Real world evidence in China
—— Current practices, challenges, strategies and developments

Xin Sun, PhD, Professor
ISPOR West China Chapter
Chinese Evidence-based Medicine Center
West China Hospital, Sichuan University, China

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study setting</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feng et al. (2007)</td>
<td>Schools in Chengdu</td>
<td>355 children with at least one visible white-spot lesion</td>
</tr>
<tr>
<td>Wei et al. (2010)</td>
<td>A general hospital in Henan Province</td>
<td>129 patients with myelodysplastic syndrome</td>
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<tr>
<td>Yu et al. (2010)</td>
<td>General and TCH hospitals in Beijing, Tianjin, Henan, Hebei, and Shandong</td>
<td>200 inpatients with ischemic stroke</td>
</tr>
<tr>
<td>Yan et al. (2011)</td>
<td>General and infectious disease hospitals across China</td>
<td>133 HIV/AIDS patients with chronic diarrhoea</td>
</tr>
<tr>
<td>Yu et al. (2011)</td>
<td>Twelve hospitals across China</td>
<td>200 inpatients with acute ischemic stroke</td>
</tr>
<tr>
<td>Li et al. (2014)</td>
<td>General and infectious disease hospitals across China</td>
<td>300 inpatients with chronic kidney disease</td>
</tr>
<tr>
<td>Tian et al. (2011)</td>
<td>General and infectious disease hospitals across China</td>
<td>127 patients with chronic kidney disease</td>
</tr>
<tr>
<td>Dong et al. (2014)</td>
<td>Schools in Chengdu</td>
<td>153 HIV/AIDS patients with chronic diarrhoea</td>
</tr>
<tr>
<td>Liu et al. (2015)</td>
<td>Rural counties and urban districts from Heilongjiang, Jiangsu, Hunan, and Chongqing</td>
<td>3,292 outpatients with new pulmonary tuberculosis (TB)</td>
</tr>
<tr>
<td>Browning et al. (2016)</td>
<td>Community Health Stations in Fengtai district, Beijing</td>
<td>669 patients with type 2 diabetes</td>
</tr>
<tr>
<td>Fu et al. (2016)</td>
<td>General hospitals in Beijing and Henan</td>
<td>200 inpatients with ischemic stroke</td>
</tr>
<tr>
<td>Li et al. (2016)</td>
<td>A psychiatric centre of a general hospital in Beijing</td>
<td>140 inpatients with severe anaemia psychosis accompanied by paranoid ideas</td>
</tr>
<tr>
<td>Chen et al. (2017)</td>
<td>Psychiatric out-patient clinics in mainland China, Hong Kong, and Taiwan</td>
<td>342 patients with schizophrenia spectrum disorders</td>
</tr>
<tr>
<td>Wu et al. (2017)</td>
<td>Endocrinology and Acupuncture out-patient clinics of a general hospital in Beijing</td>
<td>369 male smokers</td>
</tr>
<tr>
<td>Yang et al. (2017)</td>
<td>Campus advertisements from several universities in Chengdu</td>
<td>153 patients with primary dysmenorrhoeas</td>
</tr>
</tbody>
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Most pragmatic trials tested traditional Chinese medicine

- Cancer and vascular diseases staying on the top
- Searched up to June 2007

*Search up to June 2007*
### Increasing use of RWE for healthcare and policy decisions in China

<table>
<thead>
<tr>
<th>Authorities</th>
<th>Major uses</th>
<th>Relative importance of RWE for decision making</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese Drug Administration</td>
<td>Post-approval decisions</td>
<td>• Post-approval drug assessment and safety surveillance ++++</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Label changes and new indication assessment +</td>
</tr>
<tr>
<td></td>
<td>Pre-approval decisions</td>
<td>• Supporting evidence for investigational new drug approval</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(e.g. disease burden and practice pattern) +++</td>
</tr>
<tr>
<td>Medical Security Bureau</td>
<td>Drug coverage decisions</td>
<td>• Parameters for Cost-effectiveness analysis</td>
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<tr>
<td></td>
<td></td>
<td>• Cost of illness and disease burden +++</td>
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<td></td>
<td></td>
<td>• Clinical outcomes and epidemiological data +++</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Health-related quality of life and utility +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Parameters for budget impact analysis +++</td>
</tr>
<tr>
<td>National Health Commission</td>
<td>Health technology assessment</td>
<td>• Clinical outcomes for emerging technologies ++++</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cost assessment +++</td>
</tr>
<tr>
<td></td>
<td>Healthcare quality and safety surveillance</td>
<td>• Measurement of healthcare quality indicators ++++</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Safety monitoring and assessment +++</td>
</tr>
<tr>
<td>Healthcare providers</td>
<td>Clinical practice guidelines</td>
<td>• Disease burden assessment ++++</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clinical assessment if classical trials not available ++++</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Safety assessment of treatments +++</td>
</tr>
</tbody>
</table>

### Diversified real world data sources in China

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

### Challenges: RWE development still at early stage in China

Misconduct and misinterpretations are common

<table>
<thead>
<tr>
<th>Types of misunderstanding</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real world data (RWD)</td>
<td>RWD are another word for big data</td>
</tr>
<tr>
<td></td>
<td>RWD are allowed for low quality given its nature</td>
</tr>
<tr>
<td>Real world studies (RWS)</td>
<td>RWS are universally observational</td>
</tr>
<tr>
<td></td>
<td>RWS are typically cheap</td>
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<tr>
<td></td>
<td>RWS have no control group</td>
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<td></td>
<td>RWS have no quality control</td>
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<td></td>
<td>RWS should not set up restrictions to patient inclusion</td>
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<td></td>
<td>RWS do not need ethical review</td>
</tr>
<tr>
<td></td>
<td>Informed consent is not needed for any type of real world studies</td>
</tr>
<tr>
<td>Real world evidence (RWE)</td>
<td>RWE less trustworthy than classical trials</td>
</tr>
<tr>
<td></td>
<td>RWE better than classical trials in their findings</td>
</tr>
<tr>
<td></td>
<td>RWE applicable only to drug assessment</td>
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<tr>
<td></td>
<td>RWE of low quality</td>
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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 Alli ance: 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, pharmaco economics, health informatics
- Data partners: regional EHR, hospital EMR, disease registries, claims database
- Industrial collaborators: HEOR, pharmacoepidemiology, medical affairs

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

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
  - Pharmacoeconomic 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

- Pragmatic clinical trials
- Registry studies
- Retrospective database studies
- Synthesis of real world evidence
- Post-approval drug monitoring, assessment and policy
  - Target and regular drug safety monitoring
  - Effectiveness and comparative effectiveness
  - Treatment individualization and outcome prediction
  - Off-label use and new indications

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

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

- Safety signal detection
  - Case reports
  - Spontaneous reporting
  - Active monitoring

- Signal confirmation
  - Large database studies
  - Pragmatic clinical trials
  - Quality of evidence assessment
  - Causality assessment

- Recommendations
  - Independent research to confirm or refuse the signal
  - Risk mitigation management
  - Policy assessment

- Policy development
  - Policy document and implementation

- ADR Monitoring system
  - ADR spontaneous reporting
  - CHPS active monitoring
  - ……

- Research organization
  - Assess quality of evidence and strength of causation
  - Independent research to confirm or refuse the signal

Practical example 1: pragmatic clinical trial to test an ancillary therapy for patients with non-small cell lung 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

**Chinese EBM Center**
- Overall planning, protocol and CRF design, trial registration, study oversight

**Clinical sites**
- Patient recruitment and informed consent, patient management and follow up

**Chinese EBM Center**
- Data management and monitoring, data cleaning and analysis, statistical report

| Cancer data company – capacity to receive!
| Ethic review, randomization, patient follow up, project coordination, data collection |

3m 6m 12m 18m 24m 30m 36m
An integrated approach to collecting data

Baseline data from EMR
- Basic demographic characteristics
- General disease information
- Tumor information
- Surgical information
- Treatment plan after surgery
- Quality of Life Questionnaire

Informed consent and baseline (on the day of the first adjuvant chemotherapy after operation)

Primary endpoint
6m ± 7d after enrollment

Data collected from EMR
- Treatment plan
- The grading of hematological toxicity on anti-cancer drug
- Tumor information
- Infectious disease during hospitalization

Data collected from Interview
- Quality of Life Questionnaire
- Death, metastasis, recurrence
- Information on the use of ancillary therapy

During Chemo-radiotherapy (data collected 2-3 days after each chemotherapy cycle)

12m ± 7d 18m ± 7d 24m ± 7d 30m ± 7d 36m ± 7d

Data from EMR
- Tumor progression information

Data from Interview
- Quality of Life Questionnaire
- Death, metastasis, recurrence
- Information on the use of ancillary therapy
- Readmission after chemo-radiotherapy
- Treatment plan after discharge

Post-treatment follow up

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 matured 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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