

Current situation and challenge of registry in China

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AbstractIncreasing emphasis has been placed on registries for an organized system used in developing clinical research to improve health care. China has sufficient data that can be applied broadly, but the heterogeneity and irregularity of registries limit their applicability. This article aims to describe the status of registries in China and the related challenges. Patient registries for observational studies were retrieved from the International Clinical Trials Registry to quantitatively evaluate the number of comparatively high-quality registries in China. A literature search was also performed to provide support and updates. A total of 64 patient registries were retrieved from ClinicalTrials.gov using disease, product, and health service as criteria. The sample sizes ranged from 15 to 30 400, with only 12 registries marked as completed. This article describes and compares the detailed information in many aspects. The efficient use of registries has already made considerable progress in China; however, registries still require standardization, high-quality transition, and coordinated development.

KeywordsChinese; registry study; patient registries; observational study

Introduction

A randomized controlled trial (RCT) is the typical method for analyzing the effect of interventions; however, an increasing number of researchers have realized that observational studies, especially registry studies, may compensate for the inadequacy of RCTs, including their inability to quickly reflect the safety and effect of different intervention measures in the real world [1].

In 1974, a publication from the World Health Organization introduced and described registries in health information systems [2]. The first study based on a registry system, which utilized 56 000 obstetric records, was a collaborative study on cerebral palsy to analyze neuropsychological deficits in children of diabetic mothers [3]. In recent years, registry studies have attracted considerable attention. As the National Committee on Vital and Health Statistics delineated, registries are used for a broad range of purposes in public health and medicine as “an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the

occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects” [4]. At present, 875 patient registries from all over the world are enrolled in ClinicalTrials.gov; 87 of these registries are developed in China (64 in the mainland of China, 1 in Hong Kong, and 22 in Taiwan). Nevertheless, the number of registries in China still lags behind that in Europe and the United States [5].

According to *the Registries for Evaluating Patient Outcomes: A User's Guide*, most registries use three general categories with multiple subcategories and combinations to classify patients with exposure to a product or service, a particular disease or condition, or various combinations thereof [6]. In practice, these registry categories overlap, thereby complicating the classification process. For example, a registry may refer to the incidence of thrombosis after implantation of drug-eluting stents in patients with coronary artery disease [7]. An important objective of these health service registries is to generate an assessment with respect to outcomes [6]. The US Food and Drug Administration has introduced the pregnancy registry, which actively collects information on medical product exposure during pregnancy and the neonatal consequences [6].

Patient registries, which can provide a real-world view of clinical practices, patient outcomes, safety, and comparative effectiveness, have been widely utilized for scientific,

clinical, and health policy purposes [6]. Registries are frequently used to monitor product safety under real-world clinical practices; to assess effectiveness, especially of long-term treatments; to develop a post-marketing commitment to the government; to observe the natural history of diseases; to understand real-world treatment use and provide suggestions for clinical decision making; and to reduce the burden of rare conditions [1,8]. The present article aims to describe the status of registries in China and provide some suggestions on how to face the related challenges.

Current situation of registries in China

To assess the current situation of registries in China, we quantitatively evaluated the number of comparatively high-quality registries in China by retrieving “patient registries for observational studies” from www.clinicaltrials.gov [9]. A total of 64 patient registries (3 were repeated) from January 2009 to April 2014 were obtained. The sample sizes ranged from 15 to 30 400. Fig.1 shows the variation in the registries and clearly reflects the steady increase in the number of registries in China. Twenty-three registries should have been completed by the end of April 2014. However, only 12 registries have been completed thus far. Additional details are shown in Table 1.

Table 2 shows the general characteristics of the registries, including the scope of the studies and the sample sizes. Most registries in China, especially those with large sample sizes (some studies are calculated twice or thrice because of the combinations), are developed according to disease or condition.

Table 3 classifies the registries by diseases based on ICD-10. Endocrine, nutritional, and metabolic diseases have the highest percentage of relation to the registries, followed by diseases of the circulatory system and neoplasms. Drug and device registries are relatively scattered. These registries are always combined with specified diseases or conditions,

including drugs used for the following diseases: neoplasms (e.g., bevacizumab), diseases of the digestive system (e.g., pancreatic enzyme), diseases of the blood and blood-forming organs, diseases related to the immune mechanism hematological system (e.g., idarubicin), diseases of the circulatory system and cardiovascular diseases (e.g., clopidogrel), diseases of the nervous system (e.g., lurasidone), diseases of the skin and subcutaneous tissue dermatology (e.g., topical corticosteroids), traditional Chinese medicine injections (e.g., cinepazide maleate injection), biomarkers (lung cancer biomarker panel), and some devices related to medical operations (e.g., stenting and colonoscopy).

This study also compared the objectives and sponsors of the registries in China. The main purpose of the disease registries is to obtain epidemiological features, such as disease incidence [10]. Drug and device registries are developed for surveillance, such as for post-marketing safety. Combined registries serve multiple purposes, including for efficacy and safety evaluation and for social planning [11]. As sponsors, hospitals and universities are generally the main parties that develop registries; only a few registries are developed by the government and some professional associations in China.

A literature search was performed using PubMed to provide support and updates. We found that the National Cancer Registry is frequently used, with the focus mostly on the trend of mortality or prediction of breast cancer, oral cavity and pharyngeal cancer, esophageal cancer, and colorectal cancer [12–18]. Only one research was found to be related to a specific cancer, that is, the “Esophageal and gastric cardia cancers on 4238 Chinese patients residing in municipal and rural regions: a histopathological comparison during 24-year period” [19]. In addition, many publications are based on the China Quality Evaluation of Stroke Care and Treatment (QUEST) registry study [20,21], Chinese Transcatheter Interventional Therapy (TIT) of congenital heart disease registry study [22], China National Stroke Registry (CNSR) [23], Chinese Coronary Artery Bypass Grafting

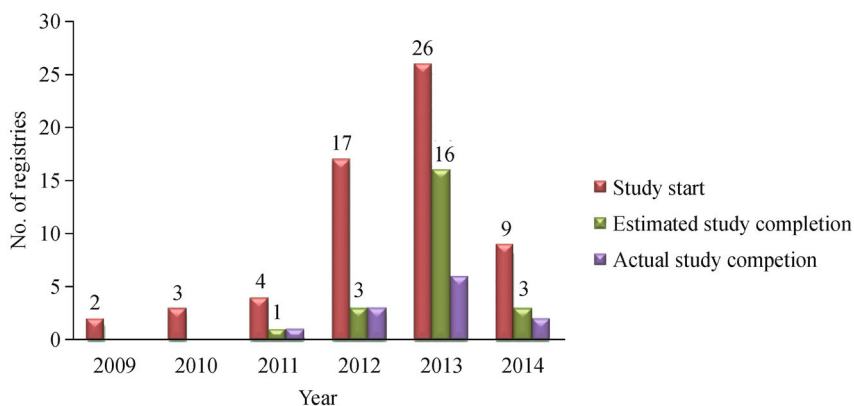


Fig.1 The variation in the number of registries in China from January 2009 to April 2014.

Table 1 Characteristics of the 12 completed registries in China

NCT number	Title	Study design	Estimated enrollment	Start date	Completion date	Population	Sponsor
NCT01779310	Clinical pathway for Alzheimer's disease in China	Case only	1024	Nov. 2012	Apr. 2013	Outpatients with clinically significant cognitive impairment per judgment of the participating physicians	Peking University
NCT02093156	A predictive score identifies patients with inadequate bowel preparation for colonoscopy	Prospective	605	Sep. 2013	Dec. 2013	Patients with digestive diseases from the Endoscopy Center	Fourth Military Medical University
NCT01939613	Colloid improves organs function in resuscitation of extensive burn patients	Case control	47	Jul. 2010	Jul. 2013	Extensive burn patients admitted within four hours after injury	Tang-Du Hospital
NCT02109120	MMP-9 monitoring particulate cerebral embolization	Cohort	48	Feb. 2012	Nov. 2013	Patients under CEA in the Peking Union Medical College Hospital (PUMCH)	PUMCH
NCT02105025	A novel clinically usable point score to prejudice the complexity of colonoscopy	Prospective	612	Oct. 2013	Jan. 2014	Patients with digestive diseases from the Endoscopy Center	Fourth Military Medical University
NCT01838629	The effect of universal salt iodization on thyroid diseases	Ecological or community	12 438	Jul. 2009	Jun. 2012	Patients with thyroid disease in Hangzhou	Weimin Xu
NCT01755351	Comparative study about the influence of diabetes distress and depression on treatment adherence in Chinese type 2 diabetes patients	Cohort	200	Dec. 2011	Dec. 2012	Patients with type 2 diabetes who visited two local hospitals between December 2011 and April 2012	Shandong Provincial Hospital
NCT01752452	Effect of ulnar styloid fracture on the outcome of distal radial fractures treated with external fixation	Case control	106	Jan. 2009	Oct. 2012	Unstable distal radial fracture patients: (1) the initial dorsal angulation > 20°, (2) with dorsal or volar comminution of the metaphysis, (3) shortening of radius > 5 mm, and (4) with an associated ulnar fracture	The Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School
NCT01867853	Volume responsiveness before spontaneous breath trial predicts the outcome of mechanical ventilation weaning in critically ill patients	Case only	82	Oct. 2012	Mar. 2013	Patients mechanically ventilated and ready to undergo spontaneous breathing trial with a T-piece	Southeast University, China
NCT01984970	Evaluation McGrath series 5 videolaryngoscope for double-lumen tube intubation	Prospective	43	Nov. 2013	Jan. 2014	Adult patients scheduled for thoracic surgery requiring double-lumen tube insertion for one-lung ventilation	Huazhong University of Science and Technology
NCT02011776	A randomized, parallel-group comparison study of topical corticosteroids in dry eye patients with Sjögren syndrome	Case control	35	Mar. 2013	Nov. 2013	People who suffered from dry eye disease caused by the Sjögren syndrome	Santen Pharmaceutical (China) Co., Ltd.
NCT02102581	Evaluation of short-term effects of tourniquet use in different ways during total knee arthroplasty (TKA)	Case control	60	Feb. 2011	Dec. 2011	Consecutive patients who underwent routine TKA	Peking Union Medical College Hospital

*This classification of study design is based on the registry applicants. Although NCT02011776 and NCT02102581 included RCT, they were also categorized as observational studies by www.clinicaltrials.gov. Moreover, we could not determine from the data whether these studies were RCTs or observational studies alone.

Table 2 Registries in China stratified by disease, drug, device, and cases

Scope	Registered cases (Total = 61)			
	10–200	201–1000	1001–5000	>5000
Disease or condition	12	12	4	6
Drug	9	2	5	3
Device	10	12	1	1

Table 3 Number of registries according to disease

Disease	No. (%)
Endocrine, nutritional, and metabolic diseases	10 (43)
Diseases of the circulatory system	10 (43)
Neoplasms	4 (17)
Diseases of the nervous system	3 (13)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	3 (13)
Diseases of the respiratory system	1 (4)
Diseases of the musculoskeletal system and connective tissue	1 (4)

(CABG) registry [24]. Sino-global registries, such as the China Non-ST Elevation Acute Coronary Syndromes registry and the Sino-Global Registry of Acute Coronary Events, were also found. Table 4 shows the characteristics of the four influential registries [25].

We also investigated some important registries that provide services or surveillance to the government without being published. These registries included reports about the registration of dialysis and transplantation in China, emergency center database, Chinese monitoring system for the rational use of drugs, Chinese birth defects registry, and infectious disease registry (e.g., tuberculosis).

The results showed that the use of patient registries varies based on priority condition, with cancer, stroke, and cardiovascular diseases having a relatively large number of registries and with rare diseases having very few registries [2]. Thus, the application of patient registries is continuously and aggressively increasing.

Given the conditions described previously, the transformation of the registry status in China still involves many issues that need to be solved [11].

Facing the challenges in the registry status of China

Enhancing the quality of registries

The quality of registries in China varies significantly. Some registries are inconclusive because of a small sample size, and only less than half of the registries in China were accomplished on time. Several quality issues emerged upon further examination of the study population preferred in China. The present study offers some suggestions based on similar rules and successful experiences abroad [1,2,6,11,26]. The first step in registry development should be to confirm the minimum sample size and to define the quality assurance requirements, including identifying the most likely errors and potential lapses in procedures [27]. Attention should be paid to the recruitment and supervision of providers and to the management of patients [6]. In fact, most data collectors in China have not been properly trained. Hence, researchers should consider how data elements are structured and defined, how personnel are trained, and how data problems are handled (e.g., missing, out of range, or logically inconsistent values) [6]. Collecting data in accordance with established procedures and guidelines recommended by experts can ensure that registries meet the requisite quality standards and consequently accomplish their purposes. Guaranteeing the criteria for each procedure, including collecting, cleaning, storing, monitoring, reviewing, and reporting registry data, is difficult but necessary [6]. Continuously evaluating registries is also important in preventing bias [9].

Developing multicenter registry and linking registry data

The fragmentation and heterogeneity of Chinese registries often limit their general applicability. The results discussed above highlight the apparent advantages and growing trend of multicenter registries, such as QUEST, CNSR, TIT, and CABG. The results also reveal the trend in the cooperative analysis of rare diseases with an adequate sample size. However, coordinating with every center, balancing financial and production benefits, and providing motivation to data providers are big challenges.

Registry data should be linked to other data sources, such as administrative and other registry data sources, to examine

Table 4 Characteristics of QUEST, CNSR, TIT, and CABG registries

Title	Study design	Enrollment	Time	Study sponsor	Publications on PubMed
QUEST	Prospective	6416 patients in 62 hospitals	Jul. 2007 to Nov. 2006	Multicenter	8
CNSR	Prospective	22 216 patients in 132 hospitals	Aug. 2007 to Jul. 2008	Hospital-based registry funded by the Chinese government	18
TIT	Retrospective	5720 patients in 23 medical centers	Jan. 2008 to Dec. 2010	Multicenter	1
CABG	Cohort	9248 patients in 35 centers	Jan. 2004 to Dec. 2005	Fuwai Hospital; multicenter	4

questions that cannot be addressed by using the registry data alone. However, the following should be considered: how to make the linkage feasible and legal, how to support the process technically, and how to solve the statistical problems (e.g., matching) in linking records. We should also focus on developing global patient registries [6].

Interfacing registries and electronic health records

Most of China's registry sponsors are hospitals. The number of hospital-based registries with electronic health records (EHRs) is increasing along with the increase in population and the standardization of EHRs. However, data exchange accuracy in software-as-a-service may be an obstacle [6]. Thus, ensuring the interoperability of syntactic and semantic communication and content is important [6]. Continuously developing, testing, and adopting open-standard building blocks toward incrementally advancing interoperability is difficult. Researchers should thus consider critical ethical practices and specify data ownership to ensure the attainability of data records in the beginning of the registry development process. Other important concerns include the transparency of activities and supervision.

Sharing and allocating benefits

One big challenge in the usage of Chinese registries is the allocation of benefits to stakeholders from multiple centers. This problem may be solved by considering an effective system design and establishing a set of benefits with incentive mechanisms.

Conclusions

The collection of real-world data and the development of observational studies, especially in patient registries, are important in evidence-based decision making [1,9,26,28,29]. Registries, along with RCTs, can promote the improvement of public health care in China, which is known for its huge population [28]. The focus of registries on actual use, such as describe natural history of disease, analyze short- and long-term safety and effectiveness, and determine meaningful health outcomes, dictate design decisions and the choice of analytic methods [6]. The status of registries in China has made considerable progress. However, the evaluation of the curative effect of registry use on policymaking is still lacking. Researchers should continue developing systematic methodologies, state-of-the-art technologies, and relevant laws and regulations [1,6,26–28]. More important, we must establish a uniform guideline through which researchers can expand the application of this study. In sum, the status of registries in China needs a standardized, high-quality transition with coordinated development [6].

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Compliance with ethic guidelines

Yang Zhang, Yuji Feng, Zhi Qu, Yali Qi, and Siyan Zhan declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval from relevant institutional review boards or ethics committees.

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