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The Clinical Innovation Network: a policy for promoting development of drugs and medical devices in Japan

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The continuous increase in the costs of developing new drugs and medical devices drives increases in medical expenses. Seventy to ninety percent of these costs are associated with clinical trials. Therefore, the development of cost-effective methods to perform clinical trials remains a challenge. One approach is to use patient registries, collections of data related to patients with a specific diagnosis, condition, or procedure. Patient registries are used in Denmark, Sweden, and the USA for the enrollment of patients into clinical trials, and to evaluate endpoints. In Japan, a national project for registry-oriented clinical research, termed the 'Clinical Innovation Network' (CIN), was initiated in 2016. Here, we provide an overview of the CIN and discuss its impact on drug and device development in Japan.

Introduction

The total costs of research and development (R&D) per approved new drug have steadily increased, and are now >US$1 billion [1,2]. The continuous increase in the costs of R&D has been a major barrier to the development of new drugs and medical devices, causing a delay in the provision of new pharmaceuticals and devices for patients. In addition, the increase in the costs of developing new drugs leads to an increase in the price of drugs, thus driving increases in national budgets for public healthcare. The drug development process can be divided into (i) preclinical research; and (ii) clinical trials in humans; most of the cost is associated with clinical trials and these costs increased tenfold between 1991 and 2003 [3]. Randomized, double-blind, placebo-controlled studies are the only reliable method to evaluate clinical outcome by controlling confounding factors in clinical trials. However, such trials are expensive and time-consuming, particularly with regard to recruiting participants, a lack of external validity, and excessive complexity [4]. As an alternative, registry-based observational studies have been performed. For example, in the International Cancer Benchmarking Partnership, observational studies using the large-scale cancer registries in six countries, including the UK, are underway [5]. Similarly, a coronary angiography and angioplasty registry is used for observational registry studies in Sweden [6]. Thus, registries are useful for identifying potential patients in a country, providing marketing information to pharmaceutical industries, and cost-effectively enrolling patients into clinical trials. A registry is also applicable as an historical control data set in a clinical trial [6,7]. Registry data can also facilitate the surveillance of real-world data and lower costs in the marketplace [3].

In Japan, the Government decided to promote registry-based clinical studies through the CIN in 2015. CIN is a network to advance clinical research and trials and to seek the consolidation of cases through collaboration among the National Centers for Advanced and Specialized Medicine (NC) and other medical institutions, with the goal of improving the environment for clinical trials (https://www.kantei.go.jp/jp/singi/kenkouiryou/en/pdf/2017_policy.pdf). Cooperation among industries, government agencies, and academia has promoted registry-based clinical trials since 2016. Here, we provide an outline of CIN and discuss the challenges to making breakthroughs in drug development in Japan.

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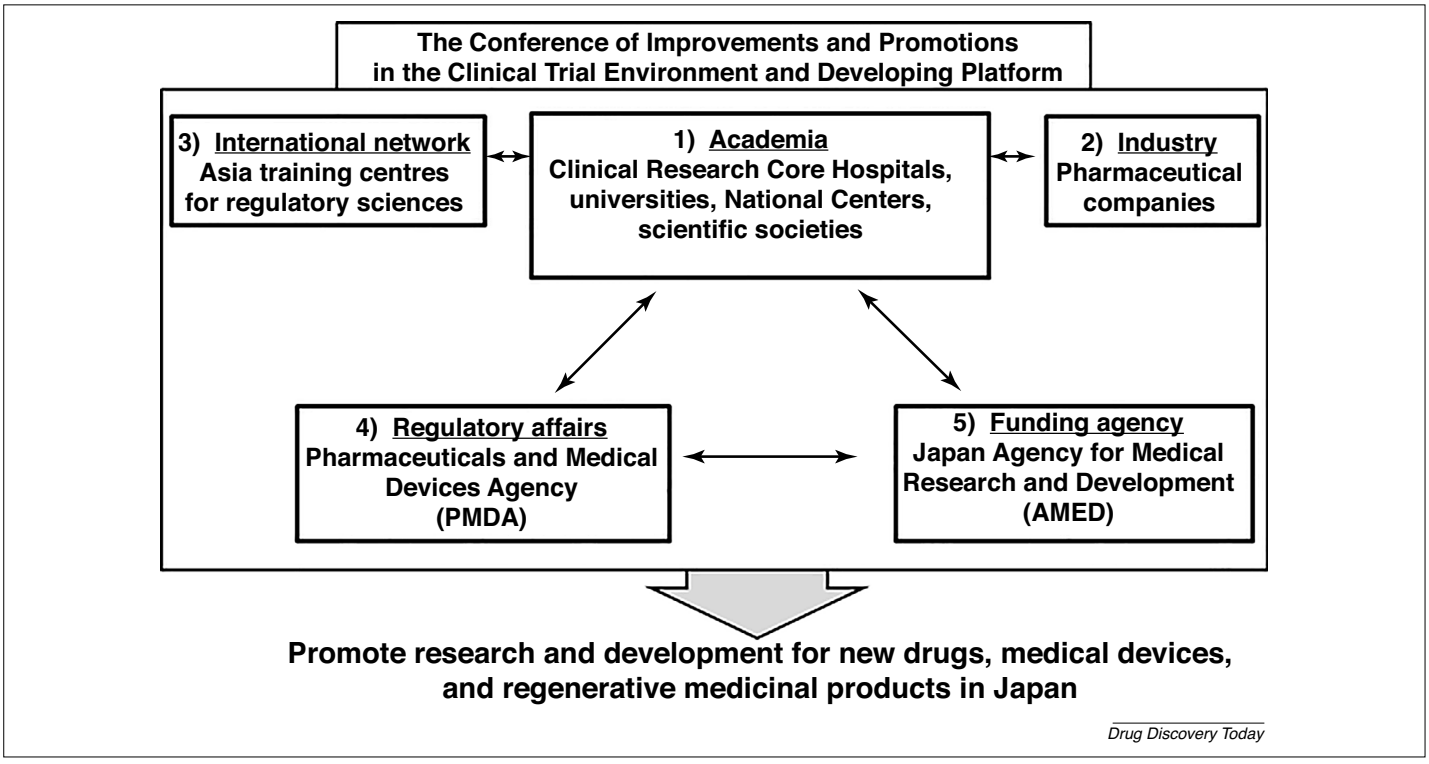

FIGURE 1

Schematic illustration of the Clinical Innovation Network (CIN). CIN is a network for the promotion of research and development for new drugs, medical devices, and regenerative medicinal products in Japan that comprises registry holders, hospitals, industries, a regulatory agency (PMDA), and a funding agency (AMED). The Conference of Improvements and Promotions in the Clinical Trial Environment and Developing Platform is the governing body of the CIN. This Conference comprises all CIN stakeholders and discusses current problems associated with the promotion of the CIN. Relationships between the stakeholders are follows: (1–2) Form a consortium for the exchange of information. (1–3) International clinical research. (1–4) Association and cooperation between academia and pharmaceutical affairs for effective and efficient promoting of the CIN. (1–5; 4–5) Support for research and development.

What is CIN?

In June 2015, the Liberal Democratic Party of Japan (LDP) elected 'the 2020 Japan Challenge' Project '10' as projects that aimed to achieve high economic growth and innovation in Japan, and to have a significant policy effect, by 2020 (http://jimin.ncss.nifty.com/pdf/news/policy/127993_01.pdf). One of the ten projects was the CIN. The CIN is a project to establish a registry-based infrastructure for the efficient clinical development of new drugs, medical devices, and regenerative medicinal products in Japan. The Government adopted the CIN as a national project in 2016 (https://www.kantei.go.jp/jp/singi/keizaisaisei/pdf/dai2_3en.pdf). The goals of the CIN are to prepare 15 registries, perform 20 registry-based clinical research and trials, and prepare five guidelines for registry-based regulation of clinical research and trials by the end of 2020 (http://jimin.ncss.nifty.com/pdf/news/policy/127993_01.pdf).

The CIN project began in 2016, and the Government budgeted ¥3.1 billion and ¥4.8 billion to promote the CIN in 2016 and 2017, respectively. The CIN stakeholders comprise medical institutes (including the Clinical Research Core Hospitals, academic societies, and NC), industry, the Pharmaceuticals and Medical Devices Agency (PMDA), and the Japan Agency for Medical Research and Development (AMED) (Fig. 1). The Conference of Improvements and Promotions in the Clinical Trial Environment and Developing Platform is the governing body for the CIN. This Conference comprises all stakeholders and enables discussion of problems associated with the promotion of the CIN (www.mhlw.go.jp/stf/shingi/other-isei.html?tid=291058). The medical institutes prepare registries, perform registry-based clinical trials, and function as an office for those trials. Industries participate in working groups in medical institutes for each disease registry, and the Conference is part of the CIN consortium. PMDA also participates in the working groups and the Conference and evaluates the use of the registries in clinical trials (www.pmda.go.jp/files/000215446.pdf). AMED provides funding for the preparation of the registries, registry-based clinical research, and regulatory science for registry-based clinical trials (www.amed.go.jp/en/program/).

TABLE 1

Clinical innovation network priorities from 2016 to 2020 in Japan

Year	Priority
2016	Networking among stakeholders
2017	Development of registries tightly associated with regulatory sciences
2018	Acceleration of registry-based clinical research
2019	Preparation of a consortium for drug development
2020	Publication of guidelines and guidance for registry-based drug development

The current CIN

The Conference for the CIN decides the goals for the CIN and sets yearly priority lists (Table 1). In 2016, CIN focused on the preparation of registries

TABLE 2

Examples of registries in Japan

Affiliation	Disease
National Center of Cancer	Lung and gastric cancers
National Cerebral and Cardiovascular Center	Stroke, congenital heart disease, fetal arrhythmia, heart failure
National Center of Neurology and Psychiatry	Muscular dystrophy, mental conditions
National Center for Global Health and Medicine	Diabetes, AIDS, hepatitis, infectious diseases
National Center for Child Health and Development	Rare childhood diseases
National Center for Geriatrics and Gerontology	Mild cognitive impairment
National Institutes for Biomedical Innovation, Health, and Nutrition	Rare diseases

for registry-based clinical trials through the collaboration of academia, PMDA, Ministry of Health, Labour and Welfare (MHLW), and industry. 6NCs and National Institutes for Biomedical Innovation, Health, and Nutrition have registries for lung and gastric cancers; congenital heart disease, stroke, heart failure, and fetal arrhythmia; mental conditions and muscular dystrophy; diabetes, AIDS, hepatitis, and infectious diseases; rare childhood diseases; mild cognitive impairment; and rare diseases (Table 2).

Some pilot studies of registry-based clinical trials have already started. For example, SCRUM-Japan is a nationwide cancer genome screening registry. Using registry data on cancer-related gene mutations, this registry aims to deliver appropriate therapeutic agents, including investigational new drugs, to suitable patients with lung and gastrointestinal tract cancers [8]. REMUDY is a registry for the enrollment of patients with muscular dystrophy into clinical trials; it contains epidemiological data and genetic information about dystrophy-related gene mutations [9]. A drug candidate for Duchenne muscular dystrophy was added to the SAKIGAKE list, which is a scheme for rapid authorization of unapproved drugs, accelerating the practical application of unapproved or off-label use of drugs for serious and life-threatening diseases (https://musculardystrophynews.com/2017/04/26/duchenne-potential-therapy-ds5141b-japan-sakigake-fast-track-designation/; www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html). Thus, REMUDY is useful for the enrollment of patients into clinical trials and the development of new drugs. J-MACS is a registry for the postapproval study of a highly pulsed, low shear-rate, continuous-flow, left ventricular assist device, EVAHEART [10]. Data on survival rates, adverse events, and quality-of-life were added to J-MACS, which contributed to the efficient and effective post approval of EVAHEART. These findings indicate that some current registries have been useful for researching market size, enrolling patients into clinical trials, and studying post-marketing approval (Fig. 2).

Pilot studies for registry-based clinical trials and post-marketing surveillance (PMS) also began recently. Single-arm clinical trials using registries as historical controls for pharmaceuticals for cancers and muscular dystrophy have been undertaken by the National Center for Cancer and the National Center of Neurology and Psychiatry, respectively. Registry-based PMS has also been initiated for amyotrophic lateral sclerosis at Nagoya University. Each project team meets to share up-to-date information about the registry with the stakeholders, and the PMDA, MHLW, and industry representatives meet to discuss any problems that arise with the registry-based drug development.

Several issues have been raised regarding the future clinical application of the registries: how is informed consent obtained from patients? What

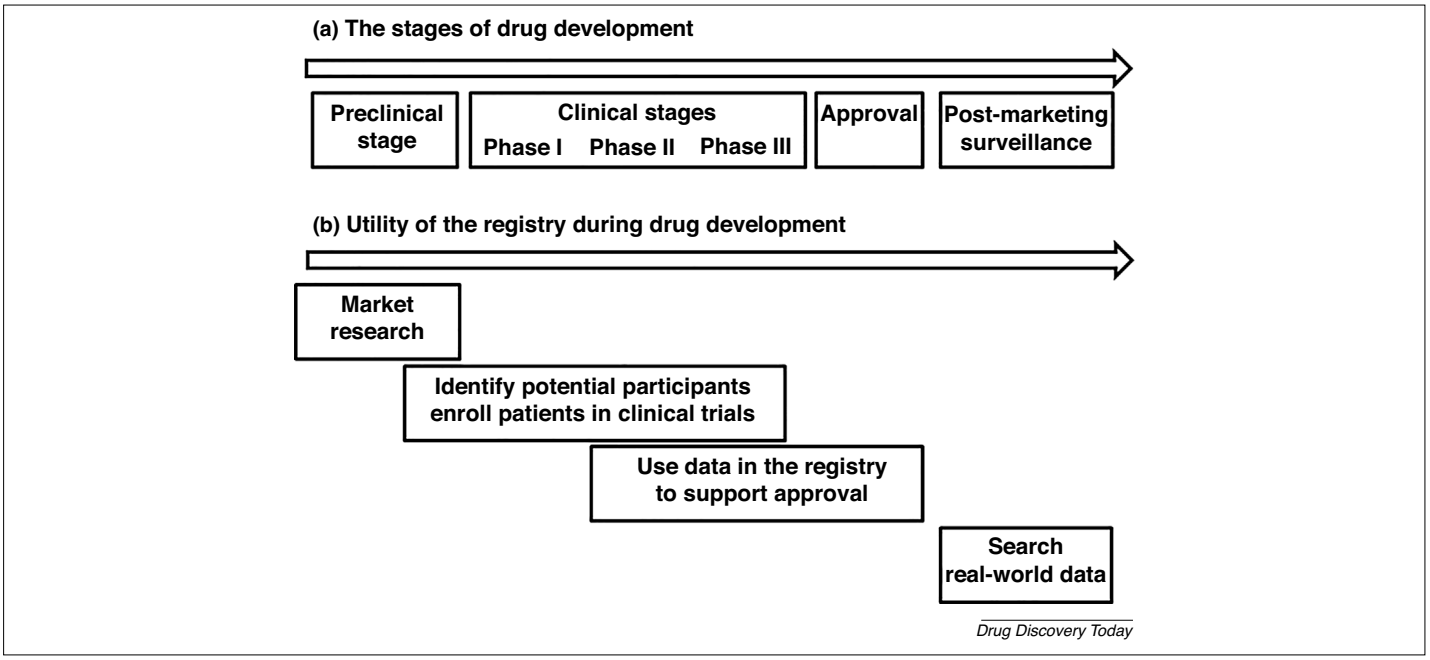

FIGURE 2

Utility of the registries in drug development. (a) Procedure for the development of drugs, medical devices, and regenerative medicinal products. The stages of drug and medical device development comprise preclinical, clinical, approval, and post-marketing surveillance stages. (b) Utility of the registry during drug and medical device development. Registries are useful to research market size, enroll patients into clinical trials, and study post-marketing approval.

TABLE 3

Individual projects to promote the CIN

Project	Purpose	Budget (million ¥) in 2017 (budget in 2016)
Preparation of registry	Registry for specified rare and intractable diseases Registry for medical devices Registry for historical control in approval Registry for postmarketing studies	2020 (740)
Registry-based clinical research	Registry-based clinical research for drugs Registry-based clinical research for medical devices	
User support program	Evaluation of registries in Japan, development of registry lists containing possible applications Provide one-stop service for users of registries	34 (0)
Regulatory sciences for registry-based drug development	Development of guidelines and guidance for approval of drugs in registry-based clinical trials	20 (20)
Preparation of infrastructure for clinical research	Cultivation of human resources for statistics and coordination of clinical research Development of hard and soft infrastructure in the Clinical Research Core Hospital Preparation of training centers for pharmaceuticals and medical devices regulatory affairs Networking clinical research worldwide	2760 (2300)

kind of contract should be in place between the registry holders (academia) and the registry users (industries and academia)? How will costs for the maintenance of the registries be met? How is patient information appropriately transferred from holders to users under the Act on the Protection of Personal Information? And, how do we validate data from registries for approval in the PMDA? To answer these questions, the AMED adopted two projects to develop solutions to these common clinical and regulatory problems (http://www.amed.go.jp/en/program/).

The future direction of the CIN

Although registries have been used to evaluate market size, patient enrollment, and post-approval study in Japan, full-scale utilization of these registries has not yet begun in Japan. Moreover, there is still no precise estimate of comparative efficacy between registry-based clinical trials and randomized, double-blind, placebo-controlled clinical trials [11]. In registry-based studies, endpoints are limited to the cases reported in the registries. Registry-based studies can examine multiple endpoints and use real-world data, including a variety of patient types and patients with comorbidity. If we can randomize data and select data sets for control groups from registries with external validity and without bias, the randomized registry-based trial would represent a breakthrough in clinical trials, transforming existing standards, procedures, and cost structures, represented by a move from randomized, double-blind, placebo-controlled studies to single-arm studies.

The key to applying a registry to a clinical trial in a single-arm experiment is whether regulatory affairs consider the data set extracted from the registry as data for approval. The PMDA established a working group with the MHLW and AMED to discuss the use of registries from the perspective of clinical medicine, statics, epidemiology, study design, reliability, and regulatory sciences to promote the CIN. The PMDA also participates in meetings on registry development projects and provides advice from the point of reviewing applications for marketing approval of pharmaceuticals and medical devices (Table 3).

Registries represent organized systems that use observational study methods to collect uniform data to evaluate specified outcomes for a population defined by a scientific, clinical or policy purpose [12]. If a registry is used for a retrospective study, in which the population is defined and the exposure and/or treatment of the data generated is determined before the initiation of the study, the variables and outcomes of interest must also be determined at the initiation of the study. How do we assure the validity of the data quality and quantity in a registry? How do we design protocols for registry-based randomized clinical trials? How do we ensure representativeness in a registry to avoid bias? These questions remain unanswered. Therefore, regulatory sciences need to be developed for clinical trials that use registries as a source of historical data.

Digital platforms provide us with real-world data from sources outside of traditional clinical trials. These sources can include large simple clinical trials, or pragmatic clinical trials, prospective observational or registry studies, retrospective database studies, case reports, administrative and healthcare claims, electronic health records, and data obtained as part of a device, procedural, or disease registry. These data are frequently derived from electric systems used in healthcare delivery to track patients' experiences during care (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM513027.pdf).

For now, registries are a tiny part of real-world data, and how to apply real-world data, particularly big data, into registry remains a challenge. Not only the amount, but also the quality of data is important for any registry. Using vast amounts of medical treatment and examination data in a safe and effective manner will contribute to the research and development of cutting-edge drugs, treatments, and medical devices.

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