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## Management of Information about Adverse Events in Clinical Trials

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Information about safety greatly affects the decision by patients as to whether or not they will participate in clinical trials. Therefore, it is important to keep all participants fully informed. However, it is very difficult to manage information about adverse events that are reported during clinical trials, mainly because the amount of information is large and the casual relationship with investigational drug administration is often unclear.

We sought to develop a method to effectively evaluate the clinical significance of reported adverse events and to also efficiently manage information. The adverse events reported to our institution by trial sponsors during the period between September 1999 and December 2001 were classified based on an evaluation of three factors: the degree of health hazard, the character (geographical location, previously known or new effect, clinical trial phase or post marketing phase), and causal relationship with the investigational drug.

Based on the results of this analysis and a questionnaire survey of trial sponsors, we recommended that adverse events should be routinely categorized into three classes in the manner described above, and the data regarding each event should be gathered in a standardized format, and electronic media should be used to transmit the data.

**Keywords** — adverse event, clinical data, clinical research coordinator, good clinical practice, information technology

### Introduction

The revised Guidelines for Good Clinical Practice (new GCP) were introduced in 1997 to ensure a unified approach to both medical science and ethics in the EU, the USA and Japan<sup>1,2)</sup>. The new GCP guidelines requires to obtain informed consent from a subject taking part in clinical trials to be based on a written explanation of the aims and risks of the trial. The decision to conduct a clinical trial depends on the balance between the expected advantages of the new medical treatment and the various costs of the trial. In particular, information about safety is a key factor in the subjects' decision to participate.

When a previously unknown (new) adverse event is reported during a clinical trial, the sponsor has a duty to inform the Ministry of Health, Labour and Welfare and the principal investigator at the trial site. The investigator must

then consider the propriety of continuing the trial. When information that might influence on the decision of the subjects to continue their participation in the trial is provided by the sponsor, the principal investigator must immediately inform the subjects and reconfirm their willingness to continue.

However, management of information about adverse events of investigational drugs provided by sponsors is not easy. The major reasons are the vast amount of information provided by sponsors and the uncertainty of the causal relationship with administration of the investigational drug<sup>3,4)</sup>.

Consequently, there is a huge workload for the principal investigator, clinical trial secretariat, clinical institutional review board (IRB) secretariat and clinical trial coordinator (CRC).

Our aim was to develop an efficient method to manage information about adverse events in clinical trials.

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## Methods

Information about adverse events provided by clinical trial sponsors was examined from the viewpoints of quantity (number of reports and cases), quality (sponsor's evaluation of causal relationship), and the evaluation of the causal relationship by the principal investigator. Furthermore, the organization to evaluate adverse events and the application of information technology for information management were investigated.

### 1. Survey of quantity and quality of adverse event reports provided by sponsors

The adverse event reports provided by sponsors were categorized as follows: (1) character of occurrence (in Japan or overseas countries, in a clinical trial or in the post-marketing phase) and (2) previously known or new type of event, and (3) likelihood of a causal relationship. The period of the investigation was 28 months from September 1999 to December 2001. A report that was subsequently withdrawn was included as one case in this examination.

Details of all adverse event reports provided by sponsors were inputted into our database using commercial spreadsheet Microsoft Excel™ (MS-Excel).

### 2. Investigation of principal investigators' assessments of adverse event reports

We evaluated the principal investigators' conclusions about adverse event reports from the viewpoints of: (1) the influence on the subjects' decision to continue participa-

tion, (2) the need for explanation and reconfirmation of subjects' willingness to participate, and (3) the propriety of continuing the clinical trial. The targets of investigation were the adverse event reports provided by sponsors to our institution between September 1999 and November 2000.

### 3. Investigation of information management by trial sponsors

The character of adverse event reporting and application of information technology for information management in 50 sponsor companies were investigated by sending a questionnaire during the period between January 11 and January 31, 2001, which was the restricted period of the investigation.

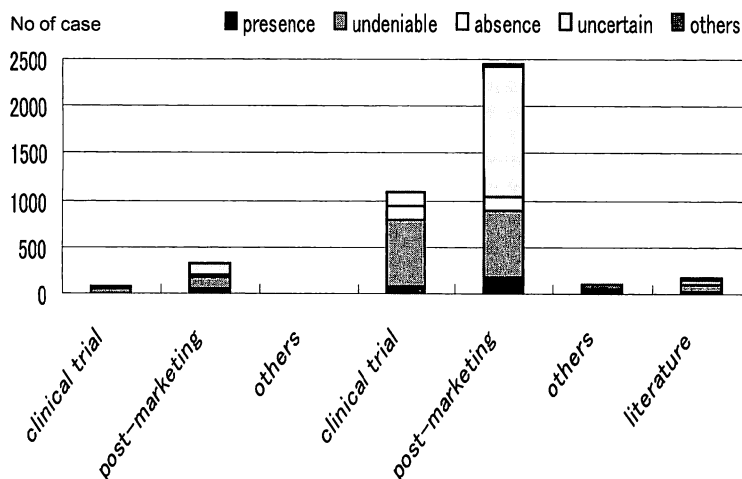
## Results

### 1. Survey of information about adverse events

The number of adverse event reports received from sponsors at our institution was 461 (16.4 per month) and the case number of adverse events was 4,185 (149.5 per month) within the investigation period (28 months between September 1999 and December 2001). All cases of adverse event notified by sponsors were recorded in our database by CRC, and the time required was about 6 hours per month.

Concerning location, 90.1% (3,770 cases) were detected in other countries and 9.9% (415 cases) in Japan (Fig. 1). Further, 66.0% (2,762 cases) were detected in the post-marketing phase, and among them, 11.7% (323 cases) were in Japan and 88.3% (2,439 cases) in other countries.

As regards a causal relationship with test drug administra-



**Japan (415 cases; 9.9%) Other countries (3770 cases; 90.1%)**

Fig. 1. Classification of Adverse Events Based on Generating Situation. (Investigational period: Sept., 1999-Dec., 2001)

Axis: ordinate/number of case, horizontal/detected phase or source of adverse events. Indicated with dividing into Japan and other countries. Presence, undeniable, absence, uncertain, and others indicate the evaluation result of causal relationship by sponsors.

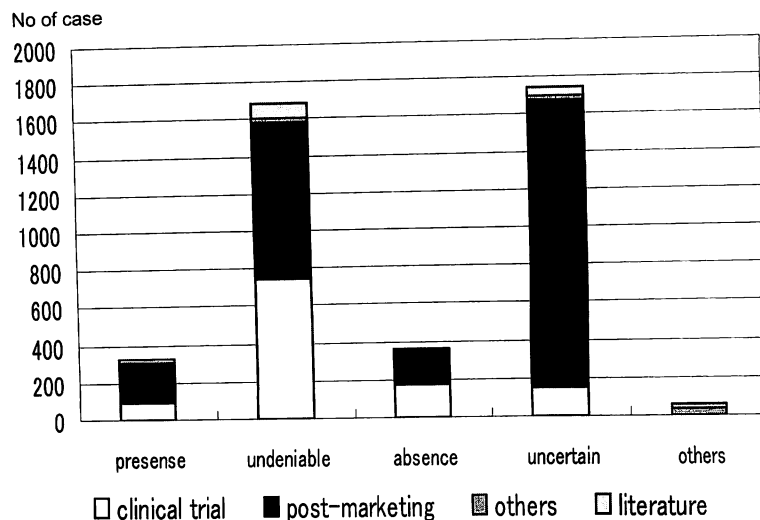


Fig. 2. Classification of Adverse Events Based Causal Relationship Evaluation. (Investigational period : Sept., 1999-Dec., 2001)  
Axis : ordinate/number of case, horizontal/the evaluation result of causal relationship by sponsors.

tion, 41.8% (1,749 cases) were classified as “causal relationship uncertain”. In the clinical trial phase, “causal relationship uncertain” accounted for 8.9% (156 cases) of all adverse events, of which 10.3% (18 cases) were in Japan, and 88.5% (135 cases) in other countries. In the post-marketing phase, “causal relationship uncertain” accounted for 55.1% (1,522 cases), and among them, 8.3% (126 cases) were in Japan, and 91.7% (1,396 cases) in other countries. Overall, 79.8% (1,396 cases) of “causal relationship uncertain” events were detected in the post-marketing phase in countries outside Japan (Fig. 2).

## 2. Evaluation of principal investigators' assessment of adverse event reports

Excluding events that did not require consideration by the IRB (such as termination of a clinical trial), 151 reports were investigated between September 1999 and November 2000.

The principal investigators in our institution considered that 53.0% (80 reports) might influence on the subjects' decision to continue participation, while 46.4% (70 reports) were “not influential”, and 0.6% (one report) reached no conclusion. The major reasons for evaluation as “not influential” by principal investigators were : (1) background information was insufficient, (2) the event was due to a distinct illness, and (3) it would not be expected to affect the subjects' decision (Fig. 3).

The 80 reports that were “influential on decision-making”, were placed in the following categories by the principal investigators : “explanatory document needs to be revised”, “explanation with supplementary document is required”, “verbal explanation is required” and “unnecessary to explain”, which accounted for 43.8%, 28.8%, 17.5% and

10% of this group, respectively. Thus, 90% among them was considered to require additional advice to subjects in some respect by the principal investigators.

Among the 70 reports that were “not influential on decision-making”, the conclusions were “explanatory document needs to be revised”, “explanation with a supplementary document is required”, “verbal explanation is required” and “unnecessary to explain” in 0%, 1.4%, 8.6% and 90%, respectively. Only 10% of this group was considered to require additional advice to subjects.

One trial was judged negatively as “discontinuation of new entry” and one as “continuation to be reexamined” among the 80 reports of “influential on decision-making” adverse events by principal investigators. No negative judgment was seen in the 70 reports considered “not influential on decision-making”.

## 3. Investigation of information management by trial sponsors

The response rate to the questionnaire survey was 100% (50 companies).

### 3-1. Organization for evaluation of adverse event reports in sponsor companies

According to this survey, 64% (32 companies) of investigated sponsors have standard criteria for evaluation of a putative causal relationship. Among them, 84% (27 companies) have their own criteria and two companies were also using the FDA standard. Naranjo Score and WHO standard criteria were used in some companies (Fig. 4). We found that 56% (28 companies) of sponsors have a full-time evaluation doctor and 44% (22 companies) were outsourcing.

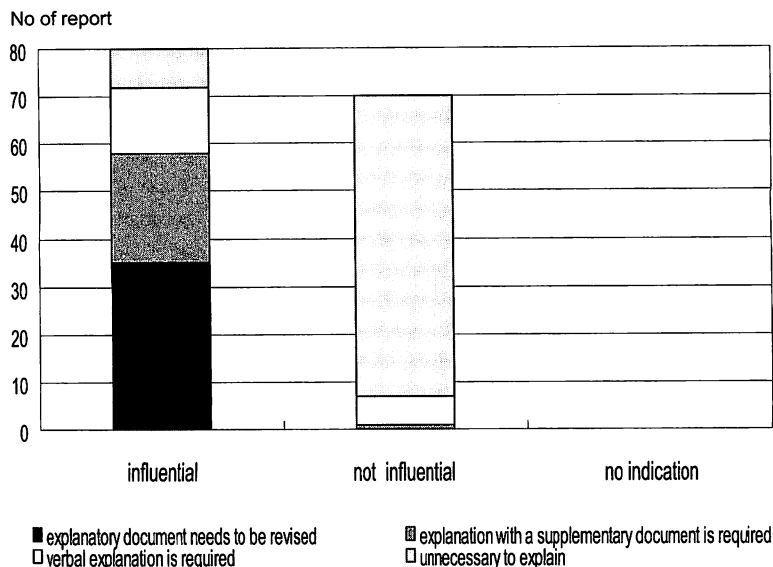
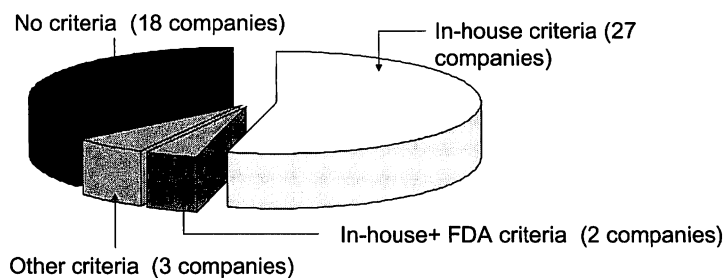


Fig. 3. Evaluation of Adverse Events Based on Influence in Subject's Decision-Making by Principle Investigators. (Investigational period : Sept., 1999-Nov., 2000)  
 Axis : ordinate/number of report from sponsors, horizontal/the evaluation result of the influence on the subjects' decision to participate clinical trials by principle investigators.  
 The reason which is "unnecessary to explain" observed in "influential" is that there is no registration of new subject.

A. Criteria for evaluation of adverse events



B. Employment of doctor for evaluation of adverse events

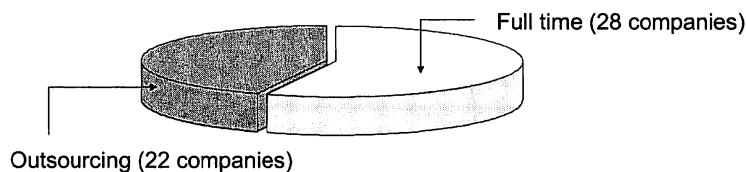


Fig. 4. Organization for Evaluation of Adverse Events in Sponsors. (Questionnaire survey to 50 sponsors, Jan. 11-21, 2001)

Regarding the frequency of meetings of the evaluation committee, the frequencies were "once per week" and "as necessary" in 36%(18 companies) and 32%(16 companies), respectively. "Every day" was seen in 2 companies and "2 or 3 times per week" was seen in 3 among foreign-financed companies.

3-2. Application of information technology to adverse event reports

As the answer to the question "Is creating a database of adverse events useful in order to provide information quickly and exactly?", "yes", "no" and "noncommittal" replies were 88%(44 companies), 0% and 12%(6 compa-

nies), respectively. The reason for "noncommittal" was that the features of the database were not specified.

As the answer to the question "What method is regarded as useful in order to arrange and to provide information efficiently?(check all that apply)", "use of the internet", "use of facsimile" and "use of electronic media such as floppy disk or CD-R" were checked by 66%(33 companies), 24% (12 companies) and 16%( 8 companies), respectively.

As the answer to the question "What are the problems of automatic report transmission via the internet ? (check all that apply)", "security of transmission", "security at the trial site", "adjustment of internal database" and "no opportunity to explain items that are difficult to document" were checked by 78%(39 companies), 42%(21 companies), 40%(20 companies) and 16%(8 companies), respectively.

## Discussion

The problem on information management about adverse event in clinical trials was shown, and then, the method for problem solution was discussed.

### 1. Problems of information management

As the number of adverse event reports from sponsors is about 150 per month, it is very difficult to manage them efficiently for a clinical trial secretariat and IRB secretariat, and to evaluate them quickly for the IRB.

Although 64%(32 companies) of sponsors have criteria to evaluate the causal relationship of adverse events to the investigational drug, 84%(27 companies) of this group use their own criteria, i.e., no standard criteria common to all sponsors. The principal investigators thought that it was difficult to evaluate the clinical significance of some adverse events because of insufficient background information.

Information concerning adverse events is considered as one of the most important factors in the decision of subjects about participation or continued participation in clinical trials. So, it seems important to create a set of standard criteria to evaluate the existence of a causal relationship as soon as possible.

The new important problem was observed, recently. According to the official notification "The handling of adverse drug reactions and infection case reports concerning investigational drugs (No.1249)<sup>5)</sup>" by the Ministry of Health and Welfare / Pharmaceutical and Medical Safety Bureau (currently the Ministry of Health, Labour and Welfare Pharmaceutical Bureau), the CIOMS (Council for International Organizations of Medical Sciences) report style<sup>6)</sup> and Med-Watch report style<sup>7)</sup> (Food and Drug Administration, U.S.A.) written in English are to be adopted for transmission of reports of adverse drug reactions detected in the post-marketing phase in overseas countries from sponsors to trial sites. Transmission using the style 2 sheet regulated by the Ministry of Health and Welfare / Pharmaceutical and Medical

Safety Bureau (notification No. 403, May 15, 1998) has become unnecessary<sup>8)</sup>.

In a survey on sponsors' response to the notification No.403, the replies were "use of English data", "no use of English data" and "no answer" from 44%(22 companies), 48%(24 companies) and 8%(4 companies), respectively. Among the 22 companies which answered "use of English data", 9 companies noted that a document written in Japanese was also attached, and 13 noted that a document written in Japanese was not attached<sup>9)</sup>. The amount of prescribing in overseas countries is huge, and the number of adverse event reports is large, so the management of information about adverse events provides a high workload for both sponsors and trial sites. If the information is only provided in CIOMS report style or MedWatch report style written in English, linguistic difficulties can be expected to cause confusion at trial sites.

### 2. Method for problem solution

#### 2-1. Classification of adverse event

For efficient evaluation by the IRB at our institute, adverse events have been classified from three points of view since September 1999 : these are ( 1 ) previously known or new, ( 2 ) the degree of severity, and ( 3 ) causal relationship is clear or not. Since an event which is new, severe and in a causal relationship with the test drug must affect the subjects' intention to continue participating in clinical trial, the explanatory document must be revised (addition of a new adverse event), and the subjects' willingness to continue must be confirmed. In our institution, about 22% of notified adverse events can be classified into the group for which reconfirmation of the subjects' intention is necessary.

As a result of information management of adverse events for five years, we have arrived at the conclusion that the influence of events detected in the post-marketing phase is not equal to that of events detected in clinical trials with strict restriction on patient selection and use of combinations of medicines. Thus, further categories (Japan or overseas, clinical trial phase or post-marketing phase) were needed in our classification<sup>10)</sup>. In fact, we have introduced a new procedure in which classification by detection characteristics is performed initially, followed by distinction of previously known or new event and the degree of severity (Fig. 5). Fortunately, we found that this procedure was very similar to that examined by the JPMA (Japan Pharmaceutical Manufacturers Association), and we have started to discuss planning adjustments with the PMS Committee and Clinical Evaluation Committee of the JPMA from the autumn of 2001. Agreement should be reached by the end of 2002 and the transmission of information about adverse events by the new procedure will be started in early 2003.

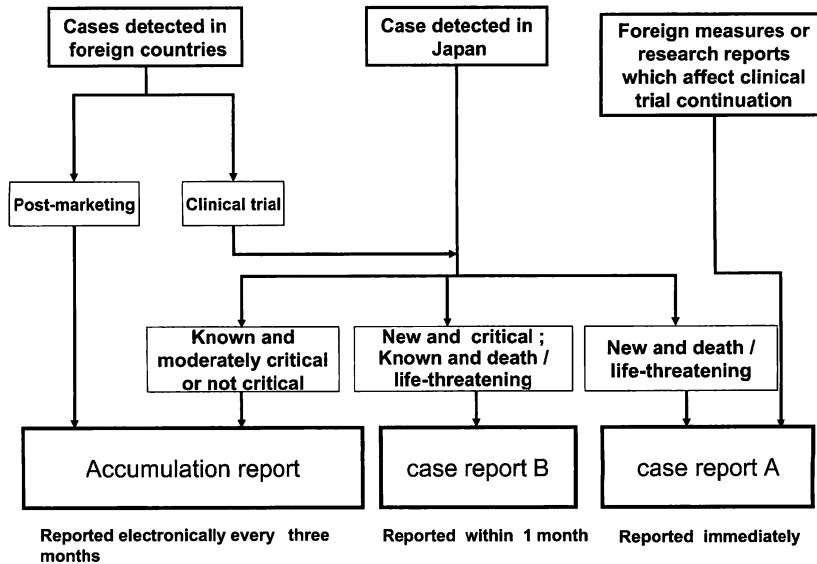


Fig. 5. Classification of the Adverse Events Information for Efficient Information Management and Transmission.

2-2. Transmission by standard electronic data

In our institution, a database of adverse events was set up in 1997 using spreadsheet software (MS-Excel™, and the data were provided on electronic media (floppy disk) by some sponsors<sup>3)</sup>. However, the major problem that remains for sponsors is responding to requests from trial sites (e.g., requests for data to be reformatted in the individual style of each institution). To solve this problem, it is considered that standard data items on which sponsors and trial sites can agreed should be set up, and the information should be provided only as standard data from sponsors to trial sites. Each trial site can then make its own modifications, if necessary. A possible data set is being reviewed with the Exploratory Committee of the JPMA (Japan Pharmaceutical Manufacturers Association) and will be put forward for common use as the standard data item set approved by the Clinical Trial Taskforce of the Japanese Society of Hospital Pharmacists<sup>10)</sup>.

Since insufficient information makes evaluation of a causal relationship difficult, requests from the sponsor side, such as enforcement of SDV (Source Document Verification; collation of source material and case report) for every case and simplification of the SDV operating procedure need to be discussed between sponsors and trial sites.

According to the MHLW notification “The handling of the side effects and infection case reports concerning an investigational drug (No. 1249)”, terms given in MedDRA/J can be used to describe adverse drug reactions. When a different term is used for a condition considered as the same, it is treated as another unknown event. Since the use of the Japanese translation (MedDRA/J) of MedDRA<sup>11)</sup> allows stan-

dardization of the terminology for adverse drug reactions, this makes the creation of database about adverse events relatively easy. Our experience over five years indicates that the creation of a database from which data can be modified individually for each trial site based on the standard data provided by the sponsors is rapid and effective. The database can also respond easily to a request for the latest information about adverse events from a subject.

By standardizing the procedure of providing information, it is expected that information management about adverse events can efficiently be done for both sponsor and trial site. For the transmission of information to the clinical site from the sponsor, electronic media such as floppy disk, CD-R, etc., are presently desirable, but the use of electronic mail and browsing software should be considered. Further, discussion should be started between sponsors and trial sites about communication of adverse events detected in trial sites to sponsors.

In the near future, information about safety currently covered by ICH E2b/M2<sup>12)</sup> will be available on electronic media, and a database for common use of the information will be installed on the internet. Although sufficient security is required, it is expected that there will be considerable advantages in information management about adverse events for both sponsors and trial sites.

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