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Compliance with Good Clinical Practice in oncology registration trials in Japan

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Background: This study aimed to examine the quality in oncology registration trials for new drug application (NDA) or supplemental new drug application (sNDA) as extensions of the indications for use in Japan based on Good Clinical Practice (GCP) audit findings.

Materials and methods: We collected audit reports of on-site GCP inspections for registration trials in 383 NDAs or sNDAs that were reviewed by the Pharmaceuticals and Medical Devices Agency between the fiscal years 2004 and 2009.

Results: Among the 40 audits for oncology drug applications, the frequencies at which one or more deficiencies ascribed to institution, investigator, sponsor, and institutional review board were found to be 15 (37.5%), 13 (32.5%), 21 (52.5%), and 10 (25.0%), respectively. The exclusion of patients from the review objective due to serious violations of GCP in 40 audits for oncology drug applications was observed in 2 (5.0%) cases, whereas that in the remaining 343 audits for other drug applications was observed in 40 (11.7%) cases.

Conclusion: The overall compliance of GCP in oncology registration trials was moderately better than that in registration trials for other diseases, although there was no statistically significant difference between them.

Key words: audit, cancer, compliance, Good Clinical Practice, inspection, registration trial

introduction

Approval of new drug applications (NDA) or supplemental new drug applications (sNDA) for extension of the range of indication and/or posology as well as the method of administration is based on collecting evidential materials from registration trials that are strictly managed in terms of quality control and quality assurance. The registration trials for applications are conducted in conformity with Good Clinical Practice (GCP) that provides corroboration of both ethics and science. The purpose of GCP is to protect the human rights and safety of the subjects and is based on the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subject in order to ensure accurate data and reliability in registration trials [1]. The Ministry of Health and Welfare [currently Ministry of Health, Labour and Welfare (MHLW)] of Japan had issued instructions regarding the old GCP guideline in October 1990, which was not legally binding [2]. In April 1997, a new GCP guideline was enforced in response to the implementation of the GCP released by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use for all Japanese registration trials that began from April 1998 onward [3, 4]. Major differences between the old and new GCP guidelines are related to the acquisition of written informed consent documents, intensification of the responsibility of the sponsor, clarification of the responsibility and role of the principal investigator, and improvements in the function of the institutional review board (IRB) and supports for registration trials [2, 3].

In Japan, the number of clinical trial protocol notifications for oncology drug applications is rapidly increasing with each passing year; oncology drug applications comprised ~15% of all clinical trial protocol notifications in the fiscal year 2007 [5]. The number of clinical trial protocol notifications among global registration trials has been increasing substantially; moreover, clinical trial protocol notifications for oncology drugs comprised 59% of global clinical trial protocol notifications, making it the largest field in drug applications in the fiscal year 2007 [6]. It appears that clinical development in the oncology drug field became both active and stable in Japan around this time. These conditions have also made it easier to carry oncology registration trials with sufficient quality according to GCP as compared with that in other drug fields.

Clinical trials for oncology drugs have many differentiating features as compared with those for other drugs. In oncology clinical trials, complicated inclusion/exclusion criteria, frequent dose modifications caused by toxic effects, numerous

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prohibited concomitant medications, tight schedules of clinical assessments, and long follow-up periods are required. In addition, since the pharmacological effects of oncology drugs generally influence cell proliferation or cell division, a large number of adverse events are frequently reported in oncology clinical trials as compared with clinical trials for other drugs. Thus, enormous effort and responsibility are imposed on trial participants, such as institutions, investigator, IRBs, and sponsors.

In this study, we examined GCP compliance in oncology registration trials in order to ensure high-quality clinical trials in Japan. The GCP compliance of the registration trials for NDA and sNDA was examined based on the Pharmaceuticals and Medical Devices Agency's (PMDA) judgment on recent overall results of on-site GCP audits. We have discussed the quality of oncology registration trials through a comparison of the deficiencies found in GCP inspections that were ascribed to the institution, investigator, sponsor, and IRB between 40 oncology drugs applications and 343 drug applications for other diseases.

materials and methods

GCP inspection of PMDA in Japan

The Office of Conformity Audit of PMDA carried out GCP inspections that consisted of document-based conformity audit at the PMDA along with on-site GCP audits [7]. The document-based conformity audit exhaustively inspects the consistency between application materials attached to the application form for approval and all evidential materials of all institutions retained by study sponsors (e.g. case report forms, monitoring records, etc.) from the viewpoint of Good Laboratory Practice, GCP, and conformity criteria of the application materials. The on-site GCP audit inspects the consistency between raw data (e.g. medical records, examination slips, and patient diaries) as evidential materials of surveyed medical institutions and evidential documents of surveyed institutions held by study sponsors (e.g., case report forms). In addition, the on-site GCP audit inspects the general institutional structure for registration trials at the institution (e.g. administration of the medical institution, IRB, maintenance of essential archives, and investigational drug accountability of the pharmacy). The objectives of on-site GCP audits in trial applications have been previously defined [8]. On-site GCP audits are generally carried out for four institutions in NDA and two institutions in sNDA. An institution in Japan or another country enrolling many patients into a pivotal registration trial of application is selected for on-site GCP audit. The PMDA finally judges GCP compliance as follows: conformation, conformation with proviso, or nonconformation. The results are sent to both the sponsor and the institution.

Conformation indicates complete compliance with the GCP in the registration trial for the application. Conformation with proviso means that the PMDA imposes the exclusion of patients from the review objective due to serious violations of the GCP and evaluates the registration trial comprising the remaining patients. If a critical GCP violation concerning ethics and/or science in the registration trial is found, the PMDA judges that all the materials in the registration trial related to GCP nonconformation should be deleted from the application for NDA or sNDA. In this case, the PMDA generally concludes in favor of rejection of the application. It should be noted that when the PMDA's judgment is nonconformation, these results are not publicly released; therefore, the frequency of nonconformations is not investigated.

data sources

In Japan, for each application, on-site GCP inspection for the registration trials—including trials conducted in Japan and overseas for the drugs—are conducted, and their comprehensive audit results are publicly released with exposures of the deficiencies found in GCP inspections that are ascribed to the institution, investigator, sponsor, and IRB [9]. In this study, 344 audits, which were reviewed by the PMDA and approved by the MHLW of Japan between April 2004 and March 2010 (fiscal years 2004 to 2009), were examined, excluding public domain approvals and audits without on-site GCP inspections [10]. For each audit, the following data were collected: medicinal classification of the approved drug, approval year, the PMDA's judgment on GCP compliance (conformation with/without proviso), the number of patients excluded due to serious violations of GCP, GCP deficiencies, and responsible participants of deficiencies (institution, investigator, sponsor, and IRB).

Fisher's exact test was used to compare the frequency distributions with respect to the deficiencies between the audits for anticancer drugs and those for other diseases. A two-sided $P \leq 0.05$ was considered to be statistically significant. All the analyses were carried out using the SAS software (version 9.1; SAS Institute Inc., Cary, NC).

results

conformation with/without proviso

The approval years and medicinal classifications for 383 audits are shown in Table 1. The audits for oncology drug applications comprised 40 (10.4%) of the 383 audits.

Table 2 shows the proportions of conformation with/without proviso overall and for each medicinal classification. Overall, 89.6% of conformation and 10.4% of conformation with proviso were observed. Among the 42 audits judged as conformation with proviso, the frequencies of audits with ≥1 deficiencies ascribed to the institution, investigator, IRB, and sponsor were 34 (81.0%), 23 (54.8%), 12 (28.6%), and 25 (59.5%), respectively. Additionally, the frequencies of audits in each deficiency ascribed to each responsible participant are shown in Table 3.

Conformation with proviso in 40 audits for anticancer drug applications were observed in 2 (5.0%) cases, whereas that in the remaining 343 audits for the other disease applications was observed in 40 (11.7%) ($P = 0.286$). The proportion of conformation with proviso in cancer registration trials tended to be smaller than that in the registration trials for other disease applications, although the number of audits varied depending upon the medicinal classification. Furthermore, although the number of excluded patients was unknown in 9 audits, among the 42 audits judged as conformation with proviso, the median number of excluded patients was 3 (range 1–182) in the remaining 33 audits.

responsible participants due to deficiencies

Table 4 shows the distributions of audits in which one or more deficiencies were ascribed to the responsible participants overall and in each medicinal classification. The proportion of approvals with ≥1 deficiencies ascribed to the institution, investigator, IRB, and sponsor were 15 (37.5%), 13 (32.5%), 10 (25.0%), and 21 (52.5%) in 40 audits, respectively, for oncology drug applications and 168 (49.0%), 145 (42.3%), 78 (22.7%), and 169 (49.3%),

Table 1. Summary of 383 registration trial approvals [*n* (%)]

Medicinal classification	Approval year, fiscal year						Total
	2004	2005	2006	2007	2008	2009	
Neurological	1 (4.2)	3 (7.3)	8 (12.3)	10 (10.9)	8 (11.0)	17 (19.3)	47 (12.3)
Metabolic	1 (4.2)	6 (14.6)	12 (18.5)	15 (16.3)	18 (24.7)	17 (19.3)	69 (18.0)
Oncology	2 (8.3)	7 (17.1)	6 (9.2)	8 (8.7)	9 (12.3)	8 (9.1)	40 (10.4)
Cardiovascular	3 (12.5)	3 (7.3)	4 (6.2)	7 (7.6)	10 (13.7)	9 (10.2)	36 (9.4)
Respiratory	1 (4.2)	1 (2.4)	1 (1.5)	2 (2.2)	0 (0.0)	5 (5.7)	10 (2.6)
Gastrointestinal	0 (0.0)	1 (2.4)	3 (4.6)	10 (10.9)	2 (2.7)	6 (6.8)	22 (5.7)
Hormonal	2 (8.3)	3 (7.3)	7 (10.8)	6 (6.5)	8 (11.0)	7 (8.0)	33 (8.6)
Urological	2 (8.3)	1 (2.4)	4 (6.2)	5 (5.4)	3 (4.1)	1 (1.1)	16 (4.2)
Antimicrobial	7 (29.2)	7 (17.1)	10 (15.4)	16 (17.4)	4 (5.5)	9 (10.2)	53 (13.8)
Biologics	2 (8.3)	4 (9.8)	5 (7.7)	6 86.5)	5 (6.8)	7 8.0)	29 (7.6)
Others	3 (12.5)	5 (12.1)	5 (7.7)	7 (7.6)	6 (8.2)	2 (2.3)	28 (7.3)
Total	24 (100)	41 (100)	65 (100)	92 (100)	73 (100)	88 (100)	383 (100)

Table 2. PMDA's judgment on GCP compliance in oncology and other drug audits [*n* (%)]

Judgments	Medicinal types		Total
	Oncology	Others	
Conformation (without proviso)	38 (95.0)	303 (88.3)	341 (89.6)
Conformation with proviso	2 (5.0)	40 (11.7)	42 (10.4)

Fisher's exact test for contingency table of judgments and medicinal types: $P = 0.286$.

GCP, Good Clinical Practice; PMDA, Pharmaceuticals and Medical Devices Agency.

respectively, in the remaining 343 audits for other drug applications. The deficiencies ascribed to the institution and investigator in the cancer registration trials tended to be lesser than those in the registration trials for other diseases ($P = 0.184$ for institution and $P = 0.309$ for investigator).

deficiencies ascribed to responsible participants

Table 5 shows the frequencies of audits in each deficiency ascribed to each responsible participant overall and in each medicinal classification. The deficiencies related to archives, eligibility criteria, and prohibited concomitant therapies in 40 audits for oncology drug applications were 1 (2.5%), 2 (5.0%), and 0 (0.0%), respectively, whereas those in the 308 other drug audits were 47 (13.7%), 43 (12.5%), and 28 (8.2%), respectively ($P = 0.043$ for archives, $P = 0.201$ for eligibility criteria, and $P = 0.099$ for prohibited concomitant therapies). On the other hand, the deficiency of 'insufficient review' by the IRB in 40 audits for oncology drug applications was higher than that in the 343 other drug audits (17.5% versus 5.5%, $P = 0.012$).

discussion

The results of the present study indicated that the overall compliance of GCP in oncology registration trials was passably better than that in registration trials for other diseases, although there was no statistically significant difference between them. According to Table 5, the problems related to archives in institutions were lesser but insufficient reviews by the IRB were more frequent in the oncology drug applications when compared with those for other diseases. Therefore, completeness of IRB reviews would enhance quality of drug applications in the oncology field.

Previous studies have analyzed a number of GCP deficiencies in registration trials for NDA or sNDA, approved by the MHLW of Japan, from the fiscal year 1997 to 2006 [11–18]. Since a white paper or annual report regarding the overall results of on-site GCP audit has not been officially published, these studies have repeatedly used the same data that were partly released by the PMDA, workshops, or symposiums. In addition, most of these studies examined GCP deficiencies immediately after the enforcement of the new GCP guidelines [11–15]. The examination of compliance with GCP in registration trials for NDA or sNDA in recent times is required.

Our study demonstrated 10.4% of conformations with proviso in registration trials overall in the past 5 years. Previous studies have reported that conformations with proviso comprised 17.6% of registration trials during the fiscal years 2001 and 2003 [16]. Based on the results of the present study and those of previous studies, compliance with GCP in Japanese registration trials has generally been improving [16, 17]. Furthermore, the present study revealed the overall GCP compliance of oncology registration trials tended to be better than that of registration trials for other drugs.

The present study revealed trial institution deviations, investigator deviations, and sponsor deviations in 40%–50% of the audits. The frequencies of deviations related to the trial institution or investigator were lower in the oncology registration trials as compared with those in the other drug registration trials. This may be because the development of oncology drugs is highly specialized; therefore, research sources—including the trial institution, investigator, and other health care professionals—for the registration trials of oncology drugs have much greater experience and can carry registration trials with greater compliance.

Table 3. Frequencies of audits in each deficiency ascribed to each responsible participant in 42 approvals judged as conformation with proviso

Responsible participants	Deficiencies	*n* (%)
Institution	Qualification requirements of hospitals were not met	6 (14.3)
	Lack of appropriate SOP	0 (0.0)
	All investigators were not identified in the contract	0 (0.0)
	Inappropriate contract	6 (14.3)
	Inappropriate informed consent	11 (26.2)
	CRFs filled incorrectly/and or insufficiently	8 (19.1)
	Problems related to archives	19 (45.2)
	Delay in communication of safety information	3 (7.1)
	Others	6 (14.3)
Investigator	Eligibility criteria were not met	13 (31.0)
	Prohibited concomitant therapies	7 (16.7)
	Laboratory tests were not performed according to the defined protocol	9 (21.4)
	Nonobservance of dose and/or schedule provided by the protocol	8 (19.1)
	Others	8 (19.1)
Sponsor	Inappropriate monitoring	24 (57.1)
	Delay in communication of safety information to institution	4 (9.5)
	Others	2 (4.8)
IRB	Qualification requirements of IRB were not met	2 (4.8)
	Lack of appropriate SOP	1 (2.4)
	Insufficient review	4 (9.5)
	Insufficient minutes of meetings	2 (4.8)
	Others	7 (16.7)

IRB, institutional review board; SOP, standard operational procedure; CRFs, case report forms.

Table 4. Frequencies of audits in which one or more deficiencies ascribed to the responsible participants were found by GCP inspection in oncology and other registered trials [*n* (%)]

Responsible participants	Medicinal type		Total	*P* value[a]
	Oncology	Others		
Institution				0.184
Yes	15 (37.5)	168 (49.0)	183 (47.8)	
No	25 (62.5)	175 (51.0)	200 (52.2)	
Investigator				0.309
Yes	13 (32.5)	145 (42.3)	158 (41.3)	
No	27 (67.5)	198 (57.7)	225 (58.8)	
IRB				0.696
Yes	10 (25.0)	78 (22.7)	88 (23.0)	
No	30 (75.0)	265 (77.3)	295 (77.0)	
Sponsor				0.740
Yes	21 (52.5)	169 (49.3)	190 (49.6)	
No	19 (47.5)	174 (50.7)	193 (50.4)	

[a]Fisher's exact test for contingency table of the presence of deficiencies ascribed to each responsible participant and medicinal types.
GCP, Good Clinical Practice; IRB, institutional review board.

Drug development generally takes considerably long due to the on-site GCP audit in response to a trial application. However, problems related to archives would essentially relate to the reliability of the registration trial regarding the existing subjects, ethics, and science. We noted no problems related to archives in the oncology drug registration trials; the frequency of this deficiency was clearly lower for oncology drugs as compared with other drugs. Thus, the compliance with GCP regarding archives was satisfactory in oncology drug registration trials.

The frequency of protocol deviation in oncology fields is lower than that for other medicinal classifications; however, protocol deviations for eligibility criteria or use of prohibited concomitant therapies would influence subject safety in registration trials. Therefore, investigators, clinical research coordinators (CRC), and other health care professionals who support registration trials should make an effort to have sufficient knowledge regarding the target disease and treatment and keep track of details regarding the protocol and GCP. The incidence of deficiencies at domestic investigational sites with CRC was 21% ($N = 270/1260$), which was lower than that of deficiencies at domestic investigational sites without CRC, i.e. 58% ($N = 188/325$) [7, 18]. Therefore, an effective approach for reducing deficiencies associated with protocol deviation would entail the careful selection of trial institutions with sufficient numbers of well-trained CRCs and suitable conditions for carrying out monitoring.

In the present study, deficiencies in monitoring were most frequent both overall and in sponsor deviations. Monitoring of the medical institution by the sponsor is enforced by GCP in order to ensure appropriate operation of the registration trial according to trial protocol and GCP. A previous study indicated that typical monitoring issues associated with sponsors in the fiscal year 2005 were as follows: operation of monitoring associated with standard operation procedure and source document verification (41%), timing of monitoring (9.5%), taking appropriate precautions to prevent deviation by monitoring report (8.5%), submission of monitoring report (5.5%), and other (35.5%) [18]. Appropriate monitoring for registration trial by a monitor who has been specifically trained and possesses scientific and clinical knowledge is important for ensuring quality control and quality assurance of registration trials. For further improvement in reducing deficiencies in monitoring, the monitor in the sponsor organization or contract research organization (CRO) should be sufficiently familiar with the protocol and GCP. Improved performance of various parties in the registration trial would not only facilitate operation of the registration trial by the sponsor but also the operation of investigator-initiated registration-directed clinical trials by the investigator, according to the revised GCP enforced from July 2003 [19].

Another major item of deficiency related to the sponsor is a delay in communicating information regarding adverse drug reactions; this is related to subject safety, ethics, and operation of the registration trial. A seamless communication system for delivering critical information is important for ensuring subject safety and appropriate operation of the registration trial. In

Table 5. Frequencies of audits in which each deficiency was found by GCP inspection in oncology drug and other drug applications [*n* (%)]

Responsible participants	Deficiencies	Oncology	Others	Total	*P* value[a]
Institution	Qualification requirements of hospitals were not met	1 (2.5)	6 (1.8)	7 (1.8)	0.541
	Lack of appropriate SOP	0 (0.0)	0 (0.0)	0 (0.0)	–
	All investigators were not identified in the contract	0 (0.0)	3 (0.9)	3 (0.8)	1.000
	Inappropriate contract	2 (5.0)	17 (5.0)	19 (5.0)	1.000
	Inappropriate informed consent	3 (7.5)	26 (7.6)	29 (7.6)	1.000
	CRFs filled incorrectly/and or insufficiently	8 (20.0)	81 (23.6)	89 (23.2)	0.696
	Problems related to archives	1 (2.5)	47 (13.7)	48 (12.5)	0.043
	Delay in communication of safety information	2 (5.0)	21 (6.1)	23 (6.0)	1.000
	Others	4 (10.0)	36 (10.5)	40 (10.4)	1.000
Investigator	Eligibility criteria were not met	2 (5.0)	43 (12.5)	45 (11.8)	0.201
	Prohibited concomitant therapies	0 (0.0)	28 (8.2)	28 (7.3)	0.099
	Laboratory tests were not carried out according to the defined protocol	6 (15.0)	59 (17.2)	65 (17.0)	0.823
	Nonobservance of dose and/or schedule provided by the protocol	5 (12.5)	23 (6.7)	28 (7.3)	0.195
	Others	5 (12.5)	48 (14.0)	53 (13.8)	1.000
IRB	Qualification requirements of IRB were not met	1 (2.5)	5 (1.5)	6 (1.6)	0.487
	Lack of appropriate SOP	0 (0.0)	2 (0.6)	2 (0.5)	1.000
	Insufficient review	7 (17.5)	19 (5.5)	26 (6.8)	0.012
	Insufficient minutes of meetings	0 (0.0)	12 (3.5)	12 (3.1)	0.623
	Others	2 (5.0)	49 (14.3)	51 (13.3)	0.138
Sponsor	Inappropriate monitoring	19 (47.5)	136 (39.7)	155 (40.5)	0.395
	Delay in communication of safety information to institution	5 (12.5)	50 (14.6)	55 (14.4)	1.000
	Others	1 (2.5)	13 (3.8)	14 (3.7)	1.000

[a]Fisher's exact test for contingency table of the presence of each deficiency and medicinal types.
GCP, Good Clinical Practice; IRB, institutional review board; SOP, standard operational procedure.

recent drug development protocols, registration trials such as randomized clinical trials are carried out globally in various trial institutions; in such a scenario, worldwide regional offices of the sponsor would be ideal for improving communication systems and ensuring smooth and timely communication.

There have been various approaches for improving social and scientific infrastructure for clinical research in Japan by academia, industry, and the government. In 2003, the MHLW drew up and published the nationwide 3-year clinical trial activation plan, under which it promoted various measures, including the creation of clinical trial networks and fostering of CRC. Subsequently, the MHLW created the office of clinical trial promotion, research, and development and launched the new 5 yearly clinical trial activation plan in 2007, which was expected to reinforce clinical research infrastructure to ensure patient safety and to secure access to new drugs and devices [20]. Furthermore, the MHLW science research grants 'research on clinical trials infrastructure development' were inaugurated to support framework development for promoting clinical trials (comprising grants to 10 leading academic medical centers). Thus, a study on 'the development of individual health care institution infrastructure models aimed at equally sharing cancer research infrastructure development' was started, and it became possible to pursue favorable institutional infrastructure development and human resources training concerning the ethical aspects of clinical research and methods of new drug development in the National Cancer Center Hospital [21, 22]. Furthermore, the Japanese Ministry of Education, Culture, Sports, Science and Technology provided grants to five universities and a clinical research organization named 'Coordination, Support and Training Program for Translational Research' in 2007 and onward [22, 23]. These various approaches promoted the establishment of a clinical trial infrastructure; we believe that an adequate infrastructure would be the optimal influence for ensuring compliance with GCP in registration trials.

Our study had certain limitations. We were not able to use the full data of on-site GCP audits for a number of trial institutions—such as the trial institution background, i.e. scale (university hospital, national hospital, private hospital, and clinic), region (Japan or other countries), number of subjects under on-site GCP audit, presence of supporting system for registered trial (CRC, site management organization, CRO, etc.)—because the PMDA review reports for on-site GCP audit are the only available data source and these do not have detailed data. Therefore, it is difficult to directly compare the results of the present study with those of previous studies. Because there

are few reports of on-site GCP audits by regulatory agencies, the present study described differences in deficiencies from on-site GCP audits between Japan and other countries. For further improving global compliance with GCP, we consider that each regulatory agency should disclose detailed results of on-site GCP audits on a regular basis.

GCP inspections have indicated certain deficiencies in the data of registration trials and the operation systems of registration trials; these were evaluated in the regulatory reviews of NDA or sNDA. However, the most important purpose of GCP inspection is to prevent a recurrence of GCP deficiencies for establishing higher quality in drug development. In 2009, the European Medicines Agency (EMEA) and the Food and Drug Administration (FDA), USA, initiated the EMEA–FDA GCP initiative that focuses upon enhanced and systematic GCP-related information exchanges between the EMEA and FDA combined with collaboration in the conduct of GCP inspections of registration trials [24]. The results of the present study suggest that the principle of compliance with GCP for registration trials has reached Japanese investigators and trial institutions, and high-quality GCP inspections are thereby being carried out by the PMDA. The clinical development of medicines is a global undertaking. Therefore, in the future, we consider it important that all regulatory agencies work in a collaborative and synergistic manner in order to achieve a system for the optimal use of GCP inspection resources and results and implement information exchanges.

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disclosure

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PHASE III STUDIES

The notorious "drug lag" for oncology drugs in Japan

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Summary This study aimed to analyze the oncology "drug lag" (i.e., the delay in time required for the approval of oncology drugs) in Japan compared with that in the United States of America (US) or the European Union (EU) and to identify the factors associated with this lag. Using publicly available information, we collected data on 42 approvals of 30 oncology drugs in Japan, the US, and the EU that included dates of drug development initiation, submission, review, and approval. Lags in each step of the process were then examined and compared among the three regions. We found that median submission and approval lag times between Japan and the US were 20.0 and 29.9 months, respectively, while those between Japan and the EU were 14.9 and 21.3 months, respectively. The median review periods for Japan, the US, and the EU were 14.3, 6.0, and 13.2 months, respectively, and the median lag in initiation of oncology drug development between Japan and the US/EU was 38.9 months. The proportion of approvals for which Japanese Phase I registration trials started after corresponding approvals in the US were 39% compared with 47% for the EU. Multivariate analysis suggests that delays in the initiation of drug development and the extended length of the regulatory review period in Japan may contribute to the longer oncology drug lag observed in Japan compared with that of the US or EU.

Keywords Oncology · Drug lag · Delay · Registration trial · Approval · Drug development

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Introduction

New drug development is a gradual process involving several stages of scientific and objective evaluation. After preclinical trials using cultured cells or animal models are conducted to evaluate a drug's potential efficacy, toxicology, or mechanism of action, Phase I clinical trials involving humans are undertaken to determine the recommended administration dose and schedule depending upon the safety profile derived from dose-limiting toxicity studies. Then, the Phase II and Phase III (or "pivotal") clinical trials are carried out to develop preliminary and confirmatory evidence, respectively, for efficacy and safety of the new agent as compared with conventional treatment.

After these registration trials, a pharmaceutical company submits a new drug application (NDA) or supplemental NDA (sNDA) that includes all trial data to the regulatory agency of the country, and the regulatory agency reviews the risk/benefit balance of the NDA or sNDA. When such an application is positively reviewed and approved, thus, patients allows to benefit from the approved drug treatment.

Each country has specific laws and regulatory controls that govern pharmaceutical affairs for NDAs or sNDAs; however, these controls often differ from country to country. Therefore, the time required for approval of an NDA or sNDA may vary depending on each country's regulatory process. In Japan, the notorious "drug lag" (i.e., the delay in time required for the approval of drugs) for

NDA and sNDA approvals has recently become a major social issue [1, 2]. One study showed that the delay between the approval of a new drug in the United States (US) versus approval of the same drug in Japan was approximately 2.5 years [3]. Another study reported that the mean time required for approval of new biologics was 3.7 months in the US, 7.5 months in the European Union (EU), and 52.6 months in Japan [4].

Oncology drugs are prescribed for the treatment of cancer, which is a major cause of mortality in developed countries; therefore, a lag in the availability of oncology drugs is a direct threat to life and is naturally of particularly high interest to the public. To the best of our knowledge, no report regarding the drug lag for oncology drugs in Japan has yet been published, and the factors associated with this problem remain unknown. Therefore, identifying the actual status of the oncology drug lag in Japan and the factors that influence the drug approval process not only in Japan but also in other countries would provide important information that could be used in efforts to resolve this issue.

In the present study, we discuss the oncology drug lag in Japan through an examination of the delays inherent in processes related to drug development, submission, and approval in Japan compared with the US/EU; we also examine in detail the timing of the regulatory review process for the three regions.

Materials and methods

Data sources and analyses

The Pharmaceuticals and Medical Devices Agency (PMDA) is a Japanese regulatory agency working in conjunction with the Ministry of Health, Labour and Welfare (MHLW) [5]. The major functions of the PMDA include conducting drug and medical device reviews, evaluating post-marketing safety, and providing relief services related to adverse drug effects. The PMDA conducts scientific reviews of marketing authorization applications for pharmaceuticals and medical devices as well as clinical trial consultations. On the basis of these reviews, the MHLW evaluates NDAs and sNDAs for Japan for approval or disapproval.

We examined 88 approvals for 53 drugs that were approved in Japan between 2000 and 2009. Multiple approvals for the same drug involved its use in the treatment of multiple malignant diseases. For these 88 approvals, the dates of drug development initiation, review submission, review duration, and approval in Japan, the US, and the EU were collected. The date of drug development initiation was defined as the date of first patient enrollment in the earliest phase registration trial for an NDA or sNDA. These data were extracted from the PMDA's review reports and from documents submitted by the application sponsors, as publicly released on the PMDA website [6]. Additionally, for each drug, the following information was collected: target cancer type (solid malignancy/hematologic malignancy), drug type (molecular-targeted drugs/small-molecular-targeted agents or antibody agents/other non-molecular-targeted drugs), application type (NDA/sNDA), review type (regular/priority), orphan drug status (yes/no), and whether approval was being sought for a public domain application (yes/no). The same data for the US and EU were also gathered from review reports of each region's regulatory agency [7–9]. Not all of these data could be collected for each approval; therefore, the analyzed number of approvals from Japan and the US/EU are not identical.

Among the 88 approvals, 16 applications were approved without registration trial data because the applications were eligible for being in the public domain (Fig. 1). Further, 30 approvals had not yet been approved in the US or EU at the time of approval in Japan. These approvals were excluded from the evaluation; therefore, 42 approvals for 30 drugs were examined in this study. The lags in the dates of development, submission, and approval between Japan and the US and/or EU and the periods required for review among three regions were calculated. The factors associated with the lag in approval between Japan and the other two regions were explored by multivariate analysis.

Results

Lags in the approval and submission process, review period, and initiation of drug development between Japan and the US/EU

The characteristics of the 42 approvals studied are shown in Table 1. The median submission and approval lags were 20.0 (N=33) and 29.9 (N=42) months, respectively, between Japan and the US, while those between Japan and the EU were 14.9 (N=24) and 21.3 (N=40) months (Fig. 2).

The median review periods for Japan, the US, and the EU were 14.3 (N=42), 6.0 (N=33), and 13.2 (N=24) months, respectively (Fig. 3). In many cases, drug development in the US and EU was initiated in parallel, so we calculated the lag time in drug development initiation between Japan and the US/EU. The median delay in the initiation of drug development for oncology drugs between Japan and the US/EU was found to be 38.9 months (N=19) (Fig. 4).

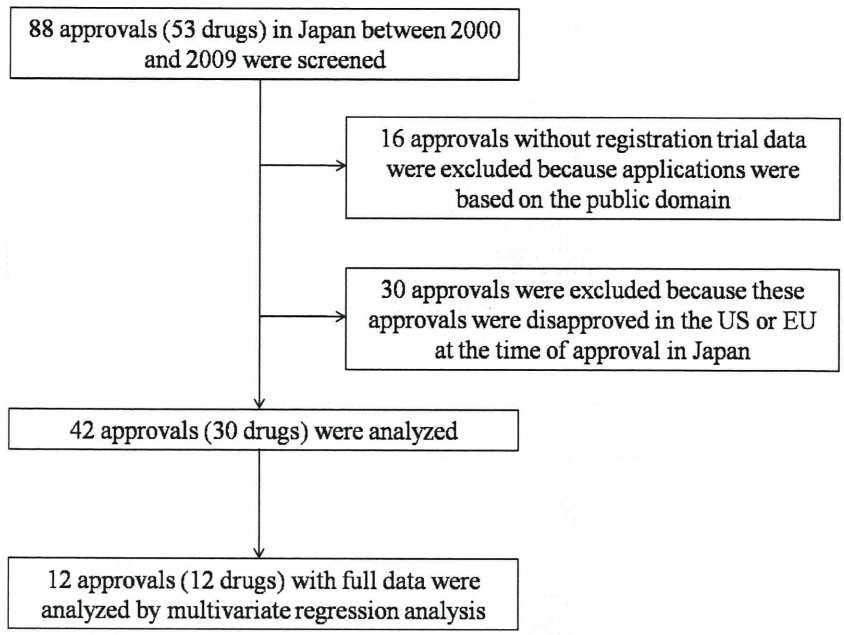

Fig. 1 Diagram of selection of study objects

Factors associated with approval lags between Japan and the US/EU

For 12 approvals of 12 drugs for which all data were completely collected, we used multivariate regression analysis to examine the impact of submission lag, review period duration, targeted cancer type (solid vs. hematologic malignancy), and drug type (molecular-targeted vs. non-molecular-targeted drugs) on the approval lag between Japan and the US/EU. The results are shown in Table 2. All of the variables, excluding submission lag, were significantly associated with the approval lag.

Additionally, the development status of drugs in the US and EU at the start date of Phase I oncology trials in Japan is shown in Table 3. The number of drug approvals for which Japanese Phase I registration trials started after the drug had been submitted for approval in the US was 13 out of 33 (39%); in the EU, this number was 16 out of 34 (47%).

Discussion

Our study indicated that several factors are significantly associated with the oncology drug lag in Japan. We observed that the initiation of drug development in Japan for many oncology pharmaceuticals began after the NDA/sNDA for these same drugs had already been submitted or approved in the US or EU. Therefore, Japanese pharmaceutical companies should coordinate oncology drug development with pharmaceutical development in other countries in order to reduce duplication of effort and minimize drug development delays. The review period required by the Japanese regulatory agency needs to be reduced in order to minimize the drug lag for oncology drugs, and this can occur only with the concerted efforts of the pharmaceutical companies, the PMDA, and concerned academia. Oncology drugs classified as "drugs for hematologic malignancy" and "non-molecular-targeted drugs" were associated with increased drug lag. This may be

Table 1 Characteristics of 42 approvals for 30 drugs approved in Japan, the US, and EU

Variables		Number of drugs (%)
Submission	NDA	24 (57.1)
	sNDA	18 (42.9)
Malignancy	Solid	29 (69.1)
	Hematologic	13 (30.1)
Drug type	Molecular-targeted drug	20 (47.6)
	Non-molecular- targeted drug	22 (52.4)
Orphan	Yes	17 (40.5)
	No	25 (59.5)
Review	Standard	9 (21.4)
	Priority	33 (78.6)

NDA new drug application; *sNDA* supplemental new drug application

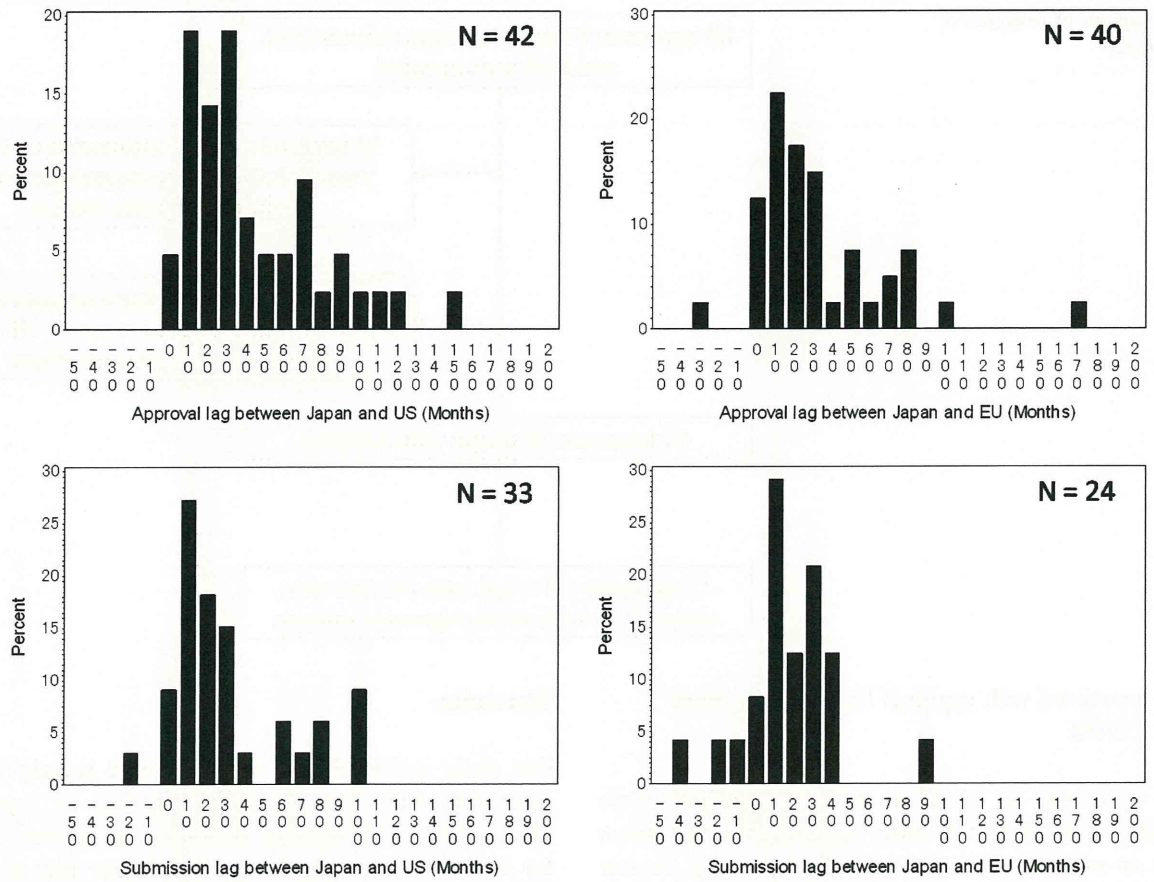

Fig. 2 Histograms of approval lags and submission lags between Japan and the US/EU

because hematologic malignancy is generally a rare disease associated with slow enrollment of patients in registration trials as compared with solid malignancy. Further, NDAs/sNDAs for molecular-targeted drugs may tend to achieve priority review status as compared to non-molecular-targeted drugs. Based on our results, both factors contributed to delays in the initiation of oncology drug development in Japan.

Drug lag is closely affected by pharmaceutical regulation. The regulatory standards for registration trials and evaluation procedures for oncology drugs in Japan have dramatically changed over the last decade following publication by the MHLW of two important notifications related to global oncology registration trials in Japan [10, 11]. "Guidelines on Methods of Clinical Evaluation of Oncology," published in November 2006, included important revisions that required evidence from confirmatory Phase III trials of survival prolongation in major cancers such as lung, breast, gastric, and colorectal cancers. "Basic Principles on Global Clinical Trials," published in September 2007, allowed the submission of clinical data from international trials with or without Japanese patients for NDAs or sNDAs. However, Japanese regulations require the submission of registration trials involving Japanese

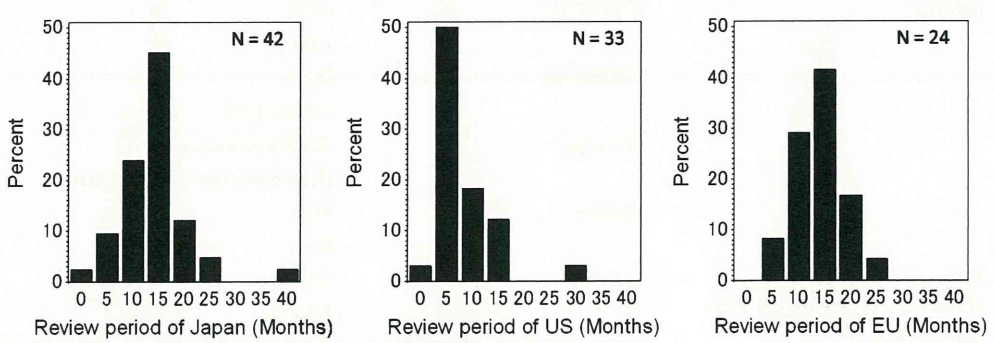

Fig. 3 Histograms of review periods in Japan, the US, and EU

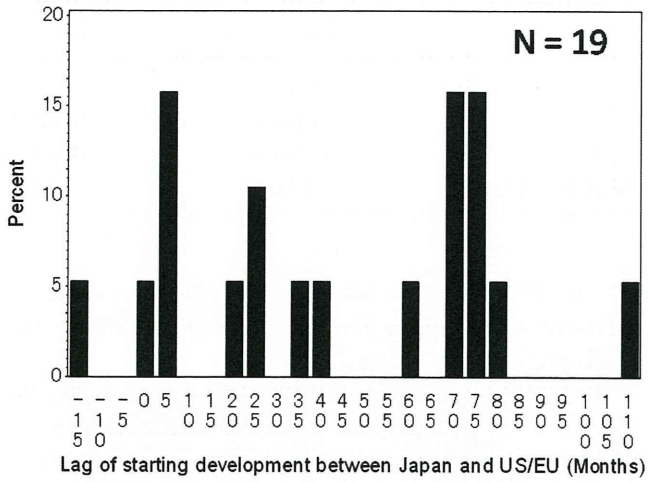

Fig. 4 Histograms of lags in starting drug development between Japan and the US/EU

patients to evaluate Japanese safety profiles. Therefore, at present, most NDAs or sNDAs must include clinical data from Japanese registration trials, which is more information than is required by NDA/sNDA submission packages in the US or EU. Thus, the current Japanese guidelines will have limited impact on resolving the oncology drug lag in Japan.

The Japanese government has initiated various direct and indirect measures for resolving and reducing drug lag. As a direct measure, in order to expand the indications of oncology drugs used in combination chemotherapy, the MHLW set up a transient special committee in 2004 that evaluated evidence of efficacy and safety for several drugs based on publications, textbooks, guidelines, and reviews. Accordingly, sNDAs for 27 drugs for use in 20 chemotherapy combinations were approved between November 2004 and September 2005 without clinical data from registration trials [12].

As an indirect measure, the MHLW set up an expert review committee for examining unapproved drugs between January 2005 and October 2009; this committee evaluated drugs that had been approved in the US or EU and additionally considered the opinions of academia and patient groups regarding the need and appropriateness of the unapproved drugs in clinical practice [1]. Thus, by incorporating these measures, the MHLW aimed to encourage pharmaceutical companies to conduct registration trials in Japan. A revision of the Pharmaceuticals Affairs Law, which came into effect in July 2003, allowed companies to perform investigator-initiated registration trials for the submission of NDAs or sNDAs that required clinical data [13]. To ensure the smooth operation of registration trials, the MHLW set up an expert review committee for defining registrations that functioned between March 2005 and September 2007 to establish an infrastructure for operating registration trials in Japan and to reduce excess responsibility on the managers of investigator-initiated registration trials [14]. Thus, the MHLW issued several notifications related to investigator-initiated trials based on Good Clinical Practice guidelines and the opinions of the expert review committee. The MHLW also launched nationwide clinical trial activation initiatives in 2003 and 2007 to support the development of a framework to promote clinical trials [15]. Continuation of this investment and support for the establishment of an adequate infrastructure for clinical trials would serve to encourage registration trials and could represent an important factor in the future reduction of the drug lag in Japan.

The present study suggests that the oncology drug lag is associated with delays in the initiation of drug development in Japan. One possible reason for the delays may be that pharmaceutical companies believe that simultaneously conducting early-phase registration trials in Japan and in the US/EU is a major financial risk. To resolve delays in the initiation of drug development in Japan, pharmaceutical companies should make an effort to enroll Japanese patients in international registration trials. Although participation in international Phase I trials would be ideal, it is imperative that pharmaceutical companies start drug development in Japan in time for participation in confirmatory-phase global trials.

The results of the present study also suggest that decreased review times by the Japanese regulatory agency would directly contribute to resolving the oncology drug lag. According to a report by Japan's Council for Science and Technology Policy, the PMDA has doubled its staff over a period of approximately 3 years to reduce submission lag and review time by 1.5 years and 1 year,

Table 2 Multivariate regression analysis for approval lag (N=12)

Variables	Coefficient	95% confidence interval		P value
Submission lag	0.1	−0.1	0.2	0.478
Review period	1.3	0.8	1.9	<0.001
Lag in initiation of drug development	0.6	0.4	0.7	<0.001
Hematologic malignancy vs. solid malignancy	−15.3	−26.7	−3.8	0.009
Molecular-targeted drug vs. Non-molecular-targeted	−34.0	−46.2	−21.8	<0.001

Table 3 Development status in the US and EU at the time of starting phase I oncology trials in Japan

Status	US	EU
Post approval, n (%)	9 (27.3)	6 (17.7)
Submitted for approval, n (%)	4 (12.1)	10 (29.4)
Starting pivotal study to submission, n (%)	12 (36.4)	10 (29.4)
Starting Phase I study to starting pivotal study, n (%)	8 (24.2)	8 (23.5)

respectively, by 2011 [16]. Between October 2006 and July 2007, an expert review committee set up by the MHLW worked to clarify the review policy, discussed post-marketing safety controls and infrastructure for consultation of registration trials, and evaluated the review system. The PMDA then released "Points to be Considered by the Review Staff Involved in the Evaluation Process of New Drug" to promote an understanding of the reviewers' standard policies and evaluation process among those in industry and academia [17]. Increasing human resources in the review system and further improving the transparency of the review process at the PMDA would further contribute to reducing review time. During the review process, the PMDA and the pharmaceutical company that developed the drug repeatedly discuss the NDA/sNDA submission until a decision regarding final approval is made by the MHLW. Therefore, both the PMDA and the pharmaceutical company are central players and have a major responsibility for reducing review time.

In Japan, every citizen is required to join universal health insurance program (i.e., employees' health insurance programs or the National Health Insurance program) and the cost of medical drugs is reimbursed by universal health insurance programs according to the indications and dosages that have been approved by the Health Insurance Bureau of the MHLW and the Central Social Insurance Medical Council. Therefore, all pharmaceutical companies have necessary to obtain pharmaceutical approval by submitting an NDA or sNDA to the PMDA in order to sell drugs under Japan's universal health insurance system. Additionally, submitting published data from non registration trials for an NDA or sNDA is not acceptable, even if the trial provides highly significant clinical evidence for treatment guidelines. The drug lag in Japan may also be a result of the relationship between pharmaceutical and medical insurance approval [18]. Thus, resolving drug lag may require changes in the health insurance approval system. A government infrastructure for the evaluation of medical insurance approval independent of pharmaceutical approval, as is embodied in the US compendia, is necessary [19]. Ideally, the PMDA would review all NDAs only that are required to evaluate the risk/benefit balance as drug with new active ingredients; this would make all additional insurance approval process to undertaken by the Health Insurance Bureau. Further, eliminating sNDA submissions for the PMDA would allow the PMDA to reduce its workload and improve the quality of the reviews, thus helping to resolve the drug lag.

In light of the realities of the drug lag in Japan, the MHLW set up a transient expert review committee in February 2010 to evaluate unapproved drugs for unmet medical needs. Although this committee is similar to the transient special committee set up in 2004, the new committee targeted all medicinal classifications of drugs rather than a specific class [20]. The 2010 committee issued three approvals for three oncology drugs without registration trial data because the applications were eligible for inclusion in the public domain [20]. Although this committee successfully led an effort to reduce temporarily unapproved drugs in Japan, its transient nature is not a long-term solution. Therefore, it is imperative that the entire regulatory system for drug and health insurance approval in Japan be reformed in order to better address the needs of Japan's patient population [21].

This study had some limitations. The number of examined approvals varied depending on region (i.e., Japan, the US, and the EU) in Figs. 2, 3, and 4, and the number of approvals examined by multivariate regression analysis was only 12. Specifically, since the imbalance of the examined approvals between Japan and the US/EU could lead to a bias of the summary statistics, the median values shown in the Results section should be carefully interpreted. Furthermore, the coefficients for the parameters shown in Table 2 may include a bias due to the small number of examined approvals, although the multivariate regression analysis showed that all variables, excluding submission lag, were significantly associated with approval lag.

In conclusion, our analysis suggests that delays in drug development initiation and the extended length of the regulatory review period in Japan may contribute to the longer oncology drug lag observed in Japan compared with that in the US/EU. To reduce this lag, the review period required by the Japanese regulatory agency should be reduced; however, this can only occur through the combined efforts of pharmaceutical companies, the PMDA, and concerned academia. We also recommend that Japanese pharmaceutical companies coordinate oncology drug development with development initiatives in other countries to reduce duplicative development efforts as well as delays.

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Conflict of interest statement Masashi Ando—Research funding: Sanofi-Aventis, Wyeth, Novartis, and GlaxoSmithKline.
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Kenji Tamrua—Honoraria: Bristol Myers Squibb and Chugai; Research Grant: MSD.
Noriyuki Katsumata—Advisory Board: Astra-Zeneca; Honoraria: Sanofi-Aventis, Chugai, Daiichi Sankyo, Novartis, Kyowa-Kirin, and Ono Pharmaceutical; Consultant for protocol: Ono Pharmaceutical, Takeda Bio, and GlaxoSmithKline; Research funding: Eisai, GlaxoSmithKline, and Astra-Zeneca.
Yasuhiro Fujiwara—Honoraria: Taiho, Sanofi-Aventis, Eli Lilly, and Chugai; Research Funding: Pfizer, GlaxoSmithKline, Chugai, Eisai, Daiichi Sankyo, Taiho, Nihon Kayaku, Amgen, Novartis, Takeda, and Astra-Zeneca.
The other authors declare no conflicts of interest.

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1. Cebul RD, Love TE, Jain AK, Hebert CJ. Electronic health records and quality of diabetes care. N Engl J Med 2011;365:825-33.
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THE AUTHORS REPLY: We welcome the opportunity to respond to Koppel and colleagues. To clarify, there were 46 practices in our cross-sectional comparisons, and we also included a longitudinal analysis of 36 practices. Although we were motivated in part by conflicting evidence from systematic reviews, there are positive summaries[1] as well as the negative summary cited. We did not have "several years" of pre-EHR observations, but our trend analyses documented both faster improvement among patients at EHR sites and higher achievement cross-sectionally. As a collaborative, we prospectively identified important measures of patient-level selection and included these as covariates in generalized-estimating-equation models that accounted for clustering within organizations. Nonetheless, we acknowledged the likelihood of underadjustment and other limitations in our discussion. We also discussed the concordance of our results with other findings[2] that highlight the greater challenges associated with improving outcomes as compared with metrics of provider care. Although we would welcome a randomized trial, we do not believe that any site in the current era would agree with random assignment to remain "in the dark" for several years.

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Since publication of their article, the authors report no further potential conflict of interest.

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Genomics, Health Care, and Society

TO THE EDITOR: Hudson, in her otherwise comprehensive review article on genomic medicine (Sept. 15 issue),[1] did not mention the issue of reimbursement and the role of payers such as the Centers for Medicare and Medicaid Services. In my outpatient clinic, many patients decline testing for a *BRCA* mutation because of the high cost (approximately $3,500 to $4,000). The tests are not approved by the Pharmaceutical and Medical Devices Agency (the Japanese equivalent of the Food and Drug Administration), nor are they covered by our universal health insurance system. Patients must bear the full cost of the mutation analysis. Furthermore, Japanese medical oncologists are struggling with the chilling effect of a limit on reimbursement (approximately $260) by the health insurance system for genetic testing for cancer. Companies that manufacture in vitro diagnostic tests are therefore reluctant to apply for regulatory approval and insurance coverage. The bloom of genomic medicine is thus constrained.

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No potential conflict of interest relevant to this letter was reported.

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