Ministry of Health & Family Welfare
Government of India

Asian Harmonization Working Party
WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

CENTRAL DRUGS STANDARD CONTROL ORGANIZATION
MINISTRY OF HEALTH, GOVERNMENT OF INDIA

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22nd Asian Harmonization Working Party Annual Meeting

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4-8 December, 2017 I New Delhi

Ministry of Health & Family Welfare
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WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

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Japan regulatory update

Hiroshi YAGINUMA

Medical Device Evaluation and Licensing Division, MHLW

12:10-12:30, Monday, December 4th, 2017

Landscape of medical device industry in Japan

- *Market size* ***JPY 2,800 billion*** *(USD 25b)*
  - *Diagnostic instruments JPY 700 b (USD 6.3 b)*
  - *Therapeutic devices JPY 1,490 b (USD 13.3 b)*
  - *Others JPY 600 b (USD 5.4 b)*

- ***2,400+*** *MD/IVD MAH's license holders*

- ***3,000+*** *Approvals/Marketing Certifications a year*

Health indicators (Source: OECD Health Statistics 2017)

Population:	127.3 million
Health spending:	4,519 USD/capita
Length of hospital stay:	16.5 days
hospital bed:	13.2 beds/1,000
inhabitants	

Legal framework

- *GHTF-harmonized*
  - *Essential Principles*
  - *Risk-based Classification*
  - *STED* *etc.*
- *ISO13485-based QMS*
- *MHLW controls nomenclature (JMDN)*
- *Third party-system covers most class II MDs/IVDs. JIS(Japanese Industrial Standards) are used as certification standards.*

Snapshot (pre-market regulations)

PMDA

PMDA's review focuses on high-risk or non-standard products.

MD/IVD Reviewers: *approx. 100*

Approvals in FY2016: *1,120 MDs and 75 IVDs*

New: 26
Improved: 269
Me too: 825

QMS inspectors: *approx. 20 + α*

QMS inspections in FY2016: *952 for MDs and 83 for IVDs*

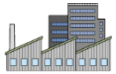
Third-party system

Conventional products are covered by the third party system and certification standards

Registered-certification bodies: *14*

Marketing certifications in FY2016: *approx. 1,800 MDs and 80 IVDs*

Scope of QMS Inspection

	Facility Registration	QMS Inspection
 MAH FRAH, designated MAH	N/A MAH license is required	**Required**
 Design Facility	Required	**Required**
 Main Assembly Plant	Required	**Required**
 Sterilizer	Required only for sterile medical device	**Required** only for sterile medical device
 Domestic (Japan) Distribution Center	Required	**Required**
 Other sites	Not Required	Depends PMDA determines based on risk assessment

Classification and conformity assessment

GHTF	Japan (As of Nov. 2017)			
	Classification	**Pre-market**	**JMDN**	**Certification Standards**
Class A extremely low risk	**General MDs** (Class I)	Self declaration (notification to PMDA)	1,197	
Class B low risk	**Controlled MDs** (Class II)	Third-party system (***certification***)	1,977	**937** Stds covering 1,702 JMDNs
Class C medium risk	**Specially controlled MDs** (Class III & IV)	PMDA's review/inspection (***approval***)	783	**11** Stds covering 43 JMDNs
Class D high risk			356	

Conformity assessment (third-party system)

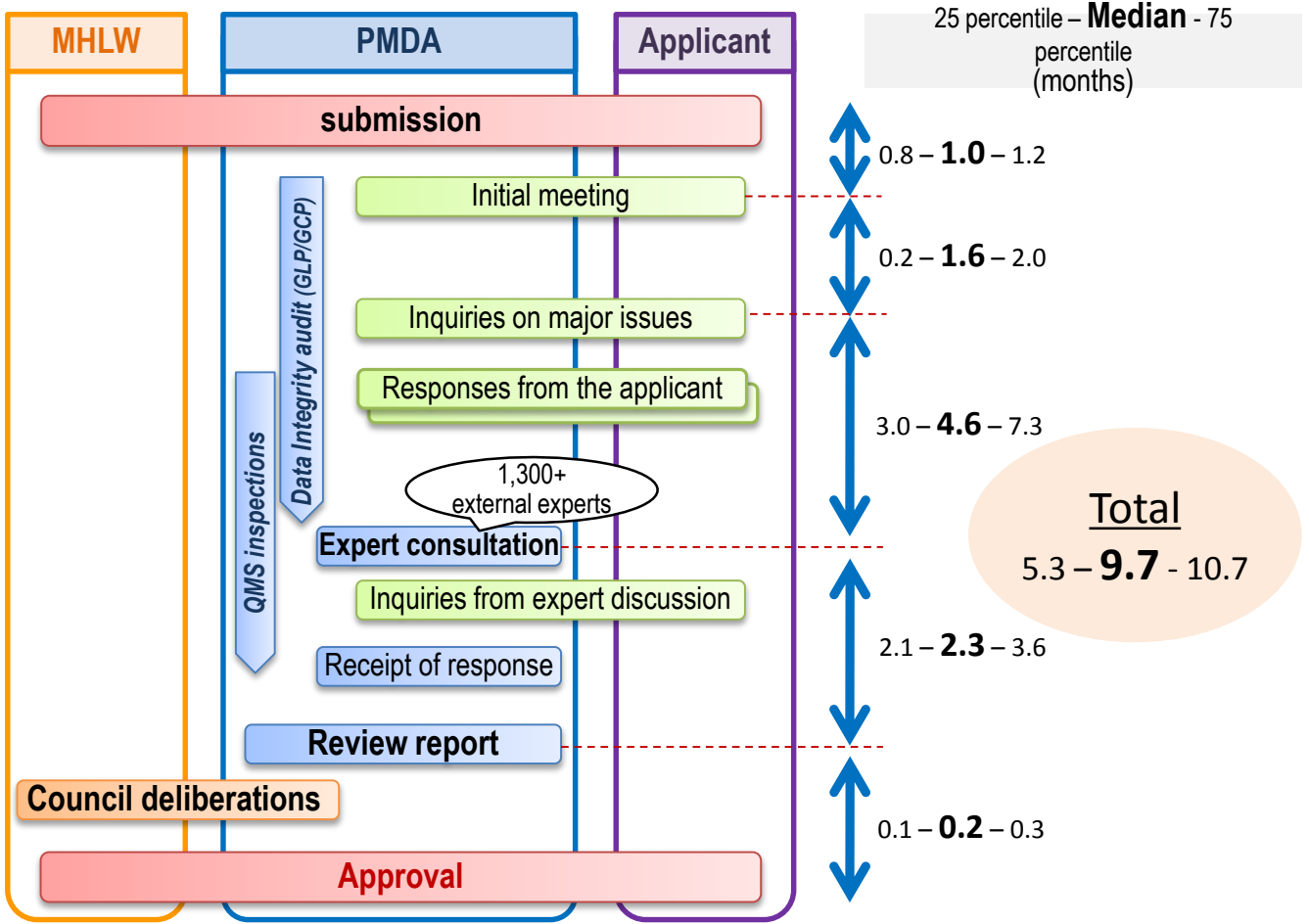
- *Registered-certification body reviews…*
  - *Scope of the indication of the product*
  - *Conformity to EP*
    - *Substantial equivalence to a marketed product*
    - *Conformity to specific JIS cited in a Certification Standards*
    - *Applicant's declaration of conformity to whole EP (checklist-style)*
  - *QMS*

offers the presumption of conformity to specific EP

(Example of a Certification Standard)

#	Applicable JMDN	Certification Standard	
		Technical standards	Indication (purpose of use)
1	1. X-ray system, diagnostic, general-purpose, mobile, analogue 2. X-ray system, diagnostic, general-purpose, portable, analogue 3. X-ray system, diagnostic, general-purpose, portable, digital 4. X-ray system, diagnostic, general-purpose, stationary, analogue 5. X-ray system, diagnostic, general-purpose,	JIS T 0601-1-3 JIS Z 4751-2-54 **IEC 60601-1-3:2008** (IDT) General requirements for basic safety and essential performance - Collateral Standard: Radiation protection in diagnostic X-ray equipment **IEC 60601-2-54:2009** (MOD) Particular requirements for the basic safety and essential performance of X-ray equipment for radiography and radioscopy	To provide the imaging information of human body for medical care used with the scintillation effect, photo-effect or ionization effect that X-ray went through a body has.

PMDA's review timeline for new MDs *(2015.1Q - 2016.2Q)*



PMDA's Performance goals and results

New MDs (excl. priority review)		2014	2015	2016	2017	2018
Performance goal	Total Review Time	14 months				
	Target Percentile	60	60	70	70	80
Result	Total Review Time (At the target percentile , Mo)	**5.6**	**10.1**	**12.0**	-	-

Me-too MDs		2014	2015	2016	2017	2018
Performance goal	Total Review Time	4 months				
	Target Percentile	52	54	56	58	60
Result	Total Review Time (At the target percentile , Mo)	**3.9**	**4.4**	**3.5**	-	-

IVDs		2014	2015	2016	2017	2018
Performance goal	Total Review Time	6 months				
Result	Total Review Time (median, Mo)	**5.3**	**7.2**	**6.4**	-	-

Joint Work Plan btw RAs and business associations

- *For smooth and speedy review, both high-quality review and submission are essential.*
- *MHLW and business associations (JFMDA, AMDD, EBC and JACRI) agreed 5-Year Joint Work Plan For Speedy Review in 2014.*

For MDs

- *Quality improvement*
  - *Training for reviewers/applicants*
  - *Training on regulatory submission*
  - *Upgrading pre-submission consultations*
  - *Identifying problems and prompt action*
- *Standard review time*
  - *Submission cohort-base*
  - *12mo for new MDs*
    (stricter than aforementioned target)*
- *Progress management*

For IVDs

- *Quality improvement*
  - *Upgrading pre-submission consultations*
  - *guidance on submission dossier writing*
- *Standard review time*
  - *Submission cohort-base*
  - *7mo for conventional IVDs*
    (stricter than aforementioned target)*
- *Increasing the number of reviewers*
- *Progress management*

Export from Japan

- *Upon request, MHLW issues following certificates regarding regulated products/facilities.*
  - *Marketing authorization (approval, certification etc.)*
  - *MAH License holder*
  - *Registered-manufacturing facility*
  - *Conformity to QMS*

(See https://www.pmda.go.jp/files/000153044.pdf)

- *While, MHLW is unable to issue a certificate regarding **non-regulated** products. A business association issues such a certificate.*

(Example)
JACRI (Japan Association of Clinical Reagent Industry) issues a certificate for reagents and calibrators that are freely marketed but not regulated as IVDs.

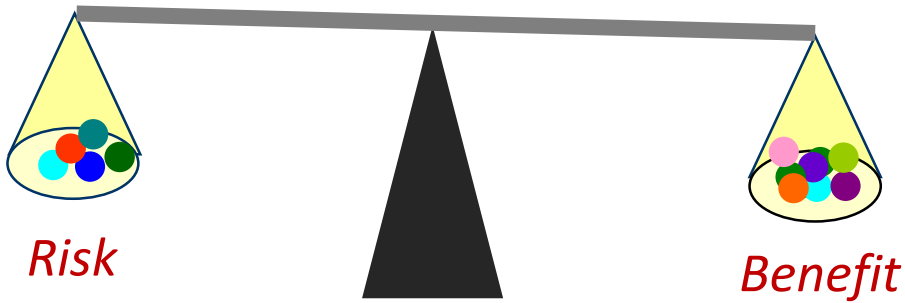
Recent updates

1. *Evolving early access scheme*
2. *Use of real world data*
3. *Re-manufacturing of SUDs*

Basic concept of reviews

- *To evaluate safety and performance (efficacy), then examine the benefit and risk balance.*

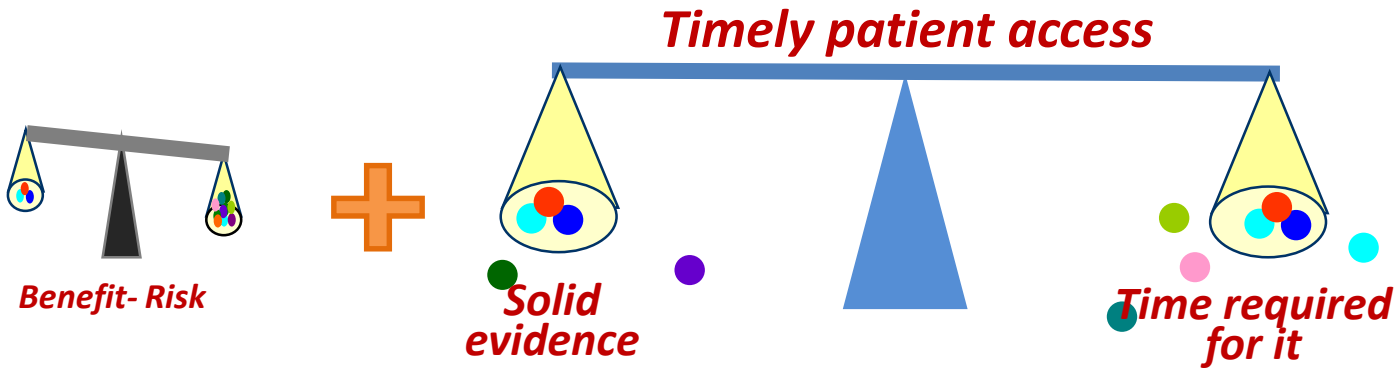
- *Also examine the appropriateness of the description of device's characteristics and the labelling that define usage circumstances.*
  (intended use, instruction for use, precautions etc.)



Additional thinking

- *It is demanded to reconsider the balance between **patient's timely access** to MDs and **considerable amount of time** required to conduct clinical trials in order for much more robust evidence.*

- *Also it's required to examine further the balance of what should be required **in pre- and post-market stage**.*



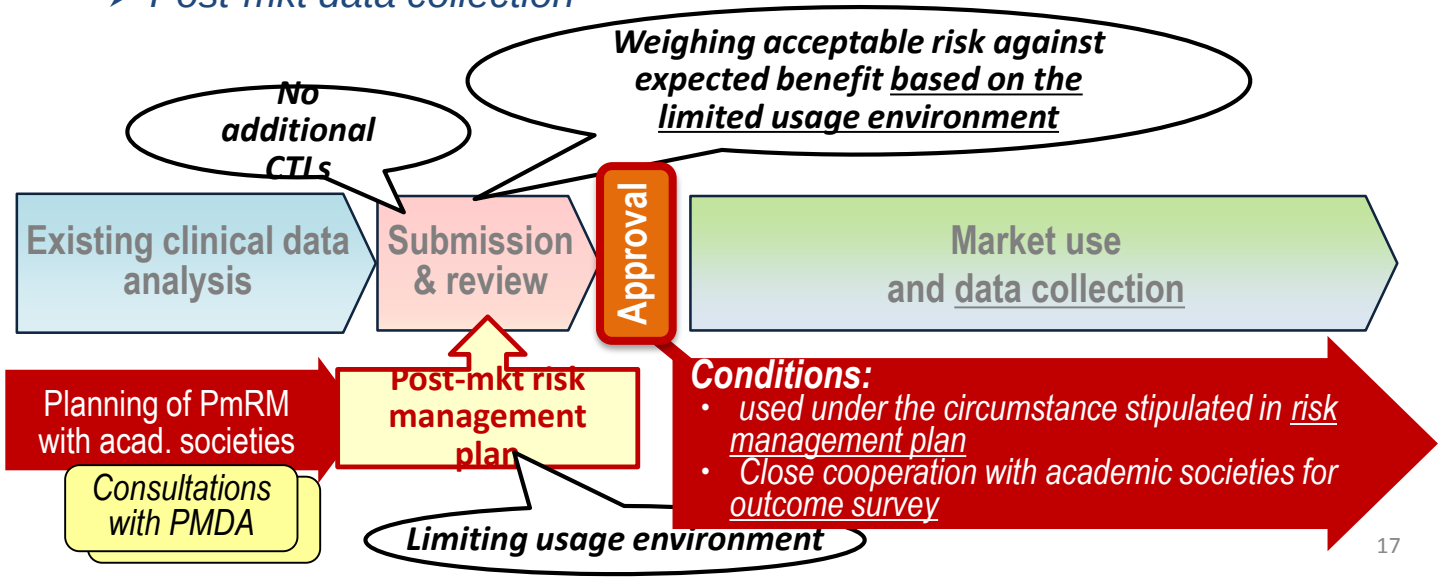
1. Evolving Early Access schemes

- *MHLW implements following measures to accommodate patient access demand.*

Type	Measures
Priority	Priority review, orphan designation
Conditional approval	**Conditional and Accelerated Approval Scheme**
Rolling submission	**Forerunner (*SAKIGAKE*) Review Assignment**

(1) Conditional and Accelerated Approval Scheme

- *MHLW clarified circumstances where new MD can be approved with exploratory trial data.* *(July 2017)*
  - *MDs for life-threating disease that has no effective treatment*
  - *Extraordinary difficulties in conducting confirmatory trial within reasonable time frame (eg. Too long period of time due to very small number of Pts)*
  - *Post-mkt risk management plan developed in conjunction with related academic societies (eg. Dr/hospital qualification, rules for proper use)*
  - *Post-mkt data collection*



(2) SAKIGAKE* Review Assignment

(* Forerunner, pioneer)

Since 2015, MHLW assigns the world's first products currently being developed with high expectation.

Assignment criteria

- *Prominent effectiveness and dire medical needs for the therapy*
- *Technological innovativeness*
- *World's first submission in the future* (incl. simultaneous submissions)

Supports from RAs

" feel like I'm riding a train going to approval, while others struggle to find their way there "

1. **Review partner** ***[A PMDA manager as a concierge]***
2. **Prioritized consultation**
3. **Substantialized pre-submission assessment**
4. **Prioritized review**

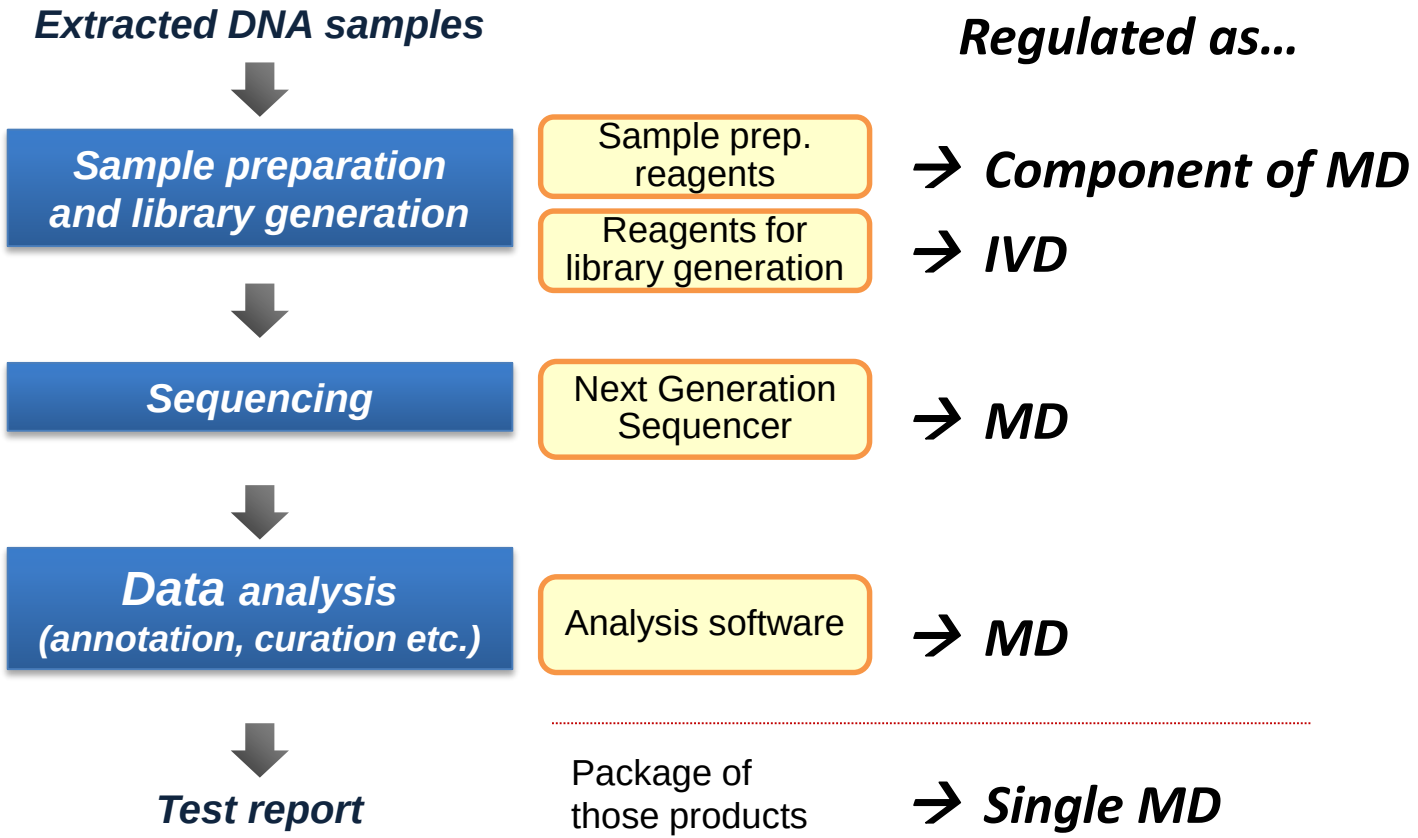
SAKIGAKE Assignment for MD/IVD

(Feb. 2016(#1), Feb.2017(#2-5))

	Name	Proposed indication	Sponsor
#1	**Titanium Bridge** (Hinge-type titanium plates)	Adduction-type spasmodic dysphonia	Nobelpharma
#2	**Tracheal prosthesis** (made of polypropylene mesh and collagen sponge)	Aiding reconstruction of tracheal while maintaining intratracheal structure after partial removal.	Daiichi Medical
#3	**Boron neutron capture therapy system** (Neutron irradiation system for BNCT)	Glioblastoma, head and neck cancer (Selective destruction of tumor cells marked by boron agents)	Sumitomo Heavy Industries, Ltd.
#4	**UT-Heart** (Software to aid CRT)	Higher accuracy prediction of effectiveness of cardiac resynchronization therapy for patients with serious heart failure.	Fuji Film
#5	**Cancer-related gene**	Collective examination of cancer-related	Sysmex

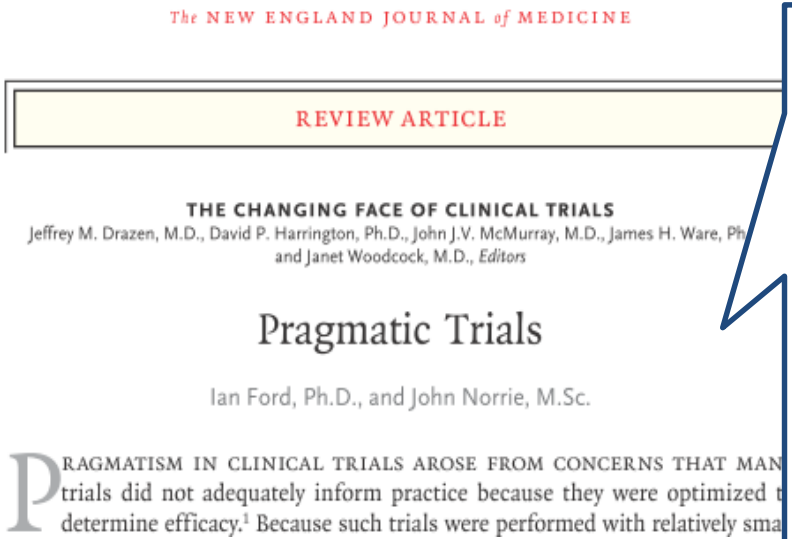
Third round of selection is underway.

Regulations for NGS-based products



2. Use of real world data

- *MHLW is developing regulatory systems supporting pragmatic trials using registries/health records.*



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph
and Janet Woodcock, M.D., *Editors*

Pragmatic Trials

Ian Ford, Ph.D., and John Norrie, M.Sc.

PRAGMATISM IN CLINICAL TRIALS AROSE FROM CONCERNS THAT MAN
trials did not adequately inform practice because they were optimized t
determine efficacy.[1] Because such trials were performed with relatively sma

An attractive alternative to trials in which **electronic health records** are used can be found in trials of alternative interventions involving patients who are already enrolled in **disease-specific or intervention-specific registries** that incorporate detailed patient phenotypes and long-term follow-up data. This framework provides **an efficient and low-cost opportunity for conducting pragmatic trials** (e.g. the TASTE trial)

Ford I. et al. NEJM 375;5, 454-463, 2016
http://www.nejm.org/doi/full/10.1056/NEJMra1510059?query=featured_clinical-trials

Examples of use of registry outcome for approval review

- **Da Vinci Surgical System**
  (Additional application of MVP & ASD)

  Comparison with results using conventional methods from the Society of Thoracic Surgeons (STS) National Database.

- **SATAKE Hot Balloon Catheter**
  (Paroxysmal atrial defibrillation therapy for high-frequency ablation catheters)

  Comparison with results using conventional methods from the Japanese Catheter Ablation Registry of Atrial Fibrillation (J-CARAF) of the Japanese Heart Rhythm Society (JHRS).

Examples of use of registry outcome for approval review

- Kawasumi Najuta Chest Stent Graft System
  (Stent graft for prevention of aortic aneurysm rupture)

  Comparison with results from surgery from the historical control group of the Japan Adult Cardiovascular Surgery Database （JACVSD).

- EXCOR Ventricular assist system (VAS)

  Comparison with the matching patient group survival rate from the ECMO treatment registry: Extracorporeal Life support Organization (ELSO).

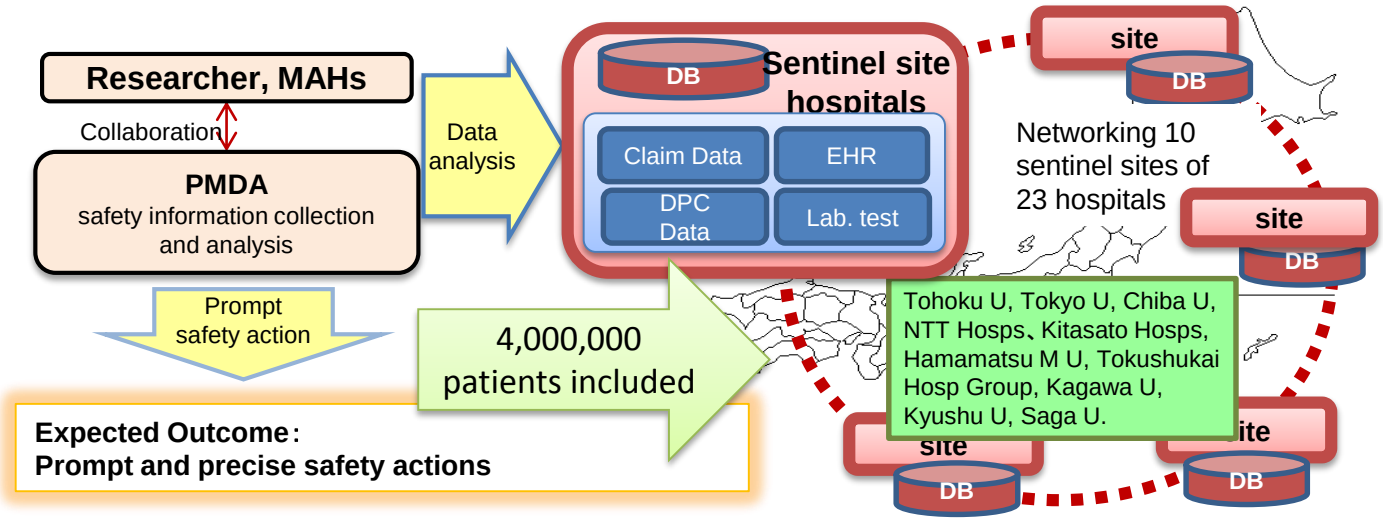
Use of electronic medical records for regulatory submission

- *MHLW published/will publish followings in 2017 as to develop the standards and general considerations for ensuring the reliability of electronic medical records (EMR) used for post-marketing studies / surveillances.*

- **Revision of Good Post-marketing Study Practice Ordinance** (Oct. 2017)
  - To address contract relations, Medical institution, DB providers and MAH to specify the information sources and responsibilities
- **General Considerations on using EMR for Drug PMS** (June 2017)
  - Scope of usable data and general consideration on study designs
  - Scientific consideration, characters of DB for PMS purposes
- **General Considerations on data reliability of EMR DBs for PMS** (tba)
  - Describe the range of data to be verified and preserved in terms of guaranteeing the reliability when using application data.

Medical Information Database Network（MID-NET）

- Promote safety measures by pharmaco-epidemiological method using medical information database.
- MHLW/PMDA have established a medical information database for collecting large-scale medical data at sentinel site hospitals and have constructed analytical systems at PMDA since FY 2011.



【History and way forward】

- ●April 2010 :「Revision of pharmaceutical administration etc. to prevent recurrence of pharmaceutical disasters (final recommendation)」
- ● April 2011 - : Start construction of MID-NET system
- ● April 2013 - : Start data quality validation to assure precision and comprehensiveness of the collected data
- ● April 2015 - : Start trial operations by PMDA and sentinel sites
- ● April 2015 - : Setting utilization rules for full-scale operation and framework of operation cost / user fees.
- ● in FY 2018 : Full scale operation, enable MAHs and researchers to use MID-NET

3. Re-manufacturing of SUDs

- *MHLW issued guidance and standards regarding reprocessing of single-use device(SUD) on July 2017*

- *Basic concept is as follows*
  1) *Reprocessed SUD is not an original MD, thus needs a different approval*
  2) *A preprocessor has to have MAH license*
  3) *Japan-closed cycle* *(Only MDs used in Japan can be reprocessed under this scheme)*

Regulatory Convergence in APEC

- *Priority Work Area "Medical Devices" established in August, 2017*
- *Co-Champions: Japan, Korea, US*
- *Draft new roadmap*
- *Possible initial subtopics:*

  Device classification principles, Recognition & use of international standards, Single Audit, Definition, IVD, Risk Management, QMS, Clinical Trial vs. Clinical Evaluation

APEC
Asia-Pacific Economic Cooperation

Regulatory Harmonization Steering Committee
APEC
Life Sciences Innovation Forum

PMDA-ATC (Asia Training Center)
Medical Devices Seminar 2017

- *November 6-10, 2017 @ PMDA*
- *30 regulators from 12 economies joined*
- *Topics covered:*

  product reviews, consultations, GCP/GLP inspections, QMS inspections, post-marketing safety measures, package inserts, registration system, international standards for medical device, in vitro diagnostics

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Thank you for your attention