Clinical Pediatric Endocrinology

Vol.29 / No.1
January 2020
pp 1–7

Review

Pediatric drug development in Japan: Current issues and perspectives

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Abstract. The number of clinical trials in Japan that aim to obtain regulatory approval for new drugs and devices has increased for adults, but not children. The following reasons have been proposed for this discrepancy: the wide range of ages from newborns to adolescents, requirements for many drug formulations, the difficulties associated with obtaining consent, and less profit for companies. The processes required to obtain regulatory approval for drugs and devices, particularly in the pediatric field, differ among Japan, Europe, and the United States (US). While clinical trials are not necessarily required for the development of new drugs or obtaining additional indications in Japan, laws in Europe and the US require clinical trials on children for newly developed drugs; however, pharmaceutical companies are entitled to a 6-mo extension for a patent when pediatric data are added to the attached documents for clinical trials. We herein discuss the current status of and issues associated with pediatric drug development, including clinical trials, in Japan as well as future perspectives.

Key words: drug development, investigator-initiated clinical trials, sponsor-initiated clinical trials, children, regulations

Introduction

Fewer advances in drug development have been achieved globally in the pediatric field than in the adult field due to rare and intractable diseases and lack of profit. Also in Japan, pediatric drug development is unsatisfactory. In the United States (US) and Europe, legislation is being introduced to promote pediatric drug development. In Japan, initiatives to promote clinical trials include giving companies incentives such as extending the re-examination period, the creation of a Working Group for selecting drugs that require development, and the establishment of a clinical trial system.

We herein discuss issues that are specific to children, the difficulties associated with pediatric drug development, the current status of pediatric drug development in Japan, and global initiatives. We also introduce some proposals to promote pediatric drug development in Japan.

Clinical Trials in Japan

The cause, prevention, diagnosis, and treatment of diseases as well as improvements in the outcomes and quality of life (QOL) of humans are the main aims of "clinical research". "Clinical trials" are performed to obtain regulatory approval for new drugs, medical devices, and regenerative medicine products. In Japan, these two types of research are conducted in different manners. Clinical research is regulated by the Ethical Guidelines for Medical and Health Research Involving Human Subjects and/or Clinical Trials Act (established in 2017, launched in 2018), whereas clinical trials are regulated by the Pharmaceutical Affairs Law and Good Clinical Practice (GCP) guidelines. With the revision of the Pharmaceutical Affairs Law in 2002, physicians and dentists are now permitted to conduct clinical trials as principal investigators, and these trials are referred to as investigator-initiated trials (IITs). While sponsor-initiated clinical trials (SITs) are conducted by companies, IITs are mainly performed when companies

Received: October 16, 2019 Accepted: November 25, 2019
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are not willing to sponsor trials for newly developed or additional indications for drugs or medical devices.

IITs differ from SITs in several aspects, with the largest difference being that IITs do not have sponsors. Thus, "physicians intending to conduct clinical trials by themselves" have to perform the majority of tasks related to clinical trials based on the Ordinance of the Ministry of Health, Labor and Welfare (MHLW) for conducting clinical trials on drugs (No. 28 of 1997) and medical devices (No. 36 of 2005). This is often referred to as GCP. The roles of IITs and SITs in conducting clinical trials are listed in **Table 1**.

Although there is a clear distinction between clinical research and clinical trials in Japan, they are often not divided in databases, leading to difficulties when searching for clinical trials. In Japan, databases of clinical research and trials include the University Hospital Medical Information Network (UMIN; https://www.umin.ac.jp/), Japan Pharmaceutical Information Center (JAPIC; https://www.japic.or.jp/), and Japan Medical Association Center for Clinical Trials (JMA-CCT; http://www.jmacct.med.or.jp/). Each database for clinical research has different features, as follows: UMIN is a database that largely deals with clinical research conducted within academia, such as in university hospitals. JAPIC is a database that is often used for the registration of clinical trials conducted by pharmaceutical companies. JMA-CCT is a database that is mainly used for the registration of IITs. The database of the National Institute of Public Health (https://www.niph.go.jp/information/) permits simultaneous searches for clinical trials registered within the three databases. Furthermore, a global database called Clinical Trials.gov. (https://clinicaltrials.gov/) allows investigators and companies worldwide to register their studies. There are differences in variables related to clinical research among the databases. Although there are clinical phase categories, including a range of ages, in these databases, they do not have a filter function to detect whether a registered study is a clinical trial or, more specifically, IIT or SIT. Therefore, difficulties are associated with selecting a clinical trial of interest within these databases.

Current Status of Clinical trials for Pediatric Drug Development in Japan

The pediatric clinical trial working group in PMDA has a website that lists pediatric clinical trials conducted in Japan. According to the online report for "the current status of pediatric clinical trials in Japan and efforts of PMDA" (https://www.pmda.go.jp/rs-std-jp/cross-sectional-project/0007.html), the number of new drug approvals in the pediatric field by the regulatory agency has remained unchanged at between 20 and 30 annually in recent years, except for public knowledge-based applications. Among new pediatric drugs being developed, the pediatric dosage and dose regimen are primarily among antibacterial and antiviral drugs (17%), respiratory system, allergy, and sensory organs (15%), and vaccines (12%). Notably, the "public knowledge-based application" is an application system that evaluates the medical need for medications requested by relevant academic societies among medicines that have already been approved in other countries with equivalent review processes for NDA to Japan and that provide medications under public health insurance without requiring extensive clinical trials.

To find clinical trials, authors performed a search using JMA-CCT, which is mainly used to register IITs. The term "clinical trial" is searched for in the free word text box with a filter for "ages between 0 and 17 yr".

As of August 09, 2019, 19 pediatric clinical trials were found. Among them, 17 trials were for drugs and the remainder for a medical device or regenerative medicine. All 19 trials were IITs. One trial started in 2006, one in 2007, two in 2008, two in 2014, one in 2015, three in 2016, two in 2017, five in 2018, and two in 2019. Eight trials were performed for refractory pediatric cancer, four for CNS diseases, two for otolaryngology, two for an influenza vaccine in healthy subjects, one for Kawasaki disease, and two for metabolic diseases. Although this search did not cover all clinical trials for children in Japan, these clinical trials were mainly for rare refractory diseases, such as pediatric cancer and cardiac and neurological diseases.

Although advances have been achieved in the development of investigational drugs in the pediatric field, further progress is needed. For example, pharmaceutical companies in Japan do not need to develop a drug formulation suitable for children of each age. Therefore, pediatricians generally prescribe tablets that are crushed to reduce doses for children in clinical practice settings (similar to other countries) because only a limited number of drugs with a formulation that is suitable for children have been approved. Furthermore, candidates for the examination of unapproved drugs at conferences of the Study Group on Unapproved and Off-label Drugs of High Medical Needs are required to be drugs that have been approved in the US, UK, France, Germany, Canada, or Australia, and new medicines under development at home and abroad are not discussed. There is currently no regulation in Japan that legally obligates pharmaceutical companies to develop pediatric drugs or suitable formulations for children. Although there is no enforcement by the Study Group to advance the development of drugs, if requested by the Study Group, industries mostly get the requested indication approved. Regarding other medicines, industries decide whether to develop the drug in Japan. Therefore, pediatricians have to use medicines with insufficient efficacy and safety data. According to an investigation by the MHLW, among drugs administered to patients younger than 18 years old, only 23% of package inserts included adequate descriptions on dosages and administration protocols for children, while the remaining 76% stated that safety had not been sufficiently established for children (1).

Table 1. Roles for investigator-initiated trials (IITs) and sponsor-initiated clinical trials (SITs) in conducting clinical trials

Tasks	IITs	SITs
Responsible person	Physicians intending to conduct clinical trials themselves	Pharmaceutical companies
Before clinical trials		
Investigator's brochure, protocol, standard operational procedure	Physicians intending to conduct clinical trials themselves	Pharmaceutical companies
Manufacture or import of investigational products	Investigational product provider (pharmaceutical companies)	Pharmaceutical companies
Sites	Medical institutions	Medical institutions
During clinical trials		
Response to the regulatory body during and after trials (submission of clinical trial notification, safety reporting)	Physicians intending to conduct clinical trials themselves	Pharmaceutical companies
Monitoring / audit	Physicians intending to conduct clinical trials themselves (or the person that is assigned by them)	Pharmaceutical companies
Documentations (data management, statistical analysis, clinical study report)	Physicians intending to conduct clinical trials themselves	Pharmaceutical companies
New drug application	Pharmaceutical companies	Pharmaceutical companies

Although an infrastructure to support clinical trials exists through the Academic Research Organization (ARO) and Contract Research Organization (CRO), which include clinical research coordinators (CRC), data centers, monitoring, and biostatisticians, there have been few opportunities for pediatricians to use these services. The main reason why sufficient advances have not been achieved in clinical trials for pediatric drug development from the point of view of pediatricians is inadequate human resources and experience. Based on reports by the MHLW, working hours for pediatricians who work at university hospitals or hospitals with a Pediatrics department are longer than those regulated by the law because they often need to work nights and provide weekend medical services, particularly for emergency patients. Therefore, pediatricians do not have as many opportunities or time to devote to clinical trials in the pediatric field (2). Furthermore, the majority of pediatricians do not have sufficient experience of conducting clinical trials, which slows the progression of trials. In addition, there are issues that are unique to the pediatric field, such as pediatricians needing to obtain assent from participants and informed consent from parents as well as limited incentives for children to join trials because of a well-developed national medical insurance system in Japan and the existence of alternative treatments. Even though pediatricians successfully enroll patients in clinical trials, children assigned to the placebo group may occasionally refuse to continue because of the lack of merit of future outcomes.

To overcome these issues, we recently proposed protocols with the option to receive a treatment regimen after completion of the follow-up period when children are assigned to a placebo group. Regarding funding to conduct IITs, pediatricians need to obtain public grants provided by the MHLW, the Japan Agency for Medical Research and Development (AMED), and other sources. It is very challenging to receive private grants from pharmaceutical companies because pediatric diseases, particularly rare diseases, are considered to be a small market. One of the reasons why clinical trials for children are not considered to be worthwhile for pharmaceutical companies may be the smaller market than the adult market. Moreover, smaller doses of drugs are prescribed due to the smaller body weight and surface of children. The combination of these factors with low cost-effectiveness results in pharmaceutical companies hesitating to develop new drugs in the pediatric field. Pediatrics covers from infancy to adolescence. According to the ICH E11 guidelines for the Clinical Investigation of Medical Products in the Pediatric Population, the immature functions of renal and liver clearance and transferability to the central nervous system need to be considered in children born prematurely, newborns, and infants. Furthermore, the influence of sex hormones, growth, sexual activity, and usage of contraceptives are important factors in adolescence (3). Despite compliance for tablets and injections generally being high in adults, powders, syrups, and suppositories may be needed in the pediatric field. The flavor of drugs is another issue that needs to be considered. Regarding neonates, international efforts are currently being made to develop

doi: 10.1297/cpe.29.1

master protocol and standardize definitions, and lab data to facilitate drug and device development, and several Japanese neonatologists are involved.

Efforts to Promote Clinical Trials in Japan

In order to advance drug development in the pediatric field, the Japanese government has attempted to enact several policies (4):

(1) Extension of the re-examination period

In the case of original drugs, the re-examination period is set for 6 yr in principle (up to 10 yr) after approval for manufacturing and sales. During this period, even if the patent expires, no other pharmaceutical companies may sell the drug. Regarding drugs expected to be used for children, the extension of the re-examination period is extended up to 10 yr if clinical trials for children with the aim of identifying appropriate doses are planned.

(2) The Project to Collect Data on Pediatric Pharmacotherapy (2005–2009)

A study group was established with a focus on off-label use for children in Japan and the collection of information on drugs approved in four countries: the US, UK, Germany, and France. Sufficient evidence for indications and appropriate dosages results in drugs being approved by the MHLW for clinical use. Six drugs have been approved through this project. This project was followed by the Study Group on Unapproved and Off-label Drugs of High Medical Needs.

(3) The Study Group on Unapproved and Off-label Drugs of High Medical Needs (2009~)

This study group was launched in 2009 to address the issue of unapproved drugs or off-label uses for drugs that are approved in four countries (the US, UK, Germany, and France), but not in Japan. This group evaluates whether a proposed drug or treatment meets high medical needs by reviewing formal petitions submitted by patient advocacy groups, academic societies, and pharmaceutical companies. Based on a review by the group, the MHLW selects the mode of the regulatory authorization process. In the case of the unapproved use of an approved drug, the MHLW decides whether the use meets the criteria for "abbreviated application of publicly known but unapproved indication (5).

(4) New Five-year Clinical Trial Promotion Plan 2012 (2012–2016)

As part of the New Five-year Clinical Trial Promotion Plan 2012, initiatives were strengthened to promote drug development for pediatric, rare, and intractable diseases for which new drugs cannot be easily developed. For example, incentives (subsidies for researchers and support for IITs) and provision of information on the clinical trials of rare and intractable diseases were introduced, creating a new framework for pediatric drug development.

(5) "Project for Drug Selection to Promote New Drug Development in Pediatrics" supported by AMED (2017~)

In this project (6), the Japan Pediatric Society plays a central role in organizing working groups in collaboration with academia, such as subcommittees and related academic societies, and pharmaceutical companies to create a list of drugs that need to be preferentially developed in Japan. The society develops an infrastructure system for conducting clinical trials for which development requests have been received from companies.

Global Efforts to Advance Pediatric Drug Development

Since the revised Pharmaceutical law of Japan was enacted in 2002, an infrastructure to support IITs has been established. As a result, the number of IITs has increased in the adult field, but not yet in the pediatric field. In order to resolve this issue, we recommend a pharmaceutical law that requires clinical trials for drugs and medical devices to obtain approval for children when these products will be used as indications for children. Additionally, we may also need to train and educate physicians who are in charge of performing and supporting clinical trials in the pediatric field.

In the US, the Food and Drugs Administration modernization act and BPCA (Best Pharmaceuticals for Children Act) (7) were established in 1997 and 2002, respectively. These laws allowed pharmaceutical companies to have exclusive rights to the drug developed for an additional 6 months in order to accelerate and heighten the motivation for research and development of new drugs. Since the PREA (Pediatric Research Equity Act) (8) was established in 2003, companies have been mandatorily required to submit pediatric data on new drug applications (NDA). Although the law was temporary legislation at that time, it became permanent in 2012 in the FDA Safety & Innovation Act (FDASIA) (9).

In Europe, similar to the US, pediatric in addition to adult data are required for NDA based on the Pediatric Regulation (10, 11), which was established in 2007. The Paediatric Committee (PDCO) (12) plays an important role in research on and the development of new drugs and devices for the pediatric field in Europe. The PDCO is responsible for the development and assessment of research, supporting clinical research and development, and updating the list of drug that physicians should use in clinical practice. The Paediatric Investigation Plan generally needs to be submitted by the end of Phase I trials on adults. In the US and Europe, all or some pediatric trials may be postponed if pediatric drug development is considered to be unnecessary or inappropriate. With respect (4) to newly approved drugs or additional indications of drugs, pharmaceutical companies may obtain a further 6-mo extension for the patent if pediatric data obtained from clinical trials are added to the attached documents. Although development is not compulsory for off-patent approved drugs, pharmaceutical companies may maintain protection for 8 yr and exclusive sales rights for 10 yr when they

doi: 10.1297/cpe.29.1

Table 2. Regulations related to pediatric drug development in the United States (US) and Europe

	US	Europe
Regulations	BPCA (2002): Best Pharmaceuticals for Children Act PREA (2003): Pediatric Research Equity Act Pediatric Priority FDASIA (2012): FDA Safety and Innovation Act	Paediatric Regulation (2007) Regulation (EC) (1901/2006)
Obligations	1. Pediatric Study Plan (PSP) must be submitted by the end of a Phase II study for adults (PREA)	Paediatric Investigation by the end of a Phase I study in adults
	2. Written Request (WR) by the FDA conducting a clinical trial for drug development (optional) (BPCA)	Plan (PIP) must be submitted.
Incentives	6 mo sales exclusivity (BPCA)	1. New drugs / patents: 6-mo patent supplement certificate Period extension 2. Orphan-designated medicines: 2 yr of market exclusivity added 3. Out-patent approved drug: 8 yr of childhood opening by Paediatric-Use Marketing Authorizations Data origin protection and 10-yr sales exclusivity

successfully obtain pharmaceutical approval from the Paediatric Use Marketing Authorization (PUMA) (13). In Europe, drug development is required for each generation. The Formulation Working Group in the PDCO cross-sectionally reviews application forms. Regulations related to pediatric drug development in the US and Europe are summarized in **Table 2**. The infrastructure for conducting IITs in the adult field has gradually increased in Japan, which will facilitate further IITs being performed in the pediatric field. Similar to European countries and the US, pharmaceutical companies in Japan need to conduct clinical trials in the pediatric field and receive approval for new drugs and devices as well as additional indications in the pediatric field. However, to reduce the responsibility on companies, further infrastructure for conducting IITs is urgently needed in order to incentivize physicians to perform clinical trials in the pediatric field.

Perspectives

To accelerate research and drug development in the pediatric field, the followings need to be considered.

(1) Efforts to secure participants

In pediatric drug development, particularly when implementing clinical trials, pediatricians occasionally cannot enroll subjects because some pediatric diseases are rare. To overcome this limitation, a network for pediatric drug development was launched in 2010 and supported by AMED as a project for clinical research and clinical trial promotion (14). To date, 45 institutions participate. In this network, there are 17 Japanese societies related to pediatric diseases for drug development. They collect and share information on new drugs being developed, examine the importance of drug development, and contribute to the preparation of clinical trials. These efforts may facilitate the performance of clinical trials. They also support global clinical trials. Although Japan conducted only 10% of international clinical trials for Investigational New Drug (IND) in 2007, this increased to 40% in 2016 (15). An international clinical trial conducted simultaneously with a solo protocol may increase efficiency by avoiding the repeated implementation of similar trials in each country, thereby reducing the total number of participants through the drug development package and resolving the drug lag issue between Japan and other countries. Efforts to collaborate with not only the European Innovative Medicines Initiative, Institute for Advanced Clinical Trials for Children and International Neonatal Consortium, but also patient associations may contribute to improving the efficiency of developing protocols and reducing efforts to find participating hospitals.

(2) Considerations for protocol development

In 2012, the Japan Pharmaceutical Manufacturers Association issued the concept of drug efficacy assessments as small clinical trials, which are defined as trials that aim to obtain results against a hypothesis under conditions in which difficulties are associated with enrolling subjects for clinical trials (16). Some ideas need to be considered in order to overcome these issues: the use of a validated surrogate endpoint, instead of a true endpoint and the incorporation of a historical control. The latter may allow trials with a single arm design to be implemented, thereby facilitating the completion of clinical trials because a smaller sample size is needed than the 2 or more arms design. The collection of more data from each participant registered in a trial has also been suggested. These efforts may contribute to more robust data being obtained with reliability in relation to the cause-effect relationship between targeting drugs

doi: 10.1297/cpe.29.1

and outcomes. The data obtained through the protocol revision may be sufficient to obtain regulatory approval even if they were collected from a small sample size.

A Biomarker Qualification Program has been developed in the US (17). When biomarkers are appropriately evaluated for reliability from a clinical aspect, these parameters are then disclosed for clinical trial usage, which may be helpful for accelerating clinical trials. More recently, real world and registry data became available for obtaining regulatory approval. While this may reduce the cost and effort associated with obtaining regulatory approval for clinical use, there may be bias in these data because of differences in patient backgrounds, clinical stages, and treatments including concomitant drugs and dosages. Therefore, we need to interpret results derived from these data with caution.

(3) Utilization of adult data

According to the ICH E11 (R1) 5.1.1 (18), the efficacy and safety of a drug can be supported for use in pediatric populations if the course of the disease and the expected response to the drug are sufficiently similar between pediatric and reference (adult or other pediatric) populations (19). Considering the special measures required for protecting the rights of pediatric subjects and preventing undue risks (ICH E11 2.6), adult data may be utilized as appropriate. Guidelines for extrapolation are already available in Europe (https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf) and the US (https://www.fda.gov/media/90358/download).

Conclusions

Greater difficulties are still associated with drug development in the pediatric field than in the adult field. However, efforts to develop a priority review system for children, particularly in the rare disease field, and construct an infrastructure for implementing clinical trials have promoted international clinical trials. An international joint clinical trial may obtain the sample sizes that cannot be easily collected only in Japan and solve problems, including drug lag, thereby addressing issues, such as off-label drug use in the pediatric field. The importance of pediatric drug development is widely recognized and expected to be accelerated by further incentives, such as amendments.

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doi: 10.1297/cpe.29.1