Applications of Real-World Data and Real-World Evidence in Decision Making in Asia Pacific

- Organized by ISPOR Asia Consortium Industry Committee
- The objective is to provide the most recent update on the use of real-world data (RWD) and real-world evidence (RWE) in regulatory, reimbursement, and clinical decision making in Asia Pacific.

May 6, 2024
ISPOR, Atlanta, GA

Agenda

- Introduction by moderator: Dr. Larry Liu
- Update of the use of RWD and RWE for regulatory and clinical decision making in China and Japan with specific case examples: Dr. Larry Liu
- Application of RWE in reimbursement decisions as well as hospital payment reform in China: Dr. Jianwei Xuan
- RWE Application in Medtech - a case study: Dr. Viva Ma
- Q&A

MERCK
INVENTING FOR LIFE

Update on the Use of RWD/E for Regulatory and Clinical Decision Making in China and Japan

Larry Z Liu, MD, PhD, Jun Zhang, MD, MPH, Tomoya Ohno, PhD
Merck & Co., Inc, Rahway, New Jersey, USA
Weill Medical College of Cornell University, New York, New York, USA

May 6, 2024

China RWD Guidance for Regulatory Decision Making

	China	Lecheng Pilot Zone, Hainan
2018	Nov. RWE to support drug development and approval guidelines	April: Guiding Opinions of the State Council on Supporting the Reform: Accelerating the development of Pilot Zone"
2019	May《 Key Considerations in Using Real World Evidence to Support Drug Development 》(Draft for Public Review)	March: 1st medical device was granted approval by NMPA Sept. 3 national agency issued "Implementation plan for pilot zone to support use of RWD in registration application
2020	Jan《 Guidelines for Real World Evidence Supporting Drug Development and Review (Trial) 》 Aug《 Guideline on Using Real-World Study to Support the Development and Evaluation of Pediatric Drugs》	April, Establishment of RWD Research and Innovation Center of Boao Lecheng Dec: Drug pilot program announcement, 3 Drug and 11 Device
2021	April: Guideline on Using Real-World Data to Generate Real-World Evidence (Trial)	March: One Drug got conditional approval from NMPA, making it the first approved new drug by using RWE to supplement traditional clinical research
2022	May: China drug real-world study design and protocol framework guidelines (Draft for comments) Guidelines for Communication of Real World Evidence to Support Drug Registration Applications (Draft for Comments)	Two drugs and four medical devices were granted approval by NMPA
2023	FEB: Guidance on the Design and Protocol Development of Real-World Studies for Drugs (Final) MAR： Guideline on communications of using real-world evidence to support registration applications for drug	Oct: The 2nd Boao International Conference on Real World Studies of Medical Products, with the theme of "international real world data research and scientific development of medical products regulation".

MERCK

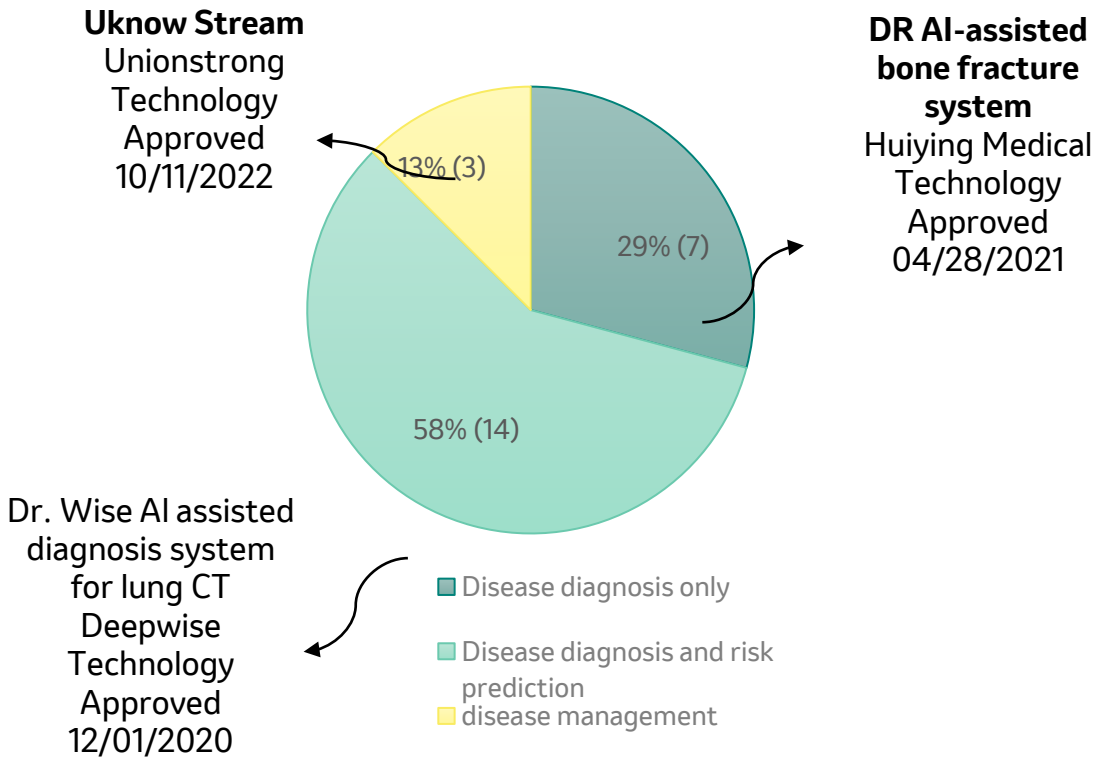
RWD Use Cases for Regulatory Approvals of Drugs in Lecheng by NMPA

Approved Drugs (4)

blueprint MEDICINES	Pralsetinib (FDA Approval Sept. 2020)	March, 2021 (NMPA approval: 6 month after FDA approval)
EYEPOINT PHARMACEUTICALS	YUTIQ (FDA Approval Oct. 2018)	June, 2022 (NDA filling on 4/2021)
G1 THERAPEUTICS	Trilaciclib (FDA Approval Feb. 2021)	July, 2022 (RWS application in Lecheng pilot Zone on 5/2021)
NOVARTIS	Inclisiran Sodium Injection (FDA Approval Dec. 2021)	August, 2023 (RWS pilot program on 8/2021

Application of RWD for Selected AI-Assisted Decision-Making System

Approved AI-Assisted software by Functions (24)



Received: 24 May 2023 | Accepted: 31 August 2023
DOI: 10.1111/jebm.12549

REVIEW

WILEY

Recent advancement in integrating artificial intelligence and information technology with real-world data for clinical decision-making in China: A scoping review

Xiwen Liao[1] | Chen Yao[1,2] | Jun Zhang[3] | Larry Z Liu[4,5]

真实世界数据和证据在我国临床决策中的应用现状

Application of Real World Data and Evidence for Clinical Decision-Making in China

廖茜雯
北京大学第一医院
北京大学临床研究所

LIAO Xi-wen
Peking University First Hospital
Peking University Clinical Research Institute

姚晨*
北京大学第一医院
北京大学临床研究所
海南省真实世界数据研究院

YAO Chen*
Peking University First Hospital
Peking University Clinical Research Institute
Hainan Institute of Real World Data

张军
默沙东研发（中国）有限公司

ZHANG Jun
MSD R&D (China) Co., Ltd.

Larry Z Liu
默沙东有限公司
威尔康奈尔医学院
Merck & Co., Inc.
Weill Cornell Medical College

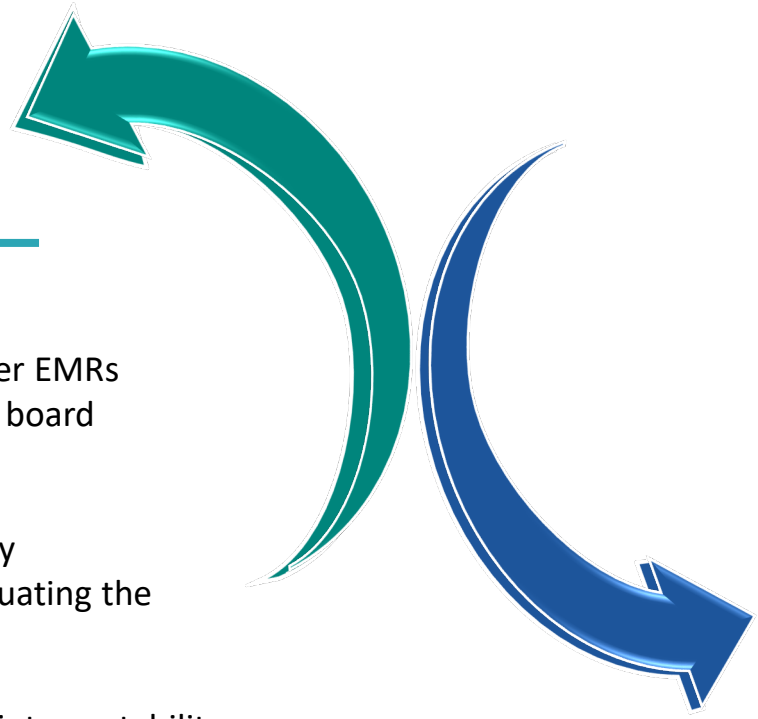
Barriers & Solutions to advance the applicability of current AI-enabled tools in clinical practice

Barriers

Data availability and accessibility
- ✓ Limited access to multi-center EMRs
- ✓ Lack of central ethics review board
- ✓ Incomplete data elements

RWD and RWE quality
- ✓ Suboptimal RWD data quality
- ✓ Lack of systematic tools evaluating the quality of RWE

Complexity of AI
- ✓ A trade-off between clinical interpretability and model complexity and performance
- ✓ Lack of transparency (Black box problem)
- ✓ Inappropriate evaluation metrics (fail to reflect reliability and clinical utility)



Solutions

Data availability and accessibility
- ✓ Adopt a collaborative approach through multi-stakeholder engagement
- ✓ Reinforce the regulation of RWD/RWE, both from the regulatory and the academic perspectives.

RWD and RWE quality
- ✓ Improve RWD data quality by strengthening source data management and adopting common source data management process.

Complexity of AI
- ✓ Visualization and the use of interpretation libraries
- ✓ Provide both local and global explanations
- ✓ Adopt an evaluation indicator of clinical utility (e.g., decision curve analysis).

Data quality and access remains the key challenges in the current RWD landscape

Data quality

- Lack of transparency in data content, quality and validation (e.g. variable definition, terminology and non-standardized coding)
- Data curation, harmonization and data validation standards are often not available

Fragmented and heterogeneous data in nature

- Patients go to multiple hospitals for outpatient care
- Lack of infrastructure and collaboration mechanism to enable record linking across hospitals

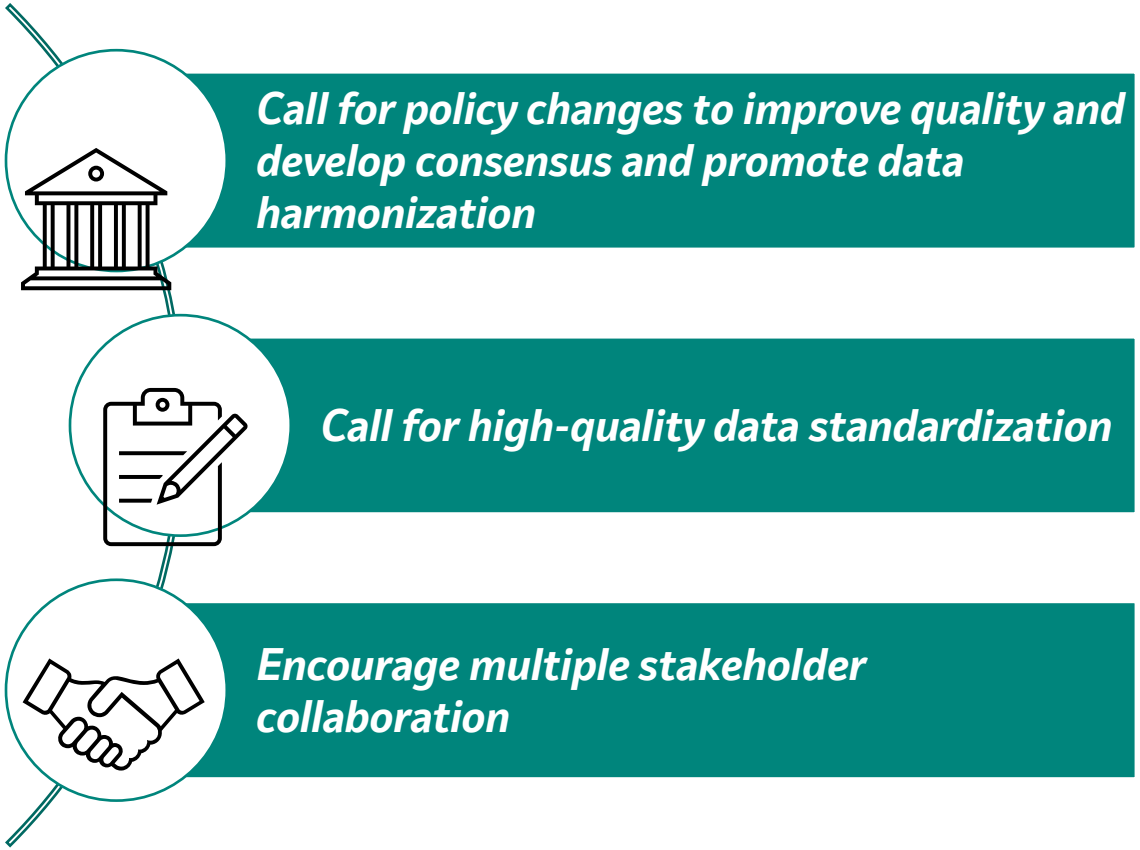
Data access

- Data access and sharing are limited and not well-defined

Efficiency and timeline

- Government and hospital regulations and requirements (Ethnics review/HGRAC review)
- Regulatory submission process
- Personal data protection law

Building the RWD foundation to further the use of RWE for regulatory and clinical decision making



ELSEVIER | Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/vhri

Systematic Literature Review

Real-World Data for Healthcare Research in China: Call for Actions

Jipan Xie, MD, PhD, Eric Q. Wu, PhD, Shan Wang, MD, Tao Cheng, MD, Zhou Zhou, MS, Jia Zhong, ScD, Larry Liu, MD, PhD

Open access Original research

BMJ Open

Existing barriers and recommendations of real-world data standardisation for clinical research in China: a qualitative study

Junkai Lai ,[1] Xiwen Liao,[1] Chen Yao,[1,2] Feifei Jin ,[3] Bin Wang ,[1] Chen Li,[4] Jun Zhang,[5] Larry Liu[6,7]

Open access Communication

BMJ Open

Advancing the development of real-world data for healthcare research in China: challenges and opportunities

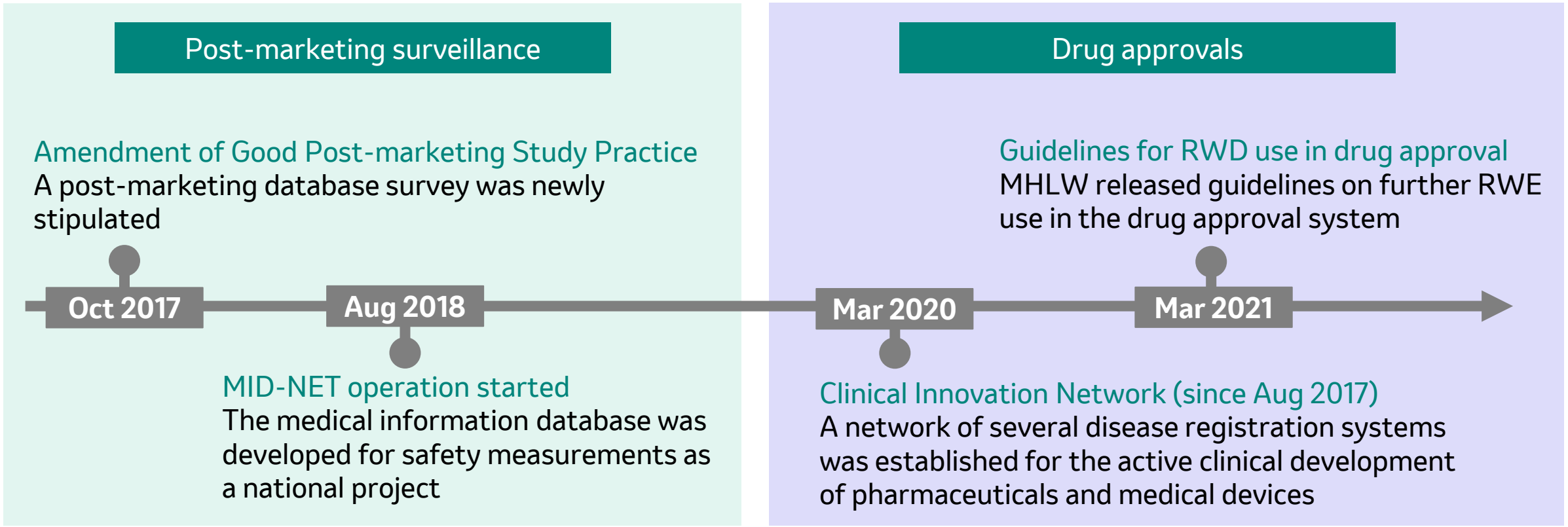
Jia Zhong,[1] Jun Zhang,[2] Honghao Fang ,[1] Larry Liu,[3,4] Jipan Xie,[5] Eric Wu[6]

MERCK
INVENTING FOR LIFE

RWD/E use for regulatory and clinical decision making in Japan

RWD use for regulatory and clinical decision making in Japan

In Japan, RWD use has been encouraged for post-marketing surveillance and drug approvals[1]



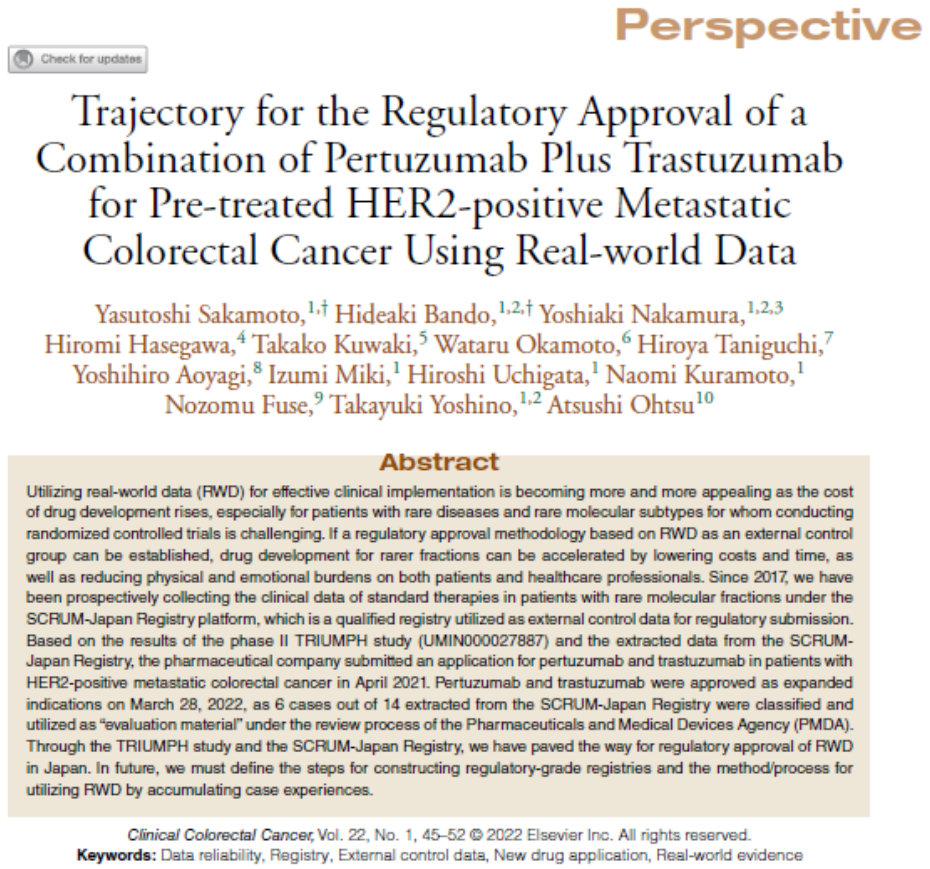
RWD: Real-World Data, MID-NET: Medical Information Database Network, MHLW: Ministry of Health, Labour and Welfare

Drug Approvals Using Real World Data in Japan

Examples of approval applications using RWD in Japan[2,3]

Generic name	Indication	Japan		
		Approval year	iNDA/sNDA	Data source
Algucosidase alfa	Pompe disease	2007	iNDA	External control medical records (overseas)
Argatroban	Heparin-induced thrombocytopenia	2011	sNDA	External control medical records (overseas)
Methotrexate	Rheumatoid arthritis	2011	sNDA	Public-knowledge application post-marketing surveillance
Tacrolimus	Interstitial pneumonitis in polymyositis/ dermatomyositis	2013	sNDA	External control published article (Japanese)
Methylprednisolone Sodium Succinate	Multiple sclerosis	2013	sNDA	Public-knowledge application post-marketing surveillance
Asfotase Alfa	Hypophosphatasia	2015	sNDA	External control electric health record (overseas) registry (overseas)

Recently, the SCRUM-Japan registry was utilized as external control data for regulatory submission[1]



Perspective

Check for updates

Trajectory for the Regulatory Approval of a Combination of Pertuzumab Plus Trastuzumab for Pre-treated HER2-positive Metastatic Colorectal Cancer Using Real-world Data

Yasutoshi Sakamoto,[1,†] Hideaki Bando,[1,2,†] Yoshiaki Nakamura,[1,2,3] Hiromi Hasegawa,[4] Takako Kuwaki,[5] Wataru Okamoto,[6] Hiroya Taniguchi,[7] Yoshihiro Aoyagi,[8] Izumi Miki,[1] Hiroshi Uchigata,[1] Naomi Kuramoto,[1] Nozomu Fuse,[9] Takayuki Yoshino,[1,2] Atsushi Ohtsu[10]

Abstract

Utilizing real-world data (RWD) for effective clinical implementation is becoming more and more appealing as the cost of drug development rises, especially for patients with rare diseases and rare molecular subtypes for whom conducting randomized controlled trials is challenging. If a regulatory approval methodology based on RWD as an external control group can be established, drug development for rarer fractions can be accelerated by lowering costs and time, as well as reducing physical and emotional burdens on both patients and healthcare professionals. Since 2017, we have been prospectively collecting the clinical data of standard therapies in patients with rare molecular fractions under the SCRUM-Japan Registry platform, which is a qualified registry utilized as external control data for regulatory submission. Based on the results of the phase II TRIUMPH study (UMIN000027887) and the extracted data from the SCRUM-Japan Registry, the pharmaceutical company submitted an application for pertuzumab and trastuzumab in patients with HER2-positive metastatic colorectal cancer in April 2021. Pertuzumab and trastuzumab were approved as expanded indications on March 28, 2022, as 6 cases out of 14 extracted from the SCRUM-Japan Registry were classified and utilized as "evaluation material" under the review process of the Pharmaceuticals and Medical Devices Agency (PMDA). Through the TRIUMPH study and the SCRUM-Japan Registry, we have paved the way for regulatory approval of RWD in Japan. In future, we must define the steps for constructing regulatory-grade registries and the method/process for utilizing RWD by accumulating case experiences.

Clinical Colorectal Cancer, Vol. 22, No. 1, 45–52
Keywords: Data reliability, Registry, External control data, New drug application, Real-world evidence

Summary

- Use of RWD/E for regulatory and clinical decision making in China improved significantly in recent years
- Exciting RWD/E opportunities in Lecheng Pilot Zone, Hainan, China
- However RWD quality and access continue to be a challenge
- Japan RWD/E use improved, but more needs to be done

MERCK
INVENTING FOR LIFE

Thank you!

RWE Application in Health Technology Assessment of China

ISPOR 2024 in Atlanta

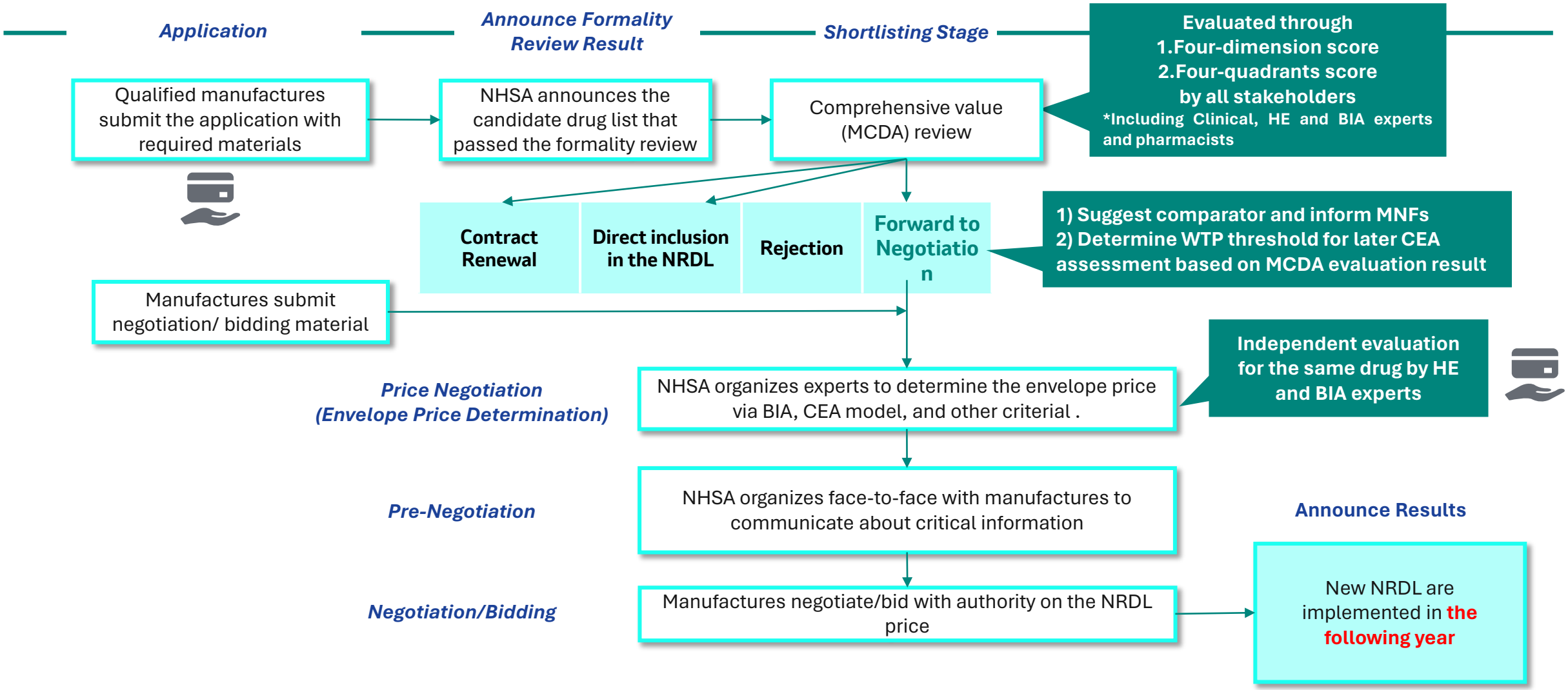
2024.05.05

01

HTA Process in China’s NRDL Negotiation

PART. 01

NRDL Process Overview in 2023



- ***HE: Health economics***
- ***BIA: Budget impact analysis***

MERCK

Shortlisting stage includes four-dimension scoring and four-quadrant assessment, which will directly impact future price estimation

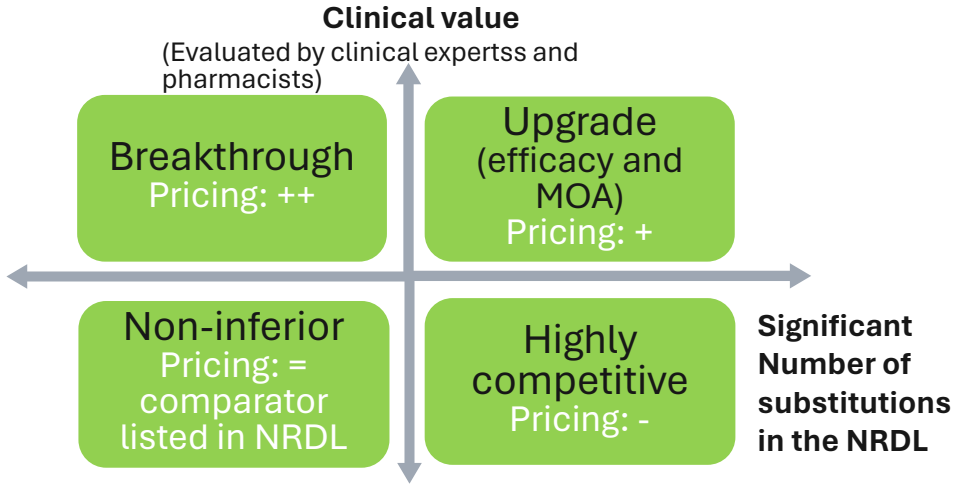
Comprehensive Review

Four-dimension Scoring

- Efficacy
- Safety
- Innovation
- Equity (including affordability)

All applied products will be scored based on four value dimensions and ranked from high to low

Four-quadrant Assessment



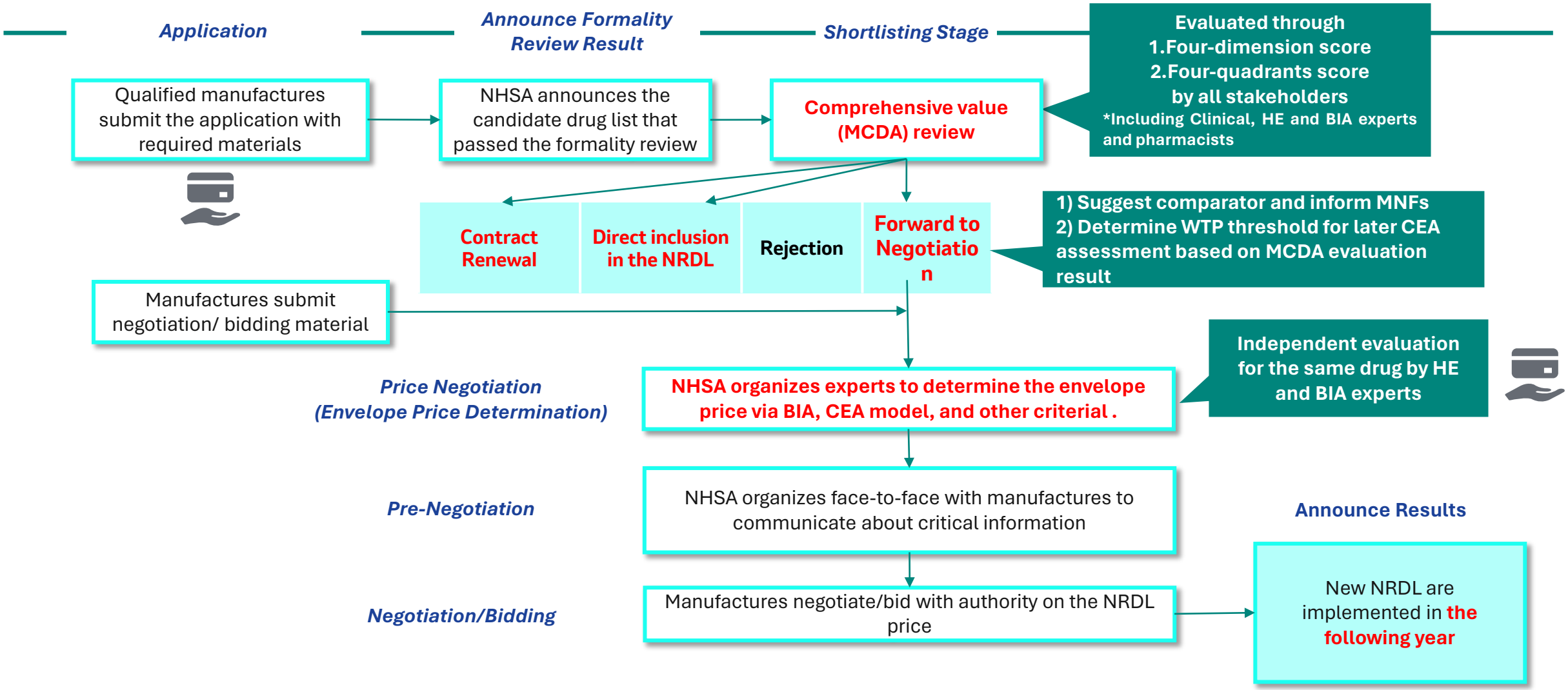
All applied products are assigned a value proposition based on four quadrants

Rating will determine whether the **product is eligible for the shortlist for the next round of negotiation**

Outcome of four-quadrant will **affect the WTP value adopted in later CEA assessment**

MERCK

RWE Potential Application In the Process



- ***HE: Health economics***
- ***BIA: Budget impact analysis***

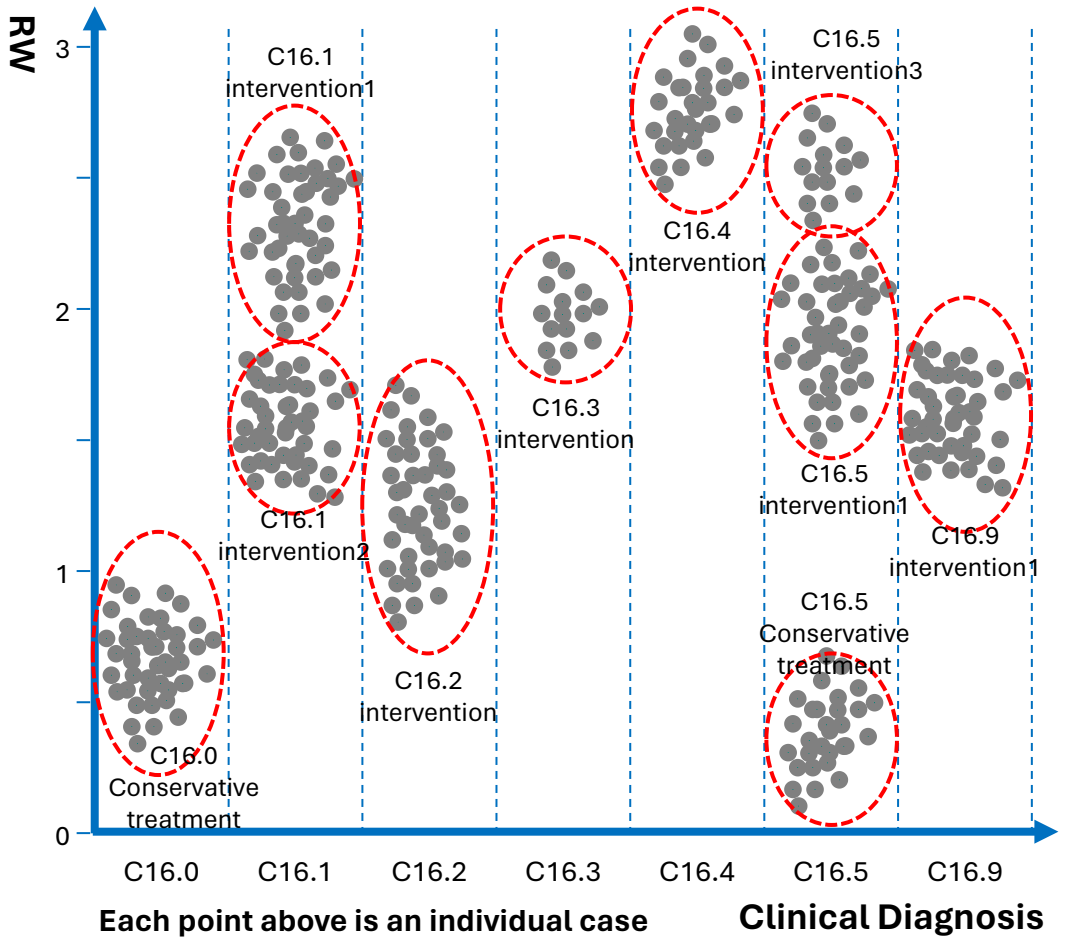
MERCK

02

Improving Hospital Management Efficiency Under DRG/DIP to Support Innovation Access

PART. 02

Grouping Illustration for BD-DIP



Reference : Xie, H., Cui, X., Ying, X., Hu, X., Xuan, J., & Xu, S. (2022). Development of a Novel Hospital Payment System – Big Data Diagnosis & Intervention Packet. Health Policy OPEN.

- According to BD-DIP, each case with the combination of disease diagnosis + intervention can correspond to the objective resource consumption level of medical services, and establish the comparative relationship of resource consumption of disease groups.

Basic elements of DIP

Packet Unit(DIPs)

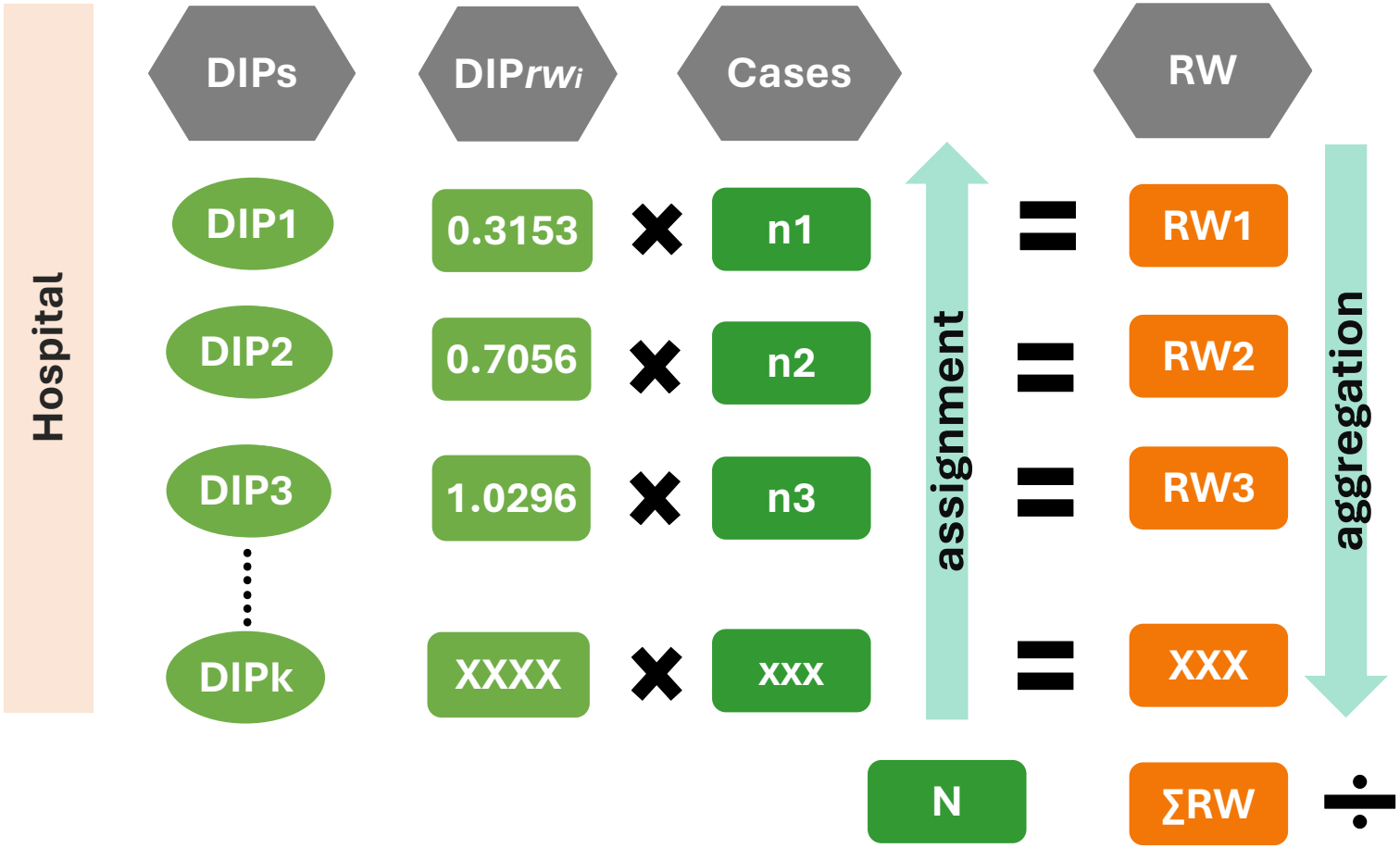
- The basic units used for analysis, evaluation, and even payment, need to have some stability (intra-group, inter-group).
- Each group is clustered naturally based on cases (as shown on the left) without human intervention.
- The number of groups should not be subjective, but rather whether the number of cases within the same group can establish comparative relationship, while considering the balance between the number of groups and the convenience of application.

Related weight (DIP*rw*)

- Related weight is based on the degree of resource consumption of each packet unit——an objective evaluation of the common characteristics of resource consumption of each unit.
- DIP*rw* is a standardized unit for different cases, reflecting the severity of disease and the complexity/difficulty of the intervention.
- The cost criteria established based on *rw* should also respond to individual differences in diseases, and fully reflect the reasonable and legitimate resource consumption of medical institutions with a sound system.

Calculation of Institution Based Overall RW and Case Mix Index (CMI)

- **RW reflects the overall service and revenue capability of hospitals.**
- **CMI value is the basis for determining the institutional adjustment factor, reflecting the overall patient disease severity and treatment complexity , as well as the service capacity at a given hospital.**



Each hospital's total RW:

$$\boldsymbol{RW} = \sum_{i=1}^{k} \mathrm{rw}_i \times n_i$$

Institutional average CMI:

$$\boldsymbol{CMI} = \frac{RW}{\sum_{i=1}^{k} n_i} \div 1000$$

Where *rwi* is DIP value for group *i*; n_i presents number of cases in DIP group *i*; and k presents the number of DIP groups in a given hospital.

The Concept of Refined Hospital Management

Note：The abscissa of the intersection of X and Y axis represents the average CMI value of the hospital

X axis：Disease's CMI value. An important indicator reflecting the level and service quality of the hospital, the higher the CMI, the higher the payment standard, and the increase in CMI effectively improves the overall capability of the institution；(Guangzhou:CMI value > 1， higher insurance pay factors), mainly depends on the complexity of the disease and management difficulties.

Y axis：Index deviation = (The actual cost of treating a patient of combination diseases in a hospital minus the standard payment threshold for this disease grouping)/negative corresponding hospital saving or better efficiency.

We Classify diagnosis related in the hospital into 4 areas, see Figure 1 below.

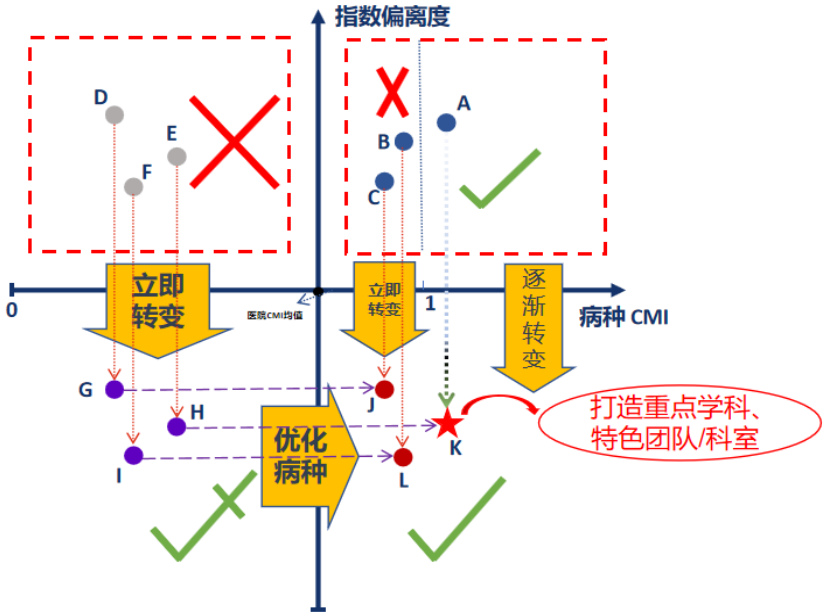
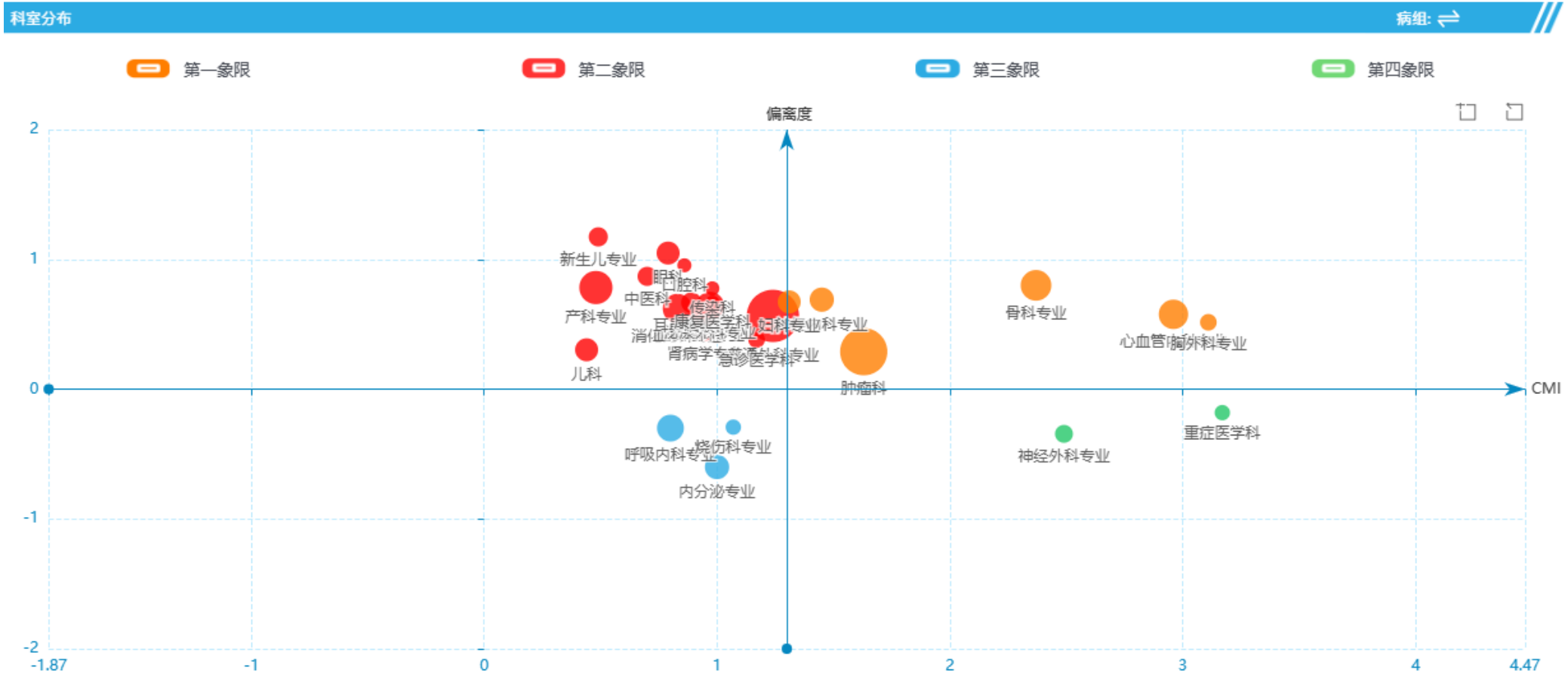


Figure 1 The number of disease groups in a hospital

Quadrant	Improvement Suggestions
First quadrant: both CMI value and index deviation **high**	CMI＜1, Reduce the index deviation through cost analysis and control of the disease groups: B immediately shift to L， C immediately shift to J. CMI ＞1， insurance positive adjustment pays. Hospitals should reasonably evaluate and balance the role of high-value products following clinical guidelines, improve medical quality, and increase CMI value to achieve performance efficiency balance.
Second quadrant: **low** CMI value, **high** index deviation	Significant problems in cost and capability, and it is recommended to improve the cost control ability through cost analysis and control patient groups, reduce the index deviation, E immediately shift to H, F immediately shift to I, D immediately shift to G
Third quadrant: CMI value is low and index deviation representing saving	Boosting CMI value by optimizing the disease management. G shift to J, H shift to K, I shift to L, improve the economic results of hospitals
Fourth quadrant: **High** CMI value and index deviation representing saving	The hospital disease treatment and diagnosis capability is higher than the average. The area needs to be rewarded internally.

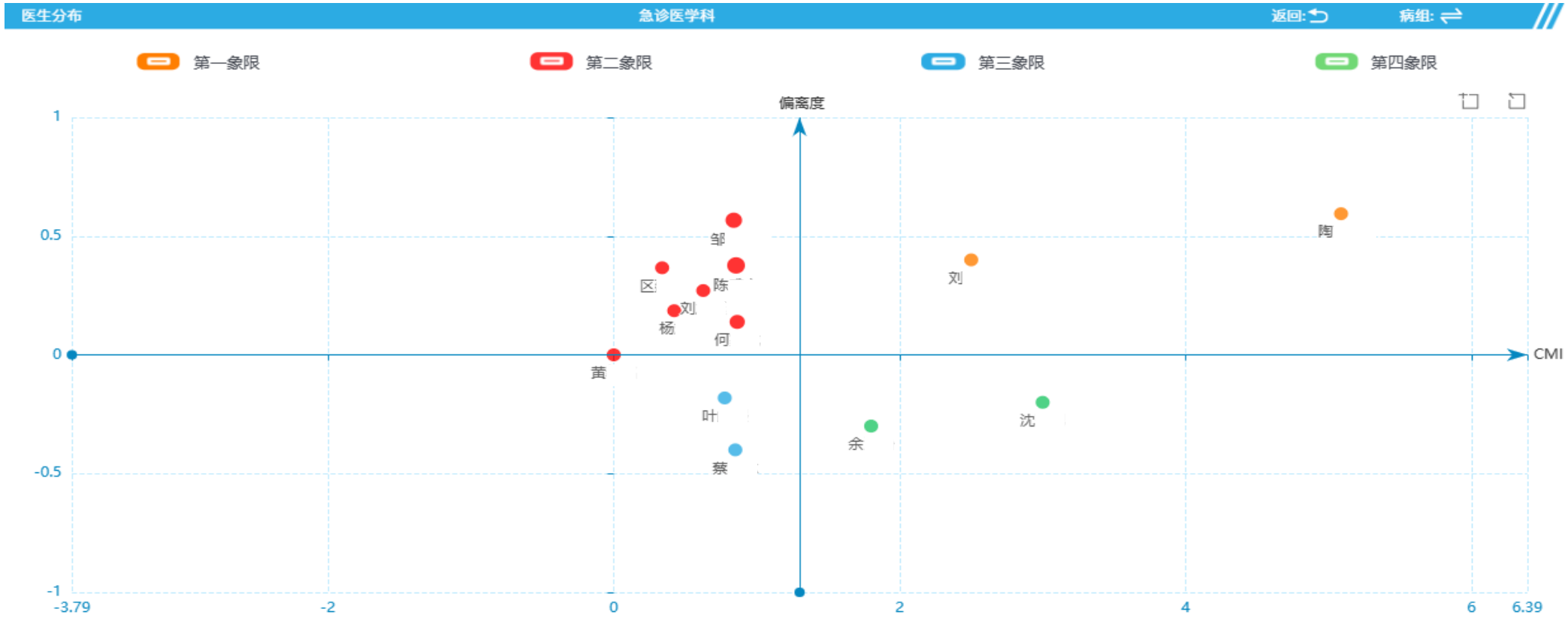
Department Analysis

Through the four-quadrant management method, we could analyze the CMI value and index deviation of various departments in the hospital



Individual Doctor Analysis

Through the four-quadrant management method, we could analyze the CMI value and index deviation of individual doctors in the hospital



Disease Analysis

Through the four-quadrant management method, we could analyze the CMI value and index deviation of various disease grouping in the hospital

Thanks

RWE Application in Medtech - a public health case study

Viva Ma, PhD, MPH, MBA

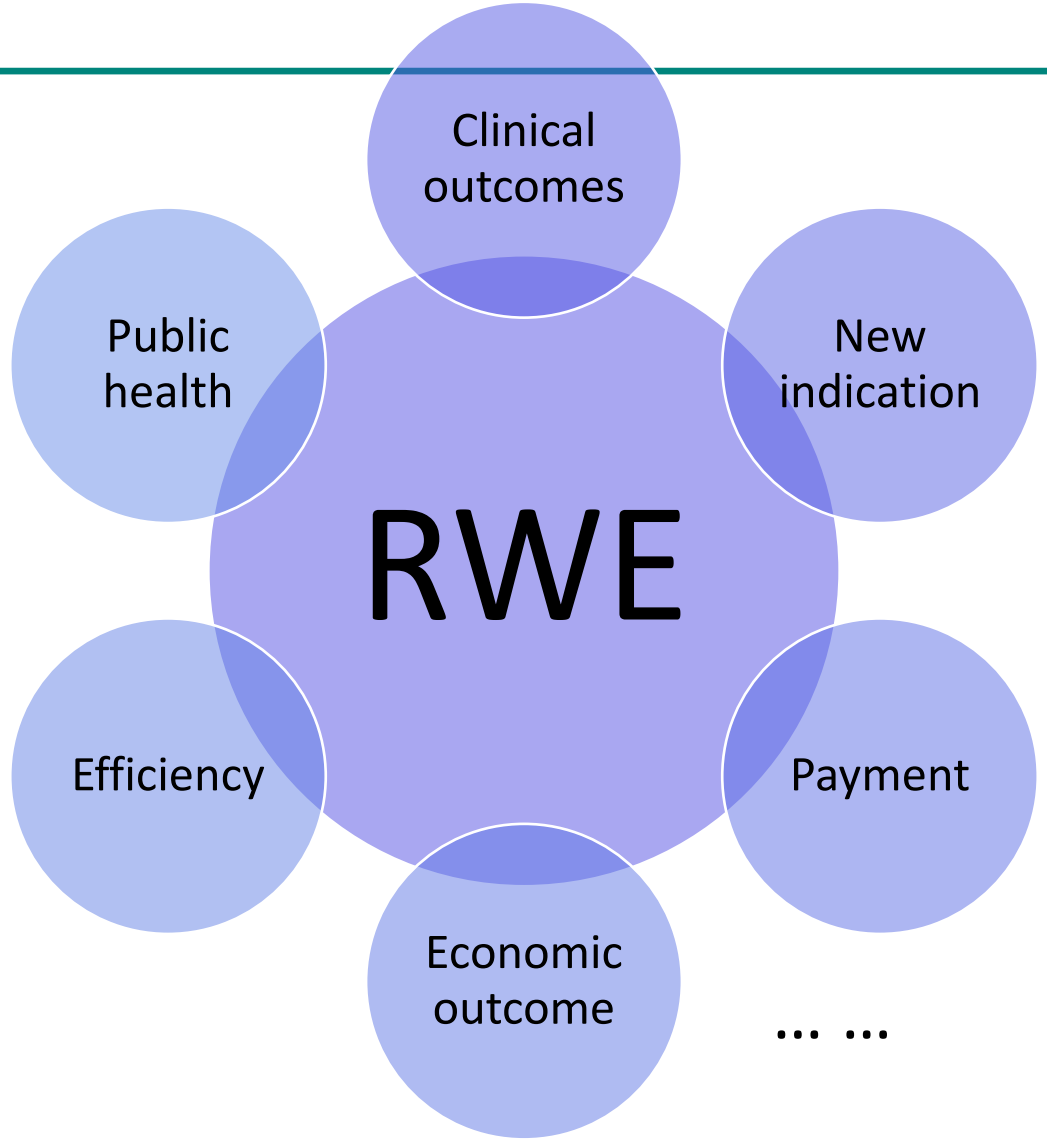
Strategic Access, Public Affairs

May 6, 2024

BD

Value of Real-World Evidence – Medtech

Real world evidence (RWE) is a demonstration of how medical technologies affect the patients, and interact with the health care system, including human, process and infrastructure factors. It not only provides information on the clinical outcomes, but also on operational and economic outcomes.



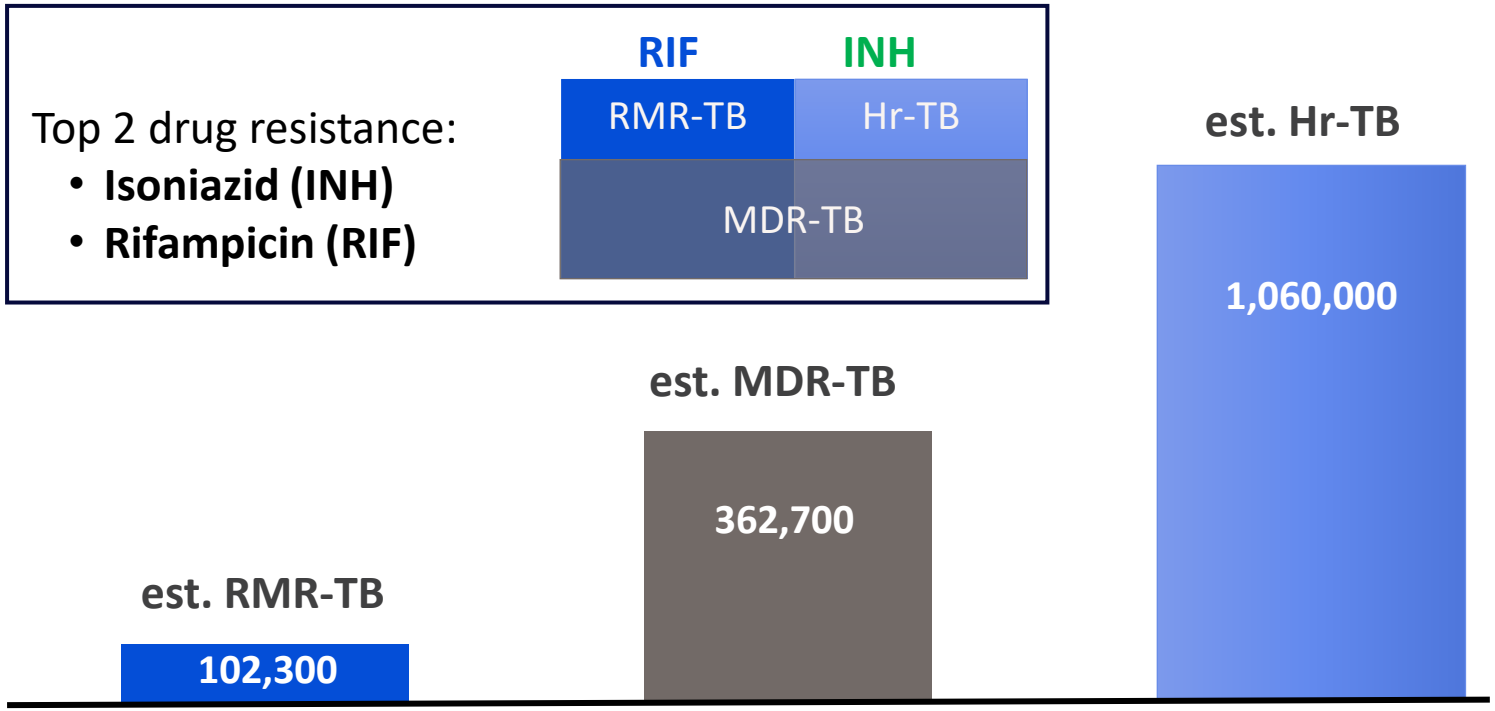
Case study on RWE informing public health strategy

In 2020, globally ~10 million people contracted TB, of which ~1.5 million died.[1]

Overall, 40% of TB patients were never diagnosed nor notified.[1] Lack of diagnosis is worse with drug-resistant TB (DR-TB).

Top 2 drug resistance:

- **Isoniazid (INH)**
- **Rifampicin (RIF)**



Issue:

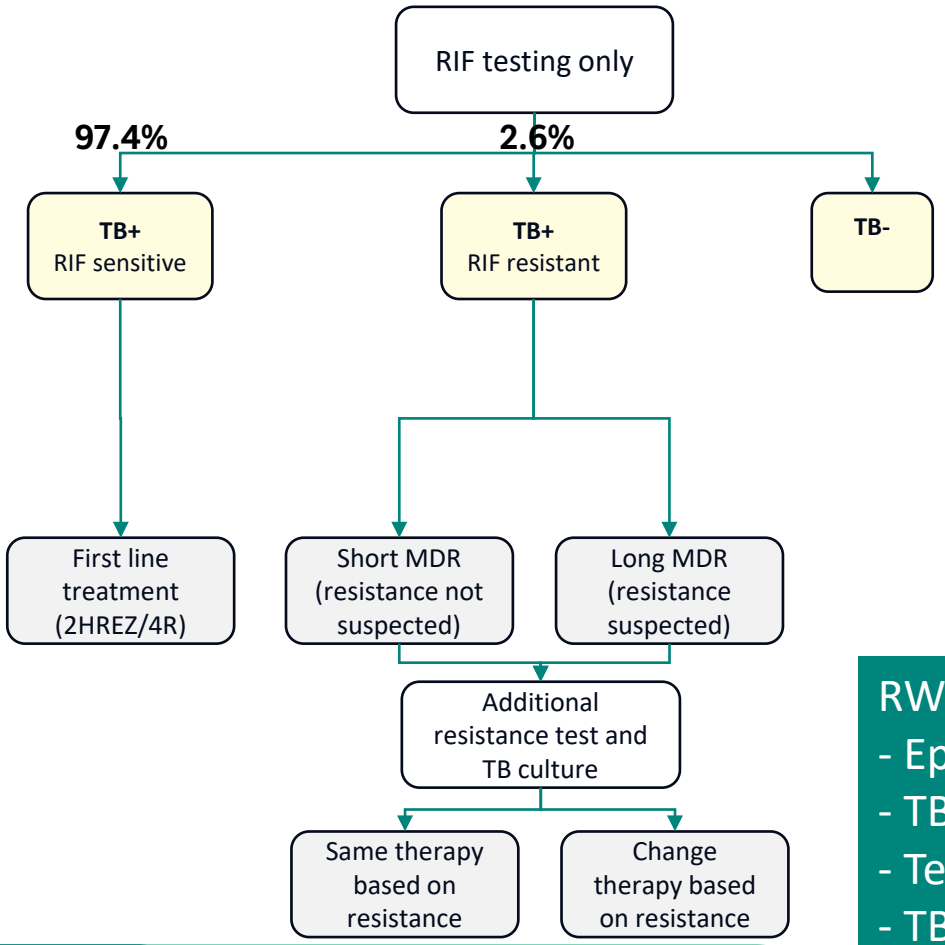
- Hr-TB is 3X more prevalent than MDR-TB, but it is not diagnosed in the first step of current algorithm.
- Treatment of Hr-TB with first line TB drugs is associated with higher treatment failure and acquisition of drug resistance.[2]

Sources:
1) World Health Organization. (2021). Global Tuberculosis Report 2021. https://www.who.int/publications-detail-redirect/9789240037021
2) Gegia M, et al . Lancet Infect Dis. 2017 Feb;17(2):223-234.

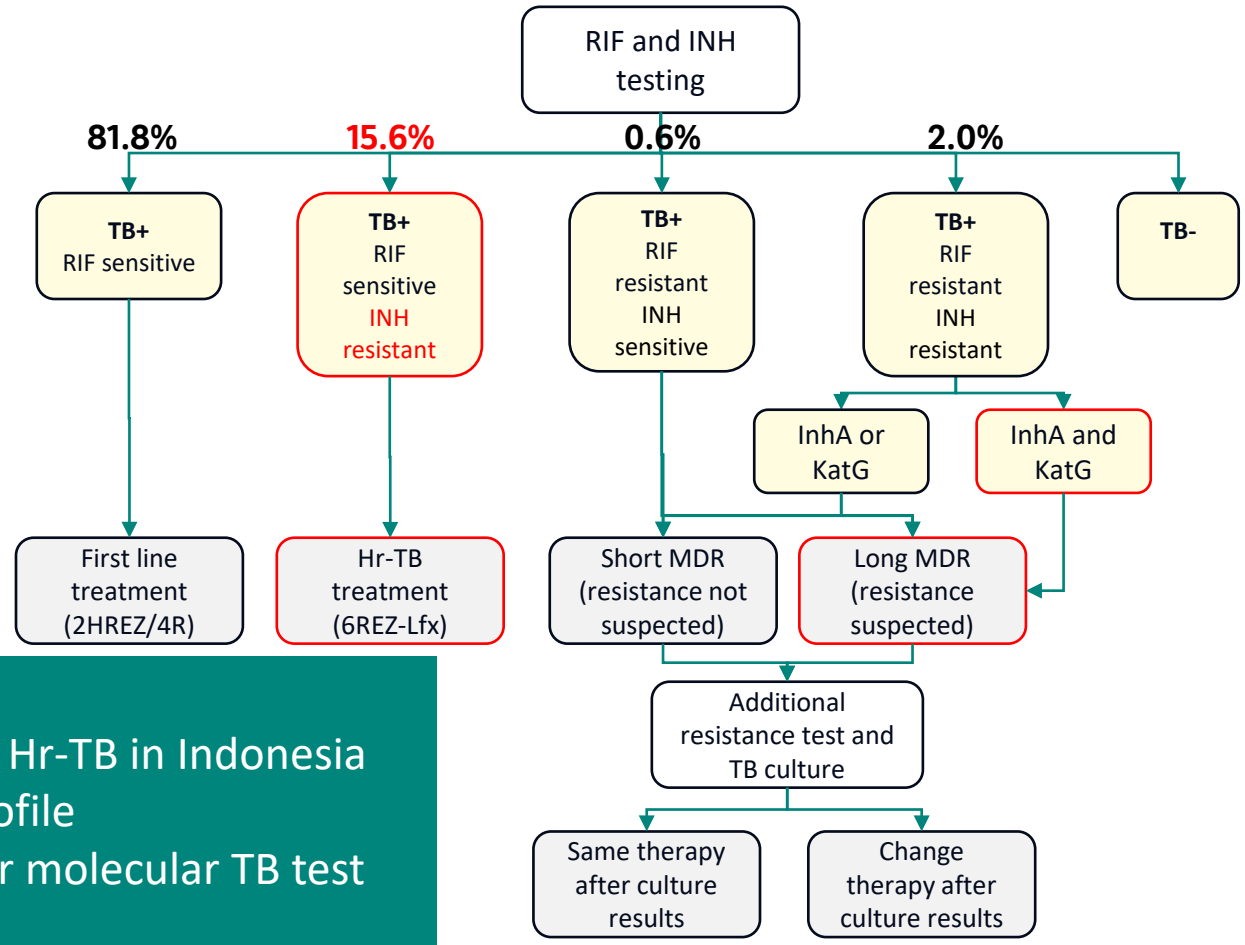
Modeling for TB elimination in Indonesia with DR-TB identification

Additional information on INH resistance allows for timely and appropriate treatment of Hr-TB and MDR-TB

Previous Algorithm



New Algorithm



RWE was used
- Epidemiology of Hr-TB in Indonesia
- TB resistance profile
- Test positivity for molecular TB test
- TB burden

Preliminary results and public health strategy (Rifampicin and isoniazid testing vs Rifampicin only)

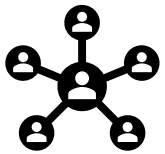
Rifampicin and isoniazid testing for TB diagnosis supports better public health resource allocation

Cost

- **4% less costly for the national TB program**

Clinical

- **5.6%** more treatment success
- **73.2%** less treatment failure
- **13.8%** lesser deaths
- **16.1%** less loss to follow up
- **21.8%** less patients with relapse



Potential transmission among contact person

- **57.1% less** active TB requiring treatment
- **57.1% less** latent TB infection requiring treatment

Resistance acquisition

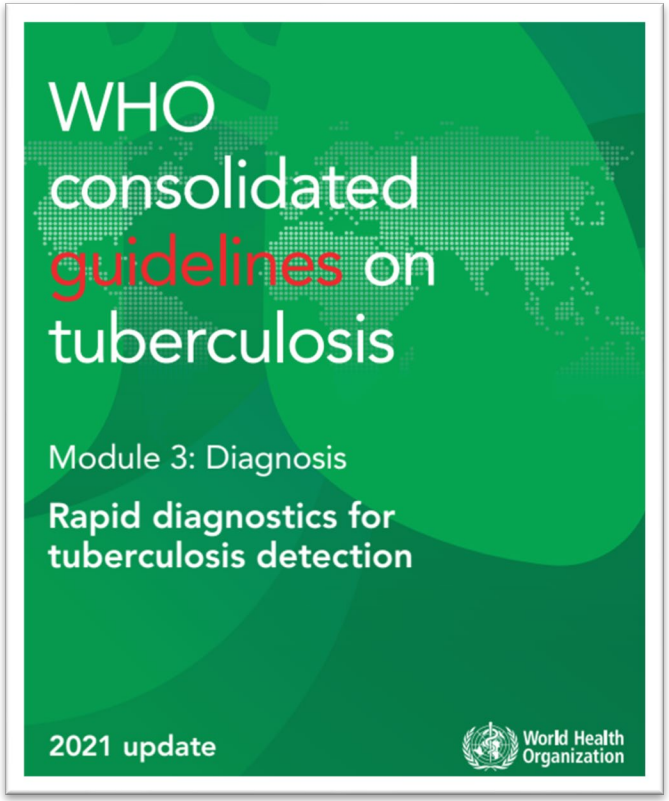
- **96.8% less** MDR-TB due to resistance acquisition

WHO Recommendation

Current TB diagnostic lacks resistance test for first-line drug isoniazid

- **Inefficient:** an extra test is needed before correct treatment can be chosen
- **Risky:** if isoniazid-resistant TB is treated with wrong drug regimen,
  - Treatment failure: ↑5x
  - Relapse: ↑ 2x
  - MDR-TB: ↑8x

WHO recommends to improve access to rapid molecular tests for the detection of TB and DR-TB:



"Globally, Hr-TB is more prevalent than MDR-TB. Thus, ***all countries need to move towards universal testing of both isoniazid and rifampicin resistance at the start of TB treatment****."*

*"**Moderate complexity automated NAATs**, recommended for the initial detection of TB and resistance to rifampicin and isoniazid"*