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ORIGINAL ARTICLE
Pediatric Cardiology and Adult Congenital Heart Disease

Pediatric Medical Devices
— Survey of Pediatric Cardiologists and Cardiovascular Surgeons in Japan —

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Background: In Japan, the choice of pediatric medical devices is limited because of 2 "device lag" problems: Japan lags behind the USA and Europe in device development, and development of pediatric devices lags behind that of adult devices. We aimed to identify the problems with and impediments to pediatric medical device development as recognized by pediatric physicians in Japan.

Methods and Results: A voluntary survey of pediatric medical devices for all council members of the Japanese Society of Pediatric Cardiology and Cardiac Surgery was conducted in 2019. The response rate was 47.1% (154/327). The respondents were 115 pediatric cardiologists (74.7%) and 39 cardiovascular surgeons (25.3%). Approximately 90% believed that difficulties in development existed. Approximately 70% were dissatisfied with the pediatric medical devices currently available in Japan, which was a result of the unavailability of medical devices approved overseas, few types and sizes, and off-label use. Factors that hindered the development of pediatric medical devices included anatomical issues specific to children with congenital heart disease, as well as system issues such as lack of corporate profitability, development cost, and amount of time for development.

Conclusions: Pediatric cardiologists and cardiovascular surgeons regard "device lag" and "off-label use" in Japan as important hindrances to the delivery of better medical care for pediatric patients with congenital heart disease.

Key Words: Device development; Device lag; Off-label use; Pediatric medical devices; Regulation

Advances in therapeutic medical devices are constant, and these devices are indispensable in the treatment of pediatric patients with congenital heart disease (CHD).[1] However, the development of pediatric medical devices lags behind that of adult medical devices in both Japan and the USA.[2] Furthermore, it takes an exceptionally long time between approval by the US Food and Drug Administration (FDA) or by the Conformité Européenne and introduction into Japan.[3] Because of these "device lag" problems, the choice and applicable range of pediatric medical devices are quite limited in Japan.[4]

The Harmonization By Doing (HBD) program was established in 2003 as a partnership among stakeholders from academia, industries, and regulatory agencies in Japan and the USA.[5] The HBD program focused on the development of adult medical devices, and the HBD working group discussed the challenges of accommodating local regulations and devised solutions by conducting proof-of-concept projects. Subsequently, the HBD-for-Children program was established in 2016, with a focus on the development of pediatric medical devices. It was a global collaboration between academia, industries, and regulatory agencies whose members investigated the possibility of aligning the regulation of pediatric medical by Japanese regulatory agencies and with that by regulatory agencies in the USA.[6] Since 2017, the findings of the HBD-for-Children working group have shown the potential for improvement in the global development of pediatric medical devices. However, pediatric physicians' perceptions of the current state of pediatric medical device development in Japan have remained unknown.

The aim of our study was to identify the problems,

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Table 1. Baseline Characteristics and Clinical Experience of Pediatric Physicians (n=154)

	Pediatric cardiologists (n=115)	Pediatric cardiovascular surgeons (n=39)
Clinical specialty		
Professional qualification for pediatric cardiology	109 (95%)	0
Professional qualification for pediatric cardiovascular surgery	0	38 (97%)
ASD or PDA closure plug certified operator	32 (28%)	0
CVIT certified operator	0	0
Catheterizations or operations as the first surgeon within previous 5 years		
0 per year	2 (2%)	3 (8%)
1–20 per year	42 (37%)	1 (3%)
21–50 per year	27 (23%)	3 (8%)
51–99 per year	24 (21%)	8 (21%)
100–199 per year	11 (10%)	10 (26%)
≥200 per year	9 (8%)	14 (36%)
Years of clinical practice		
1 to <5 years	0	1 (3%)
5 to <10 years	4 (3%)	1 (3%)
10 to <20 years	33 (29%)	9 (23%)
≥20 years	78 (68%)	28 (72%)
Age of patients being treated with medical devices		
Fetus	6 (5%)	0
Newborn to less than 1 year	83 (72%)	37 (95%)
1–6 years	98 (85%)	37 (95%)
7–12 years	77 (67%)	17 (44%)
13–18 years	26 (23%)	2 (5%)
≥19 years	28 (24%)	13 (33%)
Clinical setting for care		
University hospital	46 (40%)	19 (49%)
General hospital other than university hospital and pediatric hospital	41 (36%)	4 (10%)
Pediatric hospital	16 (14%)	13 (33%)
Specialty hospital other than university hospital and pediatric hospital	9 (8%)	3 (8%)
Clinic	3 (3%)	0
Pediatric medical devices currently mainly used		
Device closure	47 (41%)	0
Balloon	78 (68%)	0
Vascular occlusion device	76 (66%)	0
Intravascular stent	41 (36%)	3 (8%)
Arrhythmia-related devices	18 (16%)	8 (21%)
Surgical materials	3 (3%)	38 (97%)
Ventricular assist device	6 (5%)	8 (21%)
Physicians with experience in development or clinical trials	28 (24%)	10 (26%)

ASD, atrial septal defect; CVIT, cardiovascular intervention and therapeutics; PDA, patent ductus arteriosus.

impediments, and requests regarding the development of pediatric therapeutic (not diagnostic) medical devices that are recognized by pediatric physicians in Japan. We also investigated whether these problems, impediments, and requests differ according to the academic background of the physicians. We expect the results of this study to lead to recommendations for efficient development of pediatric medical devices through collaboration with academia, industries, and regulatory agencies.

Methods

This observational study was based on responses to a questionnaire. Pediatric cardiologists and cardiovascular surgeons in Japan participated in a voluntary survey about pediatric medical devices. The survey was conducted through the Questant system (Macromill. Inc., Tokyo, Japan) in 2019 from October 4 to November 18. An anonymous and optional questionnaire was sent by e-mail to all council members of the Japanese Society of Pediatric Cardiology

Table 2. Satisfaction With Current Pediatric Medical Devices and Need for New or Improved Devices According to Experience or Lack of Experience in Development or Clinical Trials (n=154)

	Lack of experience (n=116)	Experience (n=38)	P value
Difficulties in development or clinical trials	100 (86%)	35 (92%)	0.41
Intention to be involved if there is an opportunity for development or clinical trials	51 (44%)	27 (71%)	<0.01
Agreement that new pediatric medical devices must be developed	66 (57%)	30 (79%)	0.02
Dissatisfaction with pediatric medical devices currently available in Japan	80 (69%)	30 (79%)	0.30
Reason for dissatisfaction with pediatric medical devices			
Medical devices approved overseas cannot be used in Japan	59/80 (74%)	27/30 (90%)	0.07
Few types and sizes	65/80 (81%)	19/30 (63%)	0.08
Off-label use	56/80 (70%)	25/30 (83%)	0.22
Expensive	21/80 (26%)	7/30 (23%)	0.81
Poor performance and usability	12/80 (15%)	9/30 (30%)	0.10
Effect of delays in medical device development on clinical practice			
Limited options	92 (79%)	33 (87%)	0.35
Limits of adaptation	69 (59%)	24 (63%)	0.71
Poor patient quality of life	44 (38%)	19 (50%)	0.25
Poor treatment outcomes	45 (39%)	11 (29%)	0.33
Prolonged hospitalization	29 (25%)	15 (39%)	0.10
Increased health care costs	22 (19%)	14 (37%)	0.03
No effect	6 (5%)	0	0.34
Outcome obtained by promoting the development of medical devices			
Expanding the range of options	84 (72%)	30 (79%)	0.52
Wider use of minimally invasive treatments	78 (67%)	31 (82%)	0.10
Improvement in patient quality of life	65 (56%)	25 (66%)	0.35
Less need for invasive treatment	51 (44%)	25 (66%)	0.02
Prolongation of survival	48 (41%)	18 (47%)	0.57
Preservation and substitution of organ functions	41 (35%)	13 (34%)	1.00
Temporary improvement in symptoms	19 (16%)	11 (29%)	0.10

and Cardiac Surgery, which is most closely associated with pediatric therapeutic medical devices in Japan. We sent reminders twice during the survey period.

The survey was designed to elicit information about a number of aspects regarding the need for pediatric therapeutic medical devices that are fundamental in the care of patients with CHD. Personalized survey URLs allowed respondents to engage the survey intermittently at their convenience. The survey consisted of 39 closed-ended questions. Key topics included (1) satisfaction with current pediatric medical devices and the need for new or improved devices; (2) factors impeding the development of pediatric medical devices; and (3) requests by pediatric physicians that concerned the development of pediatric medical device. Professional demographic information and information about experience in development or clinical trials were also collected.

Data were calculated as numbers and percentages or as means±standard deviations. There were no missing data because respondents could not complete the survey without answering all the questions. "Very agreed" and "somewhat agreed" answers were summarized as "agreed." "Very dissatisfied" and "somewhat dissatisfied" were summarized as "dissatisfied." The response categories of factors impeding development of pediatric medical devices were ordinal: 0=no impediment, 1=small extent, 2=moderate extent, and 3=large extent. We used Fisher's exact test to evaluate categorical variables. A P value of less than 0.05 was considered significant in all analyses. JMP 11 (SAS Institute, Cary, NC, USA) was used for data analysis.

Results

Baseline Characteristics

Of the 327 council members of the Japanese Society of Pediatric Cardiology and Cardiac Surgery, 154 (47%) answered the survey. Of these respondents, 115 (75%) were pediatric cardiologists and 39 (25%) were cardiovascular surgeons. Baseline characteristics and their clinical experience involving patients with CHD are listed in **Table 1**. Most of them had extensive clinical experience with catheterizations or operations and more than 20 years of clinical practice involving patients with CHD. Conversely, only 25% of the respondents had experience in development or clinical trials of medical devices.

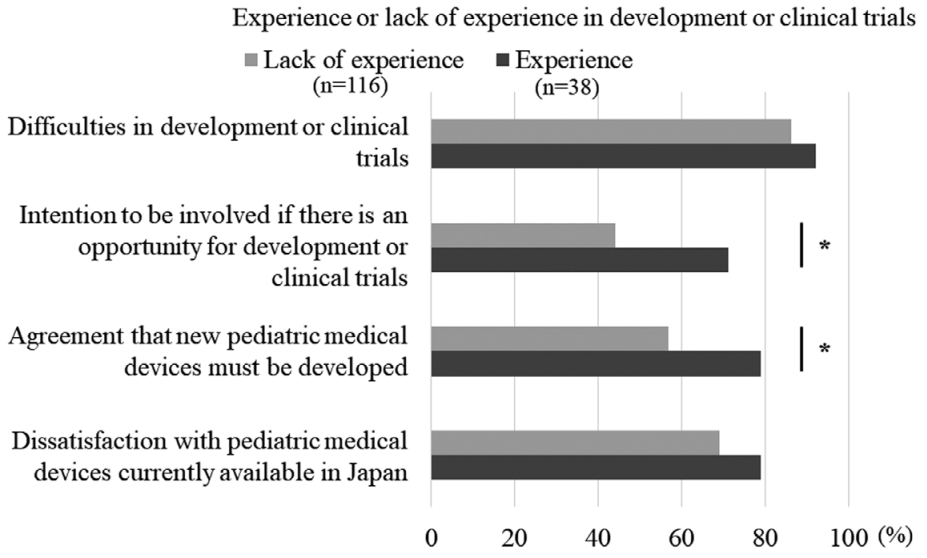

Figure 1. Attitudes towards the development of pediatric medical devices according to experience or lack of experience of pediatric physicians in Japan in development or clinical trials. Approximately 90% of respondents believed that implementing development or clinical trials of such devices would be difficult. Approximately 70% were dissatisfied with the pediatric medical devices currently available in Japan. Physicians who had experience in development or clinical trials, in comparison with those who had no such experience, were more likely to have newly developed pediatric medical devices (79% vs. 57%) and to intend to be involved if there was an opportunity for development or clinical trials (71% vs. 44%; *P<0.05).

Satisfaction With Current Pediatric Medical Devices and Need for New or Improved Devices

The respondents' satisfaction with current devices and the need for development of pediatric medical devices are summarized in **Table 2**. More than half of the respondents were interested in development and clinical trials, but approximately 90% believed that implementing them would be difficult. Physicians who had experience in development or clinical trials were more likely to than those with no such experience to have newly developed pediatric medical devices and to intend to be involved if any opportunity for development or clinical trials arose (**Figure 1**).

Approximately 70% of the respondents were dissatisfied with the pediatric medical devices currently available in Japan, which was a result of the unavailability of medical devices approved overseas, few types and sizes, and off-label use (**Table 3**). Pediatric cardiologists were more aware of off-label use as a problem than were pediatric cardiovascular surgeons (82% vs. 44%, P<0.01). In clinical practice, the majority of respondents were concerned that delays in medical device development would limit treatment options and the ability to adapt devices for individual use. They believed that promotion of medical device development could expand the range of options and increase the availability of minimally invasive treatments.

Factors Impeding Development of Pediatric Medical Devices

The 13 impediments posed in the survey as options for lack of pediatric medical device development are listed in **Table 4**. The most consequential impediments to pediatric medical device development were "disease rarity/complexity" and "various sizes to match growth", which were specific to pediatric patients with CHD. In addition, "lack of corporate profitability", "cost of development", "time for development", "government regulations", and "need for clinical trials" were also mentioned. Physicians who had experience in development or clinical trials were more concerned about "government regulations" than were those who had no experience (P<0.01). Neither clinical specialty nor experience in clinical practice affected these factors (data not shown).

Requests by Pediatric Physicians That Concerned Pediatric Medical Device Development

Respondents' requests to academic societies that are concerned with pediatric medical device development referred to "bridging with industry and regulatory authority" and "information provision". Requests to industries referred to "willingness to develop pediatric medical devices" and "cost burden on the trial implementation and approval". Requests to regulatory authorities referred to "addition of insurance points for pediatric medical devices" and "deregulation" (**Figure 2**). Requests did not differ significantly among respondents with different clinical specialties, experience in clinical practice, or experience in development or clinical trials (data not shown).

With regard to the effectiveness and safety of pediatric medical devices for patients with CHD, "comparable to standard treatment" was the most common answer by both pediatric cardiologists and cardiovascular surgeons (**Supplementary Table 1**). In the selection of treatments, there was a tendency to refer to "consulting experts", "systematic review/meta-analysis papers", and "guidelines" rather than to "textbooks" or "pharmaceutical attachments" (**Supplementary Table 2**).

Table 3. Satisfaction With Current Pediatric Medical Devices and Need for New or Improved Devices According to Clinical Specialty (n=154)

	Pediatric cardiologists (n=115)	Pediatric cardiovascular surgeons (n=39)	P value
Difficulties in development or clinical trials	101 (88%)	34 (87%)	1.00
Intention to be involved if there is an opportunity for development or clinical trials	55 (48%)	23 (59%)	0.27
Agreement that new pediatric medical devices must be developed	69 (60%)	27 (69%)	0.34
Dissatisfaction with pediatric medical devices currently available in Japan	85 (74%)	25 (64%)	0.31
Reason for dissatisfaction with pediatric medical devices			
Medical devices approved overseas cannot be used in Japan	70/85 (82%)	16/25 (64%)	0.06
Few types and sizes	64/85 (75%)	20/25 (80%)	0.79
Off-label use	70/85 (82%)	11/25 (44%)	<0.01
Expensive	21/85 (25%)	7/25 (28%)	0.80
Poor performance and usability	15/85 (18%)	6/25 (24%)	0.56
Effect of delays in medical device development on clinical practice			
Limited options	92 (80%)	33 (85%)	0.64
Limits of adaptation	74 (64%)	19 (49%)	0.09
Poor patient quality of life	51 (44%)	12 (31%)	0.19
Poor treatment outcome	44 (38%)	12 (31%)	0.45
Prolongation of hospitalization	37 (32%)	7 (18%)	0.10
Increase in health care costs	27 (23%)	9 (23%)	1.00
No effect	3 (3%)	3 (8%)	0.17
Outcome obtained by promoting the development of medical devices			
Expanding the range of options	86 (75%)	28 (72%)	0.83
Wider use of minimally invasive treatments	90 (78%)	19 (49%)	<0.01
Improvement in patient quality of life	71 (62%)	19 (49%)	0.19
Less need for invasive treatment	60 (52%)	16 (41%)	0.27
Prolongation of survival	51 (44%)	15 (38%)	0.58
Preservation and substitution of organ functions	37 (32%)	17 (44%)	0.24
Temporary improvement in symptoms	27 (23%)	3 (8%)	0.04

Table 4. Impediments and Exploratory Factors in Pediatric Medical Device Development (n=154)

	Mean±SD	None (0 pts)	Small (1 pts)	Moderate (2 pts)	Large (3 pts)
Disease rarity/complexity	2.6±0.6	0	4	30	66
Lack of corporate profitability	2.6±0.6	1	5	31	63
Various sizes to match growth	2.4±0.6	1	6	49	44
Cost for development	2.4±0.7	0	10	37	53
Time for development	2.4±0.6	1	7	45	47
Government regulations	2.2±0.7	1	13	53	33
Need for clinical trials	2.2±0.7	0	15	47	38
Technical issues	1.8±0.7	3	31	49	17
Lack of a central hospital for patients	1.7±0.8	4	35	46	15
Difficulties in determining therapeutic effects and superiority	1.7±0.7	3	37	50	10
Frequent upgrades	1.6±0.6	2	42	49	7
Reliability of medical device performance during clinical trials	1.6±0.6	1	40	55	4
Reliability of existing treatments	1.5±0.6	2	50	46	2

Data for each exploratory factor are shown as percentage. The response categories of impediments were ordinal: 0=no impediment, 1=small extent, 2=moderate extent and 3=large extent. SD, standard deviation.

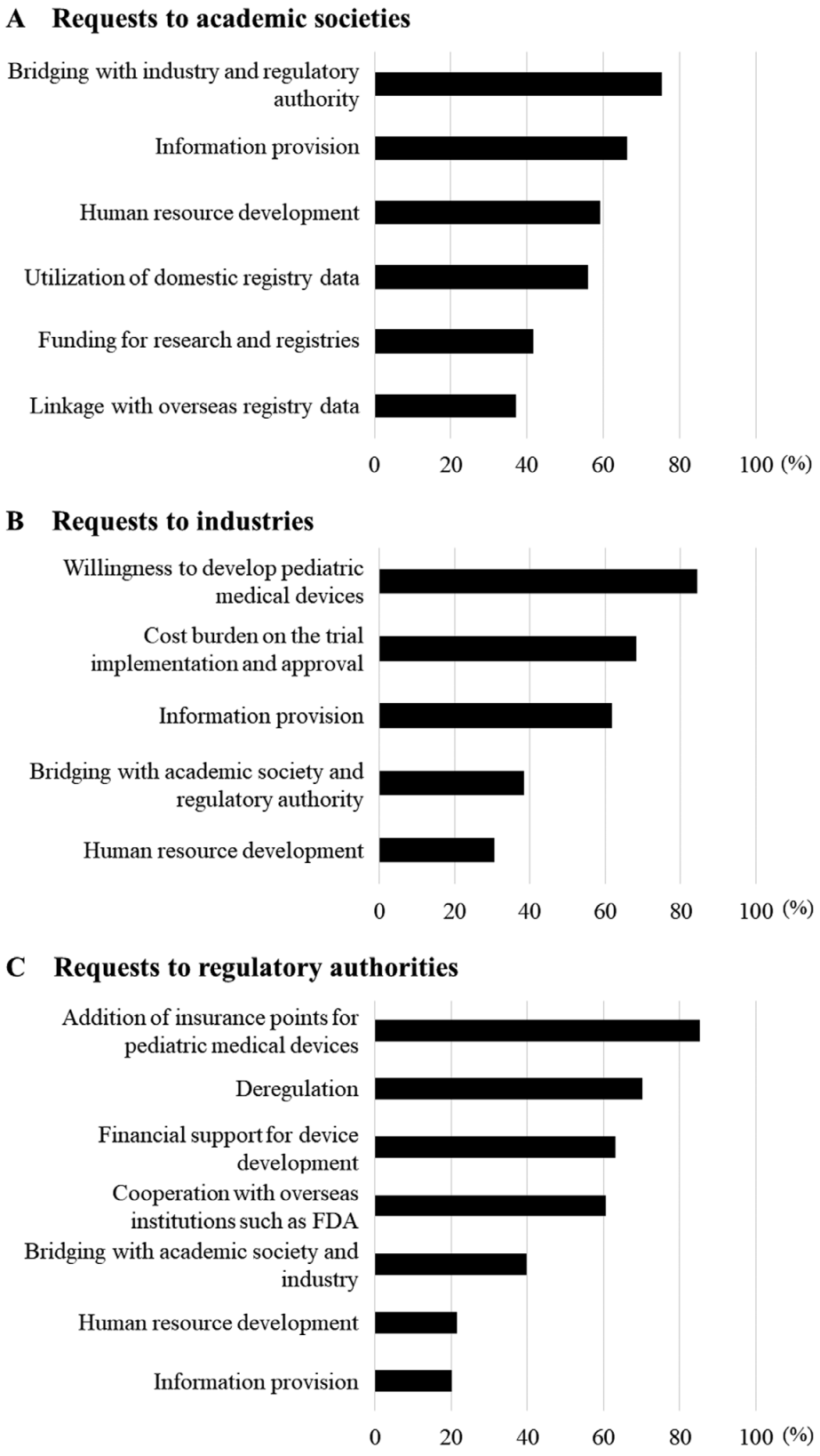

Figure 2. Requests by pediatric physicians that concerned pediatric medical device development. Percentages of requests from pediatric physicians addressed to academic societies (**A**), industries (**B**), and regulatory authorities (**C**) are presented. FDA, US Food and Drug Administration.

Discussion

The results of this survey demonstrated the problems, impediments, and requests concerning the development of pediatric medical device recognized by pediatric physicians in Japan. The respondents were pediatric cardiologists and cardiovascular surgeons with extensive knowledge and clinical experience of catheterizations or operations, but relatively little experience in the development or clinical trials of medical devices. Although the respondents recognized that device innovation is necessary to optimize care for pediatric patients with CHD, most of them believed that implementing development or clinical trials would be difficult. Those who had experience in development or clinical trials tended to have newly developed pediatric medical devices and intended to be involved in available device development or clinical trials. Therefore, the involvement of physicians is important for promoting the development of pediatric medical devices.

Approximately 70% of pediatric cardiologists and cardiovascular surgeons were dissatisfied with the pediatric medical devices currently available in Japan. A national survey of physicians who treated rare diseases in the USA revealed that more than 60% of pediatric physicians were dissatisfied with the available pediatric medical devices, and 90% confirmed the need for innovative devices.[7] Medical devices must be tailored for the care of pediatric patients, and physicians were concerned that delays in medical device development would limit treatment options. Off-label use was also a concern, especially among pediatric cardiologists. Actually, in Japan, the majority of pediatric medical devices are used off-label in clinical settings. The FDA recommends that pediatric physicians consider off-label or physician-directed use of medical and surgical devices in children as necessary and appropriate when no device that has been approved or cleared for the specific pediatric indication is available.[8] Such use may be common and appropriate practice for many childhood medical and surgical conditions, in addition to CHD.

Factors that hindered the development of pediatric medical devices include anatomical issues specific to pediatric patients with CHD, as well as system issues such as lack of corporate profitability, cost of development, time required for development, and government regulations. Respondents who had experience in development or clinical trials tended to be more concerned about time for development and government regulations than did those who had no experience. Our findings are generally consistent with those of prior studies of rare disease.[7,9] Previous surveys of physicians who treat rare diseases in the USA showed that "costs of development" and "lack of profitability to industry" were the 2 impediments to device development that were most commonly perceived.[7] A major public health need is the innovation of medical devices to care for pediatric patients with CHD.[1] Too small a market was the most significant cause of delayed development of pediatric medical devices, according to the results of a previous survey conducted in the medical device industry in Japan and the USA.[6] Because the market in the pediatric field is smaller than that in the adult field, it is difficult for pediatric industries to keep a balance between marketing cost and revenue.[2] Promotion of global clinical trials and utilization of real-world data may be needed to develop these devices.

With regard to pediatric medical devices for patients with CHD, pediatric cardiologists and cardiovascular surgeons emphasized the effectiveness and safety of these devices in comparison with standard treatment. Randomized controlled trials are considered the most robust method of proving effectiveness and safety.[10] However, the cost burden on trial implementation is critical. Because clinical trials must be conducted efficiently, single-arm studies may be more appropriate for evaluating device performance in patients with rare diseases, if the technology is very well established and if historical data about comparable treatments, lesion types, and patient demographics are sufficiently informative.[11,12] Therefore, it is important to select the study design according to the risk–benefit balance based on the characteristics of the new devices and the diseases. Speeding up development is required for both approval of and expanded indications for new pediatric devices. To obtain cooperation from industries, it is necessary to simplify the approval process and reduce costs. For that purpose, we believe that the framework of the HBD-for-Children program will enable these discussions among academia conducting studies, industries, and regulatory agencies.[6]

Study Limitations

First, the response rate to this survey was relatively low. The anonymous voluntary nature of participation may have affected the response rate. Lack of the information on the council members who did not respond the survey may be a source of potential bias. Second, we did not solicit patient or industry input; therefore, we plan to advance the investigation to identify the issues recognized by industry. Third, the proportion of the respondents who had experience in development or clinical trials of medical devices was low in comparison with that in the earlier survey of physicians treating rare diseases.[7] Their background could have been a source of bias towards dissatisfaction and wanting to develop new devices. Finally, because this study was not designed for hypothesis testing, it is difficult to draw clear conclusions that are based on biostatistics. However, despite these limitations, this survey enabled us to comprehensively assess pediatric cardiologists and cardiovascular surgeons' perspectives about the problem of availability of pediatric medical devices in Japan. Addressing the device lag will require concerted efforts by a broad range of stakeholders to develop new and enhanced solutions that will improve the development of medical devices for children living with CHD.[6]

In conclusion, we reconfirmed that device lag and off-label use in Japan are widely recognized by both pediatric cardiologists and cardiovascular surgeons as important impediments to the delivery of better medical care for pediatric patients with CHD. In the future, using the framework of the HBD-for-Children program through discussions with academia conducting studies, industries, and regulatory agencies, we hope to propose solutions to these problems.

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design, the collection, analysis and interpretation of data, the writing of the report, or the decision to submit the article for publication.

Author Contributions

T.M., A.K., S.T., M.H., and T.K. designed the study; T.M. and T.K. collected and analyzed the data; T.M. and T.K. wrote the manuscript; A.K., M.H., S.Y., H.Y., R.I., S.-H.K., and K.S. revised the manuscript. All authors read and approved the final manuscript.

IRB Information

The Ethics Committee at the National Center for Child Health and Development granted an exemption from requiring ethics approval.

Disclosure

The authors declare no conflicts of interest. The views expressed in this article are those of the authors and do not necessarily reflect the official views of the Pharmaceuticals and Medical Devices Agency or Japan's Ministry of Health, Labour and Welfare.

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Supplementary Files

Please find supplementary file(s);
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