science

CIN-WG discuss the followings:

- Requirements for the registries in terms of clinical development and post-marketing surveillance
- Methodology of the evaluation of the data in registries
- How to secure reliability etc.
For clinical development,

- Are the data items appropriate and enough?
- Is it possible to collect information about primary endpoint in the registry?
- Is the use of the registry as a control appropriate in the clinical data package?
<table>
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<tr>
<th>Product</th>
<th>Approval</th>
<th>Indication</th>
<th>Usage of disease registry</th>
<th>Category</th>
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<td>Alglucosidase alfa</td>
<td>2007.4</td>
<td>Pompe Disease</td>
<td>Use of the survival rate from retrospective cohort study in US as comparator</td>
<td>Orphan drug</td>
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<tr>
<td>Argatroban hydrate</td>
<td>2011.5</td>
<td>Hepalin induced thrombocytopenia type II</td>
<td>Selected historical controls in the same trial site by the same selection criteria with subjects</td>
<td>Orphan drug</td>
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<tr>
<td>Tacrolimus hydrate</td>
<td>2013.6</td>
<td>Interstitial pneumonia in patients with PM/DM</td>
<td>Use of the survival rate from retrospective cohort study as comparator</td>
<td>Orphan drug</td>
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<tr>
<td>Asfotase alfa</td>
<td>2015.8</td>
<td>Hypophosphatasia</td>
<td>Use of the survival rate from retrospective cohort study in US as comparator</td>
<td>Orphan Drug</td>
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平成27年度厚生労働科学研究費補助金（厚生労働科学特別研究事業）「国立高度専門医療研究センター（ナショナルセンター）等において構築する疾患登録システム（患者レジストリ）を基盤とした、新たな治験・臨床研究の推進方策に関する研究」分担研究報告書「治験対照群としての疾患登録情報の活用について」より引用、一部改変
Utilization of Registry in Medical Device development

  - Stent graft for prophylaxis of thoracic aneurysm rupture
  - As a control group, surgical outcome of descending thoracic surgery registered in Japan Adult Cardiovascular Surgery Database

- SATAKE·HotBalloon Catheter (Approval: Nov. 2015)
  - High frequency ablation catheter for paroxysmal atrial fibrillation
  - As a control, outcome of traditional treatment modality registered in the Japanese catheter ablation registry of atrial fibrillation (J-DARAF) by Japanese Heart Rhythm Society (JHRS)

- Da Vinci Surgical System (Labelling change: Dec. 2015)
  - Labelling change of robotic surgery for cardiac surgery
  - As a control, surgical outcome of traditional mitral valve repair surgery registered in the Society of Thoracic Surgeons National Database in US
New Approaches in Japan

Construct post-market registries including MAH's PMS

-under the company (MAH), government, academia collaboration-

J-MACS
June, 2010～

J-TAVI Registry
July, 2014～

Flow Diverter Registry
September, 2016～

The Challenges and Future Expectations of Postmarketing Registry System for New Medical Devices in Cooperation with industry/PMDA/Academia
(session V4-S6: Nov. 15, 14:00-15:30)
Post-market Framework of Registries in Japan

Academic societies

Cooperation

Data Center

Data Base

Case enrollment, Follow-up (Data entry)

Data access (Own company’s)

AE-reports

Participating institutions

Companies (MAH)

Making of facility criteria and/or user criteria

Cooperation

Annual Reports and re-examinations base on PMD-ACT

Investigation

Information

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Utility of Post-Market Registry in Medical Devices

- Evidence Generated from Japanese registry
  - Selection of best candidate patients for the treatment, reduction of complications and assessment of device performance
  - The evaluation of effectiveness and safety in brand new medical device

- Immediate Safety measures for incidents

- Reduction of manufacture’s burden

- Consideration for future development or modification of medical device

- Big Challenge: Is it possible to shift from pre-approval clinical trial and review to post-market evaluation?
The following problems remain,

- Funds and human resources
- Incentive for data entry of medical information by health care professionals
- Burden Reduction in healthcare professionals
- Cooperation and support from academic society
For clinical development,

- What are the points that need to be considered during the actual securing of reliability?
- Do data integrity standards differ between registries? Does it depend on the purpose of the registry?
- Is it necessary to establish new data integrity standards?
- Under discussion
Issues in current post marketing survey in Japan (“Shiyouseiseki-tyousa”)

- Primary data collection only
- Ambiguous research question, single cohort design, about 3000 patients
- Compliance: Under current GPSP

DB is going to be available for post marketing survey

- Under discussion in the working group composed of PMDA, MHLW, and industries
- Not only primary data collection but also claim data, medical records, and registry
- Clear research question, appropriate study design, with comparison control group
- Compliance: Under new GPSP (about 2018)

Two draft documents (Epidemiology and GPSP) for basic principals about post marketing survey using health information databases
(session V7-S4: Nov.15, 9:00-10:30)
For clinical development,

✓ What is the appropriate way to use registries in clinical development strategy?
✓ How do we evaluate the data from registries?
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- Expectations for Clinical Innovation Network (CIN)
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Future plans

- CIN-WG discuss the use of disease registry
  - From the various perspective (clinical medicine, statistics, epidemiology, system design, actual securing of reliability, regulatory science・・・)
  - In collaboration with MHLW and AMED
- Cooperation with academia in the study group supported by AMED
  - Discussion about the data set that need to be collected in each registry (PMDA will give advices in the consultations)
  - Data integrity standards
  - Optimal clinical trial /epidemiological study design
Future plans

1) **Proposals on** Clinical trial /Epidemiological study design

2) **Proposals on** Requirements for the Registries (Data integrity standards etc.)

Study groups regarding establishment of new registries

Offices of New Drug, offices of Medical Devices etc.
Ask