Real-world evidence for regulatory and reimbursement decisions: updates from China

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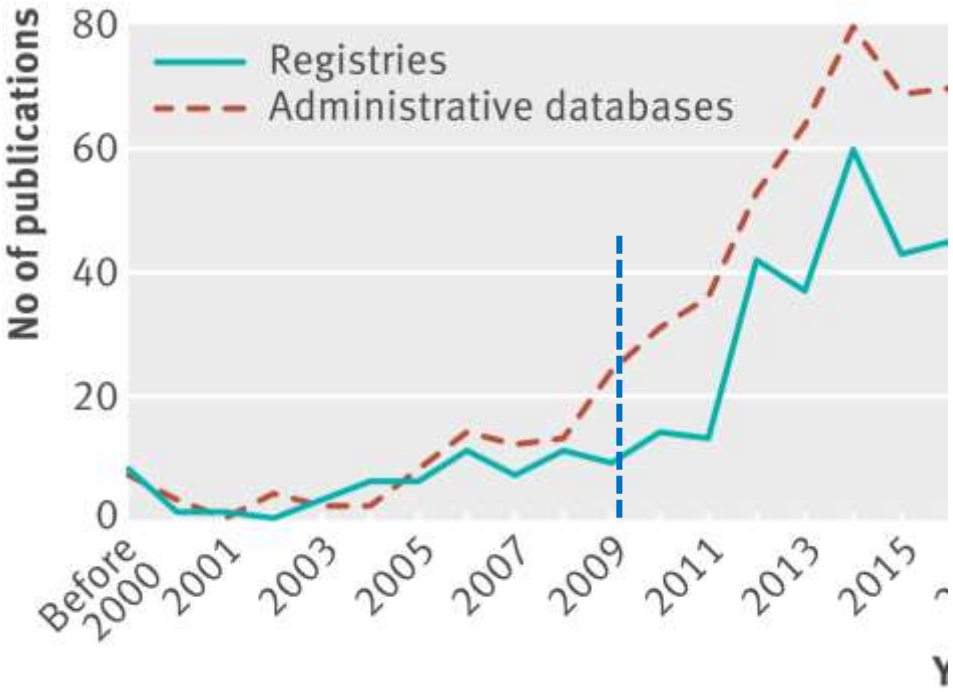
Production of RWE rapidly increased in China

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 herbal 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 health policy decisions in China

Authorities	Major uses	Relative importance of RWE for decision making
National Medical Products Administration (NMPA)	Post-approval decisions	• Post-approval drug assessment and safety surveillance +++++ • Label changes and new indication assessment +++
	Pre-approval decisions	• Supporting evidence for investigational drug development (e.g. in combination with RCT) +++
National Healthcare Security Administration (NHSA)	Coverage and payment decisions	• Clinical outcomes and epidemiological data ++ • Health-related quality of life and utility ++ • Parameters for Cost-effectiveness modelling +++ • Cost of illness and disease burden ++++ • Parameters for budget impact analysis ++++
National Health Commission (NHC)	Essential medicines selection and HTA	• Clinical outcomes for emerging technologies ++++ • Cost assessment ++++
	Drugs and devices clinical use monitoring	• Measurement of healthcare quality indicators ++++ • Safety monitoring and assessment ++++
Healthcare providers	Clinical practice guidelines Clinical Decision Support System (CDSS)	• Disease burden assessment +++ • Clinical assessment if classical trials not available ++++ • Safety assessment of treatments ++++ • Disease prediction +++++

Use of RWE for regulatory decisions: National Medical Products Administration

国家药品监督管理局
National Medical Products Administration

- NMPA Leadership efforts
  - Inclusion of RWE for approval of medical products first noted in 2019
  - Regulatory Sciences Initiatives began in 2019
    - Including two specific projects about real-world data and evidence
- Center for Drug Evaluation (CDE)
  - Guidance documents released
- Center for Medical Devices Evaluation (CMDE)
  - Use of Real-world evidence for clinical evaluation of medical devices
- Center for Drug Re-Evaluation (National Center for ADR Monitoring)
  - RWD already commonly used
  - Active surveillance - drug ADR signal detection and confirmation
  - New drug target surveillance

Guidance for Real-World Evidence to Support Drug Development and Review

https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20200107151901190.html
https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20200901104448101.html

Guidance for the Use of Real-World Data in Clinical Evaluation of Medical Devices

国家药品监督管理局
National Medical Products Administration

中 En

请输入关键字

国家药监局关于发布真实世界数据用于医疗器械临床评价技术指导原则（试行）的通告
（2020年第77号）

发布时间：2020-11-26

为规范和指导真实世界数据在医疗器械临床评价中的应用，按照国家药品监督管理局中国药品监管科学行动计划工作安排，国家药监局组织制定了《真实世界数据用于医疗器械临床评价技术指导原则（试行）》，现予发布。

特此通告。

附件：真实世界数据用于医疗器械临床评价技术指导原则（试行）

国家药监局

2020年11月24日

https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20201126090030150.html

RWE initiatives for approvals and monitoring of drugs

- **Use of RWE for approval of new drugs**
  - Boao program for new products approved by overseas authorities (e.g. FDA, EMR)
  - Approval of orphan drugs
  - Indication expansions and change of labels for drugs

- **RWE initiatives for post-approval safety monitoring**
  - Chinese Hospital Pharmacovigilence System （CHPS）
  - Using real-world data for assessing bleeding risk associated with antibiotics
  - Using regionally linked electronic health records for assessing vaccine safety
  - Using CHPS data for drug-induced liver injury
  - Methods study on devices safety monitoring

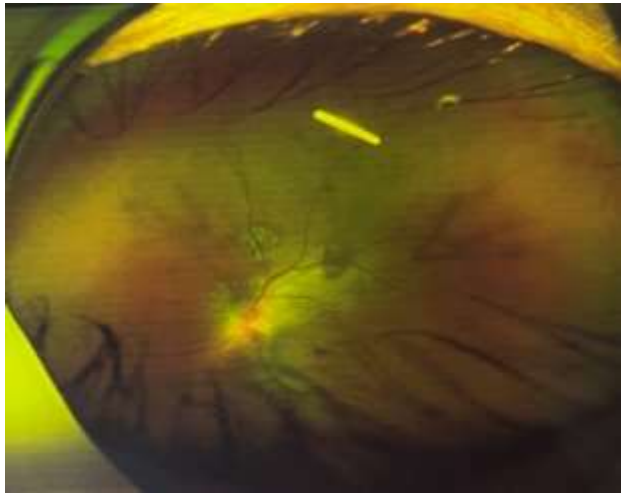
Boao RWE program

- **Drugs and medical devices used in Boao meet important requirements**
  - meet urgent clinical needs
  - used for specified medical purposes
  - not approved in China, but already approved by major regulatory bodies abroad

- **Specific patient healthcare context**
  - Patients come from all over the country
  - Receive healthcare through the special medical tourism policy
  - Conducted through solicited or unsolicited recruitment
  - Usually receive special drug at Lecheng healthcare institutions, then return home city
  - Follow up visits may be conducted at home city or Boao, depending on disease condition, drug used

FAI RWE to support regulatory decision

- First case in China that used local RWE for regulatory approval of new drug
- Study design based on self-control and external control
- In June 2022, the first drug product utilizing domestic real-world data (RWD) approved in China
- Time to marketing accelerated by 1.5 years
- R&D costs reduced less than a quarter of a normal registration trial



RWE initiatives for approval of Chinese herbal medicines

- **Center for Drug Evaluation, NMPA**

- **Regulatory Sciences initiative**
  - **Using real-world evidence (RWE) to support claims of efficacy or safety Chinese herbal medicine**
  - **Evaluation of Chinese patent medicine efficacy based on RWD**
  - **RWE to support new indications, indication expansion, and change of labels**

- **Different approaches for combining use of RWE and RCT**

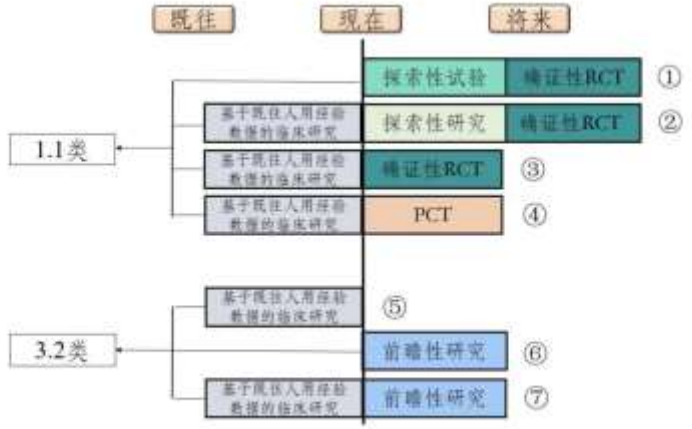
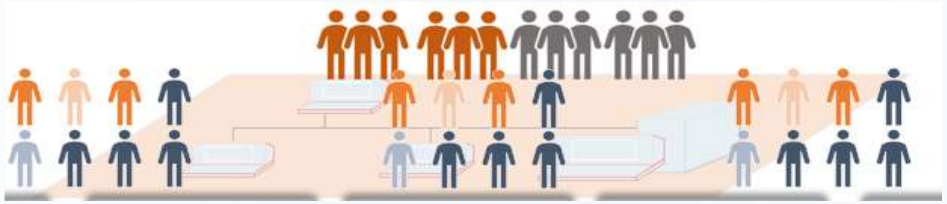
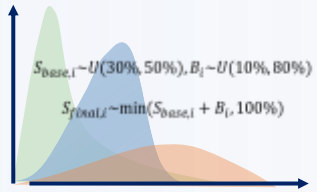


图 1 基于人用经验的中药复方制剂临床研发策略示意图*

New drug development: hospital preparation (Liuhedan) for treating acute pancreatitis

Completed the empirical study on Liuhe Dan in the treatment of acute pancreatitis





Liuhedan reduces abdominal pain and bloating symptoms and shortens recovery time of gastrointestinal function

Group	n	Time of abdominal pain disappearance	Time of gastrointestinal function recovery	Time of refeeding
Liuhe Dan	58	6.95±3.15	5.79±3.23	4.82±1.95
Control	62	6.33±3.78	7.19±3.33	5.93±3.28
t		2.27	2.47	2.29
p		0.025	0.015	0.024

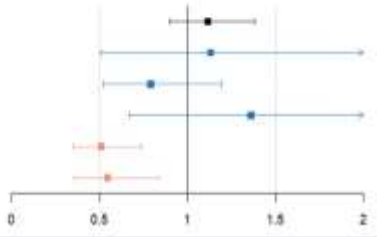
China's first class 1.1 TCM new drug for hospital preparation approved for clinical trials

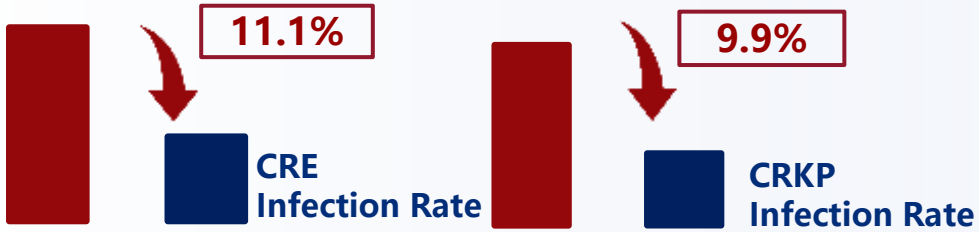
Expanding indication for Tanreqing injection: treatment for multiple resistant bacteria

Tanreqing injection reduces the risk of CRE and CRKP infections

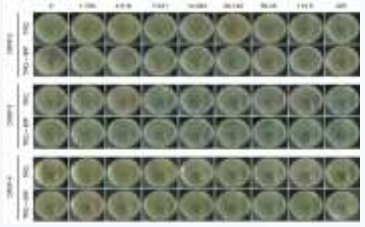
Clinical Evidence: Tanreqing injection combined with antibiotics reduces CRE and CRKP Infection Rates

Outcomes	Patients receiving combined treatment n (%) Patients with MRDO	Patients without MRDO	Adjusted OR (95% CI)
MRDOs (N=2890)	236 (16.1)	231 (16.3)	1.115 (0.900 to 1.382)
MRSA (N=626)	10 (13.9)	47 (8.5)	1.132 (0.504 to 2.543)
CRPA (N=682)	53 (16.5)	67 (18.6)	0.790 (0.521 to 1.196)
CRAB (N=1129)	176 (16.6)	12 (17.1)	1.360 (0.670 to 2.760)
CRE (N=1382)	40 (13.2)	246 (22.8)	0.510 (0.350 to 0.742)
CRKP (N=827)	35 (14.8)	140 (23.7)	0.546 (0.357 to 0.834)

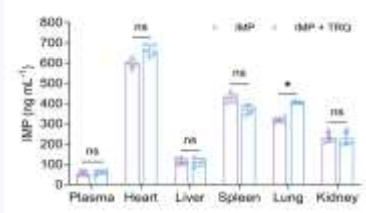




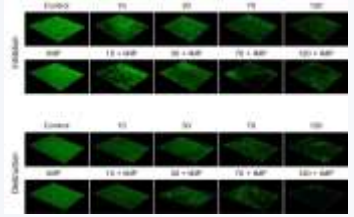
Basic Pharmacology: Four mechanisms of synergistic efficacy with antibiotics



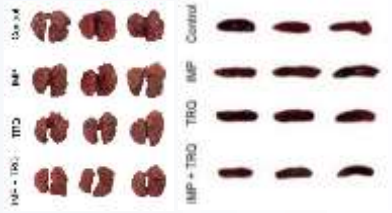
Synergistic antibacterial effect with antibiotics



Increase the pulmonary distribution of antibiotics



Cell walls disruption, Biofilms degradation



Alleviate organ inflammatory response

New indication application

Indication expansion application.

Category 2.3 - Added Indications
(Treat drug-resistant bacteria)

Phytomedicine 2025, BMC Med 2025, J Clin Epidemiol 2024

Label information change: motherwort effect on preventing postpartum hemorrhage after cesarean section

JOURNAL OF EVIDENCE-BASED MEDICINE

METHODOLOGY Open Access

A methodological framework for tackling confounding by indication when assessing the treatment effects of Chinese herbal injections in the real world

Jing Tan, Chunrong Liu, Mingxi Li, Hongcai Shang, Wen Wang, Ling Li, Yiquan Xiong, Shiyao Huang, Chaolong Rao, Xiaochao Luo, Yana Qi, Jing Wang, Kang Zou, Xin Sun

frontiers in Pharmacology

ORIGINAL RESEARCH

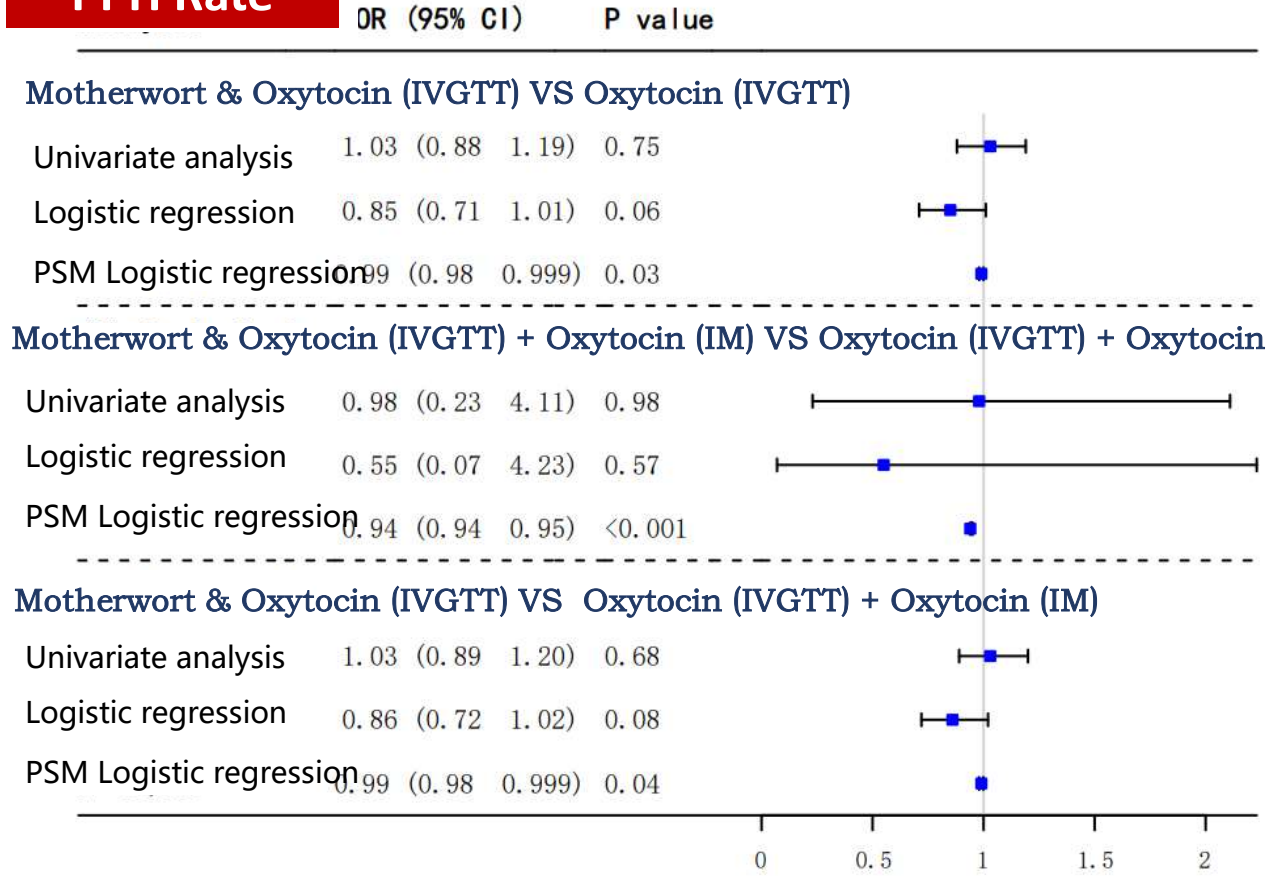
Effects of Motherwort Injection Versus Intramuscular Oxytocin for Preventing Postpartum Hemorrhage Among Women Who Underwent Cesarean Section

OPEN ACCESS

Edited by: Kevin Liu, University of South Carolina, United States

Ming-xi Li[1,2,3], Chun-rong Liu[1,2,3], Meng Chen[4], Hong-cai Shang[5], Wen Wang[1,2,3], Xiao-chao Luo[1,2,3], Ling Li[1,2,3], Ya-na Qi[1,2,3], Yi-quan Xiong[1,2,3], Shi-yao Huang[1,6], Jing Wang[1,2,3], Kang Zou[1,2,3], Xing-hui Liu[4], Jing Tan[1,2,3]* and Xin Sun[1,2,3]*

PPH Rate

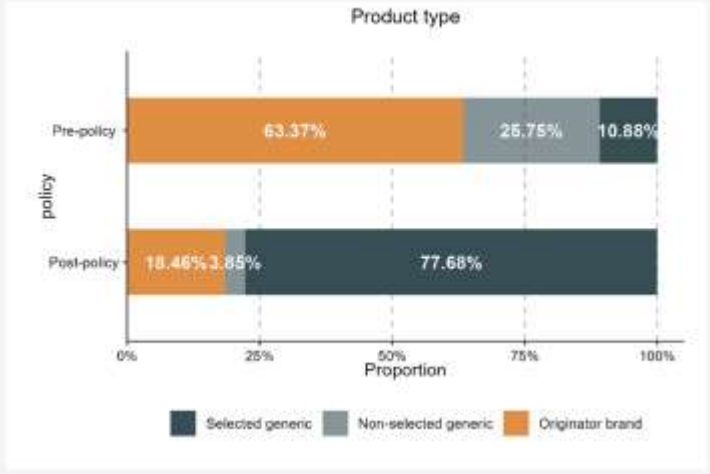


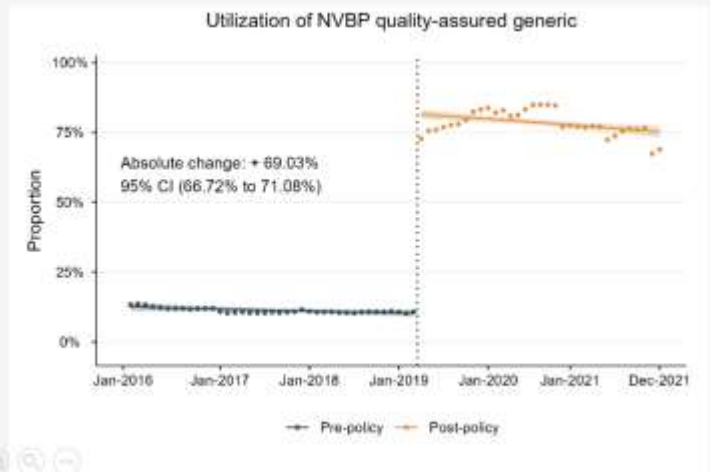
RWE initiatives for reimbursement decisions of drugs

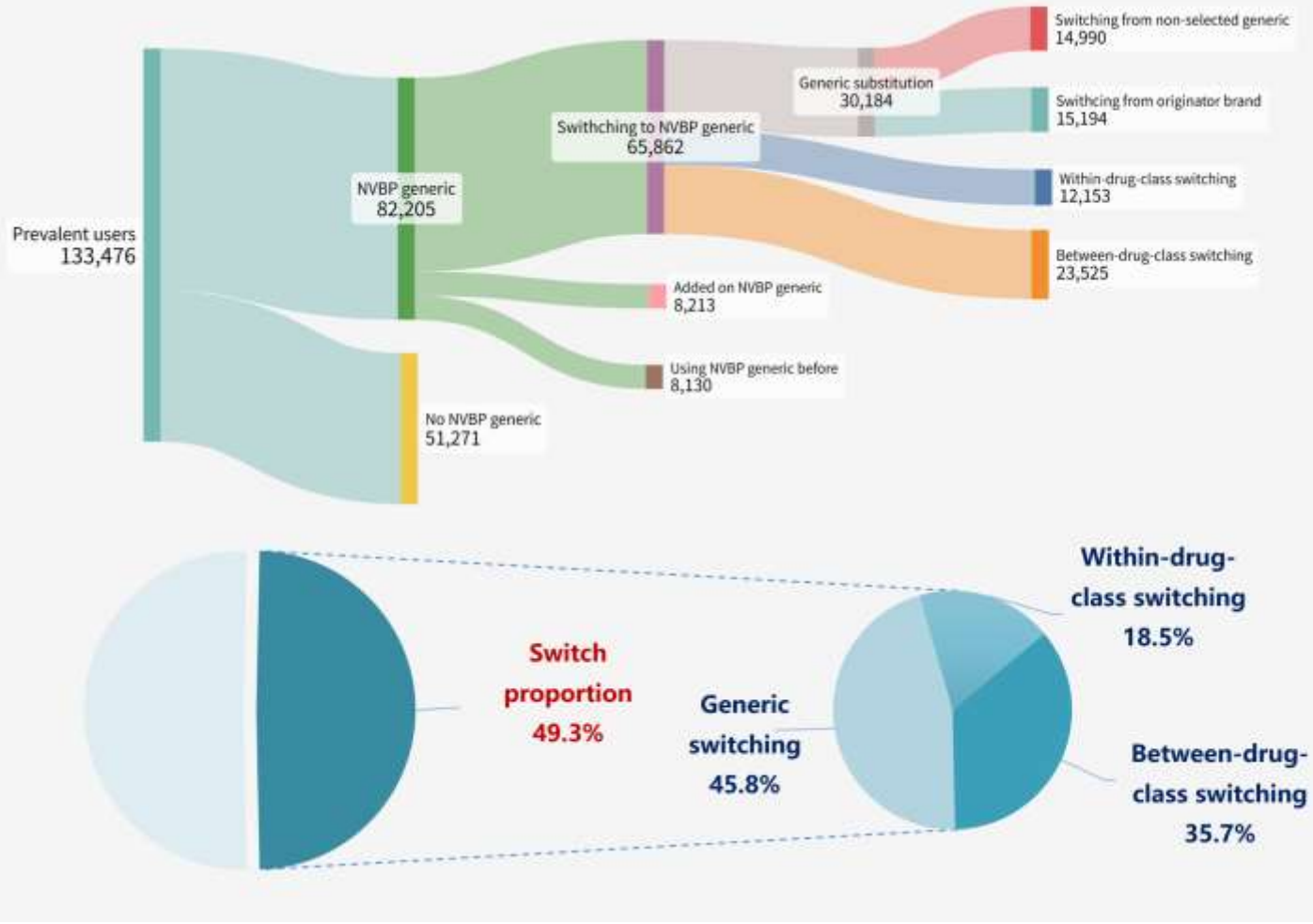
- Identifying unmet needs
- Coverage decisions for new drugs
- Coverage decisions for Chinese herbal medicines
- Boao piloting program
- National Volume-Based Procurement (NVBP) monitoring and assessment

NVBP program significantly promoted the generic substitutions

Quality-assured generic utilization increased by + 69.3% (95% CI, 66.72%% to 71.08%)
Nearly 49.3% prevalent users switched to NVBP generics during the NVBP implementation, with only 45.8% were generic switching with the same active ingredient

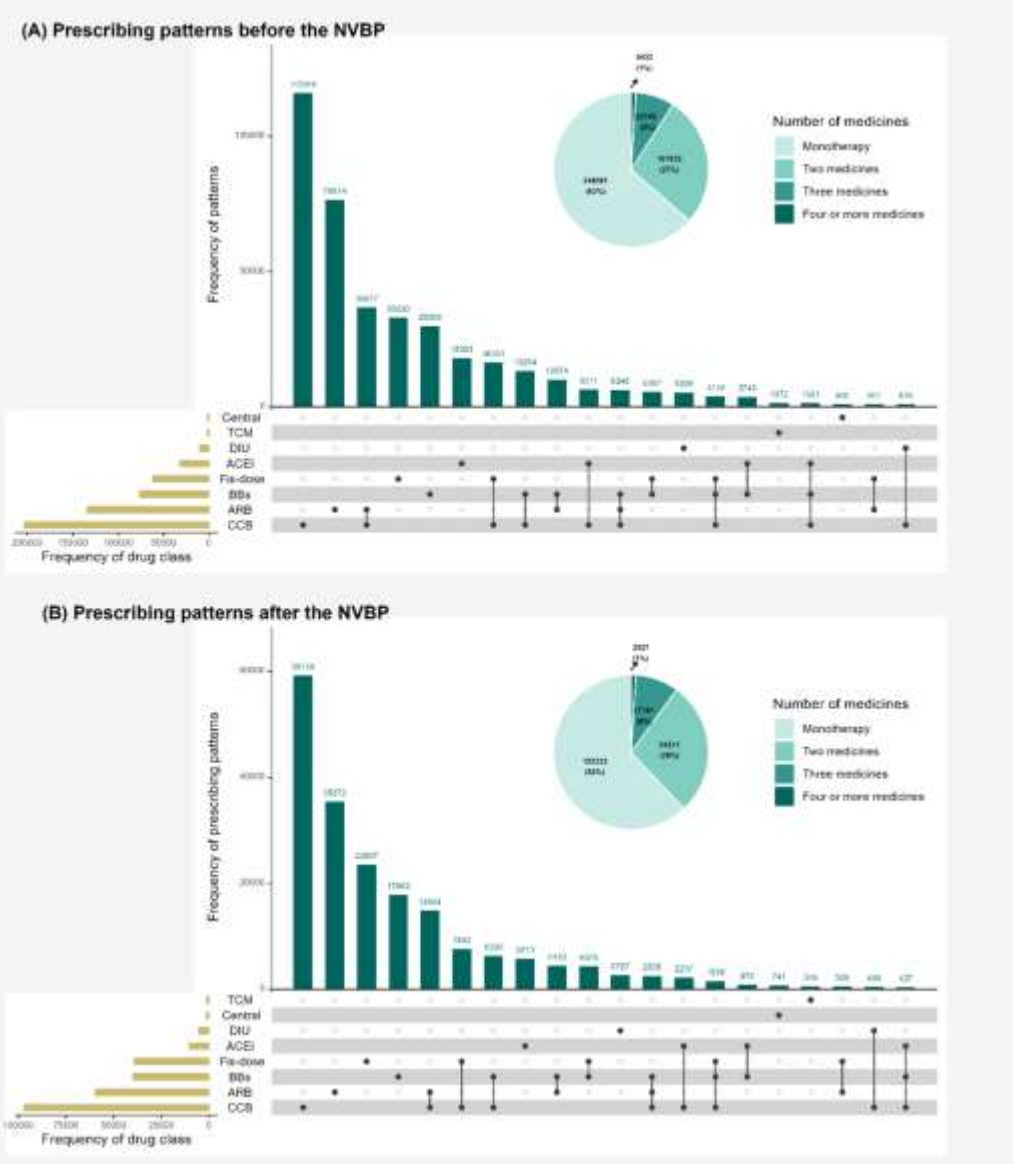






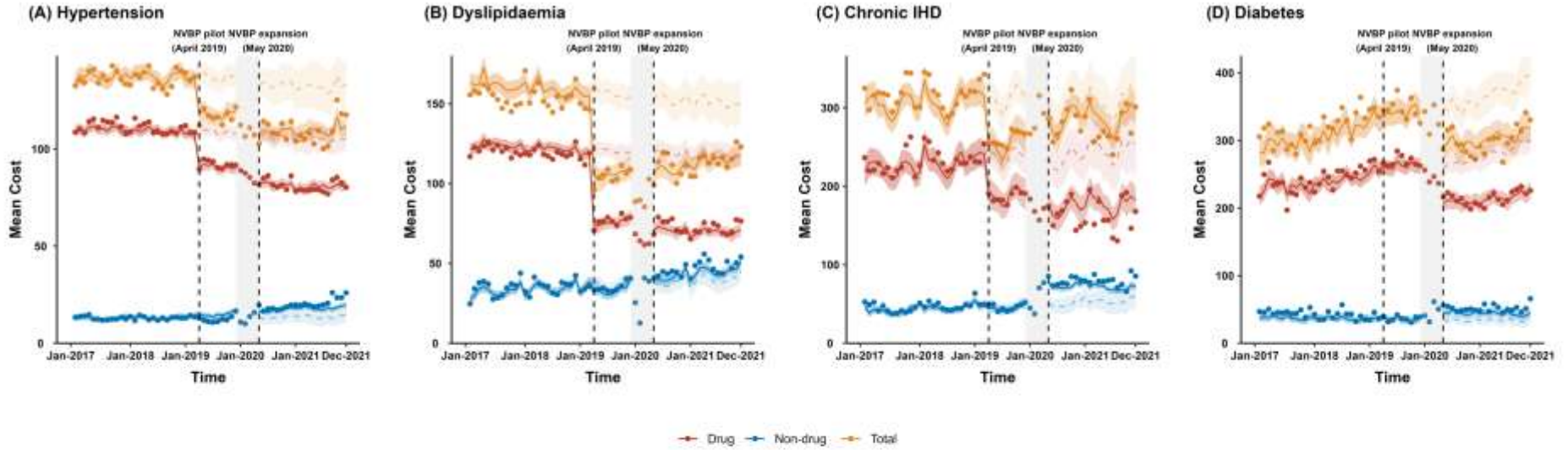
Prescribing patterns not changed significantly after NVBP and broadly complying clinical guideline recommendations

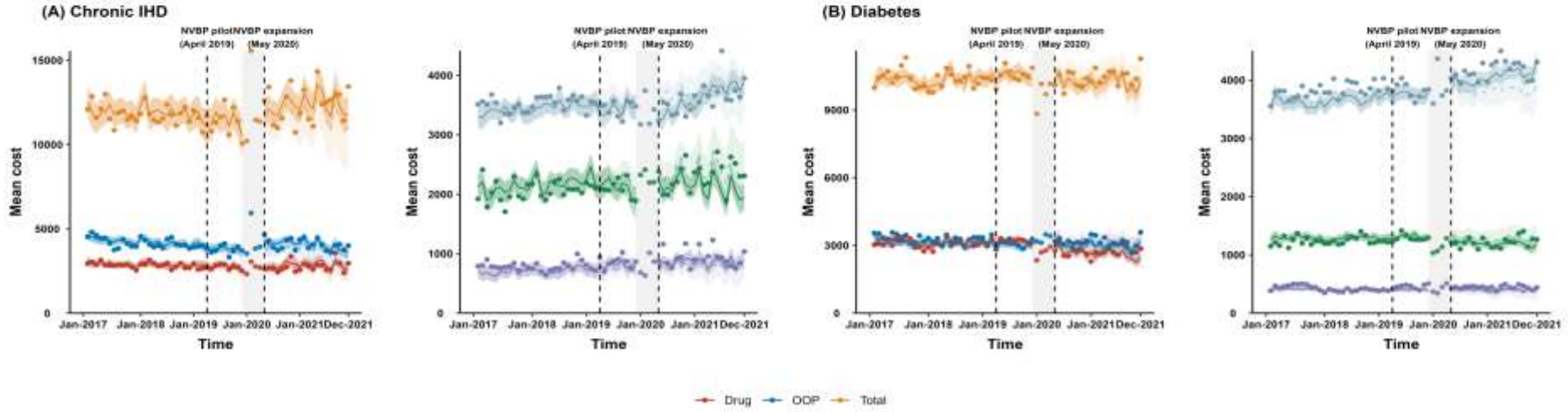
Patterns	Pre-policy (n = 399,187)		Post-policy (n = 199,541)	
	n	% (95% CI)	n	% (95% CI)
Monotherapy				
ACEI	18,023	0.045 (0.045 ~ 0.046)	5,813	0.029 (0.028 ~ 0.03)
ARB	76,514	0.192 (0.19 ~ 0.193)	35,372	0.177 (0.176 ~ 0.179)
BBs	29,909	0.075 (0.074 ~ 0.076)	17,863	0.09 (0.088 ~ 0.091)
CCB	115,916	0.29 (0.289 ~ 0.292)	59,139	0.296 (0.294 ~ 0.298)
DIU	5,309	0.013 (0.013 ~ 0.014)	2,727	0.014 (0.013 ~ 0.014)
Two medicines				
ACEI + BBs	-	-	875	0.004 (0.004 ~ 0.005)
ACEI + CCB	6,311	0.016 (0.015 ~ 0.016)	2,237	0.011 (0.011 ~ 0.012)
ARB + BBs	10,074	0.025 (0.025 ~ 0.026)	4,430	0.022 (0.022 ~ 0.023)
ARB + CCB	36,677	0.092 (0.091 ~ 0.093)	14,844	0.074 (0.073 ~ 0.076)
BBs + CCB	13,294	0.033 (0.033 ~ 0.034)	6,330	0.032 (0.031 ~ 0.032)
Fix-dose	33,030	0.083 (0.082 ~ 0.084)	23,506	0.118 (0.116 ~ 0.119)
Three or more medicines				
ARB + BBs + CCB	6,245	0.016 (0.015 ~ 0.016)	2,505	0.013 (0.012 ~ 0.013)
BBs + Fix-dose	5,387	0.013 (0.013 ~ 0.014)	4,378	0.022 (0.021 ~ 0.023)
CCB + Fix-dose	16,351	0.041 (0.04 ~ 0.042)	7,643	0.038 (0.037 ~ 0.039)
BBs + CCB + Fix-dose	3,778	0.009 (0.009 ~ 0.01)	1,518	0.008 (0.007 ~ 0.008)



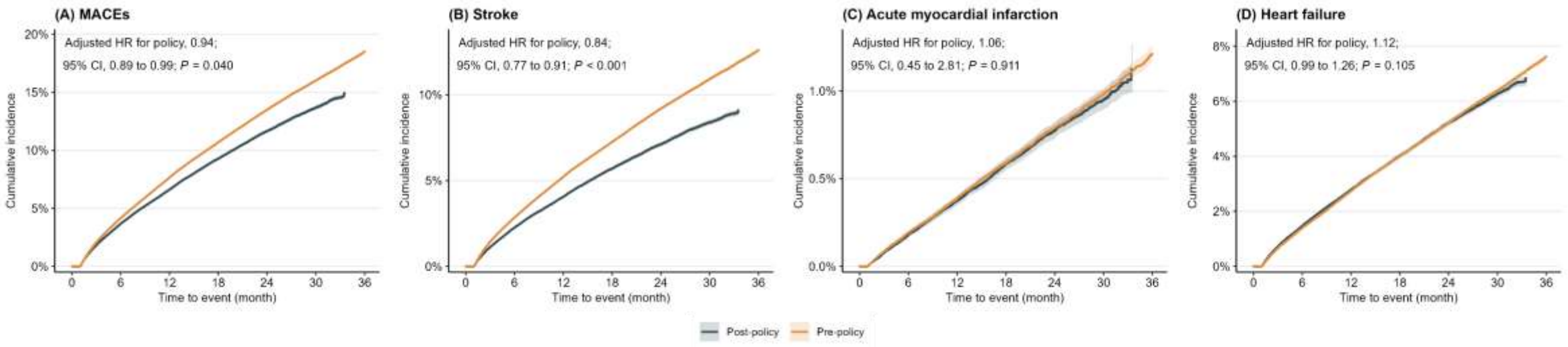
Medical expenditures for patients substantially decreased after NVBP

The average outpatient expenditures per visit decreased significantly by 15.61% for hypertension, 25.77% for hyperlipidemia, and 17.59% for diabetes.





Cardiovascular outcomes in hypertensive patients decreased following NVBP

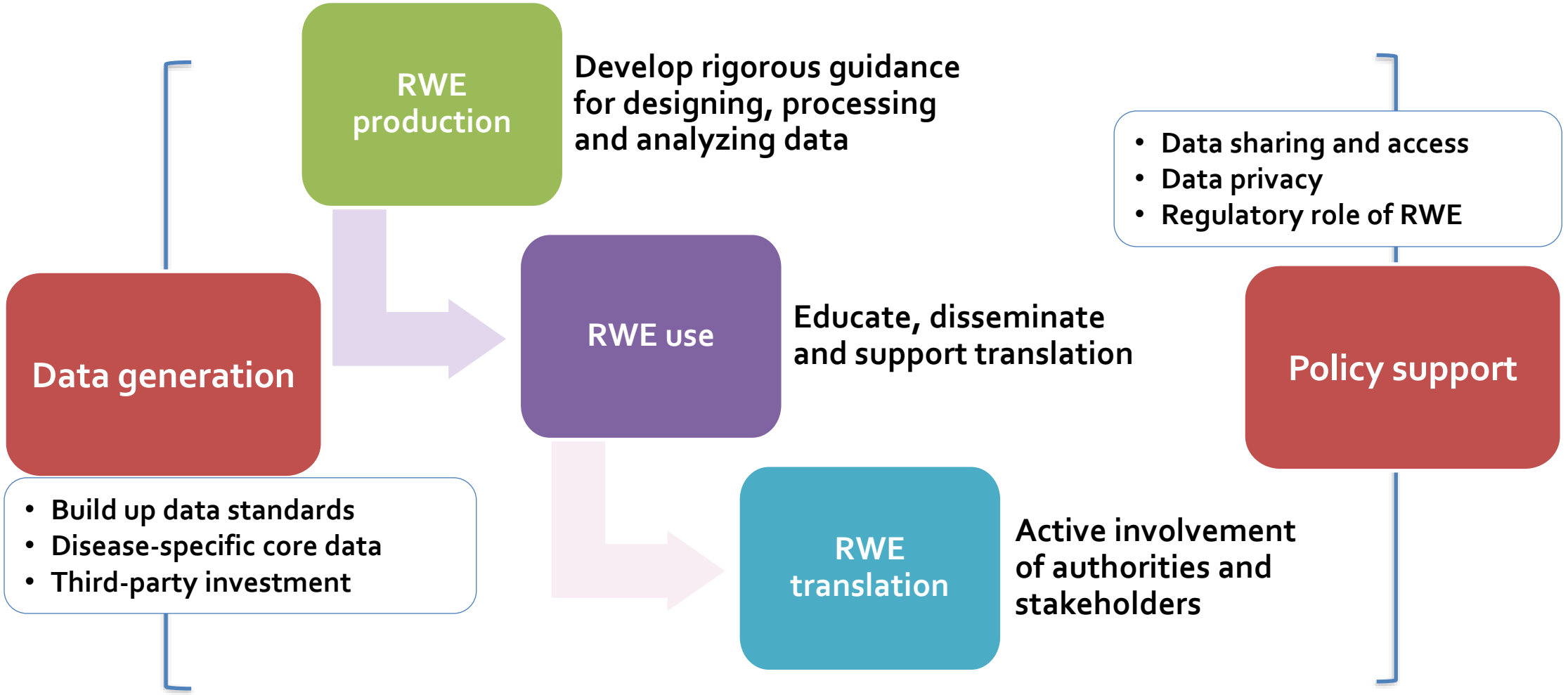


	Pre-policy		Post-policy		Absolute rate difference per 1000 person-years (95% CI)	Adjusted HR/IRR (95% CI)
	Events	Incidence rate per 1000 person-years (95% CI)	Events	Incidence rate per 1000 person-years (95% CI)		
Cardiovascular events						
MACEs	57,272	66.30 (65.76 to 66.84)	21,207	58.74 (57.95 to 59.53)	-7.55 (-8.51 to -6.60) ***	0.94 (0.89 to 0.99) *
Stroke	38,940	45.08 (44.63 to 45.52)	12,997	36.01 (35.38 to 36.63)	-9.08 (-9.84 to -8.31) ***	0.84 (0.77 to 0.91) ***
Acute myocardial infarction	3,421	3.96 (3.83 to 4.10)	1,380	3.82 (3.63 to 4.03)	-0.14 (-0.38 to 0.10)	1.06 (0.45 to 2.81)
Heart failure	22,443	25.98 (25.64 to 26.33)	9,392	26.01 (25.49 to 26.55)	0.04 (-0.59 to 0.66)	1.12 (0.99 to 1.26)
Adverse drug reactions						
Hyperkalemia	2,330	2.09 (2.00 to 2.17)	1,588	3.32 (3.16 to 3.49)	1.24 (1.05 to 1.42) ***	1.57 (1.46 ~ 1.69) ***
Hypokalemia	19,943	17.86 (17.61 to 18.10)	11,257	23.57 (23.12 to 24.00)	5.71 (5.20 to 6.21) ***	1.30 (1.26 ~ 1.33) ***
Hyponatremia	4,577	4.10 (3.98 to 4.22)	2,456	5.14 (4.94 to 5.35)	1.04 (0.81 to 1.28) ***	1.24 (1.18 ~ 1.32) ***
Hypotension	843	0.76 (0.71 to 0.81)	423	0.89 (0.80 to 0.97)	0.13 (0.03 to 0.23) ***	1.14 (1.00 ~ 1.31) *
Pedal edema	19,530	17.49 (17.24 to 17.74)	11,463	23.99 (23.57 to 24.43)	6.51 (6.00 to 7.01) ***	1.29 (1.26 ~ 1.33) ***
Bradycardia	9,372	8.39 (8.22 to 8.56)	4,595	9.62 (9.34 to 9.89)	1.23 (0.90 to 1.55) ***	1.11 (1.06 ~ 1.16) ***

Issues about data and inadequate research capacity

- **Data quality remains suboptimal**
  - Data errors and incompleteness
  - Lack of follow up
  - Data standardization not meeting requirements for research
- **Data ownership and accessibility issues**
  - Data often not readily accessible
  - Data companies do not always have the rights to use data
- **Lack of sufficient 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

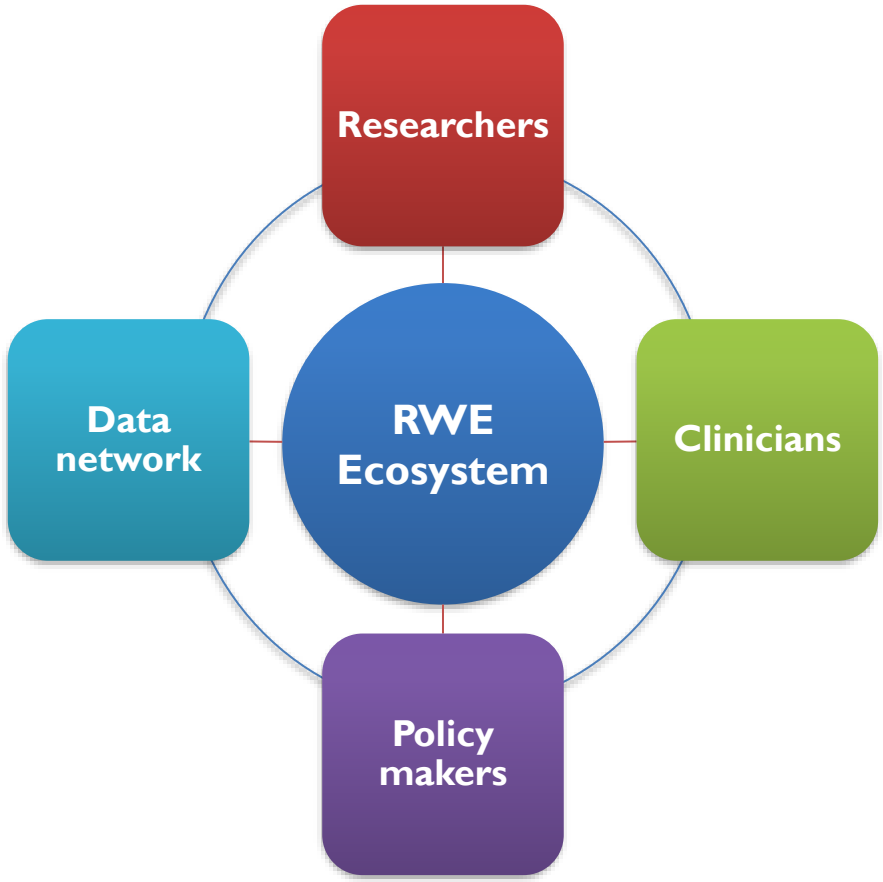
Developing an RWE ecosystem in China



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



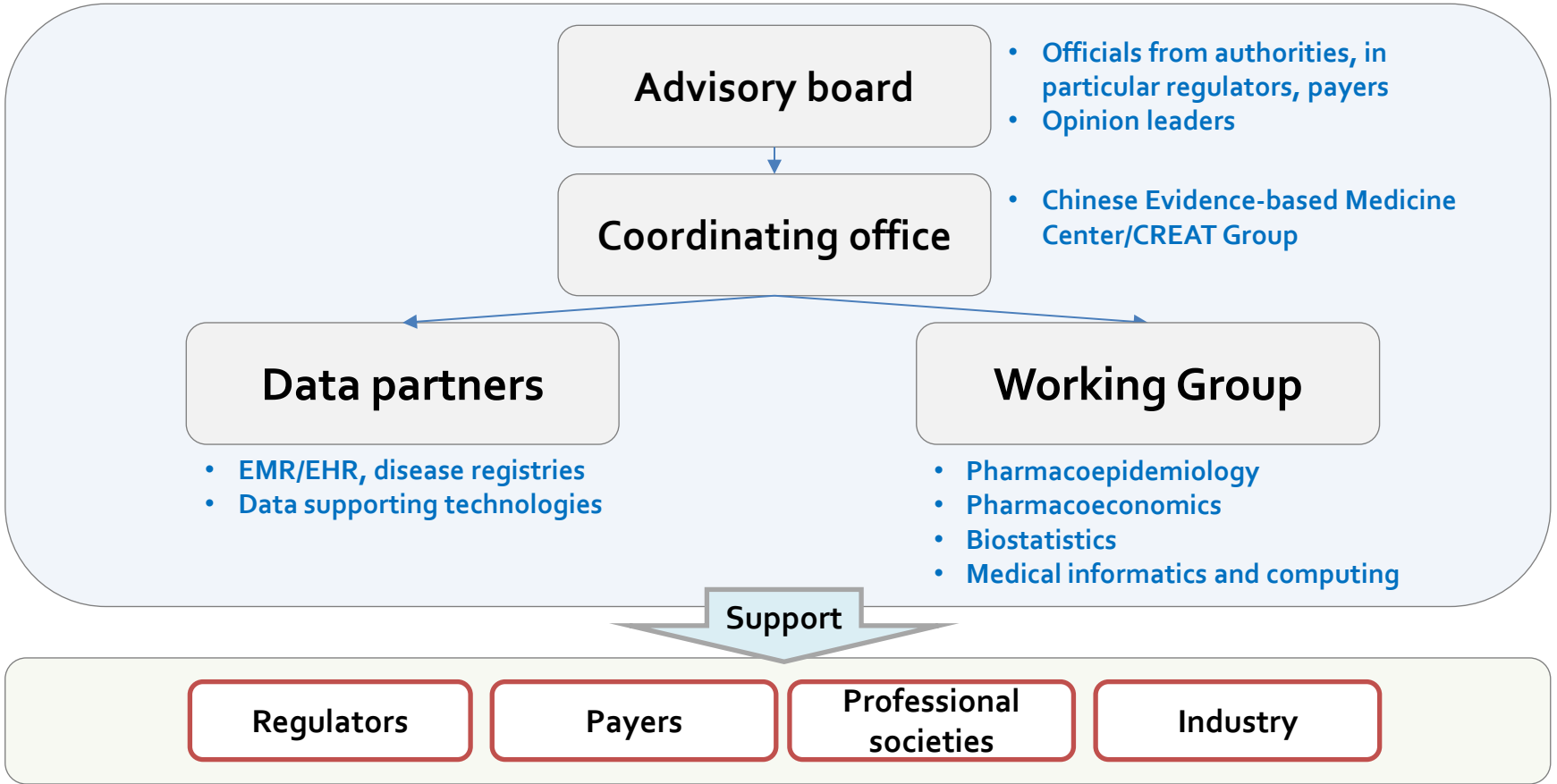
Organized by Chinese Evidence-based Medicine Center

中国循证医学中心
Chinese Evidence-based Medicine Center

ChinaREAL: a network of collaboration

Involve multiple stakeholders

- **Officials from authorities: NMPA, Healthcare Security Administration, 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**



Acknowledgements

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- ChinaREAL advisory and working group members

中国循证医学中心
Chinese Evidence-based Medicine Center

CREAT – research for better healthcare