—Regular Articles—

Items of Concern Associated with Source Document Verification of Clinical Trials for New Drugs

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In the present study, we analyzed concerns of the sponsors of clinical trials regarding source document verification (SDV) procedures performed at the University of Tokyo Hospital during April 1999 and March 2001, with special focus on the differences in description between the source document and case report form (CRF). Of 132 SDV procedures (78 protocols, 496 cases), the sponsors had problematic concerns with 348 cases (70.2%) totalling 693 items, which consisted of description inconsistencies between the source documents and the CRF (41.4%), lack of description in the CRF (39.8%), and lack of description in the source documents (8.8%). The most frequently found inconsistencies between the source documents and CRF were concerning items regarding observations, laboratory examinations, and compliance, which were associated with misdescription of clinical data and/or items for evaluation in the CRF. It was also revealed that the frequent lack of description in the CRF was associated with patient history and/or complications, adverse events, and concomitant drugs and/or therapy. In contrast, the frequent lack of description in the source documents was associated with items concerning patient background, observations, and informed consent. Further, we found that submission of a report of deviation from the protocols was required for 4.0% of the claims. These results suggest the necessity of better data management during the practice of clinical trials for the purpose of maintaining the quality of clinical trials.

Key words——clinical trials; source document verification; SDV; case report form; CRF

INTRODUCTION

Clinical trial of new drug is the final and most important step through new drug development process. It provides clinician and pharmacist with the basic information on the use of drug in patient with disease, such as target indication and disease symptom, dosage regimen and cautions for use, at the time of general clinical and dispensing practice. Therefore, clinical trial of new drug needs to be conducted under a qualified manner with well designed clinical study protocol. Clinical trial also has to be conducted under an ethically acceptable condition.

For ensuring the above, the new GCP introduced by the amendment of Japanese Pharmaceutical Affairs Law in 1997 requests a sponsor for clinical trial to monitor trial to ascertain that they are performed (or conducted) in an accurate and verifiable manner. For this purpose, source document verification (SDV) is performed, by which the sponsor inspect both the case report form (CRF), submitted by the doctors, and source documents, including medical records. At the University of Tokyo Hospital, we established a system in April 1999 to consolidate the management of such inspections, which are associated with SDV procedures, with the Clinical Research Center.[1)]

For the present study, we analyzed concerns pointed out by sponsors during the early stages of operation of this system, particularly focusing on the differences in content between the CRF and source documents. We also discuss problems experienced with the management of data obtained in clinical trials at our hospital.

METHODS

We focused on SDV procedures performed from April 1999 to March 2001, and analyzed the difference in content between the source documents and CRF by checking the monitoring/inspection report submitted

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by the sponsors to our hospital following each SDV.

The concerns pointed out by the sponsors were divided into 4 categories; lack of description in either the source documents or CRF, inconsistency between the source documents and CRF, and miscellaneous. In addition, the same concerns were also divided into 9 categories, which were use of concomitant drugs and/or therapy, patient history and/or complications, laboratory examinations, patient background, adverse events, matters regarding observation, compliance, informed consent, and miscellaneous. Both sets of classifications were subjected to analysis. We also analyzed how the doctors responded to the claims of differences between the source documents and CRF raised by the sponsors, and, based on the frequency of each kind of claim, discuss methods to solve these problems that can be implemented in the future.

RESULTS

Analysis of concerns pointed out by the sponsors: We analyzed sponsor reports regarding 496 cases, which originated from 132 SDV procedures based on 78 protocols. Among them, concerns were pointed out by the sponsors for 348 cases (70.2%), which totalled 693 individual problematic matters. These consisted of inconsistencies between the source documents and CRF (287 items, 41.4%), lack of description in the CRF (276 items, 39.8%), lack of description in the source documents (61 items, 8.8%), and miscellaneous matters including failure to obtain patient data (69 items, 10.0%).

These concerns were also classified into 9 categories, which consisted of use of concomitant drugs and /or therapy (145 items, 20.9%), patient history and/or complications (118 items, 17.0%), laboratory examinations (110 items, 15.9%), patient background (91 items, 13.1%), adverse events (68 items, 9.8%), matters regarding observation (67 items, 9.7%), compliance (39 items, 5.6 %), informed consent (39 matters, 5.6%), and miscellaneous (16 matters, 2.3 %) (Fig. 1). Each of these was analyzed based on the lack of description in either the source documents or CRF, inconsistency between the source documents and CRF, and miscellaneous, and the results are summarized in Table 1.

The most frequently found inconsistencies between the source documents and the CRF were concerning matters regarding observation (43 items, 64.2%), laboratory examinations (63 items, 57.3%), and compliance (22 items, 56.4%), which were associated with misdescription of clinical data and/or items for evaluation in the CRF. It was also revealed that the frequent lack of description in the CRF was associat-

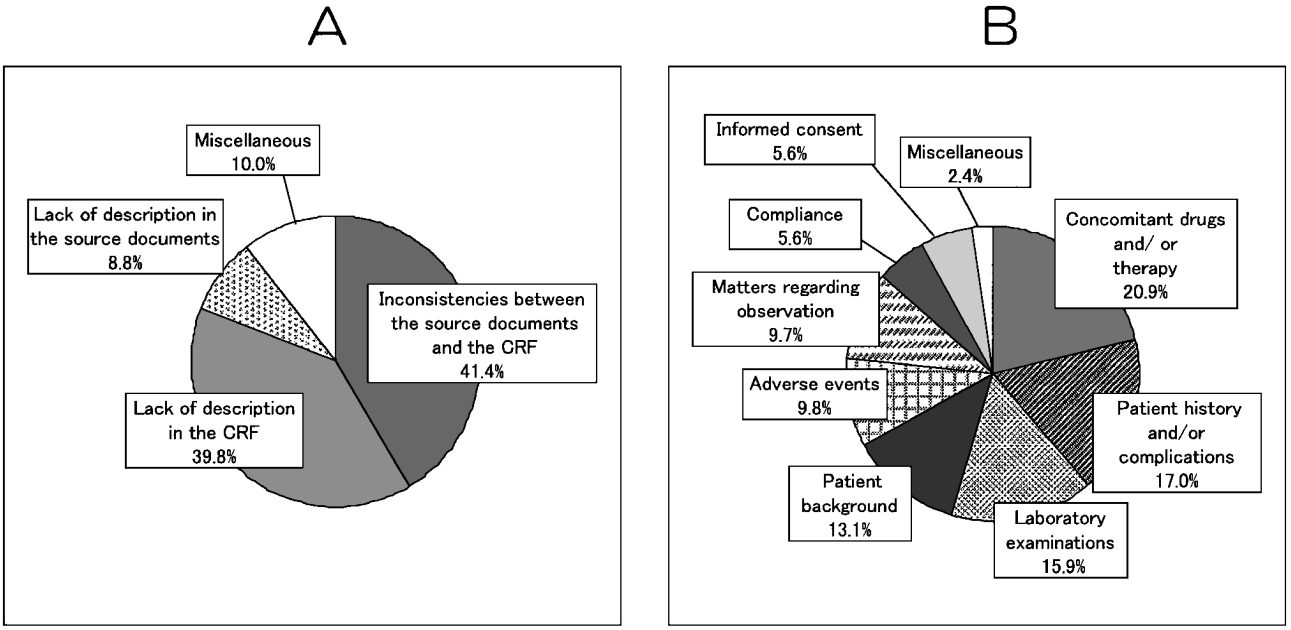

Fig. 1. Problematic Items Pointed out by Sponsors of Clinical Trials

Six hundred ninety-three separate items pointed out by the sponsors of clinical trials regarding our SDV procedures were analyzed. The concerns were analyzed from the viewpoint of consistency of the descriptions between the source documents and CRF (A), and also from the viewpoint of incorrect information entered into the source documents and/or CRF (B).

Table 1. Classification of Concerns Pointed out by Sponsors Regarding SDV Procedures.
Number of items of concern (%)

	Inconsistency between the source documents and the CRF	Lack of description in the CRF	Lack of description in the source documents	Miscellaneous	Total
Patient background	38(41.8)	33(36.3)	18(19.8)	2(2.2)	91(100)
Patient history and/or complications	25(21.2)	78(66.1)	11(9.3)	4(3.4)	118(100)
Concomitant drugs and/or therapy	68(46.9)	67(46.2)	4(2.8)	6(4.1)	145(100)
Matters regarding observation	43(64.2)	13(19.4)	11(16.4)	0(0.0)	67(100)
Laboratory examinations	63(57.3)	29(26.4)	6(5.5)	12(10.9)	110(100)
Compliance	22(56.4)	6(15.4)	2(5.1)	9(23.1)	39(100)
Adverse events	16(23.5)	41(60.3)	2(2.9)	9(13.2)	68(100)
Informed consent	7(17.9)	3(7.7)	5(12.8)	324(61.5)	39(100)
Miscellaneous	5(31.2)	6(37.5)	32(12.5)	3(18.8)	16(100)
Total					693

Six hundred ninety-three separate items pointed out by the sponsors of clinical trials regarding our SDV procedures were analyzed. The concerns were first analyzed from the viewpoint of incorrect information entered into the source documents and/or CRF. Then, each entry was further analyzed to determine consistency between the source documents and CRF. Numbers in parentheses represent the percent of total number of problematic items for each entry.

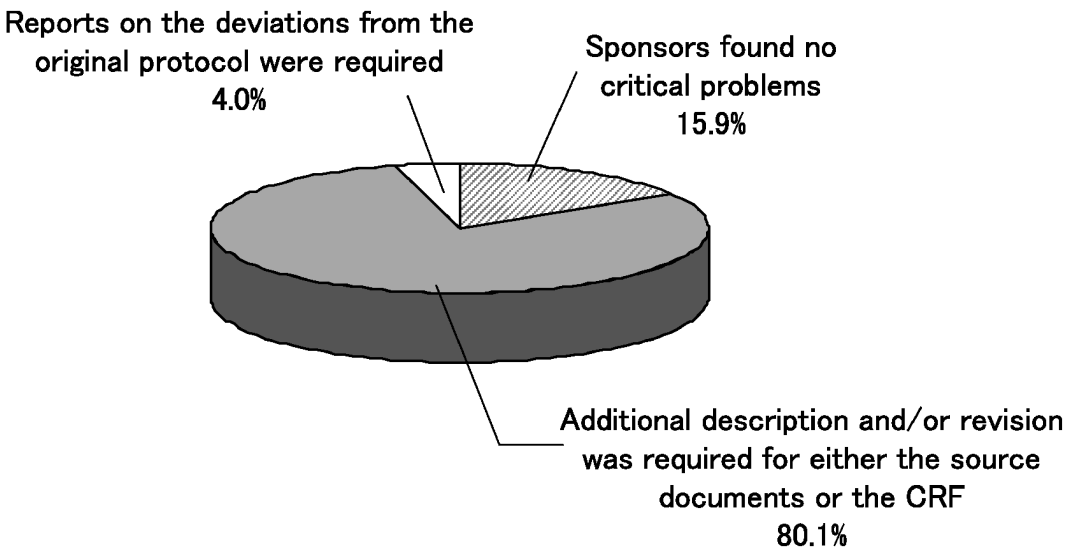

Fig. 2. Responses from Doctors to Claims from the Sponsors
We analyzed the responses from doctors regarding the 693 items pointed out by the sponsors of clinical trials regarding SDV procedures at University of Tokyo Hospital.

ed with patient history and/or complications (78 items, 66.1%), adverse events (41 items, 60.3%), and concomitant drugs and/or therapy (67 items, 46.2 %). In contrast, the frequent lack of description in the source documents was associated with items concerning patient background (18 items, 19.8%), mattres regarding observation (11 items, 16.4%), and informed consent (5 items, 12.8%).

Concerning the 693 individual items, we surveyed each doctor responsible for the respective clinical trial regarding the claims raised by the sponsors. For 110 items (15.9%), the sponsors found no critical problems (Fig. 2). However, for 555 items (80.1%), additional description and/or revision was required for either the source documents or the CRF, and for 28 items (4.0%), reports on deviations from the original protocol were required (Fig. 2).

DISCUSSION

From the present survey results, we found that an item of concern was pointed out for 70.2% of the examined cases. Most were about an inconsistency be-

tween the source documents and CRF, regarding the description or lack of description in either the source documents or CRF (Fig. 1A).

The classification most frequently pointed out by the sponsors as problematic was use of concomitant drugs and/or therapy (Fig. 1B and Table 1), and we considered that one of the important factors for this result might be related to the CRF forms.[2] We considered that many of the claims could be ascribed to the variety of types of information required on the CRF forms to describe the use of concomitant drugs and/or therapy, which was dependent on the sponsors and protocols utilized for clinical trials. It is proposed that application of uniform CRF forms for this information is required in order to maintain the quality and consistency of data presented.

Concerning the content of the problematic concerns pointed out by the sponsors, inconsistencies between the source documents and CRF were most frequently found for matters regarding observations, laboratory examinations, and compliance (Fig. 1B and Table 1). These inconsistencies were associated with misdescription of clinical data and/or items for evaluation in the CRF. Since it is possible that differences of description between the documents and CRF may have a large effect on the evaluation of cases, greater attention must be paid to accurately describe these items in the CRF.

It was also revealed that the frequent lack of description in the CRF was associated with items regarding patient history and/or complications, adverse events, and concomitant drugs and/or therapy. The fact that these points were described in the source documents indicates that the doctors did not elaborate on them in the CRF. In contrast, the frequent lack of description in the source documents was associated with items regarding patient background, observations, and informed consent. It is possible that the doctors described these items on the CRF, however, did not transcribe them to the source documents.

Our results showed that 96.0% of the concerns raised by the sponsors were not associated with serious problems or could be rectified by additional description and/or revision. However, for 4.0% of the claims, submission of a report regarding a deviation from protocol was required. These deviation cases, which were associated with such problems as a lack of patient data, alerted us to potential inaccuracies in the results of clinical trials.

In order to assure ethical and scientific aspects as well as the reliability of clinical trials, it is important to perform precise trials and give accurate data back to the sponsors, thus, a properly completed CRF is required. Ohashi et al.[3] noted that it is necessary for hospitals to examine the verification rate, inconsistency rate, and deviation occurrence rate involved with SDV procedures, in order to evaluate the quality of data management in medical institutions. In the present study, we analyzed recent clinical trials performed by our institution by examining feedback reports submitted by sponsors. As a result, we found it necessary for our hospital staff to compare descriptions between the source documents and CRF in order to evaluate the quality of clinical trials.

The results of the present analysis suggest the necessity of good data management, including the accuracy of the various pieces of information required by sponsors, as well as consistency between the source documents and CRF. Recently, it was suggested that the involvement of clinical research coordinators would be effective for maintaining the quality of clinical trials.[4] Since clinical research coordinators have begun to support the preparation of CRF forms in our hospital, it will also be necessary to examine their contribution toward solving the problems raised in the present study.

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