

**ARTICLE**

# Regulatory and operational challenges in conducting Asian International Academic Trial for expanding the indications of cancer drugs

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**Abstract**

There are many differences between Asian regions in terms of the regulatory requirements and operational procedures in conducting international academic clinical trials for the approval of new drugs. The National Cancer Center Hospital in Japan has launched an international investigator-initiated registration-directed trial (IIRDT) in Japan, Korea, Taiwan, and Singapore, aiming at obtaining pharmaceutical approval in participating regions. Differences in regulatory and operational procedures were identified while coordinating the trial. In Japan, regulatory authority reviews should be performed after approval by institutional review boards for IIRDT, whereas in other regions these can be done in parallel. There were disparities in Good Manufacturing Practice-related documents between regions. Several differences were found regarding investigational product (IP) management, specifically concerning labeling, import/export procedures, and customs clearance costs. On the other hand, safety reporting procedures were relatively well-harmonized in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH-E2A). Regions also differed in per-patient costs, due to varying regulations for academic registration-directed trials. In conclusion, the observed differences among Asian regions should be harmonized to facilitate international academic trials in Asia and thus resolve unmet patient needs worldwide.

**Study Highlights****WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

International clinical trials have become common because they make it possible to accrue patients faster and obtain new drug approval in wider areas. However, pharmaceutical regulatory differences hinder the efficient conduct of international clinical trials, especially in academia.

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### WHAT QUESTION DID THIS STUDY ADDRESS?

We conducted an academic international clinical trial on new drug applications in four Asian countries and clarified pharmaceutical regulatory differences and operational difficulties.

### WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The study identified differences between countries in terms of regulatory affairs, institutional review board (IRB) review processes, investigational new drug (IND) dossiers, investigational product (IP) management procedures, and clinical trial costs, while safety reporting procedures were relatively harmonized. Japan utilizes investigator-initiated registration-directed trials, an advanced regulatory system for new drug application by academia, but the other countries do not.

### HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Harmonization of pharmaceutical regulations and trial initiation procedures, and regulatory reform of clinical trial costs are important to accelerate academic international clinical trials for new drug applications.

## INTRODUCTION

International clinical trials have become common because they make it possible to accrue patients faster and obtain new drug approval in wider areas, although there are some complexities in conducting trials, such as the need to identify intrinsic and extrinsic factors and different regulations of each country. The number of international industry-sponsored trials is increasing and the speed of treatment development has been accelerated. However, although pharmaceutical companies are eager to invest in common cancers, they are not always interested in rare cancers or multimodal treatments due to small market sizes, despite unmet medical needs. In order to meet such needs, international academic clinical trials should play a larger role.

Many international clinical trials are conducted by academic research groups in the United States<sup>1</sup> and Europe.<sup>2</sup> The population in Asian regions is growing and the average life expectancy is increasing, which will lead to more demand for international academic trials.

The National Cancer Center Hospital (NCCH) in Japan is one of the largest cancer research institutions in Asia. The NCCH has participated in numerous international industry-sponsored trials and has led a number of domestic academic clinical trials. Based on the expertise derived from this involvement, the NCCH has launched an Asian international investigator-initiated registration-directed trial (A-IIRDT) involving four Asian regions (Japan, Korea, Taiwan, and Singapore). As far as we know, this is the first study in Asia to be sponsored by an academic institution, with aims to obtain pharmaceutical approval in the participating regions.

To facilitate this A-IIRDT and further expand academic clinical trial networks in Asia, here, we describe the

differences identified by the A-IIRDT regarding regulatory requirements and operational procedures in the four participating Asian regions.

## METHODS

In 2018, the NCCH initiated an international randomized phase III trial in 4 regions in Asia: Japan, Korea, Taiwan, and Singapore (PATHWAY trial). Through the experience of coordinating that trial, we accumulated regulatory and operational information to inform the initiation and conduct of future academic trials in these regions. In this paper, we report differences in (a) the clinical trial review processes of regulatory authorities (RAs) and institutional review boards (IRBs), (b) investigational new drug (IND) dossiers, (c) IP management procedures, (d) safety reporting requirements, (e) study site procedures, and (f) subject reimbursement costs.

### PATHWAY trial

The PATHWAY trial is a randomized, double-blinded, placebo-controlled, phase III trial for hormone receptor (HR)-positive, HER2-negative advanced, or metastatic breast cancer (NCT03423199). Palbociclib or placebo was administered in combination with tamoxifen. The primary end point is progression-free survival. A total of 185 patients has been randomized 1:1 to the palbociclib or placebo arm from 12 sites in Japan, 6 sites in Korea, 3 sites in Taiwan, and 2 sites in Singapore. Palbociclib was first approved in the United States in 2015, and, as of 2020, it has been approved in more than 90 countries. Palbociclib has been approved by the regulatory authorities in participating

regions in combination with letrozole for the treatment of postmenopausal women with locally advanced or metastatic HR-positive, HER2-negative breast cancer, and in combination with fulvestrant for the treatment of patients whose disease has progressed after endocrine therapy. However, the process of obtaining approval for cancer drug indications is generally fragmented; for example, the initial indications are for recurrent and metastatic disease, then for first-line therapy, and finally for postoperative adjuvant therapy; clinical trials are then needed to obtain additional indications. Thus, the PATHWAY trial was initiated to expand the indications of palbociclib in combination with tamoxifen in the participating regions. Therefore, the trial is being conducted in full compatibility with the International Conference on Harmonization–Good Clinical Practice (ICH-GCP). To achieve compliance with local regulations, the trial is being performed in Japan as an IIRDT in accordance with the Japanese Pharmaceuticals and Medical Devices Law.<sup>3</sup> Details of Japanese regulation of academic clinical trials are described elsewhere.<sup>4</sup> In other regions, the trial was conducted as a registration-directed trial, and clinical trial notifications (CTNs) were submitted to each local regulatory authority before trial initiation. The IPs, investigator's brochure (IB), and safety information, such as the suspected, unexpected, serious adverse reactions (SUSAR) line listing, and the Development Safety Update Report (DSUR) were provided by Pfizer, the industry partner of the PATHWAY trial.

## RESULTS

### Clinical trial review processes of RAs and IRBs

Clinical trial review processes of RAs and IRBs are stipulated in GCPs,<sup>5–8</sup> Pharmaceutical Affairs Laws,<sup>9–11</sup> and other related regulations<sup>12–14</sup> of each region. Clinical trial review processes of RAs and IRBs are shown in Table 1. There are no significant differences in regulatory review processes regardless of the presence of global regulatory approval. The most significant difference between countries is that in Korea, Taiwan, and Singapore, RA reviews of CTNs and IRB reviews are performed in parallel regardless of the type of study sponsor; in Japan, however, these are performed in parallel in industry-sponsored trials, whereas in IIRDTs, CTNs must be submitted after approval by at least one IRB.

### IND dossiers

Table 2 shows the list of documents that should be attached to CTNs of approved drugs in each region. The regions differ

in terms of the essential dossiers that require translation in the local language. In addition, there are disparities regarding Good Manufacturing Practice (GMP)-related documents.<sup>15–17</sup> In principle, all nonclinical data related to the manufacture and quality of investigational drugs should be described in GMP documents. However, these can be omitted in Japanese registration-directed trials, and a cross-reference letter is valid in Korea to avoid duplicate submission by a marketing authorization holder (an owner of the Chemistry, Manufacturing and Control [CMC] information). When conducting a clinical trial using an investigational drug developed by academia, the GMP documents can be a hurdle for academic investigators. This process can vary depending on local regulations, the indication of the investigational drug, etc.

In the case of a registration-directed trial for a New Drug Application (NDA), compensation is required in all regions, in accordance with the ICH-GCP. In fact, the study sponsor purchased the clinical trial insurance in the PATHWAY trial, and an insurance certificate is required in Korea, Taiwan, and Singapore.

### IP management procedures

Requirements for IP management are stipulated in GCPs, GMPs, and other related regulations.<sup>18,19</sup> IP management procedures are summarized in Table 3. There were several differences between regions regarding labeling, import/export procedures, and the customs clearance cost. The shipping and storage procedures of IPs, including the approaches to label attachment and central storage, should be determined after thorough exploration of local regulations concerning customs clearance and import/export expenses.

### Safety reporting

Requirements for safety reporting to regulatory authorities are stipulated in Safety Reporting Regulations<sup>20–24</sup> of each country. Each site investigator should report to the IRB all serious adverse events that occur at their site according to the site standard operating procedures (SOPs) listed in Table 4, which demonstrate slight differences in reporting deadlines between regions and institutions. Each site investigator should also immediately report all serious adverse events to the study sponsor. The reporting procedure and deadline are specified in the protocol so that there is no difference between regions. Although the study sponsor should report all SUSARs to regulatory authorities according to ICH of Technical Requirements for Pharmaceuticals for Human Use, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH-E2A<sup>25</sup>), there are

**TABLE 1** RA and IRB review processes

	Japan	South Korea	Taiwan	Singapore
Regulatory authority	PMDA MHLW	MFDS NIFDS	TFDA DOH CDE	HSA, the MOH
Related regulations	Japanese-GCP <sup>5</sup>	Korean-GCP <sup>6</sup>	Taiwan-GCP <sup>7</sup>	ICH-GCP <sup>8</sup>
IND and IRB review process	Industry-sponsored trials: parallel review possible. IIRDT: submit IND after IRB approval.	Parallel review is possible.	Parallel review is possible.	There are 3 clinical trial submission routes: 1. CTA, for trials on locally unregistered therapeutic drugs or locally registered but not used in accordance with approved indications 2. CTN, for trials on locally registered therapeutic drugs used in accordance to its approved indications 3. CTC, for trials of medicinal products (cell, tissue, and gene therapy products or complementary health products) Parallel review is possible for CTA and CTN.
Local IND holder / in-country clinical caretaker	Required (investigator can be IND holder in IIRDT)	Required	Required (a power of attorney is submitted to DOH by study sponsor)	Required
IND application form and language	Clinical trial notification form (in Japanese)	IND application can be made through web site (in Korean)	The official application format is in Chinese. English is acceptable.	IND application can be made through web site (in English)
Requirements regarding IND amendments	Major revisions require timely IND amendment. Minor revisions can be submitted every 6 months.	IND amendment is required for any revision of protocol or IB. Progress/Annual Report is required every year.	IND amendment is required for any revision of protocol, ICF, or IB.	IND amendment is required for any revision of protocol or IB. Progress/Annual Report is required every 6 months.
Requirements of local patient data for a New Drug Application <sup>a</sup>	Japanese data required.	Participation of domestic medical institutions required.	Taiwanese data required. The required number of subjects varies depending on the trial scale and the presence of FDA/EMA approval.	Singaporean data are not mandatory for drugs already approved in overseas countries.
Clinical Trial Compensation Guidelines	Japanese-GCP <sup>5</sup> Japan Pharmaceutical Industry Legal Affairs Association Guideline <sup>29</sup> (Reference)	Korean-GCP <sup>6</sup>	Taiwan-GCP <sup>7</sup>	ICH-GCP <sup>8</sup> The Association of the British Pharmaceutical Industry Guideline <sup>30</sup> (Reference)

(Continues)

**TABLE 1** (Continued)

	Japan	South Korea	Taiwan	Singapore
Provision of research samples transfer to overseas laboratories	Possible	Possible	Possible Detailed description of the measurement items and organizational information of the laboratory is required in the protocol and informed consent form.	Possible Description of research samples transfer to overseas laboratories is required in informed consent form.

Abbreviations: CDE, Center for Drug Evaluation; CTA, Clinical Trial Authorization; CTC, Clinical Trial Certificate; CTN, Clinical Trial Notification; DOH, Department of Health; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GCP, good clinical practice; HAS, Health Science Authority; IB, investigator's brochure; ICF, informed consent form; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human; IIRDT, investigator-initiated registration-directed trial; IND, Investigational New Drug; IRB, institutional review board; MFDS, Ministry of Food and Drug Safety; MHLW, Ministry of Health, Labour and Welfare; MOH, Ministry of Health; NIFDS, National Institute of Food and Drug Safety Evaluation; PMDA, Pharmaceuticals and Medical Devices Agency; RA, regulatory authority; TFDA, Taiwan Food and Drug Administration.

<sup>a</sup>Exact required number depends on negotiation with the regulatory authority.

some differences in requirements depending on drug approval status.

### Study site procedures

All sites participating in the PATHWAY trial have previous experience participating in one or more global industry-sponsored trials, as well as well-standardized systems, such as IRBs, clinical research coordinator (CRC) support, and investigational drug management, with minor differences, as summarized in Table 5.

### Subject reimbursement costs

There were differences between regions in the reimbursement of clinical trial costs by public health insurance. In Japan, for example, 70–90% (depending on age) of fees for examinations, such as blood and imaging tests and for concomitant medications, are covered by public health insurance, and the remaining 10–30% is paid by the patients, according to “Special or Specified Medical Care Coverage.”<sup>26,27</sup> When a clinical trial is conducted as an industry-sponsored trial, the sponsor should pay all of these costs. In Korea, Taiwan, and Singapore, on the other hand, these costs must be fully covered by sponsors of registration-directed trials, regardless of whether they are industry-sponsored or academia-initiated. Table 6 shows estimations of the average annual examination fee per subject based on the PATHWAY trial, assuming a standard phase III oncology trial.

## DISCUSSION

This study is the first to elucidate regulatory and operational differences between countries identified while conducting an academic international IIRDT. The four regions demonstrated discrepancies in RA and IRB clinical trial review processes, IND dossiers, and IP management procedures; on the other hand, safety reporting procedures were relatively well-harmonized in accordance with ICH-E2A guidelines. In most Asian countries in particular, such regulatory and operational information is not translated into English (with the exception of Singapore, where English is the official working language); therefore, the results described here will be of great help in conducting academic clinical trials in Asia. If the original English version is accepted for all CTN dossiers submitted to each regulatory authority, the burden on academia will be reduced. On the other hand, it may be reasonable to use local languages for some study documents submitted to study sites and IRBs, because these documents are utilized by many local users.

Operational issues can be managed by understanding local procedures in each country, but financial issues can be the most difficult barrier in international trials. For example, per-patient costs vary between regions due to differences in regulations of academic registration-directed trials. Japan has an IIRDT regulation that enables investigators to be study sponsors, and a proportion of the per-patient cost is reimbursed by public health insurance. For example, the costs of examinations and concomitant medications are covered by public health insurance based on “Special or Specified Medical Care Coverage.” On the other hand, in Korea, Taiwan, and Singapore, the study

TABLE 2 Essential IND dossier and its language

	Japan	South Korea	Taiwan	Singapore
Protocol	Yes (in Japanese)	Yes (in Korean) Korean protocol synopsis is also required.	Yes Either Chinese or English version is acceptable. The Chinese synopsis is required.	Yes (in English)
ICF	Yes (in Japanese)	Yes (in Korean)	Yes (in Chinese)	Yes (in English)
IB	Yes (in Japanese) Local formatting changes are not needed. Annual IB update is required.	Yes (in Korean) Korean summary of IB is also required. Local formatting changes are not needed. Annual IB update is required.	Yes Either Chinese or English version is acceptable. Local formatting changes are not needed. Annual IB update is required.	Yes (in English) Local formatting changes are not needed. Annual IB update is required.
Investigator's CV	No	No Information of investigational sites, investigators is required.	Yes For both PI and Sub-I, either Chinese or English version is acceptable.	Yes CV of PI in English is required.
CRF	No CRF template is not necessary.	No CRF template is not necessary	Yes Either Chinese or English version is acceptable.	Yes (in English)
Study subject compensation documents	No	Yes (subject compensation letter and insurance certificate)	Yes (insurance certificate)	Yes (insurance certificate)
CMC documents	No	Yes If the original document is written in foreign language, Korean document should be attached to the original document. If the CMC document has been submitted in another CTN for the same IP, a cross-reference letter may be submitted instead.	Yes CMC data is required either in English or Chinese.	Yes
GMP certificate of the investigational drug	No	Yes	Yes	Yes
DSUR	Yes If another sponsor such as a Marketing Authorization Holder has created a DSUR for the study drug and submitted it to the regulatory authority, it can be omitted.	Yes If another sponsor such as a Marketing Authorization Holder has created a DSUR for the study drug and submitted it to the regulatory authority, it can be omitted.	Yes If another sponsor such as a Marketing Authorization Holder has created a DSUR for the study drug and submitted it to the regulatory authority, it can be omitted.	Yes If another sponsor such as a Marketing Authorization Holder has created a DSUR for the study drug and submitted it to the regulatory authority, it can be omitted.

Abbreviations: CMC, chemistry, manufacturing, and control; CRF, Case Report Form; CTN, clinical trial notification; CV, curriculum vitae; DSUR, Development Safety Update Report; GMP, good manufacturing practice; IB, investigator brochure; ICF, informed consent form; IND, investigational new drug; IP, investigational product; PI, principal investigator; Sub-I, sub-investigator.

TABLE 3 Investigational product management procedures

	Japan	South Korea	Taiwan	Singapore
Procedure for IP import / export	<p>Drug import license or Yakkan certificate is not required. Only CTN is needed to pass customs clearance.</p>	<p>Drug import license is not required. Standard Customs Clearance Schedules Report form needs to be issued by Korea Pharmaceutical Trading Association. Annual update required.</p>	<p>IP import license is required. The license specifies the valid period and upper quantity limit. It takes 3–4 weeks to obtain or update the license.</p>	<p>IP import license is not required. Clinical Research Material Notification needs to be submitted to the Health Science Authority by the study sponsor at time of study license application or after obtaining the study license.</p>
Items to be listed on the IP label	<ul style="list-style-type: none"> <li>• For clinical trial use (protocol number)</li> <li>• Title and address of the sponsor-investigator</li> <li>• Chemical Name/Laboratory code</li> <li>• Lot or batch number identifying content and packaging operation of the product</li> <li>• Storage Conditions</li> <li>• Expiration date (if necessary)</li> <li>• Quantity per IP bottle (if necessary)</li> </ul>	<ul style="list-style-type: none"> <li>• For clinical trial use (protocol number)</li> <li>• Study sponsor (Local IND holder)</li> <li>• Chemical Name/Laboratory code</li> <li>• Quantity per IP bottle</li> <li>• Storage Conditions</li> <li>• Dosage and administration</li> <li>• Lot or batch number identifying content and packaging operation of the product</li> <li>• Expiration date</li> </ul>	<ul style="list-style-type: none"> <li>• For clinical trial use (protocol number)</li> <li>• Study sponsor</li> <li>• Chemical Name/Laboratory code</li> <li>• Quantity per IP bottle</li> <li>• Storage Conditions</li> <li>• Dosage and administration</li> <li>• Lot or batch number identifying content and packaging operation of the product</li> <li>• Expiration date</li> </ul>	<ul style="list-style-type: none"> <li>• For clinical trial use (protocol number)</li> <li>• Study sponsor</li> <li>• IP manufacturer</li> <li>• Chemical or name of substance, strength or potency, quantity of units</li> <li>• Name/Laboratory code</li> <li>• Quantity per IP bottle</li> <li>• Storage Conditions</li> <li>• Pharmaceutical form, Dosage and route of administration</li> <li>• Lot or batch number identifying content and packaging operation of the product</li> <li>• manufacturing date</li> <li>• Expiration date</li> </ul>

Abbreviations: CTN, clinical trial notification; IND, investigational new drug; IP, investigational product.

TABLE 4 Safety reporting requirements

	Japan	South Korea	Taiwan	Singapore
Safety Reporting Regulations	<ul style="list-style-type: none"> <li>• Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (PAB/ED No. 227 dated March 20, 1995)<sup>20</sup></li> <li>• Reporting of Adverse Drug Reactions Occurring in Clinical Trials to PMDA (PFSB Notification No. 0330001 dated March 30, 2004)<sup>21</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Korean-GCP</li> <li>• Korea MFDS guidelines on SUSAR reporting<sup>22</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Taiwan-GCP</li> <li>• Taiwan National Adverse Drug Reactions Reporting system Q&amp;A<sup>23</sup></li> </ul>	<ul style="list-style-type: none"> <li>• ICH-GCP</li> <li>• Expedited Safety Reporting Requirements for Therapeutic Products and Medicinal Products used in Clinical Trials<sup>24</sup></li> </ul>
Safety Reporting to regulatory authority (in case drug is approved)	<ul style="list-style-type: none"> <li>• Death or life-threatening cases (only SUSARs); within 7 calendar days from the investigator's awareness</li> <li>• Non-death or non-life threatening cases (only SUSARs), death or life-threatening cases (non-SUSARs); within 15 calendar days from the investigator's awareness</li> <li>• Research Reports</li> <li>• Reports of Safety Measures</li> <li>• Annual safety update (DSUR)</li> </ul>	<ul style="list-style-type: none"> <li>• Death, fatal, or life-threatening cases (only SUSARs); within 7 calendar days from the investigator's awareness</li> <li>• Non-death or non-life threatening cases (only SUSARs); within 15 calendar days from the investigator's awareness</li> <li>• Annual safety update (DSUR)</li> </ul>	<ul style="list-style-type: none"> <li>• Death or life-threatening cases (only SUSARs); within 7 calendar days from the investigator's awareness</li> <li>• Non-death or non-life threatening cases (only SUSARs); within 15 calendar days from the investigator's awareness</li> <li>• Annual safety update (DSUR)</li> </ul>	<ul style="list-style-type: none"> <li>• Death or life-threatening cases (only SUSARs); within 7 calendar days from the investigator's awareness</li> <li>• Non-death or non-life threatening cases (only SUSARs); within 15 calendar days from the investigator's awareness</li> <li>• Annual safety update (DSUR)</li> </ul>

Abbreviations: DSUR, development safety update report; GCP, good clinical practice; ICH, International Council for Harmonisation; MFDS, Ministry of Food and Drug Safety; PAB/ED, Pharmaceutical Affairs Bureau / Examination Division; PESB, Pharmaceutical and Food Safety Bureau; PMDA, Pharmaceuticals and Medical Devices Agency; Q&A, questions and answers; SUSAR, suspected, unexpected, serious adverse reaction.



TABLE 5 Study site procedures

	Japan	South Korea	Taiwan	Singapore
Certification of study site by the government	No	Yes: Certified by MFDS according to Ordinances for Institution Designation	Yes: Available only at government-certified medical sites	No
IRB	Central IRB is applicable (not mandatory)	Central IRB is applicable (not mandatory)	Central IRB is applicable (central IRB is recommended but not mandatory for multicenter trials)	Central IRB is applicable
Renewal of IRB approval	Required (annually)	Required (annually)	Required (annually)	Required (annually)
ICF language	Japanese IRB information and investigator name should be described in accordance with Japanese GCP requirements	Korean If gene-/embryo cell-related testing is included, additional ICF is required (Bioethics and Safety Act, Article 24. Consenting to Genetic test) <sup>31</sup>	Chinese If central IRB is used, informed consent form template of TFDA shall be used (CDE Notification 2017/9/26) <sup>32</sup>	English, Chinese, Tamil, and Malay
Language of clinical trial agreement (for international clinical trials)	Japanese in principle (English with translation can be used in some sites)	English available	Chinese in principle (English with translation can be used in some sites)	English
SAE reporting timeline to IRB	Immediately submit all relevant institutional SAE reports to the head of the medical institution/IRB (per site's own SOP)	Death or life-threatening cases (including SUSARs); within 7 days from the investigator's awareness and within 15 days from the initial reporting SAE; within 15 days from the investigator's awareness. Accumulated SAE data will be submitted every 6 months (per site's own SOP)	Death or life-threatening cases (including SUSAR): within 7 business days from the investigator's awareness Non-death or non-life threatening cases (only SUSARs); within 15 business days from the investigator's awareness (per site's own SOP)	Death or life-threatening cases (only SUSARs); within 24 h from the investigator's awareness Non-death or non-life threatening case (only SUSARs); not later than 15 calendar days from the investigator's awareness (per site's own SOP)
Accessibility to source data documents during monitoring/audit <sup>a</sup>	No restriction	No restriction	No restriction	Certified copy checks (the policy was not to grant CRAs or Auditors access to electronic health records) Occasional spot-checks of electronic health records by CRAs allowed with site supervision and over-the-shoulder access.

Abbreviations: CDE, Center for Drug Evaluation; CRA, clinical research associate; GCP, good clinical practice; ICF, informed consent form; IRB, institutional review board; MFDS, Ministry of Food and Drug Safety; SAE, serious adverse event; SOP, standard operating procedures; SUSAR, Suspected, Unexpected, Serious Adverse Reaction; TFDA, Taiwan Food and Drug Administration.

<sup>a</sup>Status at participating sites in the PATHWAY trial.

**TABLE 6** Subject examination fee borne by study sponsor (based on the PATHWAY investigator-initiated trial experience)

	Estimated reimbursement per subject (Study treatment duration, 13 months)
Japan	US \$0 <sup>a</sup> Special or specified medical care coverage
South Korea	US \$5500–15,000
Taiwan	US \$10,000–12,000
Singapore	US \$10,000–14,000

<sup>a</sup>Partial expenses such as infectious disease test, pregnancy test, image copying fee, etc. are borne by each hospital.

sponsor (academia) must bear all study-related costs when conducting academic clinical trials for NDA submission. In the PATHWAY trial, the total estimated laboratory and registration fees paid to study sites are \$200–300 per patient. A reimbursement system similar to that of Japanese IIRDTs is desirable in other Asian countries in order to facilitate academic clinical trials for NDA submission and thereby resolve unmet patient needs. In the United States, Medicare Clinical Trial Policies<sup>28</sup> of the US Centers for Medicare & Medicaid Services stipulates that Medicare covers the routine costs of qualifying clinical trials, as well as reasonable and necessary items and services used to diagnose and treat complications arising from participation in all clinical trials.

Academia also needs to make an effort to reduce research costs. There are several operational tasks that academia cannot effectively undertake when conducting international clinical trials, for instance, functioning as the local IND holder, performing overseas site monitoring or auditing, IP labeling, and storage and transportation of IPs. Similar to most pharmaceutical companies, these tasks are commonly outsourced to contract research organizations, which can be quite expensive. One way to reduce these costs is to establish collaborative networks among academic research organizations. Such networks will enable local liaison offices to handle IND submissions, safety reporting, monitoring, etc., as a local study sponsor in each region in accordance with common study-specific SOPs. Expanding these networks should facilitate international academic trials with reduced cost. The Japanese IIRDT system provides significant benefits related to supporting study costs and improving drug access for patients with rare diseases, although some procedural rules should be improved. International harmonization of pharmaceutical regulations and clinical trial guidelines is important to encourage academic clinical trial activity not only in Japan but throughout Asia. Another way to reduce labor costs is to collaborate with an industry partner. For example, if academia can obtain an IB and DSUR from the industry partner, it would reduce labor costs and be an important logistical advantage for academia.

## CONCLUSIONS

During an academic registration-directed trial in Asia, several differences regarding regulatory and operational procedures were noted between regions. These differences should be harmonized to facilitate international academic trials in Asia and thereby resolve unmet patient needs.

## CONFLICT OF INTEREST

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## AUTHOR CONTRIBUTIONS

T.H., K.N., E.N., and Y.F. wrote the manuscript. T.H., K.N., K.Y., E.N., M.W., K.T., and Y.F. designed the research. T.H., J.S., Y.S.L., and Y.S.Y. performed the research. T.H., K.N., E.N., and Y.F. analyzed the data.

## REFERENCES

1. National Cancer Institute's Clinical Trials Network. <https://www.cancer.gov/research/infrastructure/clinical-trials/nctn>. Accessed September 6, 2020.
2. European Organisation for Research and Treatment of Cancer. <https://www.eortc.org/>. Accessed September 6, 2020.
3. Pharmaceuticals and Medical Devices Law. Ministry of Health, Labour and Welfare, Japan. <http://www.japaneselawtranslation.go.jp/law/detail/?id=3213&vm=04&re=01>. Accessed September 6, 2020.
4. Nakamura K, Shibata T. Regulatory changes after the enforcement of the new Clinical Trials Act in Japan. *Jpn J Clin Oncol*. 2020;50(4):399–404.

5. Japanese-Good Clinical Practice (J-GCP). <https://www.pmda.go.jp/files/000236359.pdf>. Accessed September 6, 2020.
6. Korean-Good Clinical Practice (K-GCP). <http://www.law.go.kr/법령/의약품안전규칙>. Accessed September 6, 2020.
7. Taiwan- Good Clinical Practice (T-GCP). <https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=L0030056>. Accessed September 6, 2020.
8. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, E6 Good Clinical Practice. <https://www.ich.org/page/efficacy-guidelines>. Accessed September 6, 2020.
9. Act on securing quality, efficacy and safety of products including pharmaceuticals and medical devices. Ministry of Health, Labour and Welfare, Japan. <http://www.japaneselawtranslation.go.jp/law/detail/?ft=1&re=01&dn=1&x=29&y=9&co=01&ia=03&ja=04&ky=%E8%96%AC%E4%BA%8B%E6%B3%95%E6%96%B-D%E8%A1%8C%E8%A6%8F%E5%89%87&page=1>. Accessed September 6, 2020.
10. Pharmacist Law. Ministry of Health and Welfare, Korea. <http://www.law.go.kr/법령약사법>. Accessed September 6, 2020.
11. Pharmaceutical Affairs Law. Ministry of Health and Welfare, Taiwan. <https://db.lawbank.com.tw/Eng/FLAW/FLAWDAT0201.aspx?lsid=FL013783>. Accessed September 6, 2020.
12. Health Products Act. Health Sciences Authority, Singapore. <https://sso.agc.gov.sg/Act/HPA2007>. Accessed September 6, 2020.
13. Regulations on Human Trials. Ministry of Health and Welfare, Taiwan. <https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=L0020162>. Accessed September 6, 2020.
14. Health Products Act Health Products (Clinical Trials). Health Sciences Authority, Singapore. <https://sso.agc.gov.sg/SL/HPA2007-S331-2016>. Accessed September 6, 2020.
15. Regulation on Good Manufacturing Practices (GMP) for Medicinal Products. Ministry of Food and Drug Safety, Korea. [https://www.mfds.go.kr/eng/brd/m\\_18/view.do?seq=71475](https://www.mfds.go.kr/eng/brd/m_18/view.do?seq=71475). Accessed September 6, 2020.
16. Pharmaceutical Good Manufacturing Practice Regulations. Ministry of Health and Welfare, Taiwan. <https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=L0030073>. Accessed September 6, 2020.
17. Guide to Good Manufacturing Practice for Medical Products. The Pharmaceutical Inspection Co-operation Scheme (PIC/S). <https://picscheme.org/en/publications>. Accessed September 6, 2020.
18. Labelling of Therapeutic Products and Medicinal Products Used in Clinical Trials. Health Sciences Authority, Singapore. [https://www.hsa.gov.sg/docs/default-source/clinical-trials/hsa\\_ctb\\_guidance\\_labelling\\_mp\\_tp\\_31jan2018.pdf](https://www.hsa.gov.sg/docs/default-source/clinical-trials/hsa_ctb_guidance_labelling_mp_tp_31jan2018.pdf). Accessed September 6, 2020.
19. Medicines (Clinical Trials) Regulations. Health Sciences Authority, Singapore. <https://sso.agc.gov.sg/SL/MA1975-S335-2016>. Accessed September 6, 2020.
20. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. Ministry of Health, Labour and Welfare, Japan. <https://www.pmda.go.jp/files/000156127.pdf>. Accessed September 6, 2020.
21. Reporting of Adverse Drug Reactions Occurring in Clinical Trials to PMDA. Ministry of Health, Labour and Welfare, Japan. <https://www.mhlw.go.jp/hourei/doc/tsuchi/T200901I0160.pdf>. Accessed September 6, 2020.
22. Korea MFDS guideline of SUSAR reporting. Ministry of Food and Drug Safety, Korea. <https://nedrug.mfds.go.kr/bbs/38/67/#>. Accessed September 6, 2020.
23. Regulations for Reporting Severe Adverse Reactions of Medicaments. Ministry of Health and Welfare, Taiwan. <https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=L0030049>. Accessed September 6, 2020.
24. Expedited Safety Reporting Requirements for Therapeutic Products and Medicinal Products used in Clinical Trials. Health Sciences Authority, Singapore. [https://www.hsa.gov.sg/docs/default-source/clinical-trials/hsa\\_ctb\\_guidance\\_expedited\\_safety\\_reporting\\_2may2017.pdf](https://www.hsa.gov.sg/docs/default-source/clinical-trials/hsa_ctb_guidance_expedited_safety_reporting_2may2017.pdf). Accessed September 6, 2020.
25. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. <https://www.ich.org/page/efficacy-guidelines>. Accessed September 6, 2020.
26. Health insurance law. Ministry of Health, Labour and Welfare, Japan. <http://www.japaneselawtranslation.go.jp/law/detail/?ft=1&co=01&ia=03&ja=04&x=0&y=0&ky=%E5%81%A5%E5%BA%B7%E4%BF%9D%E9%99%BA%E6%B3%95&page=15&re=02>. Accessed September 6, 2020.
27. Rules for Health Insurance-covered Medical Facilities and Medical Practitioners. Ministry of Health, Labour and Welfare, Japan. [https://elaws.e-gov.go.jp/search/elawsSearch/elaws\\_search/lsq0500/detail?lawId=332M50000100015\\_20190701\\_501M60000100020&openerCode=1#125](https://elaws.e-gov.go.jp/search/elawsSearch/elaws_search/lsq0500/detail?lawId=332M50000100015_20190701_501M60000100020&openerCode=1#125). Accessed September 6, 2020.
28. Medicare Clinical Trial Policies. Centers for Medicare & Medicaid Services, US <https://www.cms.gov/Medicare/Coverage/ClinicalTrialPolicies>. Accessed September 6, 2020.
29. Guideline for Compensation of Subjects, Japan Pharmaceutical Industry Legal Affairs Association, Japan. [https://www.ihoken.or.jp/pdf/guideline\\_20181225.pdf](https://www.ihoken.or.jp/pdf/guideline_20181225.pdf). Accessed November 8, 2020.
30. ABPI Clinical trial compensation guidelines, Association of the British Pharmaceutical Industry, UK. <https://abpi.org.uk/publications/ct-compensation/>. Accessed November 8, 2020.
31. Bioethics and Safety Act, Ministry of Health and Welfare, Korea. [http://elaw.klri.re.kr/eng\\_mobile/viewer.do?hseq=33442&type=part&key=36](http://elaw.klri.re.kr/eng_mobile/viewer.do?hseq=33442&type=part&key=36). Accessed November 8, 2020.
32. c-IRB Drug Clinical Trial Informed Consent Form Sample, Center for Drug Evaluation, Taiwan. [https://www.cde.org.tw/news/news\\_more?id=117](https://www.cde.org.tw/news/news_more?id=117). Accessed November 8, 2020.

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