Real world evidence in China

—— Current practices, challenges, strategies and developments

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Outlines

1. Short history and current practices
2. Challenges in the production and use of RWE
3. Proposed strategies for developing a RWE ecosystem
4. Current development with special reference to regulatory decisions

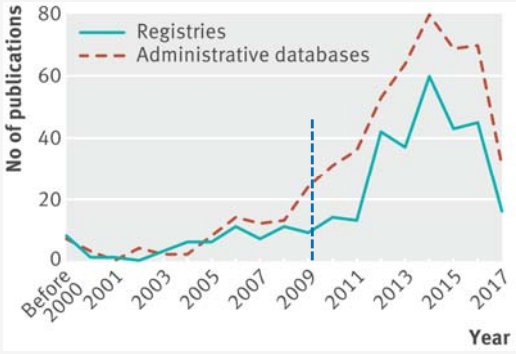
A short history of RWE in China

- 2000 and on: early efforts on outcomes research and big data
  - Early development synergized with the promotion of outcomes research by ISPOR
  - Active roles of multi-nation Pharma, primarily used for post-approval clinical assessment and marketing access
  - The China's big data initiative further boosted the development
- 2010: official introduction of RWE concept
  - The concept first introduced by researchers from traditional Chinese medicine
- 2012: parallel efforts on CER
  - Professional societies (e.g. EBM subcommittee of the Chinese Medical Doctor Association) introduced the comparative effectiveness research concept
- 2016 and on: systematic introduction of RWE framework
  - The Chinese Evidence-based Medicine Center and ISPOR West China Chapter officially and systematically introduced the concept and methodology across the country

Production of RWE rapidly increased over the past years in China

Sun X* et al. *BMJ*. 2018;360:j5262

Retrospective database studies and registry studies rapidly increased after 2009



cancer and vascular diseases staying on the top

* Searched up to June 2007

Most pragmatic trials tested traditional Chinese medicine

Reference	Study setting	Participants
Feng *et al.* (2007)[1]	Schools in Chengdu	305 children with at least one visible white-spot lesion
Wei *et al.* (2010)[2]	A general hospital in Henan Province	176 patients with myelodysplastic syndrome
Yu *et al.* (2010)[3]	General and TCM hospitals in Beijing, Tianjin, Henan, Hebei and Shandong	300 inpatients with ischemic stroke
Tian *et al.* (2011)[4]	General and infectious disease hospitals across China	153 HIV/AIDS patients with chronic diarrhoea
Ye *et al.* (2011)[5]	Twelve hospitals across China	700 inpatients with acute ischemic stroke
Li *et al.* (2012)[6]	Henan Province	50 HIV/AIDS patients who were receiving highly active anti-retroviral therapy
Li *et al.* (2014)[7]	Hospitals in Shanghai	127 patients with chronic kidney disease
Dong *et al.* (2014)[8]	Schools in Chengdu	177 school children with at least one visible white-spot lesion
Liu *et al.* (2015)[9]	Rural counties and urban districts from Heilongjiang, Jiangsu, Hunan and Chongqing	4,292 outpatients with new pulmonary tuberculosis (TB)
Browning *et al.* (2016)[10]	Community Health Stations in Fengtai district, Beijing	669 patients with type 2 diabetes
Fu *et al.* (2016)[11]	General hospitals in Beijing and Henan	260 inpatients with ischemic stroke
Li *et al.* (2016)[12]	A pancreas centre of a general hospital in Chengdu	140 inpatients with severe acute pancreatitis accompanied with paralytic ileus
Chien *et al.* (2017)[13]	Psychiatric out-patient clinics in mainland China, Hong Kong and Taiwan	342 patients with schizophrenia spectrum disorders
Wei *et al.* (2017)[14]	Township hospitals in central Zhejiang province	28,130 patients at high risk of cardiovascular disease (CVD)
Wu *et al.* (2017)[15]	Endocrinology and Acupuncture out-patient clinics of a general hospital in Beijing	369 male smokers
Yang *et al.* (2017)[16]	Campus advertisements from several universities in Chengdu	152 patients with primary dysmenorrhea

Increasing use of RWE for healthcare and policy decisions in China

Authorities	Major uses	Relative importance of RWE for decision making
Chinese Drug Administration	Post-approval decisions	• Post-approval drug assessment and safety surveillance ++++ • Label changes and new indication assessment +
	Pre-approval decisions	• Supporting evidence for investigational new drug approval (e.g. disease burden and practice pattern) +++

Medical Security Bureau	Drug coverage decisions	• Parameters for Cost-effectiveness analysis
		  • Cost of illness and disease burden ++++
		  • Clinical outcomes and epidemiological data +++
		  • Health-related quality of life and utility +

		• Parameters for budget impact analysis ++++
National Health Commission	Health technology assessment	• Clinical outcomes for emerging technologies ++++ • Cost assessment ++++
	Healthcare quality and safety surveillance	• Measurement of healthcare quality indicators ++++ • Safety monitoring and assessment ++++
Healthcare providers	Clinical practice guidelines	• Disease burden assessment ++++ • Clinical assessment if classical trials not available ++++ • Safety assessment of treatments ++++

Diversified real world data sources in China

Typical data sources	Examples	Strengths	Limitations
Regional electronic health records	• Xiamen municipal city regional EHR • Yinzhou district regional EHR • Fuzhou municipal city regional EHR	Most comprehensive data; may develop longitudinal follow up	Data may not be accessible
Electronic medical records from single care institutions	• West China Hospital, Sichuan University	Well documented clinical data, particularly during hospitalization	Lack of follow up data; incomplete outpatient data
Disease registries	• National cancer registry • Bianque chest pain registry	Data collected in a structured manner, often comprehensive	May not be accessible
Claims databases	• National claims database • Chengdu municipal city regional claims database	Good for cost analysis	Lack of clinical and lab data

Chinese Evidence-based Medicine Center and ISPOR West China Chapter move forward China's RWE initiative

- 2013
  - Initiated the RWE initiative
- 2014
  - ISPOR West China Chapter: focus on the production and use of RWE to support regulatory and coverage/payment decisions
- 2015
  - National grants to support the methodology development for drug safety surveillance using real world data
- 2016
  - Chinese FDA funded the assessment of antibiotics safety using EMR
  - First national methodology workshop on real world studies
- 2017
  - Forum on Real World Evidence and Healthcare Practice and Policy
  - China Real World Evidence Alliance (ChinaREAL) established
- 2018
  - Invited analysis paper on real world evidence in China
  - The First Congress on Real World Data and Studies

Real World Evidence Initiative

Challenges: RWE development still at early stage in China

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Misconduct and misinterpretations are common

Types of misunderstanding	Examples
Real world data (RWD)	• RWD are another word for big data • RWD are allowed for low quality given its nature
Real world studies (RWS)	• RWS are universally observational • RWS are typically cheap • RWS have no control group • RWS have no quality control • RWS should not set up restrictions to patient inclusion • RWS do not need ethical review • Informed consent is not needed for any type of real world studies
Real world evidence (RWE)	• RWE less trustworthy than classical trials • RWE better than classical trials in their findings • RWE applicable only to drug assessment • RWE of low quality

Lack of coordination and inadequate research capacity

Lack of coordination at the national level

- Limited collaboration between organizations
- Insufficient interactions between research organizations and RWE users

Absence of authority technical guidance

- No research guidance applicable to the Chinese setting
- No standards for data acquirement, processing, and quality

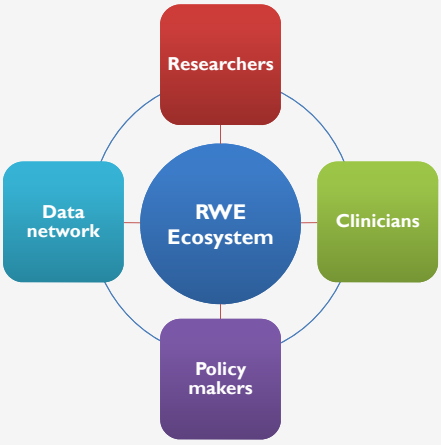
Insufficient research capacity

- Small number of research groups with expertise in data application
- Very small number of higher education programs

China REal World Data and Study ALliance: ChinaREAL

Missions and goals

- Develop an RWE ecosystem for China
- Advocate for the quality production and understanding of RWE
- Focus on medical products and disease management
- Liaise with multiple stakeholders to promote the use of RWE for healthcare and policy decisions

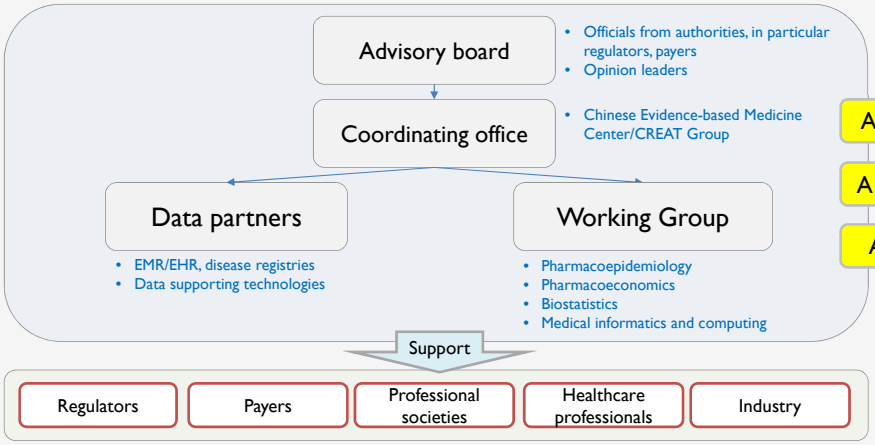


Co-organized by the Chinese Evidence-based Medicine Center, ISPOR West China Chapter, and CREAT Group

ChinaREAL: a network of collaboration

Involve multiple stakeholders

- Officials from authorities: State Drug Administration, Medical Security Bureau, National Health Commission
- Opinion leaders and leading scientists: Epidemiology, biostatistics, pharmacoeconomics, health informatics
- Data partners: regional EHR, hospital EMR, disease registries, claims database
- Industrial collaborators: HEOR, pharmacoepidemiology, medical affairs



Major themes

- A platform for communication
- A station for education/training
- A consortium of researchers

China's First Congress on Real World Data and Studies

June 21-23, 2018 Chengdu, China

- Explore the value of real world evidence for regulatory and coverage decisions
- Over 700 participants across the country
  - International experts from ISPOR (Marc Berger), The BMJ, and University of Oxford
  - Experts from national authorities (Chinese Drug Administration, Medical Security Bureau)
  - National opinion leaders
  - Researchers from over 20 universities
  - Over 15 pharmaceutical companies

Reporting by the ISPOR

Synergized education and training programs

- Master and PhD degree programs
  - Sichuan university, Peking University, Fudan University, Sun Yat-Sen University……
- Specializations focusing on the use of real world data
  - Drugs and devices monitoring and assessment
  - Pharmacoeconomics and drug policy
  - Rational drug use and clinical translation
  - Disease management
- University courses

- National training workshops
  - 2-day focused training
- Delivered in short courses
  - Retrospective database studies
  - Registry studies
  - Pragmatic clinical trials
  - Issues about bias and confounding
  - Issues about data privacy and ethic review

First national workshop on RWD methodology
2016 Chengdu, China

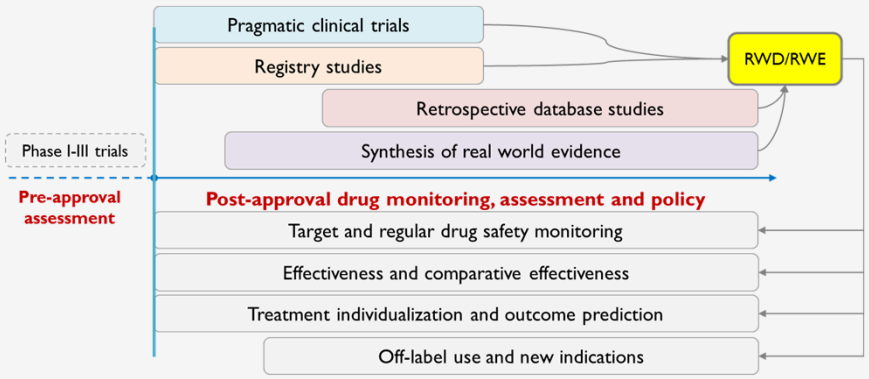
Consortium of research scientists across the country

- A group of over 40 research scientists, expertise with real world data
  - Pharmacoepidemiology and clinical epidemiology
  - Medical statistics or biostatistics
  - Health economics or pharmacoeconomics
  - Health informatics and computing
- Special interest groups (SIG): specialized applications of real world data
  - Clinical outcomes assessment and guideline translation for medical products
  - Pharmacoecnomic assessment and policy on medical products
  - Disease management
  - Statistical methods
- Internal annual meetings to discuss cutting-edge methods and issues

Recent developments: The use of real world studies for regulatory decisions – experience from the State Drug Administration

- Mainly used for post-approval drugs and devices surveillance and evaluation
- Center for Drug Re-Evaluation and National Center for ADR Monitoring
  - RWD already commonly used
  - Active surveillance - drug ADR signal detection and confirmation
  - New drug target surveillance
  - Analysis of drug utilization
- Center for Drug Evaluation (CDE)
  - At the pilot phase
  - Currently used for generic/non-patent drug re-evaluation

Developed the research framework for post-approval drugs monitoring and evaluation

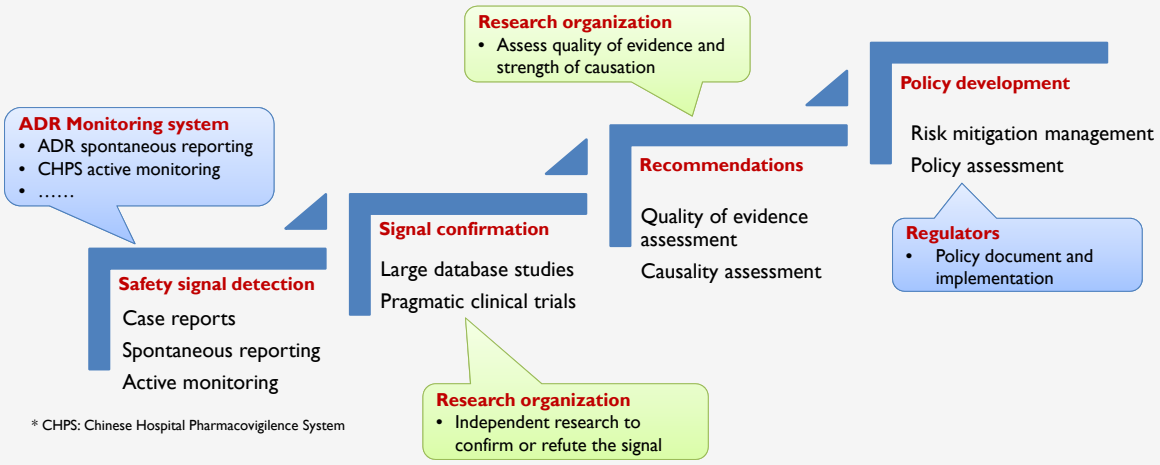



基于真实世界证据的上市后药品评价技术框架体系：思考与建议

Chinese Journal of Evidence-based Medicine. 2018; 18:277-283

Streamline post-approval drug safety monitoring, evaluation, recommendation and action

The framework for using RWD to support ADR identification, confirmation, and policy translation

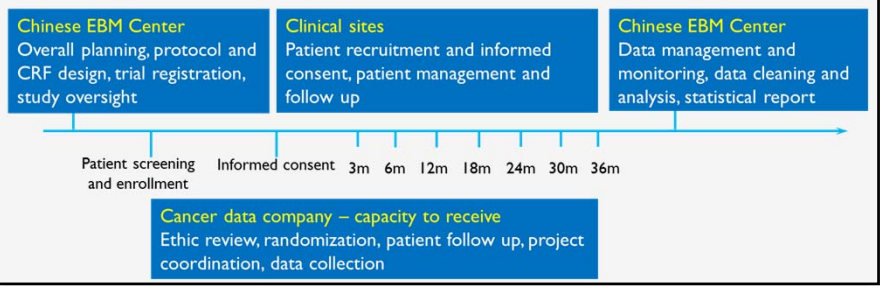


* CHPS: Chinese Hospital Pharmacovigilence System

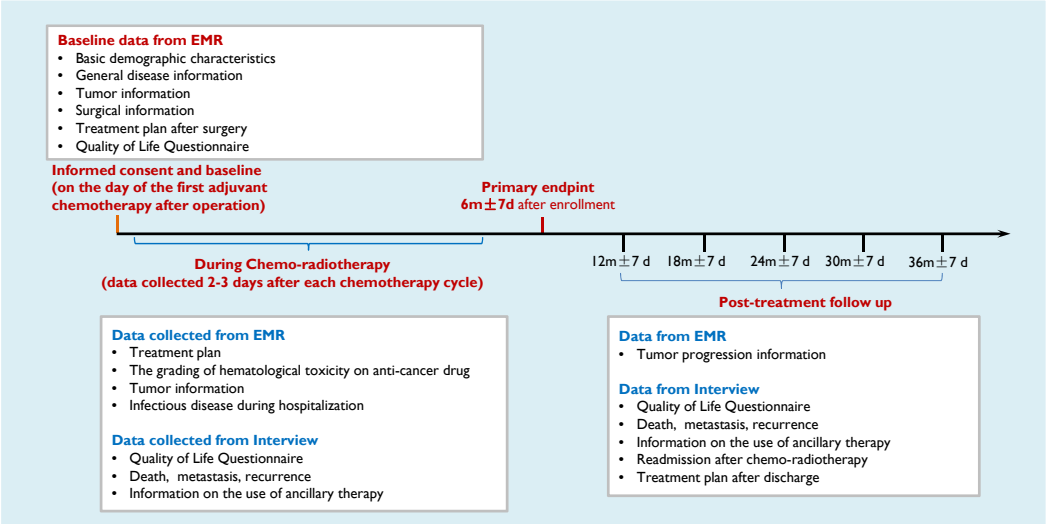
Practical example 1: pragmatic clinical trial to test an ancillary therapy for patients with non-small cell lunge cancer (NSCLC)

Study overview

- Primary aim: test whether ancillary therapy could reduce toxic effects of regular chemotherapy in the real-world setting
- Multi-center, open label, randomized controlled trial
- Patients with operable NSCLC (stage II and IIIa) who receive chemotherapy
- Use versus not use of ancillary therapy
- Anti-cancer guideline-recommended treatments available for both groups
- Treatment variations allowed among patients to reflect real-world setting
- Primary outcome: risk of severe toxic events measured by WHO guideline
- A randomization ratio of 1:1
- A planned 3-year follow up



An integrated approach to collecting data



Practical example 2 : Use of EMR database to assess risk of bleeding and coagulation disorders of an antibiotic

Background

- Signal first identified by the National Center for ADR Monitoring through spontaneous reports
- Sporadic adverse events reported in medical literature, with no convincing evidence
- Laboratory and animal studies suggested antibiotics with NMTT chain carries risk of coagulation disorder, platelet aggregation, and bleeding
- A study to ascertain the association between the antibiotic and bleeding risk commissioned by the National Center for ADR Monitoring

Research objectives

- Understand the proportion of bleeding or coagulation disorder among hospitalized patients who used antibiotic A
- Investigate whether the use of antibiotic A would be associated with increased risk of bleeding and coagulation disorder
- Explore the factors associated with bleeding and coagulation disorders

West China Hospital has one of the best EMR databases in China

One of the leading academic medical center in China – ranked first in medical research

- EMR established in 2008 and maturated in 2010
- Annual number of hospitalizations: 200,000
- Validated ICD-10 coding
- Linked data

Storage of data:

- Excel dataset
- TXT file with comma separated

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