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< Review >

**Research and development on intractable & rare diseases in Japan:  
Contribution of the National Institute of Public Health to research  
program management**

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**Abstract**

This paper outlines the history of research and development (R&D) for intractable & rare diseases in Japan, and describes how the National Institute of Public Health (NIPH) has been involved in and contributed to R&D and how the NIPH will address it.

Since 1972, R&D for intractable & rare diseases had been implemented in accordance with the “Outline of Intractable Disease Measures”, which was a policy guideline for implementing national measures for addressing intractable & rare diseases. Because the outline listed “promotion of survey/research” as high priority measure, a wide range of research, including basic, clinical, and epidemiological research, was promoted for years. However, the goal of the research was not so clear, and on the other hand, it was not focused on development of orphan drugs, unlike in other countries. The R&D projects on intractable diseases were mainly implemented in the Research Program for Overcoming Intractable Diseases, funded by the Ministry of Health, Labour and Welfare. After the budget for the program was increased substantially, to 10 billion yen in 2009, the R&D was divided in two directions: “Expansion of target diseases for survey/research”, and “Development and clinical application of innovative medical technology such as pharmaceuticals”. Then, the NIPH became the Funding Agency for the program in 2010, and addressed clarification of the goal of research projects and development of the management system of the research program. As a result, disease concepts and diagnostic criteria were established for many diseases for which surveys and research had scarcely been conducted. Moreover, clinical trials and regulatory approvals were completed for several drugs and medical devices.

Since the enactment of the Act on Medical Care and Social Supports for Patients with Intractable/Rare Diseases in 2014, and the foundation of the Japan Agency for Medical Research and Development in 2015, the framework of R&D for intractable & rare diseases has changed significantly. Research programs had been divided into two programs: the Research Program on Policy of Measures for Intractable/Rare Diseases, and the Research Program on Practical Application of Measures for Intractable/Rare Diseases. The NIPH had the role of the funding agency for the former research program, and had the responsibility for providing a scientific basis for supporting the medical cost subsidy system and the medical services delivery system under the act, which meant establishing diagnostic criteria, disease severity classifications, and clinical practice guidelines.

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Since 2014, the NIPH has established a new research program management system as follows: (a) The goal of the research program was set as maximizing the number of diseases for which diagnostic criteria, disease severity classifications, and clinical practice guidelines were developed or revised by the research projects, and were approved by the relevant academic societies; (b) It was required for each research project to set the goals for each disease to be studied, such as development of diagnostic criteria and disease severity classifications, revision of clinical practice guidelines, approval for the clinical practice guidelines by academic societies, etc.; (c) Annual submission of the research outcome report was made mandatory for each project in order to implement progress management and evaluate the research outcome. As a result, diagnostic criteria and disease severity classifications were developed or revised for many intractable & rare diseases at the end of 2017 (85% and 78% of 582 target diseases, respectively). On the other hand, the number of cases of development or revision of clinical practice guidelines remained at one half, and therefore, it is necessary to have projects set an appropriate goal in accordance with the program policy.

In the future, the NIPH is willing to continue to proactively conduct the management of the Research Program on Policy of Measures for Intractable/Rare Diseases in order to achieve many research outcomes that contribute to intractable & rare disease policy.

**keywords:** intractable & rare diseases, research and development (R&D), program management, project management, research management

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## I. Introduction

In Japan, the national program for addressing intractable & rare diseases was implemented in accordance with the “Outline of Intractable Disease Measures[1]” compiled in 1972[2]. It was one of the oldest programs on disease control. However, the outline was not an act but a guideline; therefore, the measures were implemented based on an annual budget request. The Act on Medical Care and Social Supports for Patients with Intractable/Rare Diseases[3] (hereinafter called the Intractable/Rare Diseases Act) was then enacted in 2014, and the legal grounds for the measures were established for the first time in more than 40 years.

From 1972, a wide range of research on intractable & rare diseases, which included basic research, clinical research, development research, public health research, and so on, were promoted for the purpose of overcoming them. However, the goal of each research project was not clear because a research management system did not exist. In 2010, the National Institute of Public Health (NIPH) had the role as the Funding Agency (FA) for the national research program on intractable & rare diseases, and the clarification of the goal of research projects, development of the management system of the research program, and efficiency of the research fund were addressed. Moreover, the restructuring of the research and development (R&D) management system and the establishment of new goals for R&D have been progressing since the enactment of Intractable/Rare Diseases Act in 2014 and establishment of the Japan Agency for Medical Research and Development (AMED) in

2015.

This paper outlines the history of R&D for intractable & rare diseases in Japan, and describes how the NIPH was involved in and contributed to the R&D and how the NIPH will address it.

## II. History of Intractable & Rare Disease Measures in Japan

Intractable & rare diseases are called *nambyo* in Japanese. However, as the Japanese characters do not themselves contain the meaning “rare,” the meaning is limited to “intractable disease.” This characterized Japan’s R&D with respect to intractable & rare diseases, which took a pathway that differed from that of other countries.

### 1. Initial Intractable Disease Measures

It was the occurrence of subacute myelo-optic neuropathy (SMON) during the 1960s that triggered efforts to address intractable diseases. In response to SMON, for which the cause was unknown, in 1969 a large-scale study group was formed in collaboration with the then Ministry of Health and Welfare and the then Science and Technology Agency, which conducted a multidirectional and intensive survey and research, including nationwide epidemiological studies. As a result, Kinoholm (Clioquinol, Chinoform, or Quinoform), an antidiarrheal drug, was revealed to be the cause of SMON in 1972, which was only three years later[4,5]. The ministry then banned the sales of the drug, and the incidence of SMON decreased drastically. A lesson learned from this experience was that even in cases involv-

ing an intractable disease with unknown cause, it is possible to reduce the occurrence of diseases by promoting a survey and research. Therefore, “promotion of survey/research” became the first measure listed in the Outline of Intractable Disease Measures that was established in 1972. (Table 1) There is no policy for diseases that R&D is given priority over elsewhere (e.g., “promotion of research & development” is specified under Article 19 of the Cancer Control Act[6]).

Another characteristic of the Outline of Intractable Disease Measures is that the definition of intractable disease does not include “rarity”. In other countries, survey and research is being conducted with the concept of a rare disease, with the central aim of the development and dissemination of orphan drugs (i.e., drugs that would not be developed by sponsors under the usual market mechanism due to the small number of patients). For example, in the United States, the Rare Diseases Act[7] was enacted in 2002, following the enactment of the Orphan Drug Act[8] in 1983, indicating that drug development has priority. In contrast, in Japan, the survey and research specified in the Outline of Intractable Disease Measures was widely conducted to obtain an understanding of patient status such as in an epidemiological study, basic research such as an elucidation of pathogenesis and pathophysiology, and clinical research such as an evaluation of treatment method, but was not necessarily focused on development research for drugs and medical devices.

## **2. Progress of Intractable Disease Measures and the Involvement of the NIPH**

The major national measures that have been undertaken for the survey/research of intractable diseases were the Research Program for Overcoming Intractable Diseases and the Research Project on Treatment for Specified Diseases. The former is one of the research programs operated by Health, Labour and Welfare Sciences Research Grants, a competitive research fund provided by the Ministry of Health, Labour and Welfare (MHLW), aiming for the promotion of the survey/research specified in the Outline of Intractable Disease Measures. On the other hand, regarding the latter, although it was named a research project, its main objective was medical cost subsidy for patients (i.e., the reduction of copayment of medical fees). At the same time, many epidemiological studies have been conducted utilizing patient data from medical expense subsidy applications[9].

The number of target diseases has increased yearly, and in 2009 the number of target diseases for the Research Program for Overcoming Intractable Diseases reached 130, while that for the Research Project on Treatment for Specified Diseases reached 56. In addition, the budget for the

Research Program for Overcoming Intractable Diseases, which had been kept at around 2 billion yen since 1998, was increased substantially to 10 billion yen in 2009, in accordance with the intention of the then Minister of Health, Labour and Welfare. In response, the survey/research was extended and promoted in two directions: “Expansion of target diseases for survey/research” and “Development and clinical application of innovative medical technology such as pharmaceuticals.” In addition, in order to efficiently manage the research program in accordance with these directions, the NIPH became the FA for the Research Program for Overcoming Intractable Diseases, replacing the MHLW in 2010.

With regard to “Expansion of target diseases for survey/research,” “Encouraged Research Projects” were newly launched in order to establish disease concepts, elucidate pathogenesis and pathophysiology, and develop diagnostic criteria for rare diseases, for which survey and research had scarcely been conducted, excluding the 130 diseases covered in the Research Program for Overcoming Intractable Diseases. By 2012, a total of 234 diseases were studied, and disease concepts and diagnostic criteria had become established for them.

With regard to “Development and clinical application of innovative medical technology such as pharmaceuticals,” although research projects had been conducted focusing on innovative diagnostic and treatment methods since 1996, from 2012 onward research projects were conducted with regulatory approval as the eventual goal of them. Specifically, “Step 1” research projects, in which good laboratory practice (GLP) studies preparing for clinical trial and protocol development for clinical trial were performed to shift to investigator-initiated clinical trials, as well as “Step 2” research projects, in which investigator-initiated clinical trials were performed, including the submission of investigational new drug (IND), Phase I, Phase II, and obtaining proof of concept (POC), were conducted. In this research area, the completion of clinical trials and regulatory approvals were achieved for some drugs and medical devices, by clearly indicating the expected outcome (such as the report of GLP studies, reports of clinical trials, and an Investigator’s Brochure) under funding opportunity announcements of research projects and strictly conducting the progress management of each research project (such as hearings with principal investigators and site visits to research institutes) [10,11].

Meanwhile, regarding medical cost subsidy, not only the number of target diseases but also the number of target patients has increased, reaching 780,000 by the end of fiscal year 2011. Subsequently, the annual budget for the Research Project on Treatment for Specified Diseases reached

more than 40 billion yen, which made the project difficult to manage smoothly. In addition, for medical cost subsidy, due to an increasing number of opinions requesting the expansion and revision of target diseases, it was becoming necessary to reexamine the methodologies for selecting target diseases and recognizing target patients.

**3. Enactment of Intractable/Rare Diseases Act and the Subsequent Promotion of Intractable & Rare Disease Measures**

Discussions on what measures for intractable & rare diseases should be taken began around 2011 at the Committee on Disease Control of the Health Science Council of MHLW, and a few reports were presented. In addition, it was stipulated in the “Outline of the Comprehensive Reform of the Social Security and Tax Systems[12]” in 2012 that a fairer and more stable support system was to be established for subsidizing the medical expenses of patients with intractable & rare diseases, including legislation and expansion of the range of eligible intractable & rare diseases.

Then, the Act on Medical Care and Social Supports for Patients with Intractable/Rare Diseases[3] was enacted on May 23, 2014, and came into effect on January 1, 2015.

The purposes of this act were: (1) to establish a fairer and more stable system by enabling the allocation of consumption tax revenues to the subsidy of medical cost expenses for patients with intractable/rare diseases, as a measure based on the law related to promoting the reform in order to establish a sustainable social security system; and, (2) to take measures such as the development of basic policy, promotion of research on medical care for intractable/rare diseases, and the implementation of community-based health/medical care and welfare services. In this manner, a stable medical cost subsidy system was established for even more patients with intractable/rare diseases than so far.

The definition of intractable/rare diseases and the measures for intractable/rare diseases stipulated in the Intractable/Rare Diseases Act are shown in Table 1. While intractable/rare diseases are clearly defined by four requirements, “Designated Intractable/Rare Diseases” are defined as those that also meet the following two additional requirements: (5) the number of patients in Japan is less than a specified level (approximately 0.1% of the population); and, (6) objective diagnostic criteria (or the equivalent) have been established, and they have become a target disease for medical cost subsidy. The accreditation criteria for medical

**Table 1 Comparison between Outline of Intractable Disease Measures and the Intractable/Rare Diseases Act**

	Outline of Intractable Disease Measures[1]	Act on Medical Care and Social Supports for Patients with Intractable/Rare Diseases[3]
Year of the establishment	1972	2014
Definitions of diseases addressed	<p>(1) A disease which cause has not yet been detected and for which there is no established therapy, and which may likely leave an aftereffect</p> <p>(2) A disease which is chronic and poses not only financial problems, but a heavy burden on the patient’s family due to the great deal of effort required in caring for the patients, including potential psychological burdens</p>	<p>(1) The cause of the disease is not clear.</p> <p>(2) The treatment method of the disease is not established.</p> <p>(3) The occurrence of the disease is rare.</p> <p>(4) A long-term cure for the disease is needed.</p> <p>Requirements for Designated Intractable/Rare Diseases, in addition to the above:</p> <p>(5) The number of patients in Japan is less than a certain level (approximately 0.1% of the population).</p> <p>(6) Objective diagnostic criteria (or the equivalent) have been established.</p>
Implementation Methods	<p>(1) Promotion of survey/research</p> <p>(2) Establishment of medical institutions</p> <p>(3) Reduction of copayment of medical fees</p>	<p>(1) Development of basic policy</p> <p>(2) Development of a new, fair, and stable system for the subsidization of specific medical expenses related to intractable/rare diseases</p> <ul style="list-style-type: none"> <li>• Provide subsidies for medical costs to patients with intractable/rare diseases targeted by medical cost subsidies (designated intractable/rare diseases)</li> <li>• Appointment of medical institutions that implement medical care for designated intractable/rare diseases</li> <li>• The certificates to be attached to a subsidy application are to be prepared by a designated doctor</li> </ul> <p>(3) Promotion of research on medical care for intractable/rare diseases</p> <p>(4) Implementation of community-based health/medical care and welfare services</p> <p>(Intractable/rare disease consultation/support center service, home-visit nursing care)</p>

cost subsidy are stipulated as “patients with a certain level of severity, as defined by the disease severity classification, and who have difficulty in their daily or social lives.” With regard to Designated Intractable/Rare Diseases, 110 diseases were designated in January 2015, with 196 diseases designated in July 2015, then 24 diseases designated in April 2017, and one disease designated in April 2018, reaching a current total of 331 diseases.

On the other hand, survey and research has changed significantly due to reform of the research and development framework in the medical field. In April 2015, the Japan Agency for Medical Research and Development (AMED) was founded. It promotes top-down research by unifying the management of the research and development budget in the medical field, which had previously been under the jurisdiction of multiple ministries, based on the “Healthcare Policy[13]” in 2014.

In response, Health, Labour and Welfare Sciences Research was categorized into “policy research” and “practical research,” with the former falling under the jurisdiction of the MHLW and the latter under the AMED. With regard to intractable & rare diseases, while basic research, clinical research, development research, and public health research had previously been conducted in a comprehensive manner under the Research Program for Overcoming Intractable Diseases, since 2014 it has been conducted under two research programs: (1) the Research Program on Policy of Measures for Intractable/Rare Diseases, funded by MHLW, which aims to understand the current status of patients based on epidemiological studies, establish diagnostic criteria and disease severity classifications, and establish and widely disseminate evidence-based clinical practice guidelines; and, (2) the Research Program on Practical Application of Measures for Intractable/Rare Diseases, funded by the AMED, which aims to elucidate pathogenesis and pathophysiology as well as develop innovative diagnostic and treatment methods. In particular, the latter is positioned as the Rare/Intractable Disease Project of Japan, which is one of the AMED’s nine main projects, and it is being conducted intensively with a budget of approximately 10 billion yen, aiming to achieve at least 11 regulatory approvals or indication expansion of drugs and medical devices for intractable & rare diseases by 2020. Moreover, the policy research program and the practical research program are conducted systematically, in joint cooperation.

### **III. The NIPH’s Approach to Intractable & Rare Disease Research**

#### **1. Outline of the Funding Agency at the NIPH**

The FA at the NIPH is responsible for assessing research

proposals to be applied, selecting research projects to be valued, and allocating research funds for the projects. It also supports the appropriate implementation of the projects of research programs[14]. In the FA, Program Directors (PD) and Program Officers (PO) have also been instituted. They are responsible for the following operations:

- (1) Assessment of research proposals, including selection of assessment committee members, conduct of the meetings of the committee, provision of information and reports to the committee, and summarization of the results of assessment and the comments from committee members, etc.;
- (2) Progress management of research projects, including attendance at project meetings and consultation about the research plan, hearings, site visits, etc.

In addition, they identify research areas and research projects that should be the focus of promotion by taking into consideration trends in related research and developments and make proposals for the funding opportunity announcement.

#### **2. The Past Contributions of the NIPH**

In the past, the NIPH has contributed greatly to the development of measures for intractable & rare diseases. In 2011 serious discussion began regarding the Intractable/Rare Diseases Act, which was supported by the substantially increased research budget from 2009, as well as progress in intractable & rare disease research resulting from the activities of the FA at the NIPH. Specifically, the diagnostic criteria for rare diseases established by “Encouraged Research Projects” were used as the basic reference when selecting Designated Intractable/Rare Diseases. In addition, the framework for the R&D established by the NIPH is still used at the AMED.

On the other hand, through the enactment of the Intractable/Rare Diseases Act, the positioning of intractable & rare disease research has changed greatly. While research itself was the main purpose of the Outline of Intractable Disease Measures, in the Intractable/Rare Diseases Act, it was positioned as a scientific basis for supporting both the medical cost subsidy system and the medical services delivery system for intractable & rare diseases. Therefore, under the Act, a research program should be conducted for the purpose of developing: (1) “diagnostic criteria” contributing to the selection of Designated Intractable/Rare Diseases; (2) “disease severity classifications” contributing to fair and appropriate certification of patients with Designated Intractable/Rare Diseases; (3) “clinical practice guidelines” contributing to improvement of the quality of medical care

for patients with intractable & rare diseases; and, (4) innovative diagnostic and treatment methods (drugs and medical devices) contributing to overcoming intractable & rare diseases.

### 3. A New Challenge in Research Program Management at the NIPH

From 2010, the NIPH was responsible as the FA for all intractable & rare disease research. However, in 2014 it became responsible as the FA for the Research Program on Policy of Measures for Intractable/Rare Diseases, which primarily aims to develop diagnostic criteria, disease severity classifications, and clinical practice guidelines. This resulted in a need to revisit research program management. As little research[15-17] had been performed on the management of research programs or projects, it was necessary for the NIPH to develop a methodology on its own.

In the process of implementing program management, the first effort was to establish the goals of the program, as well as the indices enabling a clear understanding of progress toward and achievement of the goals. As the purpose of the Research Program on Policy of Measures for Intractable/Rare Diseases is “to improve the standards of medical care for intractable & rare diseases by understanding the current status of patients based on epidemiological studies, establishing diagnostic criteria and disease severity classifications, and establishing, disseminating, and revising evidence-based clinical practice guidelines of intractable & rare diseases[18]”, the indices of program management was set as (a) the number of diseases developed or revised through diagnostic criteria, disease severity classifications, and clinical practice guidelines, and (b) the number of diseases of which diagnostic criteria, disease severity classifications, and clinical practice guidelines developed or revised were approved by the academic societies related to them, while the goal of the research program was to maximize (a) and (b). Approval by academic societies is considered as one of the effective measures to “disseminate” research outcomes.

Secondly, in order to achieve the program goal, it was necessary to set goals for the research projects funded by the program. At the time of invitation of public subscriptions, it was required to select one or more intractable & rare diseases to be studied and to set one or more goals for each disease among the following:

- (1) Development or revision of diagnostic criteria
- (2) Development or revision of disease severity classifications
- (3) Development or revision of clinical practice guidelines
- (4) Approval by academic societies for diagnostic criteria
- (5) Approval by academic societies for disease severity classifications

- (6) Approval by academic societies for clinical practice guidelines

In this manner, we tried to establish the R&D management system to achieve the goal of the program effectively and efficiently by setting attainable goals for each project.

Lastly, it was necessary for the status of achievement to be “reported” for the goals of each project, in order to implement progress management to achieve the goal of the entire program. The Research Outcome Report Form was created as the common format. Contents of the report to be stated were as follows:

- target diseases
- goals by each disease (stated above)
- deadline
- status of achievement of each goal (date of achievement, expected month and year of achievement, or unachieved) at the end of each year

When the goal has been achieved, documented evidence to prove the outcome was to be attached to the following pages (such as developed or revised diagnostic criteria, disease severity classification, and clinical practice guideline).

Annual submission of the outcome report was made mandatory for each project and was used for midterm and/or final evaluation of the project and progress management. By this means, the PD and PO were able to monitor the status of goal achievement for each disease targeted by each project, and the principal investigators of the projects were able to proceed with their research with an awareness of the status of goal achievement.

As of the end of 2017, the total number of ongoing projects stood at 113, targeting a total of 582 diseases. Among these diseases, Designated Intractable/Rare Diseases accounted for 342, while others accounted for 240. Among these 331 Designated Intractable/Rare Diseases, some are considered to form a “disease group” (e.g., lysosomal storage diseases, congenital anomaly syndrome, and hereditary autoinflammatory diseases). It should also be noted that since there are projects that are addressing multiple diseases that are individually included in a single Designated Intractable/Rare Disease, the actual number of target diseases (342) is larger than those of Designated Intractable/Rare Diseases (331).

Table 2 shows the status of development and revision of diagnostic criteria, disease severity classifications, and clinical practice guidelines for the target diseases of this research program at the end of 2017 (obtained by tabulating the contents of the research outcome reports of each research project). The number of diseases for which diagnostic criteria, disease severity classifications, and clinical practice guidelines were developed was 494 (85%), 456 (78%), and 293 (50%), respectively.

**Table 2 Current status of target diseases**

	diagnostic criteria		disease severity classification		clinical practice guideline	
	No. of diseases	%	No. of diseases	%	No. of diseases	%
Has been developed (Breakdown)	494	84.9%	456	78.4%	293	50.3%
Year of development or revision						
Before 2008	29	5.9%	14	3.1%	12	4.1%
2009 to 2013	73	14.8%	33	7.2%	57	19.5%
2014	110	22.3%	114	25.0%	40	13.7%
2015	130	26.3%	156	34.2%	54	18.4%
2016	81	16.4%	83	18.2%	66	22.5%
2017	53	10.7%	44	9.6%	61	20.8%
Unknown	18	3.6%	12	2.6%	3	1.0%
Academic society approval						
Yes	341	69.0%	252	55.3%	238	81.2%
No	153	31.0%	204	44.7%	55	18.8%

Among the diseases for which development or revision was achieved, the proportion of those in and after 2014 was 76% for diagnostic criteria, 87% for disease severity classifications, and 75% for clinical practice guidelines. The percentage of diseases approved by the relevant academic societies was 69% for diagnostic criteria, 55% for disease severity classifications, and 81% for clinical practice guidelines.

As described above, diagnostic criteria and disease severity classifications were developed or revised for many intractable & rare diseases under the Research Program on Policy of Measures for Intractable/Rare Diseases implemented since 2014. This suggests that the NIPH's program management method on goal and deadline setting, and progress monitoring has a certain level of effectiveness.

On the other hand, the number of cases of development or revision of clinical practice guidelines, which plays a crucial role in the standardization of medical care for intractable & rare diseases, remained at one half. In addition, for roughly one quarter of diseases, diagnostic criteria and clinical practice guidelines have not been revised for more than five years. Possible reasons for pending development

or revision include, for example, that there is no need for revision due to a lack of new evidence, or that it is not possible to develop evidence-based clinical practice guidelines due to extremely limited evidence.

Table 3 shows the current status of designated versus nondesignated intractable/rare diseases. A higher percentage of Designated Intractable/Rare Diseases have developed diagnostic criteria, disease severity classifications, and clinical practice guidelines. These results suggest that the outcome of this research program contributed to intractable & rare diseases measures, especially, the standardization of medical care for Designated Intractable/Rare Diseases. It has been reported that the utilization of research outcomes into policy was accelerated by the active involvement of a PO in the research process of each project[19]. Similarly, in this research program, the PO's attendance at project meetings and advice on the implementation of research projects is considered to have contributed to the improvement of the research process of each project.

Since 2017, not only the development and revision of diagnostic criteria, disease severity classifications, and clinical practice guidelines, but also public awareness (sup-

**Table 3 Current status of target diseases for Designated versus Nondesignated Intractable/Rare Diseases**

	Designated (342 diseases)		Nondesignated (240 diseases)		Total (582 diseases)	
	No. of diseases	%	No. of diseases	%	No. of diseases	%
Has diagnostic criteria	318	93.0%	176	73.3%	494	84.9%
Has a disease severity classification	306	89.5%	150	62.5%	456	78.4%
Has clinical practice guidelines	203	59.4%	90	37.5%	293	50.3%

porting patient advocacy group, holding symposiums, etc.), operation of a patient registry[9,20], transition from pediatric to adult health care[21], and collaboration with related research were expected as the goal of the Research Program on Policy of Measures for Intractable/Rare Diseases. Therefore, it is necessary to conduct progress management of them by setting appropriate indices (e.g., whether or not and how often a symposium is held, whether or not and how many patient registries are available, etc.).

In the near future, the NIPH is willing to continue to proactively conduct object management, progress management, and outcome management of the Research Program on Policy of Measures for Intractable/Rare Diseases in order to achieve many research outcomes that contribute to intractable & rare disease policy, as the FA of intractable & rare disease research.

### Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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## 日本の難病に関する研究開発の動向 —研究開発管理における国立保健医療科学院の貢献—

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### 抄録

本稿では、日本の難病に関する研究開発の歴史を概観するとともに、国立保健医療科学院のこれまでの難病研究への関与と貢献、そして今後の取り組みについて論述する。

日本の難病に関する研究開発は、1972年から、国の難病施策の指針の「難病対策要綱」にしたがって実施されてきた。この要綱では「調査研究の推進」が難病施策の第一に掲げられており、基礎研究、臨床研究、疫学研究など、幅広い調査研究が推進されてきた。しかし調査研究が広範であるがゆえにその目標は明確ではなく、また諸外国と異なり、必ずしも希少疾病用医薬品（オーファンドラッグ）の開発に重点が置かれたわけではなかった。難病に関する研究課題（研究プロジェクト）は、主に厚生労働省の資金提供による「厚生労働科学研究費補助金（難治性疾患克服研究事業）」で実施されてきた。2009年度に事業予算が100億円に大幅に増額されたことを受けて、調査研究を「研究対象疾患の網羅的な拡大」と「画期的な医薬品等医療技術の開発・実用化の推進」の2つの方向性で拡充することとなった。またその方向性にしたがって研究事業を円滑に運営するために、2010年度より国立保健医療科学院が本研究事業に係る研究費配分機関（Funding Agency：FA）となり、研究課題の目標の明確化、研究事業（研究プログラム）の管理システムの構築を行った。その結果、これまでほとんど調査研究が実施されてこなかった多くの難病で疾患概念の確立と診断基準の策定がなされ、また複数の医薬品・医療機器で治験の完了や薬事承認を達成することができた。

2014年の「難病の患者に対する医療等に関する法律（難病法）」の制定、2015年の日本医療研究開発機構（AMED）の設立によって、難病に関する研究開発の枠組みは大きく変化した。つまり、これまでの難治性疾患克服研究事業が「難治性疾患政策研究事業」と「難治性疾患実用化研究事業」に分割され、国立保健医療科学院は前者のFAとして、難病法に基づく医療費助成制度や難病医療提供体制を支える科学的基盤である診断基準、重症度分類、診療ガイドラインの確立を進めることとなった。

国立保健医療科学院は、2014年度から、新たな研究事業の管理システムを構築し、運用している。具体的には、(a)研究事業の目標を、診断基準、重症度分類、診療ガイドラインが策定・改訂された疾患数、及びそれらが関係学会で承認された疾患数の最大化に設定したこと、(b)各研究課題に、研究対象とする各疾患に関して、「診断基準」、「重症度分類」、「診療ガイドライン」のいずれか、あるいは全てについて、「策定・改訂」、「学会での承認」のいずれか、あるいは両方を目標として設定させたこと、(c)各研究課題に「研究成果申告書」を毎年提出することを義務づけ、進捗管理と研究評価を徹底したこと、などが推進された。その結果、2017年末までに、多くの難病の診断基準、重症度分類が策定・改訂された（582の対象疾患の85%、78%）。しかし一方で、診療ガイドラインの策定・改訂は半数にとどまり、今後は研究課題が「自ら」目標を設定するだけでなく、「研究事業の方針に従って」適切な目標を設定できるよう支援する必要がある。

国立保健医療科学院は、今後も難病研究のFAとして、難病政策に資する多くの研究成果を上げるために、難治性疾患政策研究事業の目標管理、進捗管理、成果管理を積極的に行っていくつもりである。

キーワード：難病・希少疾患、研究開発（R&D）、プログラムマネジメント、プロジェクトマネジメント、健康関連研究開発管理