Global Harmonization Working Party
GHWP Towards Medical Device Harmonization

北京大学
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Hybrid Registry and Electronic Health Records based Active Surveillance System Design for Medical Device

Pei Gao

Department of Epidemiology and Biostatistics

Peking University

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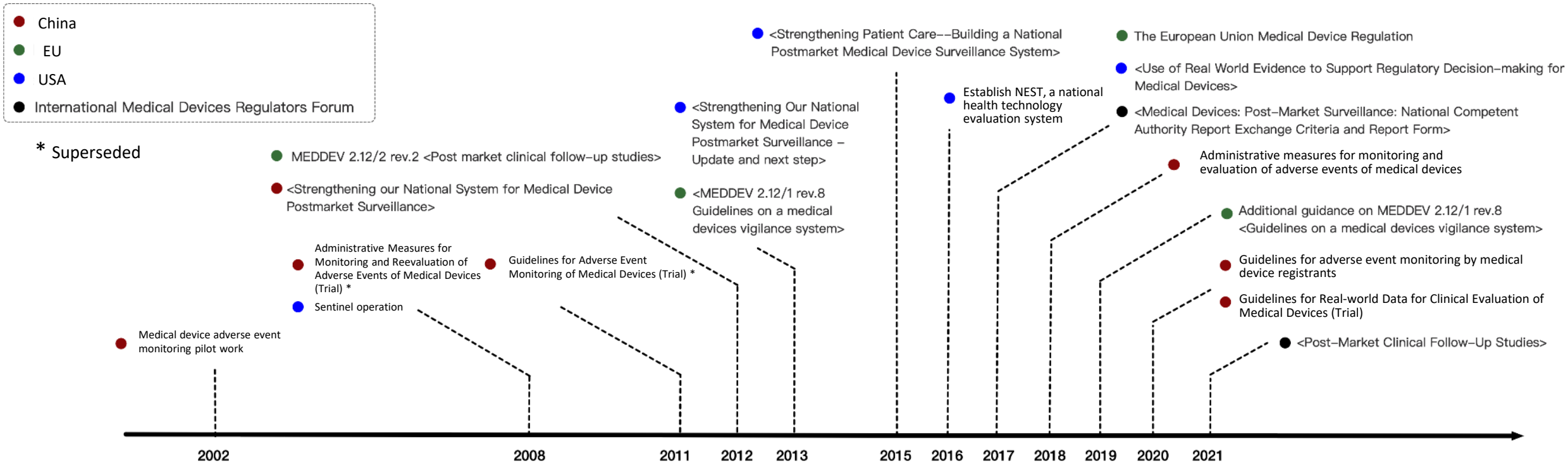
Shanghai International Convention Center

Regulatory Progress in Post-marketing Monitoring of Medical Devices



Teng et al， Progress in the application of real world data in post-marketing monitoring of medical devices， Chinese Journal of Pharmacovigilance， 2022, 19(3): 233-238.

Adverse Event Monitoring of Medical Devices in China

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- ✓ Currently, the post-marketing monitoring of medical devices in China is mainly based on spontaneous reporting methods such as the national adverse event database

  There are problems such as low reporting rate, high underreporting rate, large arbitrariness, poor data availability, and the incidence of adverse reactions cannot be calculated

In recent years, China has also been actively carrying out relevant research work：

- ✓ 100 medical device varieties were selected to be specially monitored during the 12th and 13th “Five-Year Plan” period respectively;
- ✓ The “Administrative Measures for the Monitoring and Re-evaluation of Adverse Events of Medical Devices” revised in 2018 added a chapter of “key monitoring”, clarified the principles and processes for determining the varieties of key monitoring devices, and put forward the concept of monitoring sentinels;
- ✓ In 2022, 105 hospitals will be identified as the first batch of medical device monitoring sentinels;

- ✓ In 2021, the "Technical Guidelines for the Use of Real-world Data in the Clinical Evaluation of Medical Devices (Trial)" was published by CMDE
- ✓ In 2022, the "Expert Consensus on Post-market Risk Monitoring Technology for High-risk Implantable Passive Medical Devices Based on Real-world Data" was published
- ✓ In 2023, the "Guidelines for the Registration and Review of Real-world Research Design and Statistical Analysis of Medical Devices (Draft for Comments)" was published by CMDE
- ✓ Cooperation with various professional committees of the Chinese Medical Association to explore and carry out patient registration studies on implantable high-risk medical devices, such as pacemakers, heart valves, coronary stents etc.

RWE

European and American national registration databases are used for active post-marketing monitoring

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Registration database plays an important role in active post-marketing monitoring of medical devices in Europe and the United States.

Medical Device	Data source type	Study population and sample size	Study design	Monitoring time	Evaluation Index
Excor ventricular assist devices	The enterprise establishes its own registration database	At least 62 pediatric patients, (all visiting population, pediatric age range only, under 22 years old)	There is no control, and the data is simply recorded and monitored.	5 year	**Primary end points**: Observed overall stroke incidence; Data of anticoagulation regimen **Secondary endpoints**: thrombotic event rate, adverse event rate, patient outcomes (e.g., transplant survival time, survival time recovery time)
HeartWare ventricular assist system	INTERMACS registration database	600 HeartWare users and 600 non-Heartware recipients	Compared with patients not eligible for the device.	2 year	**Primary endpoint:** success within 180 days (e.g., survival, recovery, transplant). **Secondary endpoints**: overall device survival, re-hospitalization, adverse events, quality of life, functional status, post-stroke quality of life, functional and neurocognitive assessments
TransMedics Organ Care System	United Network for Organ Sharing (UNOS) database TOP registration database	All patients using OCS devices	No control, recording and monitoring data were provided.	5 year	**PAS001 Primary endpoint:** 5-year survival (BOS and mortality) without obliterated bronchiolitis syndrome (BOS) **PAS002 Primary endpoint :**12-month survival of patients and grafts after double lung transplantation
Ceramax hip prosthesis	United Kingdom National Joint Register Database Australian Orthopaedic Association National Joint Replacement Registry database	At least 500	No control, recording and monitoring data were provided.	Short term, medium term, long term (" long term "generally refers to 10 years or more)	**Primary endpoints:** equipment survival, revision, and mortality
IN.PACT Admiral paclitaxel coated balloon catheter	SVS VQI registration database	300	There is no control, and the data is simply recorded and monitored.	3 year	**Primary endpoint:** Target lesion revascularization within 12 months. **All-cause mortality (12 and 24 months)TLR(24 months) Target vessel revascularization (TVR)(12 and 24 months) Major limb amputation (12 and 24 months) Follow-up up to 36 months**
GORE-TAG aortic stent	SVS VQI registration database	At least 60	Comparison of different brands of aortic stents.	5 year	**Primary endpoints:** 1 year follow-up group: No discaline-related deaths during 1 year, technical success of the device at the time of surgery (successful delivery, successful and accurate deployment, and successful exit from the delivery system)5-year follow-up group: 5 years free of disintercalation-related deaths, successful device technique at the time of surgery (successful delivery, successful and accurate deployment, and successful exit from the delivery system), 30 days successful device procedure (successful device technique, no of the following major adverse events [MAE] subsets within 30 days, primary intimal tear with false chamber perfusion, retrograde extension of the dissection, and unintentional rupture of the intercalation interval).
Micra leadless pacemaker	The enterprise establishes its own registration database	Patients implanted with the Micra transcatheter pacing system	There is no control, and the data is simply recorded and monitored.	9 year	**Primary endpoints:** 1) Incidence of acute complications associated with the MICRA system or implantable gymnastics (≤ 30 days)2) long-term complication free survival
Impella RP® left ventricular assist device	cVAD registration database	60 adults 15 children	Surveillance was carried out in different subgroups of peoplePost-discharge data will be collected by phone contact and viewing medical records.	Adult population: 1 year Children: 180 days	**Primary endpoints (two populations)** : survival at 30 days after transplantation, bleeding, hemolysis, and pulmonary embolism at 30 days after discharge, discharge instrument failure, central venous pressure, cardiac index, and left ventricular diastolic functional flow.

U.S. Food and Drug Administration. Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions. Published online 2021:183.

European and American registry databases are used for active post-marketing monitoring

Medical Device	Data source type	Study population and sample size	Study design	Monitoring time	Evaluation Index
Peripheral vascular stent	ANCHOR registration database	not clear	The short neck renal vascular cohort was followed up without control.	5 year	**Primary endpoints:** aneurysmal-related mortality, aneurysm rupture, aneurysm enlargement, type Ia internal leakage, migration, type III internal leakage, secondary intervention, device-related adverse events, and device integrity. Analyze data every year.
HeartWarelef t ventricular assist device	The enterprise establishes its own registration database	300	No control, recording and monitoring data were provided.	5 year	**Primary endpoint:** No disabling stroke or device failure requiring replacement, implant, or emergency transplant. **Secondary endpoints**: Early stroke incidence (≤ 2 years after implantation) and stroke risk factors were observed. Incidence of late stroke (more than 2 years after implantation) and risk factors for late stroke, as well as stroke severity.
Left auricular occluding device	ACC LAAO registry data for the first 2 years of follow-up / 3 years of follow-up after CMS supplement	At least 2000 consecutive patients enrolled	Performance goals are set and hypotheses are tested.	5 year	**Primary endpoints:** Implantation success rate; Surgical safety; The left auricle is effectively closed; Compound stroke and all-cause death; Ischemic stroke or systemic embolism; Long-term outcomes associated with CMS were monitored for five years for perioperative events
S-ICD implantable cardioverter defibrillator	US National Registry Dat data generat remote mon devices, Mec data, and Na death regist	•NCDR ICD Registration (N=2100)			**Primary endpoint:** **NCDR:** The first primary endpoint assessed the incidence of type 3501 implants and perioperative ar incidence of model ncidence of ospitalization. ce of death from any cidence of requiring re- electrode
Edward SAPIEN 3 transcatheter heart valve model 9600TFX	The STS/A registry pro year follow-up data /CMS supplements 5-year follow-up data	patients using the device within 2 years of marketing	recording and monitoring data were provided.	5 year	) 30-day and 12-month ds, perioperative at surgery; Neurological s and 12 months; (4) 2 to 5 years after **End points of mitral valve replacement** :(1) all-cause mortality, heart failure rehospitalization, and mitral valve reintervention at 30 days and 12 months; (2) 6-minute walking distance, KCCQ, NYHA functional level changes at 30 days and 12 months; (3) Device or surgery-related adverse events, major bleeding complications, stroke and other cerebrovascular events, myocardial infarction, new dialysis requirements, new episodes of atrial fibrillation, and other events or complications at 30 days and 12 months (4) mitral valve hemodynamics at 30 days and 12 months; (5) Repeat surgery for all-cause mortality, total stroke, and valvular related dysfunction 2 to 5 years after implantation

For patients with specific diseases (or using specific medical devices), the registry database can be prospectively collected data, data collection schemes can be designed in advance, the data structure and integrity are good, and the data of the full follow-up cycle of patients can be collected, and it has gradually become a common data source for active monitoring of international medical devices after the market.

Patients' registry database in China

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Examples of existing domestic registry databases in China

Disease Type	Sample registry database
Cancer	National Central Cancer Registry, NCCR A population-based cancer registry Shanghai Cancer Registry
Cerebrovascular disease	China National Stroke Registry, CNSR ChinaQUEST（QUality Evaluation of Stroke Care and Treatment） Registry China Interventional Stroke Registry, CISR Nanjing Stroke Registry Chengdu Stroke Registry
CVD cardiovascular disease	Chinese Atrial Fibrillation Registry, CAFR Chinese Coronary Artery Bypass Grafting Registry Chinese registry of acute coronary events, CRACE Chinese Cardiac Surgery Registry China-OASIS Registry
Twins	Chinese National Twin Registry, CNTR Twin Registry in Southwestern China, TRiSC Guangzhou Twin Registry
Organ Transplantation	China Liver Transplant Registry, CLTR China Bone Marrow Transplantation） Registry Chinese Scientific Registry of Kidney Transplantation, CSRKT
Birth Defect	Chinese Birth Defects
Immunological Diseases	Chinese SLE Treatment and Research group, CSTAR registry
Diabetes	Shanghai Diabetes Registry, SDR Chinese IDDM registry
Other	National registry of hemophilia Chinese Alliance for Research in Thymomas (ChART) registry Chinese maxillofacial trauma registry Shanghai Dialysis Registry

CVD Registry Database in China

In 2019, Prashant et al. counted cardiovascular device registry databases in the U.S. and found a total of **138 registry databases** [1], including the aforementioned Transcatheter Valve Therapy (TVT), Vascular Quality Initiative (VQI), and other well-known registry databases.

Domestic cardiovascular registry database in China

Domestic cardiovascular surgery/Disease Registry Database
Chinese Atrial Fibrillation Registry Database
Chinese Coronary Artery Bypass Graft Registry Database
Chinese Acute Coronary Events Registry Database
Chinese Cardiovascular Surgery Registry Database
Chinese Acute Ischemic Syndrome Registry Database

- ✓ Less domestic registry databases;
- ✓ Most of the outputs of the registry studies were to obtain the epidemiological characteristics of the patients/diseases, such as incidence;
- ✓ Post-market surveillance of medical devices is not the purpose of registry studies: data on relevant information required for post-market surveillance of medical devices are not collected;
- ✓ Less sustainable.

Lack of case studies in China for post-market active surveillance of medical devices using registries

1. Rajan PV, Holtzman JN, Kesselheim AS, Yeh RW, Kramer DB. Landscape of Cardiovascular Device Registries in the United States. *J Am Heart Assoc*. 2019;8(11):e012756. doi:10.1161/JAHA.119.012756

Real-world Data Sources

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① **Hospital Information System，HIS**: Similar to electronic health records, it includes both structured and unstructured patient records, such as the demographic characteristics of the patient, clinical characteristics, diagnosis, treatment, laboratory tests, safety, and clinical outcomes, etc.

② **Medical Insurance System**: Data that contains structured fields such as basic patient information, medical service utilization, diagnosis, prescription, billing, medical payment, and planned care.

③ **Disease registry system**: A database of patients with a specific disease (usually chronic), usually derived from a hospital's disease population cohort registry.

④ **Natural population cohort and specific disease cohort database**: The database of natural population cohort and specific disease cohort that has been established or is being established in China.

⑤ **Omics related database**: A database that collects omics related information about patients' physiological-biological health behaviours and possible environmental interactions, such as pharmacogenomic metabolomics and proteomics.

⑥ **Death registration database**: A database formed by the death registration jointly confirmed by hospitals, the Centers for Disease Control and Prevention, and the Household Registration Department.

⑦ **Patient-reported outcome data**: Self-assessed or measured data reported by patients.

⑧ **Data from mobile devices**: Medical mobile devices, such as wearable devices, are used to detect relevant data obtained by subjects.

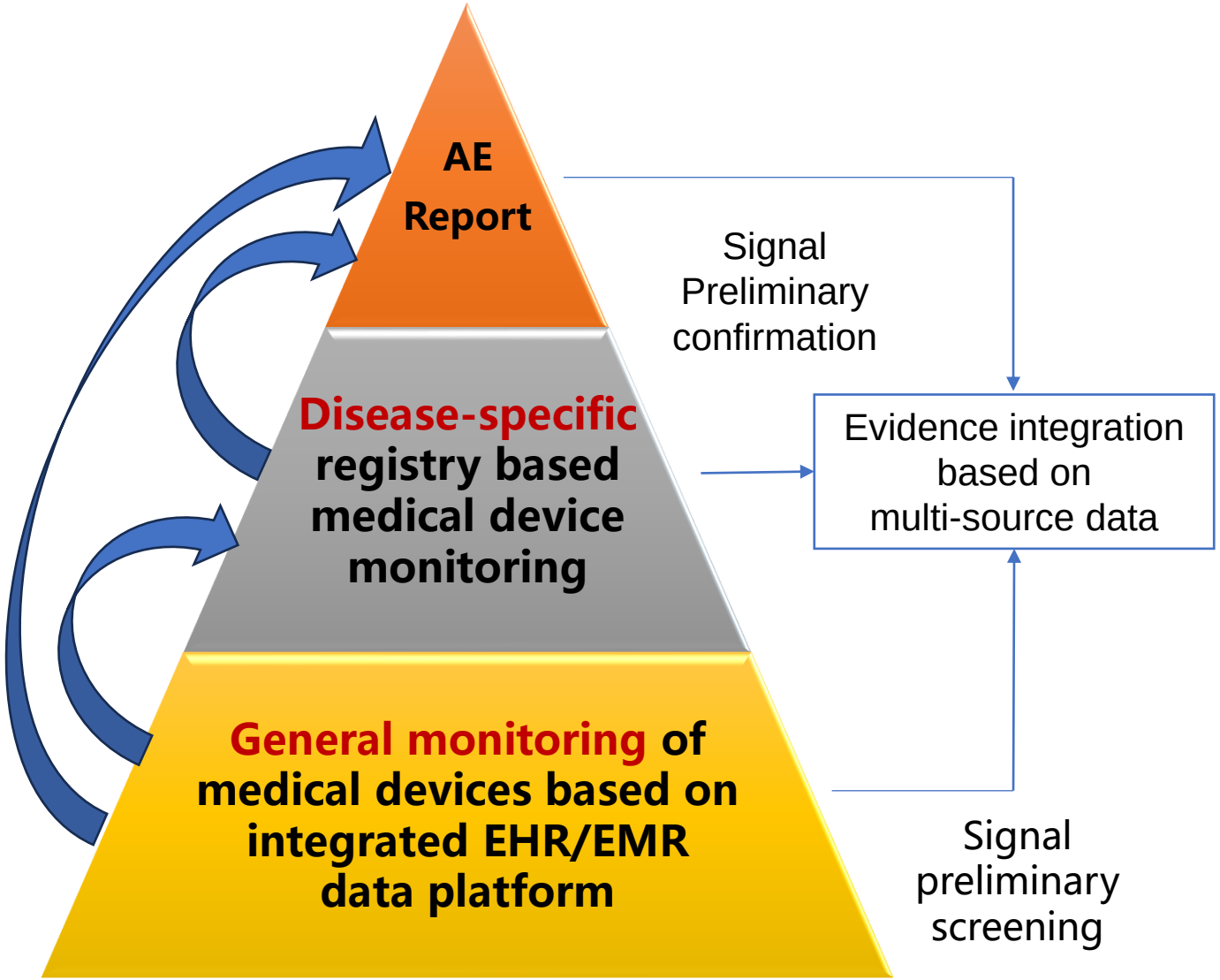
⑨ **Other special data sources**: Relevant data generated by medical institutions in some regions for specific medical purposes due to urgent clinical needs to import a small amount of overseas marketed drugs in accordance with relevant policies and regulations; and databases created for special purposes, such as the database of notifiable infectious diseases and the database of the National Immunization Program.

Medical Device Monitoring System Based on Multiple Data Sources

Medical Device	Year	Nation	Data source type	Research Purpose
Venous duct	2022	Australia	Data from five EHR systems in Queensland	An exploratory study linking electronic health record data to monitor the quality of intravenous catheter care
Hip prosthesis	2020	America	Mercy Medical Group's hospital and outpatient orthopedic database	A comparative study on the revision rate of different brands of hip prostheses
Intraocular lens	2018	Britain	7 cataract clinics using the Medisoft eye electronic medical record system	To compare the incidence of Nd:YAG capsulotomy and posterior capsular opacification (PCO) in different types of Iols
Ophthalmic laser treatment machine and other instruments	2022	China	Data of more than 360 medical institutions in Zhejiang Province	Research on software system of integrated online data collection and statistics
Breathing machine	2022	China	Hospital infection registration system in ICU of West China Hospital	Study on the association between fluid balance volume and adverse events of ventilator ventilation
Coronary drug-coated stents	2021	China	Hospital electronic medical records, charge data	To evaluate the safety, efficacy and economy of different coronary drug-coated stents

- ✓ **There is no mature monitoring system or platform for "ideal medical device monitoring system"** in China and abroad, but there have been cases of countries and regions trying to **gather multiple data sources to form a monitoring platform;**
- ✓ A multi-dimensional and multi-level **high quality data monitoring system for active surveillance of medical devices is proposed**

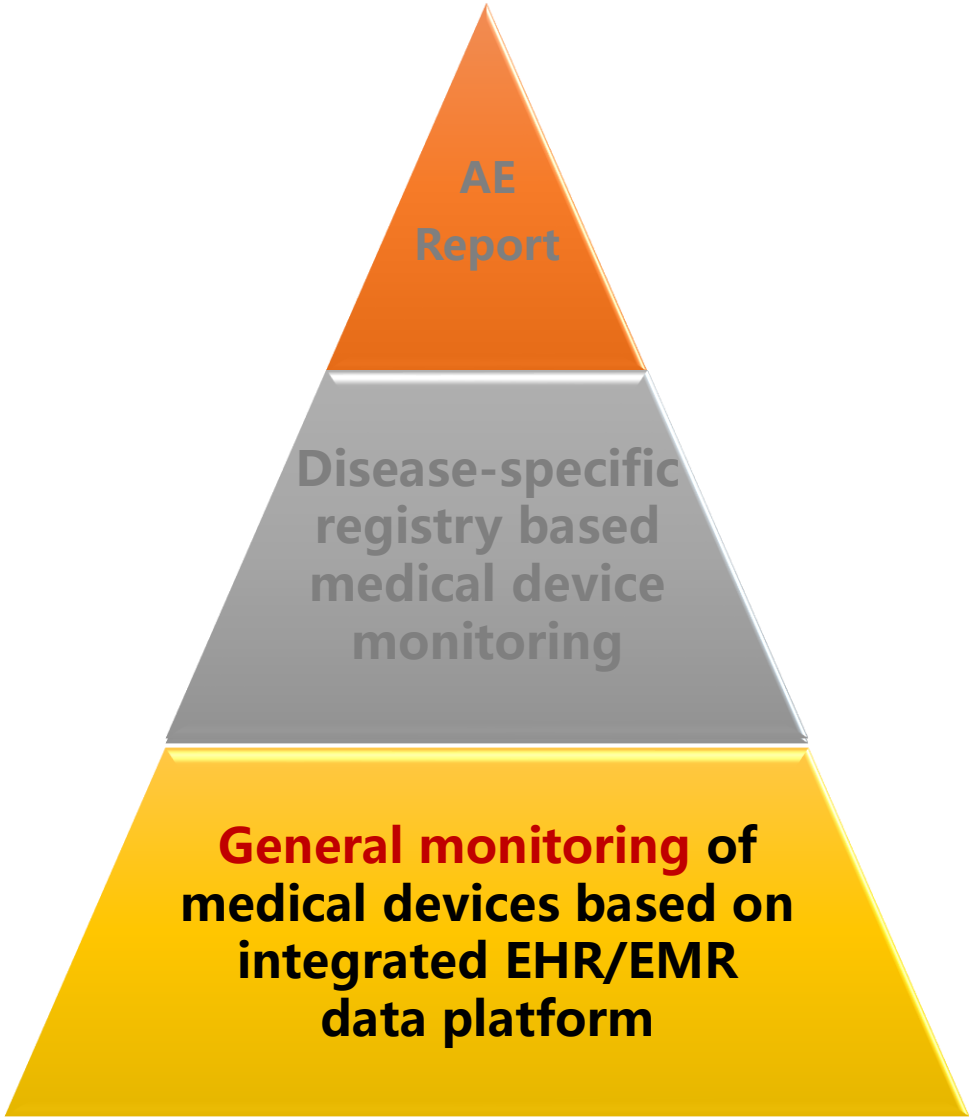
Multi-level medical device AE monitoring system



Hierarchical design can obtain richer information from different sources, and the difficulties mainly include:

- **Balance of sensitivity and specificity of signal detection:** the bottom layer system obtains more information, the middle layer system is more targeted, how to control false positives while monitoring widely is needed to consider.
- **Methods of evidence integration**: how to empower evidence from different levels of systems, and how to develop quantitative, semi-quantitative or qualitative evidence integration systems is difficult.
- Establish **a reliable system verification and evaluation mechanism and** carry out performance evaluation on a regular basis.
- **Security**: data security and privacy protection of patients' sensitive information.
- **Sustainability**: infrastructure for resources, team, collaboration, etc

Multi-level medical device AE monitoring system



CHERRY
Check In & Carry out

- ✓ Sample size: 1.05 million
- ✓ Follow-up: 12years

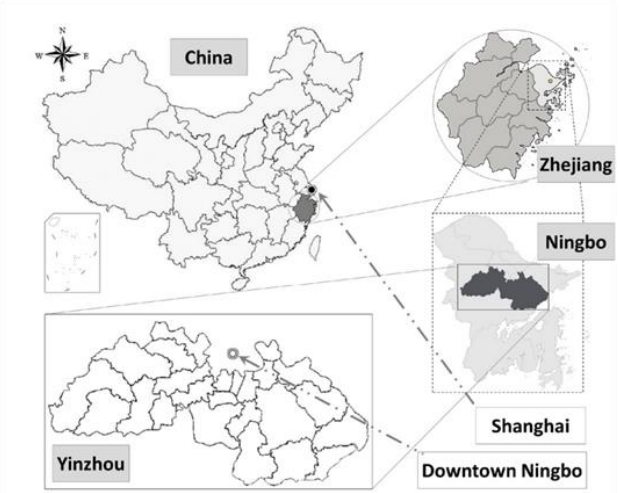


Figure 1 Study location for the CHinese Electronic health Records Research in Yinzhou (CHERRY) study.


Environment International 165 (2022) 107280

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journal homepage: www.elsevier.com/locate/envint

Full length article

Long-term exposure to o: Chinese cohort

Shudan Liu, Yi Zhang, Runme Jingyi Zhang, Ping Lu, Xun T

ESC European Society of Cardiology

European Journal of Preventive Cardiology (2023) 00, 1–11

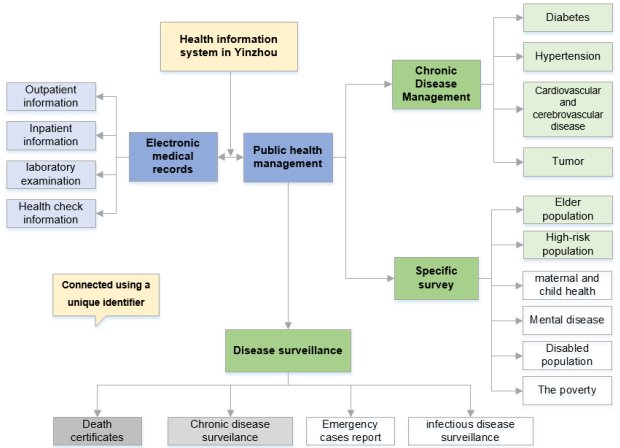
https://doi.org/10.1093/eurjpc/zwad198

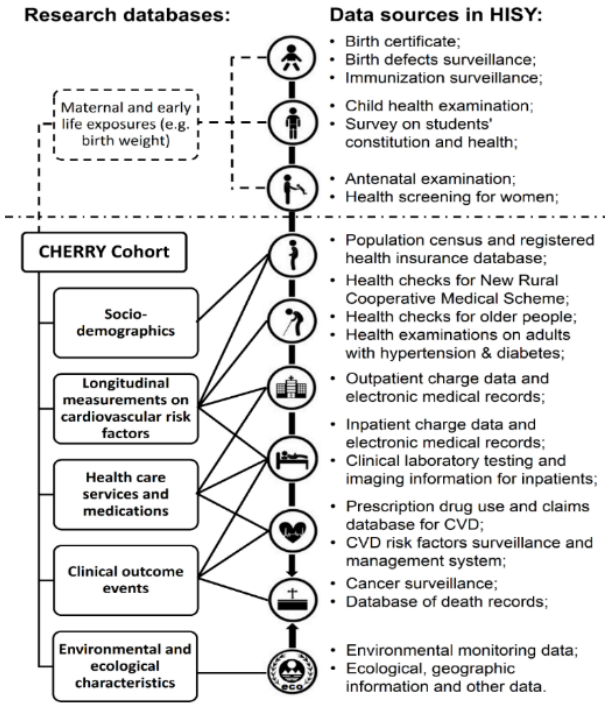
FULL RESEARCH PAPER

Risk prediction/assessment & stratification

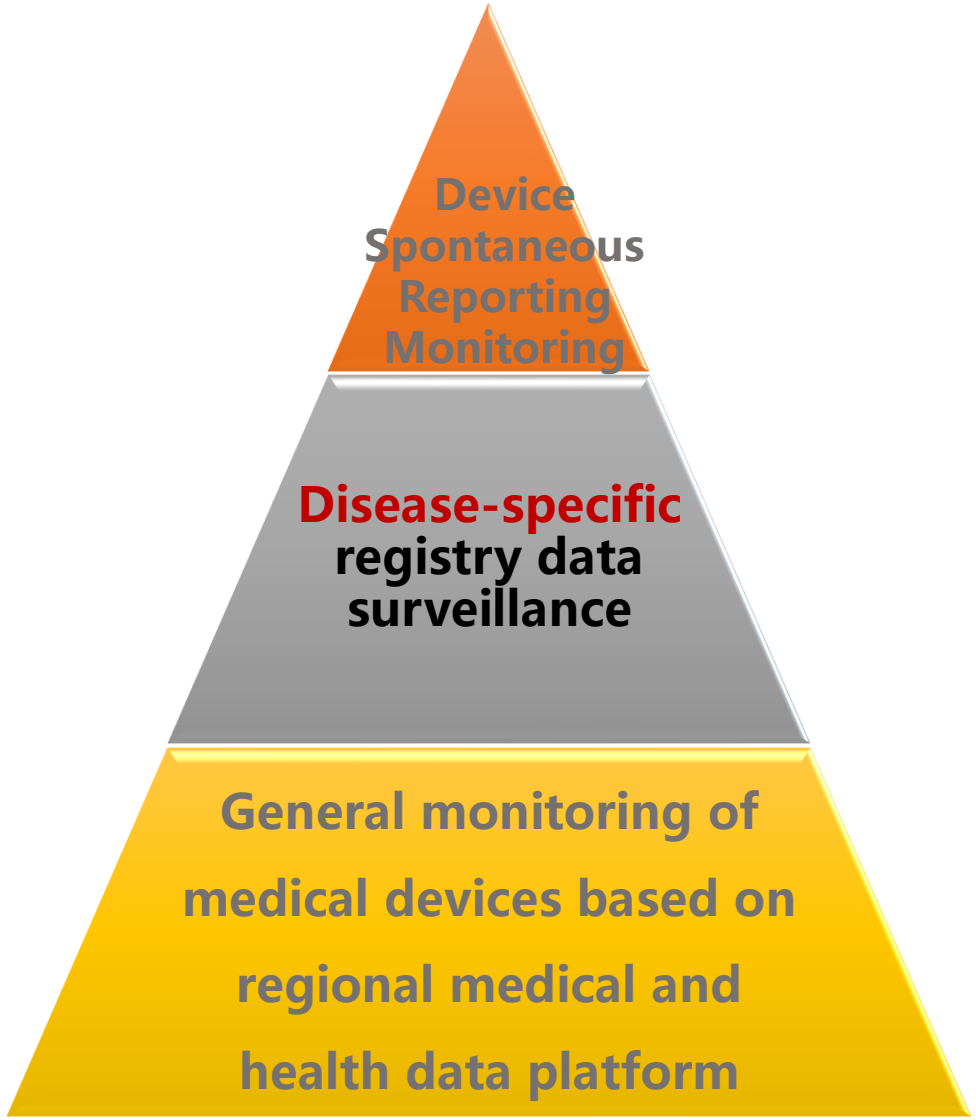
Validation and comparison of cardiovascular risk prediction equations in Chinese patients with Type 2 diabetes

Jingyuan Liang, Qianqian Li, Zhangping Fu, Xiaofei Liu, Peng Shen, Yexiang Sun, Jingyi Zhang, Ping Lu, Hongbo Lin, Xun Tang, and Pei Gao





Multi-level medical device AE monitoring system

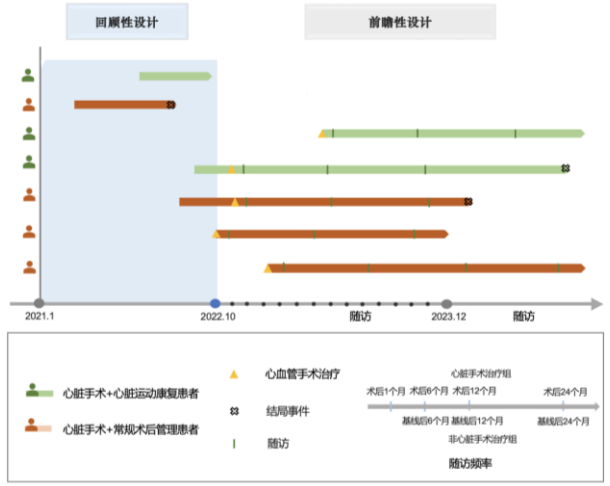


RESCUER

北京大学第三医院 Peking University Third Hospital

REgiStry-based Cardiovascular qUality improvEment Research

	Baseline	Discharge	Follow-up visit (Postoperative 1 Months)	Follow-up visit (Postoperative 6 Months))	Follow-up visit (Postoperative 12 Months)	Follow-up visit (Postoperative 24 Months))
General demographic information	√					
vital signs	√					
health checkup	√					
History of past illness	√					
Past drug history	√					
family history	√					
Scales (nicotine and alcohol dependence, exercise, sleep, quality of life, diet) were assessed	√		√	√	√	√
blood routine examination	√	√	√	√	√	√
routine urine test	√	√	√	√	√	√
blood biochemistry	√	√	√	√	√	√
renal function	√	√	√	√	√	√
coagulation function	√	√	√	√	√	√
hemorheological examination	√	√	√	√	√	√
pancreas islet function	√	√	√			
ECG	√	√	√			
ultrasonic cardiogram	√	√	√			
myocardial infarction marker	√	√	√			
interventional surgery information	√	√				
date of discharge		√				
discharge diagnosis		√				
Complications during hospitalization		√				
NYHA classification /Killip classification		√				
survival status		√	√			
discharge medication		√				
change of the illness			√			
Follow-up medication			√			
compliance			√			



RECRUITING

REgiStry-based Cardiovascular qUality improvEment Research (RESCUER)

ClinicalTrials.gov ID NCT06137885

Sponsor Peking University Third Hospital

Information provided by Peking University Third Hospital (Responsible Party)

Last Update Posted 2023-11-17

Multi-level medical device AE monitoring system

Multi-source data

- National Medical Device Adverse Event Monitoring Information System
- Regional integrated Health Information Platform
- Disease Registries

Preliminary design

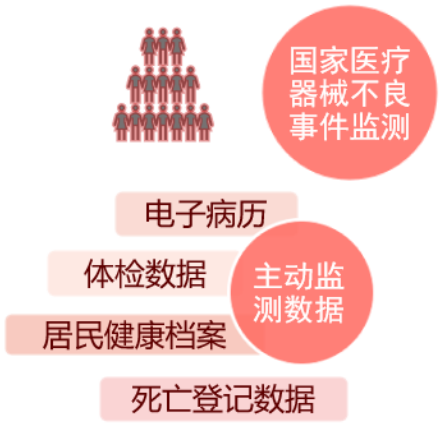
- Top-level design
- Establish mechanisms
- Data aggregation
- Data governance
- Analytical monitoring

Pilot study

- Select pilot varieties according to risk and device technical characteristics
- Complete application closed loop
- Form research analysis reports

Evaluation

- Degree of automation
- Data quality evaluation
- Clinical Epidemiology
- Expert argumentation



Event-driven evaluation

Data-driven evaluation

Granularly scaled Data sharing permission management system

Data-driven Monitoring automatic early warning upgrade system

Data granularity and time node

Analysis module and threshold management

Multi-level medical device AE monitoring system

1. **It is urgent to promote the establishment of an active monitoring system with multi-source data integration** (the domestic medical device industry is developing rapidly, and the number of innovative medical devices has increased significantly every year, including global medical devices).

2. **For specific varieties of devices, establish a pilot distributed multi-level medical device monitoring system with the registry database as the core and the regional integrated HER/EMR database as the support**.

3. **Establish a cooperative mechanism for sustainable development that allows all parties to participate and benefit**. Realize the interconnection and interoperability of health data and form a medical big data that can be used for the whole life cycle monitoring of medical devices (pre-market evaluation + post-market monitoring).

4. **Solve key technical problems**: automatic early warning system for data granularity scaling, including data granularity level division for monitoring, threshold management, time nodes, permission sharing mechanism, and development of analysis modules.

Regulatory agency

Modernize regulatory approaches

Doctors

Better grasp the clinical advantages and disadvantages of different design products

Colleges and institutes

Conduct large-scale, high-quality researches

Manufacturers

Complete the evaluation of the safety and effectiveness of the product with less money and resources

Medical insurance sides

Formulate relevant policies more rationally

Thanks!

Comments are welcomed.