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Scientific misconduct in sponsored clinical trials in Japan: published cases are the "tip of the iceberg"

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Abstract. Although cases of research misconduct in sponsored clinical trials have been sporadically reported, no systematic reviews or national surveys on this topic have been conducted in Japan. Thus, this study aimed to: 1) systemically review publicly available information on scientific misconduct reported through sponsored clinical trials, and 2) carry out a national survey to examine incidents of scientific misconduct using the following three approaches. First, a systematic review of publicly available information on scientific misconduct using Google search, Japan Medical Abstracts Society database, and PubMed.gov; second, a survey of sponsors using an anonymous web questionnaire; and third, a national survey of clinical research coordinators (CRCs) using an anonymous web survey by snowballing sampling. The systematic review identified five cases of misconduct; however, all five cases were already well-recognized in the public domain. In the survey of sponsors, five of the 12 sponsors responded that they had reported other cases to PMDA. In the national survey of CRCs, 22 of 164 (13.4%) responders reported being aware of at least one instance of "fabrication or falsification" in the past three years. These data suggest that not all instances of misconduct in sponsored clinical trials in Japan had been reported to PMDA and that not all instances reported to PMDA had been disclosed to the public. The publicized cases represent only the "tip of the iceberg." A centralized process for reporting instances of scientific misconduct to Japanese regulatory authorities with pertinent public disclosure may improve the quality of clinical trials.
Key words: scientific misconduct, Japan sponsored clinical trial, data integrity, fabrication, falsification

Highlights

This study aimed to systemically review publicly available information on scientific misconduct reported through sponsored clinical trials and conduct a national survey to examine incidents of scientific misconduct in Japan. Not all instances of misconduct in sponsored clinical trials in Japan had been reported to PMDA, and moreover, not all instances reported to PMDA had been disclosed to the public. The study showed that the publicized cases represent only the "tip of the iceberg" in Japan.

Introduction

Research integrity includes the following aspects: 1) the use of honest and verifiable methods in proposing, performing, and evaluating research, 2) reporting research results with particular attention to adherence to rules, and 3) adherence to regulations, guidelines, and commonly accepted professional codes or norms [1]. Therefore, research integrity can be defined as active adherence to ethical principles and professional standards during the practice of research [2]. A number of studies, including case studies [3, 4], national surveys [5–7], and meta-analyses [8], on research integrity and/or scientific misconduct in clinical research, have been conducted by academia and regulatory agencies worldwide.

In Japan, some cases of research misconduct have been reported, including those involving investigator-initiated clinical studies on valsaltan in 2013 [9]. One of the causes of the misconduct in the valsaltan studies was that these studies were not performed under any legally mandated regulation, such as Good Clinical Practice (GCP) [10, 11].

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Consequently, the Ministry of Health, Labour and Welfare (MHLW) issued the Clinical Trials Act, which came into effect on April 1, 2018. The development of strict regulations is one of the steps to prevent misconduct; however, it can occur despite the presence of strict regulations. For example, scientific misconduct by clinical research coordinators (CRCs) from the site management organization (SMO) in sponsored clinical trials conducted under the Japanese GCP (J-GCP) was reported in 2013 [12, 13]. The CRCs involved in misconduct purposely altered the heights of five of 72 enrolled participants to meet the sponsor's request regarding the participants' BMI distribution. In 2015, another instance of scientific misconduct involved the falsification of a sodium value in a screening test for a healthy volunteer was reported [14]. The identification of these instances of misconduct resulted in extensive discussions on scientific misconduct in relation to research integrity in sponsored clinical trials under J-GCP. However, these discussions occurred only through limited conferences and workshops [15, 16], including the GCP workshops held by the Pharmaceuticals and Medical Devices Agency (PMDA) from 2014 to 2018 [17]. Several articles [18, 19] on the disclosed cases have been published to guide general considerations; however, no systematic reviews or national surveys have been carried out in Japan. Therefore, it is not clear whether the published cases constitute the "tip of the iceberg." Thus, the aims of the present study were as follows:

1) To systemically review publicly available information on scientific misconduct reported through sponsored clinical trials under J-GCP.

2) To conduct a national survey to examine incidents of scientific misconduct and compare them with US survey data.

Materials and Methods

Definition of misconduct

In this study, we focused on fabrication, falsification, and spoofing as fundamental forms of misconduct by the CRC; these were defined as follows.

- Fabrication: making up data or results and recording or reporting them [20].
- Falsification: manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record [20].
- Spoofing: using another person's ID/password or signature.

We aimed to identify instances of misconduct in sponsored clinical trials under the J-GCP (chi-ke-n) through the following avenues.

(1) Systematic review of publicly available information on scientific misconduct

Electronic records of relevant instances of scientific misconduct were searched using Google search, the Japan Medical Abstracts Society database, and PubMed.gov. In addition to Google search, the Japan Medical Abstracts Society database was selected as the most common literature search tool in the Japanese language, whereas PubMed.gov. was selected as the most common literature search tool in English. The data sources and selection of keywords were agreed upon by the authors prior to the initiation of the data search.

Google search was performed in June 2019 by combining the following keywords in Japanese. The search was conducted by a single person, but twice.

"chi-ke-n (clinical trial)" OR "ri-n-sho-shi-ke-n (clinical study)"

AND

"fu-se-i (misconduct)" OR "fu-te-ki-se-tsu-ko-i (inappropriate behavior)" OR "ne-tsu-zo (fabrication)" OR "ka-i-za-n (falsification)" OR "na-ri-su-ma-shi (spoofing)"

Furthermore, the Japan Medical Abstracts Society database was searched by combining the same keywords in Japanese. The search covered references published from 2010 to 2019, and included an abstract. The search was conducted by a single person, but twice.

"chi-ke-n (clinical trial)" OR "ri-n-sho-shi-ke-n (clinical study)"

AND

"fu-se-i (misconduct)" OR "fu-te-ki-se-tsu-ko-i (inappropriate behavior)" OR "ne-tsu-zo (fabrication)" OR "ka-i-za-n (falsification)" OR "na-ri-su-ma-shi (spoofing)"

After the search, the title and abstract were reviewed to determine whether the study discussed misconduct in a sponsored clinical trial in Japan.

PubMed.gov was searched using the following keywords in English. The scope of the search included references and studies published in 2010–2019. The search was conducted by a single person, but twice.

"Japan clinical study" OR "Japan clinical trial"

AND

"misconduct" OR "fraud" OR "research integrity" OR "fabrication" OR "falsification" OR "spoofing"

After the search, the title and abstract were reviewed to determine whether the study discussed misconduct in a sponsored clinical trial in Japan. The review was conducted by a single person.

(2) Survey of sponsors

An anonymous web questionnaire containing three questions was sent to 13 pharmaceutical companies (7 US-based, 3 EU-based, 3 Japan-based) who had a Japan R&D office as members of PhRMA-Japan or TransCelerate Biopharma Inc. (TransCelerate) (a total of 18 pharmaceutical companies: 10 US-based, 5 EU-based, 3 Japan-based) with prior agreement to respond. PhRMA-Japan and TransCelerate were selected because both are well-recognized as representative pharma industry groups in Japan that allowed us to conduct a survey by contacting their member companies. The sample size of the survey of sponsors in this research was small, especially considering Japanese domestic companies. However, since the purpose of this survey was to investigate whether there were other cases of scientific misconduct in addition to the five published cases, we considered it acceptable that the number of Japanese domestic companies was relatively smaller. The survey was conducted through SurveyMonkey® from July 23, 2019, to August 15, 2019.

(3) National survey of CRCs

An anonymous web survey was conducted through SurveyMonkey® by snowball sampling for two months from January 15, 2018 to March 15, 2018. Initially, the questionnaire was sent to the participants of the opinion exchange meeting about research integrity on clinical trial operations hosted by the Tokyo Metropolitan Society of Health System Pharmacists in February, 1998, and members of the clinical trial center network "GCP meeting room" with a request for forwarding it to colleagues. In addition, we asked the Japan SMO Association, the largest network of SMOs in Japan, to inform CRCs of their member companies. The questionnaire for this survey was drafted by referring to a previous study conducted by the United States Office of Research Integrity (ORI) [5], and incidents of "fabrication or falsification" were compared between Japan and the USA.

Results

(1) Systematic review of publicly available information on scientific misconduct

In the systematic review of publicly available information on scientific misconduct, five cases of misconduct were identified in the Google search. The details of these cases are summarized in Table 1. All five instances of misconduct were well-known and had been already presented by the PMDA at the GCP workshop [17]. Moreover, they had been performed by clinical trial staff, mainly CRCs. Three of the five instances involved data falsification, one involved fabrication, and one involved spoofing. Four of the five cases were brought to light by whistleblowers within the investigator sites. For the first three cases, detailed informa-

Table 1. Instances of misconduct identified in a Google search

Year*	Type	Description	Agents responsible for the misconduct	Disclosed in detail
2013	Falsification	In a study of anti-obesity drugs, the SMO accepted a study with difficult temporal and conditional participant requirements, which eventually resulted in a shortage of participants. Because of the inadequate response and based on the instructions of the SMO manager, the height data for five of 72 participants were falsified by the CRC to values 4.7–9.7 cm below the actual values after obtaining the agreement of the investigator to meet the BMI distribution requested by the sponsor. The misconduct was brought to light by whistle-blowing staff at the medical institution.	SMO CRC	○
2015	Falsification	The serum sodium level of a healthy adult volunteer fell outside the normal range (138–144 mEq/l) at 137 mEq/l; thus, the laboratory technician falsified the value to 138 mEq/l to meet the reference level, and the volunteer was invited to participate in the study. The falsification was partly attributed to the fact that laboratory technicians had been informed of the desire to prevent losses in the organization both in the conduct and management of the clinical trial by enrolling participants with as few dropouts as possible. Thus, the study was conducted with practices such as repeated tests when the screening test values were slightly outside the normal range. The misconduct was brought to light by the accusations of the laboratory technologist who performed the falsification.	Laboratory technician	○
2015	Spoofing	A CRC (1) overwrote the part written in pencil by the participant in the patient diary. A subsequent CRC (2) asked the participants to rewrite the patient diary overwritten by the CRC (1) to a new patient diary form for similar content and discarded the original patient diary. CRC (2) checked the blank checkboxes in the patient diary and changed or added some values and dates in the patient dairy or medical chart without confirmation from the doctor or the participant who entered the record. The misconduct was discovered by the CRA in charge.	SMO CRC	○
2016	Falsification	In the protocol-specified "Blood Pressure Measurement and Subsequent Blood Sampling" procedure, blood pressure measurement was required after blood sampling. However, the CRC performed blood pressure measurement before blood sampling. Therefore, the time of blood pressure measurement was falsified on the worksheet. The falsification was discovered in the course of subject correspondence by another CRC after an SMO merger.	SMO CRC	×
2017	Fabrication	To compensate for missing tests as specified in the protocol, the CRC independently requested sample collection on days other than the specified dates while requesting measurements in accordance with collection on the specified dates. The medical institution asked the SMO to confirm the facts because the date of collection on the test request form was a few weeks ago, leading to the discovery of the fabrication.	SMO CRC	×

*Year of disclosed the information. SMO, site management organization; CRC, clinical research coordinator.

Table 2. Survey of sponsors results (N=12)

Question	Yes	No
In addition to the five published cases, has an inquiry about the reliability of application data in relation to non-conformance cases that occurred at other investigator sites after the application from PMDA been received?	3	9
In addition to the five published cases, are there any GCP non-compliance/inappropriate practices reported to PMDA from your company other than sharing ID / Password?	5	7
Are there any GCP non-compliance/inappropriate practices that have not been reported to PMDA?	2	10

GCP, Good Clinical Practice.

tion, such as background, internal investigation results, root causes, and action plans, was available; however, for the last two cases, only high-level summaries were disclosed in the public domain. Therefore, the case details of these two instances could not be determined from public information.

[Japan Medical Abstracts Society database]

A total of 298 references were identified using the keywords. Examination of the titles and abstracts, and further examination of the references did not reveal any references discussing misconduct in sponsored clinical trials in Japan.

[PubMed.gov]

A total of 160 references were identified using the keywords. Examination of the titles and abstracts and further examination of the references did not reveal any references discussing misconduct in sponsored clinical trials in Japan.

(2) Survey of sponsors

Twelve of the 13 pharmaceutical companies from PhRMA-Japan or TransCelerate responded to the questionnaire by the end of the survey period (response rate: 92.3%). This was 66.7% of the total member companies of PhRMA-Japan and TransCelerate. The responses are tabulated and summarized in Table 2.

(3) National survey of CRCs

A total of 164 responses were received during the survey period. The backgrounds of the responders are shown in Table 3. The response results are presented in Table 4. In the survey, 22 of 164 (13.4%) responders reported at least one "fabrication or falsification" in the past three years. In a previous US study [5], 128 of 2,212 (5.8%) responders reported at least one "fabrication or falsification" or unknown case over the last three years.

Table 3. Background of the responders to the clinical research coordinator (CRC) survey (N=164)

Working history as CRC	
<3 yrs	31 (18.9%)
3–10 yrs	85 (51.8%)
>10 yrs	47 (28.7%)
No answer	1 (0.6%)
Affiliation	
Medical institute	36 (22.0%)
SMO	128 (78.1%)
Medical background	
Nurse	26 (15.9%)
Pharmacist	21 (12.8%)
Lab technician	52 (31.7%)
Other	26 (15.9%)
No medical background	39 (23.8%)

SMO, site management organization.

Discussion

This study provides the first systematic review and national survey on research misconduct in Japan, focusing on CRC or site staff in sponsored clinical trials. The findings of (1) a systematic review of publicly available information, and (2) a survey of sponsors, indicated that not all instances of misconduct that occurred in Japan were reported to the PMDA and that not all the instances of misconduct reported to the PMDA had been disclosed in the public, especially in detail. Under Japanese regulations, only GCP violations resulting in study discontinuation at the clinical trial site must be reported to the PMDA. Although the PMDA recommends voluntary reporting of all cases of misconduct, this is not a regulatory requirement. In contrast, some health authorities overseas such as the Medicines & Healthcare products Regulatory Authority (MHRA, UK) [21] and the regulatory authorities in Australia [22], Serbia, and Singapore [23] require reporting of all serious breaches under their regulations/guidelines. From January 31, 2022, serious breach reporting expanded to all European Economic Area (EEA) countries per the new Clinical Trial Regulation [24]. As an example of public disclosure, the MHRA collects information regarding all instances of misconduct in the country as serious breaches and issues annual reports [25].

The findings of the CRC survey indicated that the most common type of misconduct witnessed by CRCs was spoofing, followed by falsification. This tendency was also noted in the public information survey. Spoofing may be particularly prevalent in relation to electronic systems because of the practice of sharing login credentials. Furthermore, falsification may be considered an easier type of misconduct than fabrication because alteration of a part of the data may seem less wrong, with 74.4% of the CRCs reporting that they had at least one experience of back-dating some clinical trial-related documents in the past three years. Completely prohibiting the practice of backdating clinical study documents may help prevent future cases of misconduct.

Because 73.1% of CRCs responded that they worked in an environment where they could forge or fake data, environmental improvement can be an effective approach to prevent misconduct. However, this can require a higher clinical trial budget and is often challenging in practice. In

Table 4. Results of the clinical research coordinator (CRC) survey

Q1: Have you or your facility ever witnessed or noticed any fraudulent activity in the clinical trial over the past three years, such as fabricating, falsifying, or spoofing data? (N=164)				
Yes	41 (25.0%)	No		123 (75.0%)
Type of misconduct*		Role who conducted the misconduct*		
Fabrication	6.1% (3)	Doctor		20.9% (9)
Falsification	38.8% (19)	CRC**		69.8% (30)
Spoofing	55.1% (27)	Other staff		9.3% (4)
Q2: What is the most likely motivation for a CRC to commit fraud in clinical trials? (N=157)				
Pressure by Investigator/Institution				16 (10.2%)
Pressure by Sponsor				39 (24.8%)
Pressure by Supervisor/Site management organization (SMO)				15 (9.6%)
Pressure not to deviate from the protocol				73 (46.5%)
Others				14 (8.9%)
Q3: Number the following in the order of importance in the quality of trial. (N=161)				
	1st	2nd	3rd	4th
Source document reliability	14 (8.7%)	72 (44.7%)	71 (44.1%)	4 (2.5%)
Protocol compliance	13 (8.1%)	72 (44.7%)	74 (46.0%)	2 (1.2%)
Enrollment as planned	0 (0.0%)	3 (1.9%)	5 (3.1%)	153 (95.0%)
Patient protection	134 (83.2%)	14 (8.7%)	11 (6.8%)	2 (1.2%)
Q4: Is your environment where you could forge or fake data? (N=160)				
Yes	117 (73.1%)	No		43 (26.9%)
Q5: Have you backdated or have you asked a doctor or medical staff to backdate any documents in the last three years in a clinical trial? (N=164)				
Yes	122 (74.4%)	No		42 (25.6%)
Type of backdated document*				
Institutional review board (IRB) related essential document				24 (19.7%)
Non-IRB related essential document				37 (30.3%)
Worksheet				94 (77.0%)
Medical chart				7 (5.7%)
Informed Consent Form				2 (1.6%)
Investigator's signature on lab report				47 (38.5%)

*: Multiple answers available. **: Included "CRC conducted by CRC under the direction of a doctor" into CRC.
Note: For Q5, some responders answered that the backdated documentation was requested by or added in agreement with the sponsor clinical research associate (CRA).

the book "Other People's Money," the author noted that "pressure," "rationalization," and "opportunity" were commonly related to fraud [26]. Thus, "motivation" and "justification" may be realistic solutions to avert fraudulent behavior. Considering that "motivation" and "justification" are personal aspects, training on research integrity may be effective in enforcing these aspects. Although 97.2% of the responders reported receiving training on research integrity in a survey conducted by the Japan SMO Association in 2018 [27], the effectiveness of this training was not measured. If feasible, workshops using real cases should be employed in training to ensure that participants understand all aspects of potential misconduct. Four of the five public cases were brought to light by whistleblowers at the investigator sites. Thus, the presence of individuals with high levels of integrity at investigator sites may improve the possibility of prompt reporting of misconduct. Accordingly, it is essential to build a system that does not unfairly penalize whistleblowers.

For comparison with research in the USA [5], Fisher's exact test was used to analyze the incidence of fabrication or falsification in the Japanese and US results. This exploratory analysis revealed that the reported incidence of misconduct was higher in Japan than in the USA (P=0.0006). Whether there was a significant difference in misconduct incidences between Japan and the USA needs to be clarified. Furthermore, it is difficult to compare the true difference, if any, between the responder's groups (CRCs in Japan vs. scientists in the USA) and with dissimilar methods (the web survey by snowball sampling vs. the survey administrated to National Institutes of Health (NIH)-funded scientists). Despite these apparent differences, the ORI survey reporting the incidence of each type of misconduct (fabrication, falsification) was selected to allow comparative analysis in this research. Based on a survey of CRC in the USA by Pryor *et al.* [6], the perceived prevalence of falsifying data within one year was 28.7%. In addition, the meta-analysis [8] showed a variety of misconduct rates; a pooled weighted average of 1.97% (N=7, 95%Cl: 0.86–4.45) of scientists who admitted fabricated, falsified, or modified data or results at least once. At this stage, considering the complexity of comparative data, we should not definitively conclude that

the incidence of misconduct in Japan is higher than that in the USA.

Reasons for committing misconduct vary [28], but the high expectations for protocol compliance have been suggested to be a motivating factor for misconduct by CRCs in Japan. These expectations are led not only by the investigator or the clinical trial site, but also by the sponsor. Human errors should be tolerated by avoiding setting all errors to zero, and the perception of the risk-based approach cited in ICH-GCP (R2) can help prevent clinical misconduct. In the CRC survey in the USA [6], CRCs reported that pressure influenced misconduct, and that workload, including the number and intensity of protocols for which the CRC was responsible, as well as insufficient involvement or low interest of the PI were aggravating factors. Thus, controlling the workload of CRCs and ensuring the PI's commitment to the clinical study may help reduce the CRC's motivation for misconduct. These findings are also applicable to Japan. In addition, some responders commented on the influence of complicated e-learning requests by the sponsor. Based on the Institution Sponsor Efficiency Improvement Project (ISEI-PJ) survey [29], the median number of passwords used simultaneously was 10 and the maximum number was 40, but the median and maximum numbers of passwords memorized and used were two and 12, respectively. A shared investigator platform and site qualification and training (GCP and EDC System Training Mutual Recognition), which have been implemented by TransCelerate, may help decrease ID/Passwords and duplicated e-learning [30].

While four cases of misconduct were reported by whistleblowers, only one was detected by monitoring, indicating that the clinical research associate (CRA) could not detect the misconduct during monitoring in the first four cases. Central monitoring with statistical analysis is a cost-effective way to incorporate the detection of potential misconduct [31]. According to the TransCelerate survey [32], 14 of 18 companies used central monitoring, whereas 8 of 18 companies used advanced statistical analysis with traditional methods (monitoring, auditing, and data review).

This research focused on misconduct in sponsored clinical trials (chi-ke-n) by CRC, because the Clinical Trials Act applicable to investigator-initiated clinical studies was made effective recently (effective date: April 1, 2018), whereas quality activities (e.g., monitoring, audit, and data management) vary across trials. The focus on CRCs is attributed to the fact that the well-known cases of misconduct in sponsored clinical trials in Japan involved CRCs [12–14]. Although the number of CRCs who responded to the survey in this study represents less than 5% of the total CRCs in Japan, the data obtained are valuable because there has been no similar research reported in Japan to the best of our knowledge.

In general, scientific misconduct includes fabrication, falsification, and plagiarism [20], but plagiarism has been excluded from the definition of "misconduct" in this research because plagiarism is typically performed by an investigator, not by other site staff, including the CRC. Instead, spoofing was included because the PMDA recently identified this as a GCP problem in some conferences [17].

Conclusions

Our research indicated that not all instances of misconduct in sponsored clinical trials in Japan were reported to the PMDA, and that some instances of misconduct that were reported to the PMDA were not disclosed in public. Thus, the publicized cases of misconduct represent only the "tip of the iceberg." A centralized process for reporting all instances of scientific misconduct to Japanese regulatory authorities and disclosure of these instances in the public domain may improve the quality of clinical trials.

Furthermore, this study could not conclude whether the incidence of misconduct in Japan was higher or lower than that in the USA. Additional national surveys and meta-analysis comparisons are needed for this evaluation.

Moreover, effective proactive solutions should be implemented to prevent scientific misconduct and improve the quality of future clinical trials, including: 1) effective training, 2) controlling CRC workloads, 3) improving PI commitment levels, 4) adherence to a risk-based approach, 5) prohibition of backdating for all clinical trial documents, and 6) introduction of central monitoring.

Conflict of Interest

The authors have no conflict of interest directly relevant to the content of this article.

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