An Attempt to Evaluate the Quality of Clinical Trial Data by the Investigational Medical Institution Itself : Survey of Quality of Clinical Trial Data from the Source Documents Verification (SDV) Viewpoint

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The aim of this study was to look at the clinical trials from the viewpoint of medical institution's own data management. From source documents verification (SDV) from 33 clinical trials (126 cases) carried out in Nippon Medical School Hospital between June 1999 and July 2000, the verification rate, inconsistency rate and occurrence state of deviation were surveyed.

In the SDV of 126 cases, the mean verification rate was $97.5 \pm 4.0\%$ [mean $\pm$ SD (range : 85.8~100%)]. The data with the lowest verification rate was on items for "evaluation" (82.9%) followed by "others", "side effects/adverse events" and "withdrawal/dropout". The major reason for the impossibility to verify was due to the fact that investigators entered the records directly to CRF without recording on to medical charts (no statement was made to regard data entered to CRF as source data). Other reasons were due to the monitor's inappropriate interpretation of the medical chart, insufficient preparation of source documents for SDV. There was no case which source data was missed.

Among the 26,628 data verified, inconsistency was found between CRF and the source documents in 333 data [$1.7 \pm 2.3\%$ (range : 0~8.1%)]. Inconsistency was caused mainly by inaccurate entering of data to CRF and by incomplete data of CRF due to omission of entry. Other reasons were miscalculation, misspelling, and contradiction between source documents.

In 126 cases 68 deviations were found. The majority was that laboratory tests had not been carried out. Serious deviations observed were those of exclusion/inclusion criteria, inappropriate informed consent, and omission of the evaluation.

Data error observed in this survey were considered to be within the acceptable range. We conclude that by reviewing the verification rate, the inconsistency rate and the occurrence state of deviation as measurements of quality of clinical trial data, each medical institution can achieve their own data management.

Key words : verification rate, inconsistency rate, deviation, and data management

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Fig. 1 Multiple steps of data collection and process flow to final reports in a clinical study

Introduction

The aim of this study was to examine clinical trials from the viewpoint of data management. Confirmation of whether the data reported from the investigator to the sponsor is accurate and reliable is a fundamental requirement of Good Clinical Practice (GCP)¹⁾. Monitors in the sponsor side carry out this confirmation through source documents verification (SDV) process. However, it is the medical institution that collects data through the clinical trial and prepares case report forms (CRF) based on the data (Fig. 1). Therefore, it is of significant importance for the medical institution to have a self-check function to evaluate the quality of the clinical trial by checking whether the data reported from the investigator to the sponsor was accurate and complete. In Nippon Medical School we tried to test the self-check system through the model project²⁾ using SDV by direct access to medical charts from October to December 1997, just before the full enforcement of new GCP. During that process, the percent-

age of the amount of data verifiable in SDV to the total amount of data in CRF was calculated as the verification rate. A verification rate of $86.4 \pm 12.9\%$ [mean $\pm$ SD (range : 63.7~99.7%)] was achieved at that time (Table 1). For clinical trials 2 years after the first survey, the same survey was carried out to find which measurements of quality are appropriate to monitor the change in the level of clinical trials. The purpose of this survey was to identify the factors to be taken into account in order to allow the medical institution itself to execute an effective and proper clinical trial management system and to determine the future direction to proceed.

Method

For the result of SDV from 33 clinical trials (126 cases) carried out in Nippon Medical School Hospital between June 1999 and July 2000, the following matters were reviewed by checking of CRF, inquiring of the monitor in charge and IRB survey by the members of IRB office carried out simultaneously with SDV in

Table 1 Percentage of Amount of SDV-possible Data to All Amount of Data in CRF as Verification Rate

	Drug	Disease	Stage	Total data of CRF	SDV-possible Data (verification rate%)		SDV-impossible Data	
1	Antiarrhythmic (Class Ib)	VPC	late phase II	310	285	91.9%	25	8.1%
				310	284	91.6%	26	8.4%
2	Immunosuppressive drug	Aplastic anemia	phase III	94	89	94.7%	5	5.3%
				405	259	64.0%	146	36.0%
3	Antiemetics	Reflux esophagitis	early phase II	405	258	63.7%	147	36.3%
				405	348	85.9%	57	14.1%
4	Antiarrhythmic (Class Ic)	VPC	phase III	343	281	81.9%	62	18.1%
5	Specific hypsensitization therapeutic drug	Nasal allergy (Cedar induced)	phase II	249	242	97.2%	7	2.8%
6	Anticancer agent	Cancer	phase I	82	71	86.6%	11	13.4%
7	Cardiac failure	Acute heart failure	early phase II	539	494	91.7%	45	8.3%
8	Brain metabolic stimulant	Cerebral thrombosis	late phase II	862	603	70.0%	259	30.0%
9	Consciousness stimulant	Cerebral infarction (acute stage)	late phase II	750	720	96.0%	30	4.0%
10	Anticancer agent	Non small cell lung cancer	late phase II	709	707	99.7%	2	0.3%
				383	381	99.5%	2	0.5%
Total (mean±sd)				429.6±258.9	86.4±12.9%		13.6±12.9%	

(1997 Oct.~1997 Dec.)

order to evaluate the accuracy and completeness of data.

1) Analysis of data possible to verify : Data on each item of CRF were classified into the following 3 groups and the possible verification rate, that is, the percentage of (I) + (II) to the total amount of data in CRF was calculated.

(I) Data possible to do SDV [Data recorded in medical charts and possible to verify the original records (raw data)]

(II) Conditional data possible to do SDV (Data recorded in medical charts but impossible to verify the original records)

(III) Data impossible to do SDV

2) The details of (III) data impossible to do SDV were analyzed.

3) The details and frequency of inconsistency

between CRF and source documents among data possible to do SDV [(I) + (II)] were surveyed.

4) State of appearance of deviation was surveyed.

Results

(1) For SDV of 33 clinical trials (126 cases), the mean $97.5 \pm 4.0\%$ (range : 85.8~100%) of the average data amount 820.4 ± 764.7 (range : 36~3,773) was possible to verify (Table 2).

(2) Data having a high verification rate (95% or higher) were on accompanying symptom (99.9%), observation period (98.7%), laboratory examinations (98.3%), items for observation (98.1%), hospital/patient-related information (96.9%), and the patient's background (96.1%). On the other hand, the data with a

Table 2 Percentage of Amount of SDV-possible Data to All Amount of Data in CRF as Verification Rate and Percentage of Amount of Inconsistent Data to That of SDV-possible Data as Inconsistency Rate

Drug	Disease	Stage	SDV cases	Total data of CRF	SDV-possible data (verification rate %)		SDV-impossible data		Inconsistent data (inconsistency rate %)	
1 β -blocker	Chronic heart failure	phase II	1	198	174	87.9%	24	12.1%	13	7.5%
2 Na ⁺ /H ⁺ transporter inhibitor	Acute myocardial infarction	early phase II	2	595	585	98.3%	10	1.7%	18	3.1%
3 Angiotensin II antagonist	Hypertension	phase III	3	810	806	99.5%	4	0.5%	40	5.0%
4 HMG-CoA reductase inhibitor	Hyperlipidemia	phase III	2	158	155	98.1%	3	1.9%	0	0.0%
5 Insulin sensitivity inducer	NIDDM	phase II	3	752	752	100.0%	0	0.0%	0	0.0%
6 Inducer		phase II	6	1,813	1,813	100.0%	0	0.0%	12	0.7%
7 Antidiabetic	NIDDM	phase III	2	36	36	100.0%	0	0.0%	1	2.8%
8 Angiotensin II antagonist	Diabetic nephropathy	phase III	1	240	240	100.0%	0	0.0%	11	4.6%
9 5-HT _{1D} agonist	migrain	late phase II	8	749	746	99.6%	3	0.4%	0	0.0%
10 Antiulcer agent	Gastric ulcer	phase IV	1	153	153	100.0%	0	0.0%	4	2.6%
11 Antifungal	Deep mycosis	phase II	2	676	580	85.8%	96	14.2%	3	0.5%
12 Agent of anti-influenza	Influenza	phase III	1	859	859	100.0%	0	0.0%	0	0.0%
13 NSAIDS	Pain of cancer	late phase II	3	429	429	100.0%	0	0.0%	27	6.3%
14 Muscarine agonist	chronic dry mouth	phase III	3	1,210	1,201	99.3%	9	0.7%	2	0.2%
15		phase III	2	476	468	98.3%	8	1.7%	0	0.0%
16 Thrombomoduline/Thrombin complex	DIC	phase III	1	1,126	1,113	98.8%	13	1.2%	0	0.0%
17			4	3,773	3,746	99.3%	27	0.7%	0	0.0%
18 Serotonine•norepinephrine reuptake inhibitor	Depression	phase III	1	224	200	89.3%	24	10.7%	0	0.0%
19 5-HT _{1A} agonist	Disturbance	early phase II	3	485	449	92.6%	36	7.4%	5	1.1%
20 AChE Inhibitor	Alzheimer disease	phase II	1	474	474	100.0%	0	0.0%	0	0.0%
21 Benzodiazepin partial agonist	Dementia due to AD, CVD	early phase II	1	557	505	90.7%	52	9.3%	6	1.2%
22 ACh • monoamine releaser	Alzheimer disease	early phase II	2	699	670	95.9%	29	4.1%	0	0.0%
23 H ₁ antagonist	Nasal allergy (Cedar induced) infants	late phase II	6	1,089	1,062	97.5%	27	2.5%	10	0.9%
24 Extracts of cedar pollen	Nasal allergy (Cedar induced)	phase III	10	1,172	1,159	98.9%	13	1.1%	15	1.3%
25			7	831	820	98.7%	11	1.3%	10	1.2%
26 TXA ₂ antagonist	Nasal allergy (Cedar induced)	late phase-II	2	129	119	92.2%	10	7.8%	1	0.8%
27 Vitamine D ₃ analogue	psoriasis vulgaris	phase III	3	677	658	97.2%	19	2.8%	12	1.8%
28		phase III	3	1,961	1,941	99.0%	20	1.0%	17	0.9%
29 $\alpha_{1L, 1A}$ antagonist	Prostate hypertrophy	early phase II	2	158	158	100.0%	0	0.0%	4	2.5%
30 α_1 -blocker	Urinary disturbance due to Prostatic hypertrophy	late phase II	2	104	104	100.0%	0	0.0%	1	1.0%
31 Gd for MRI	Hepatic tumor	early phase II	6	828	825	99.6%	3	0.4%	12	1.5%
32 β -blocker	Arrhythmia (during surgical operation)	phase III	10	2,356	2,356	100.0%	0	0.0%	6	0.3%
33 Acetated Ringer's solution	Surgical patients	phase III	22	1,276	1,272	99.7%	4	0.3%	103	8.1%
Total (mean $\pm$ sd)			126 (3.8 $\pm$ 4.1)	27,073 (820.4 $\pm$ 764.7)	26,628 (97.5 $\pm$ 4.0%)		445 (2.5 $\pm$ 4.0%)		333 (1.7 $\pm$ 2.3%)	

(1999 Jun.~2000 Jul.)

Table 3 Analysis of SDV-possible Data (Verification Rate)
in Relation to 10 Categories of Data

Items of data	Number of protocols	Amount of SDV-possible data	Verification rate
① Hospital/patient-related information	33	29.8±19.8 (6~77)	96.9±8.0% (57.5~100%)
② Patient's background	32	77.3±69.8 (3~310)	95.9±6.5% (76.5~100%)
③ Observation period	25	88.6±169.1 (1~845)	98.7±3.9% (81.6~100%)
④ Items for observation	32	256.7±362.3 (3~1,774)	98.1±6.7% (63.6~100%)
⑤ Laboratory examinations	32	240.7±233.0 (2~1,070)	98.3±4.8% (81.5~100%)
⑥ Accompanying symptom	17	100.4±216.9 (1~894)	99.9±0.5% (98.0~100%)
⑦ Adverse drug reactions or adverse events	29	30.7±32.6 (1~138)	90.0±23.0% (0~100%)
⑧ Discontinuance	29	8.7±15.8 (1~88)	92.8±19.7% (25.0~100%)
⑨ Items for evaluations	24	81.0±128.7 (2~435)	82.9±0.2% (0~100%)
⑩ Miscellaneous	14	49.1±73.5 (2~217)	85.7±36.3% (0~100%)
Total (mean±SD)	33	820.4±764.7 (36~3,773)	97.5±4.0% (85.8~100%)

low verification rate was that on items for evaluations (82.9%) followed by miscellaneous (85.7%), adverse drug reactions or adverse events (90.0%), and discontinuance (92.8%) (Table 3).

(3) The reasons for impossibility to verify reported by the monitor could be classified into 5 categories as shown in Table 4.

A total of 386 of 445 data which were impossible to verify (86.7%) fell into (C); the investigator entered the records directly into CRF without entering medical charts (no statement was made with regard to data entered to CRF as source data). A total of 26 data (5.8%) fell into (D); data were impossible to verify because of the monitor's inappropriate interpretation of medical charts. A total of 21 data (4.7%) fell into (B); nothing was entered to medical charts and no raw data such as laboratory test slips and medical charts of other department were prepared for SDV. No original data were missed (A). Miscellaneous causes were noted in 12 data (2.7%) as follows (E):

- Doctors did not check the medications the patients had received at previous hospitals.

- No abnormality on urine test, blood pressure and heart rate was seen in CRF but no statement of "no abnormality was found" was made in the medical charts. Because of that it was impossible to verify.
- Doctors did not understand how to enter the data in CRF because the CRF entry form was ambiguous. (A statement was made that the attached copy of the electrocardiogram was regarded as original data. However, there was confusion in the form where the time that the ECG was taken had to be entered separately.)
- The state of compliance to medication and concurrent treatment were unable to verify because the patient stopped visiting in the middle of the clinical trial.

(4) Among the total number of data (I + II : 26,628) in which verification could be made, inconsistency was found between CRF and the source documents in 333 data. Thus, the inconsistency rate was $1.7 \pm 2.3\%$ (range : 0~8.1%) (Table 2). The details of inconsistency were roughly classified into 2 categories (Table 5): data entered in CRF were not the same as those

Table 4-1 Causes of Impossible Source Document Verification

A. Loss of source documents B. Insufficient preparation of source documents for SDV
 C. The data directly recorded in case report form, not in medical note
 (No identification the data recorded in CRF to be the source data)

D. Inappropriate reading of information in the medical note E. Miscellaneous

① Hospital/patient-related information

Item	No.	Cause of impossible SDV
Data of writing CRF	3	C
Initial of name	2	D
Age	2	D
Date of confirming the check rist	1	C
Diagnosis	1	D
Eligibility criteria	1	C
Exclusion criteria	9	C
Name of doctor	1	D
Data of checking source documents	2	C
Occupation	1	C
Code of patient	2	C
Other therapy	1	C
Date of final writing CRF	6	C

② Patient's background

Item	No.	Cause of impossible SDV
Body weight	7	C
Cigarette habit	4	C
Comment	1	D
Occurrence of disease	1	C
Former medicine	1	E
Previous therapy	1	E
Coronary angiographical findings	1	B
Complication	2	C
Other treatments	17	B
Height of body	5	C
Psychiatric cause	6	C
Reasons of former drug changed	4	C
Diagnosis	4	C
Suspected date of fungal infection	2	C
Chief antigen	2	D
Dual antigen	4	D
Global severity	10	C
Incidence period	4	C
Presence of complication	2	C
Judgement of risk	1	C
Pregnancy or Lactation	1	C

③ Observation period

Item	No.	Cause of impossible SDV
Concomitant therapy	3	D
Reasons for dose escalation	4	D
Concomitant drugs	5	C
Present illness	2	C
Allergic symptoms	1	C
Contrast medium for CT	3	B

④ Items for observation

Item	No.	Cause of impossible SDV
Compliance	3	C
Reasons for concomitant therapy	29	C
Dose of concomitant drug	2	C
Compliance at 2nd week	1	E
Presence of concomitant therapy	1	E
Blood pressure	1	C
Heart rate	1	C
Reasons of concomitant drug changed	1	C
Subjective symptom	10	C
Medical findings	9	C
Nasal hemorrhage	1	C

⑤ Laboratory examinations

Item	No.	Cause of impossible SDV
Blood pressure	8	C
Presence of abnormality	37	C
Fraction of WBC	5	D
Judgement of abnormality	6	E
Comment	4	C
Causality	12	C

⑥ Accompanying symptom

Item	No.	Cause of impossible SDV
Accompanying symptom	1	C

Table 4-1 (continued)

⑦ Adverse drug reactions or adverse events			⑨ Items for evaluations		
Item	No.	Cause of impossible SDV	Item	No.	Cause of impossible SDV
Grade	16	C	Severity	3	C
Causality	10	C	Global safety	10	C
Occurrence	1	D	Comment	3	C
Disappearance	1	C	Global evaluation	4	C
Judgement	2	C	Time performing ECG	2	E
Classification of severity	18	C	Global improvement	29	C
Comment	2	C	Effective % of clinical finding	3	C
Treatment and process of abnormality	1	C	Micological effect	3	C
Yes or No	17	C	Serologically effectiveness	3	C
Symptomatic therapy	2	C	Image diagnostic effectiveness	3	C
Another drug	1	C	Final effect	2	C
⑧ Discontinuance			Impression of Pt.	1	C
Item	No.	Cause of impossible SDV	Judgement of side effect	11	C
Follow up study	1	C	Presence of clinical or hemorrhagic symptom	15	C
Yes or No	1	C	Follow up study till pretreatment	5	C
Date	1	C	⑩ Miscellaneous		
Cause	5	C	Item	No.	Cause of impossible SDV
Comment	5	C	Summary and comment	2	C

Table 4-2 Frequency and Causes of SDV Impossibility

Cause	No.	(%)
A : Loss of source documents	0	0.0%
B : Insufficient preparation of source documents for SDV	21	4.7%
C : The data directly recorded in case report form, not in medical note (No identification the data recorded in CRF to be the source data)	386	86.7%
D : Inappropriate reading of information in the medical note	26	5.8%
E : Miscellaneous	12	2.7%
Total	445	100.0%

recorded in source documents because of inaccurate entry in CRF ; incomplete data due to omission of entry. Others were miscalculation, misspelling, and contradiction between source data (Table 5). The type of inconsistency produced was characterized by the kind of data. Omission of entry in CRF was frequently found in the data of patient's background, items for observation, side effects and previous or concomitant medication were also frequently missed. On the other hand, inconsistency due to inaccurate entry to CRF was the most often found in laboratory tests : this is called transcription error which occurred when the investigator transferred the data from laboratory test slip to CRF. Details of inconsistency are shown in Table 5.

Table 5 The Details of Inconsistency between Data Entered in CRF and Those in the Source Documents

* shows a representative case of same kind of inconsistency observed

(1) Hospital/patient-related information

Inaccurate entry in CRF	The date of informed consent	1	• The date entered in CRF is different from that in written informed consent. [3/26/1999] in CRF, [4/1/1999] in written informed consent
	The registration number and age of subject	4	* Age entered in CRF is different from that in medical chart. [63 years old] in CRF, [67 years old] in medical chart
Omission of entry	Drug therapy	1	• No entry in CRF ; There are entries about 3 different drugs in medical chart

(2) Patient's background

Inconsistency between original documents	Time of onset	1	• The description in CRF is the same as that in worksheet but a different description is found in medical chart
	Complication	1	• The descriptions in CRF, medical chart and worksheet are different from one another
Inaccurate entry in CRF	Complication	2	• [No complication] is entered in CRF but complicated diabetes was ascertained from his (her) doctor • [Gastritis, Insomnia] in CRF, [Constipation] in medical chart
	Past history	2	• [Old myocardial infarction] in CRF, [Myocardial infarction in 1987] in medical chart • [Hepatitis] in CRF, [Operation of cholelithiasis] in medical chart
	History of allergic disease	1	• Described in CRF, [Nil] in medical chart
	Dose of concomitant drug	1	• Description about 1 drug in CRF is different from that in medical chart
	Presence or absence of contraindicated drug to take	1	• [Nil] in registration card, [Presence] in medical chart
	The date of starting concurrent medication, The date of myocardial infarction onset, Duration of pain, Duration of sickning	4	• Description in CRF is different from that in medical chart
	Induced nose reaction, Severity of blood pressure	2	• Severity entered in CRF is different from that in medical chart
	Diagnosis	1	• [Congenital left aural fistula] in CRF, [Congenital aural fistula (left)] in medical chart
	The date of obtaining informed consent	1	• [9/6/1999] in CRF, [9/7/1999] in medical chart
	Medical chart number, Initial	2	• Number and initial entered in CRF are different from those in medical chart
	Weight	1	• Weight at the end of clinical trial is entered in CRF while weight at the date of obtaining informed consent is entered in medical chart

Table 5 (continued)

Miswritten	Complication, previous disease	2	<ul style="list-style-type: none"> • Wrong word of [cataract] • Wrong word of [chronic pancreatitis]
Omission of entry	The name of concomitant drug	2	* [Nitrate agent tape] is entered in medical chart besides those entered in CRF.
	Past history	10	<ul style="list-style-type: none"> * Additional previous diseases are entered in medical chart besides that entered in CRF (Only [Colon polyp] is entered in CRF while [Chronic otitis media] etc. are entered in medical chart besides colon polyp) * [Nil] in CRF, Previous diseases such as [Herpes zoster] etc. are entered in medical chart
	Complication	37	<ul style="list-style-type: none"> * No complication is entered in CRF but [Hypertension], [Hyperuricemia], and [Borderline diabetes] are entered in medical chart * There are many cases having entries such as [Cancer+], [Allergy+], and [Hypertension+] etc. * Additional complications are entered in medical chart besides that entered in CRF
	Daily dose of concomitant drug, Duration of concomitant drug use	2	• Information on 1 drug is entered in CRF but information on other drugs is entered in medical chart
	The name, route of administration, and daily dose of previous therapeutic agent, Site and duration of previous therapeutic agent used	10	• Information on 2 drugs is omitted in CRF
	Presence or absence of severe ventricular arrhythmia	1	• [Absence] in CRF, [Presence] in medical chart
	The name of underlying disease	1	• [Multiple myeloma] is marked in CRF but not selected whether it is primary or recurrent condition. According to the medical chart, it is recurrent one
	Diagnosis	1	• [Thyroid cancer] is entered in CRF, but [rt thyroid ca] is entered in medical chart
	The name of operation	1	• Additional name of operation is entered in medical chart besides that in CRF
	Family relationship of proxy giving informed consent	1	• It is entered in medical chart but no entry is made in CRF
Mis-calculation	Gender	1	• [Male] in CRF, [Male, F] in medical chart
	Family history of hypertension, maternal	1	• [Nil] in CRF, [Unknown] in medical chart
	Duration of anesthesia	1	• Miscalculated duration of anesthesia derived from starting and terminating time of anesthesia

Table 5 (continued)

(3) Observation period

Inaccurate entry in CRF	Duration of concomitant drug administration. The quantity of concomitant drug consumed The name of concomitant drug. The date of evaluation. Laboratory tests implemented during observation period	13	• Information in CRF is different from that in medical chart
	Frequency of concomitant drug administration	1	• A tranquilizer [3 times/day] is entered in CRF but [2 times/day] in medical chart
	The time of examination	1	• [9:09] in CRF, [8:55] in medical chart
	Observation period weeks	4	• [~May 8th] in CRF, [~May 10th] in medical chart
	Treatment period 4 weeks : The date of the III drug evaluation	1	• [July 19th~] in CRF, [July 6th~] in medical chart
Omission of entry	The name of concomitant drug	7	• There is a drug entered in medical chart without being entered in CRF
	Duration of concomitant drug used	1	
	The purpose of concomitant drug use. The quantity of concomitant drug consumed	9	• There is entry in medical chart but no entry in CRF
Inconsistency between original documents	Prescribed tablet	2	• Description in medical chart is consistent with that in CRF but inconsistent with the description in investigational drug control table

(4) Items for observation

Inaccurate entry in CRF	Cumulative amount of bleeding	5	• Amount of bleeding in CRF is different from that in medical chart
	TIMI classification, The time of starting reperfusion	4	• Information in CRF is different from that in medical chart
	The date of blood pressure and pulse measurement	1	• [4/26/2000] in CRF and worksheet, [5/3/2000] in medical chart, Collection of the date in CRF
	Heart rate, blood pressure	2	• Incorrect value in CRF

Table 5 (continued)

Inaccurate entry in CRF	Judgement of hypotensive effect. Basal blood pressure-blood pressure at the time of judgment. Basal blood pressure. Confirmation of dose escalation criteria	16	<ul style="list-style-type: none"> • The values in CRF are different from those in medical chart
	Concomitant drug	4	<ul style="list-style-type: none"> • Description in CRF is different from that in medical chart * The date of drip infusion in CRF is different from that in medical chart
	Investigational drug, Duration of investigational drug prescription	3	<ul style="list-style-type: none"> * [The II drug] in CRF, [The I drug] in medical chart • The duration is inconsistent between CRF and medical chart
	Cumulative dosage	1	<ul style="list-style-type: none"> • [1,310 ml] in CRF, [1,210 ml] in medical chart
	Induction agent	1	<ul style="list-style-type: none"> • [7 ml] in CRF, [5 ml] in medical chart
	Duration of suffering	1	<ul style="list-style-type: none"> • [~8 weeks] in CRF, [~1 month] in medical chart
	Weight	1	<ul style="list-style-type: none"> • Corrected weight in CRF is different from the weight in original data
	Signal intensity	2	<ul style="list-style-type: none"> • The values of background noise and kidney (40~120 minutes after administration) are inconsistent between CRF and medical chart
	Concomitant symptom	1	<ul style="list-style-type: none"> • No entry in CRF [Stopped injection due to fever 37.3°C] is entered in medical chart
	Judgement of MMSE correct answers	2	<ul style="list-style-type: none"> • The date of implementation in CRF is incorrect • Correct answer is mistakenly interpreted as incorrect
	Secretory rate (before administration)	2	<ul style="list-style-type: none"> • [+] in CRF, [3+] in original document (diary) • [-] in CRF, [2+] in original document (diary)
	Secretory rate (2 weeks after administration)	1	<ul style="list-style-type: none"> • [+] in CRF, [2+] in original document (diary)
Omission of entry	Concomitant drug (the name of drug, dosage, time of administration, unit, duration of prescription, purpose of treatment)	21	<ul style="list-style-type: none"> * Slash mark in CRF, [Gastric agent] in medical record • Part of concomitant drugs entered in medical chart are not entered in CRF * Only [Bosmin 4 cc, 9:30] is entered in CRF but [1% Xylocaine 4 ml, 9:34] is entered in medical chart besides Bosmin * [Nil] is marked in CRF but [Bosmin physiological saline solution, 9:00] is entered in medical chart
	Change of concomitant drug (the name of drug, dosage regimen, dose, duration of administration, reason)	8	<ul style="list-style-type: none"> • It is entered in medical chart but no entry is made in CRF.
	The name of operation	1	<ul style="list-style-type: none"> • [Chronic otitis media] in CRF, [Tympanoplasty, Left antrotomy] in medical chart
	Electrocardiogram findings	1	<ul style="list-style-type: none"> • No entry in CRF, [sinus bradycardia] in medical record

Table 5 (continued)

Omission of entry	Subjective symptom and objective symptom	4	* [Nil] in CRF, [Feeling of headache] in medical record * [0 (nil)] in CRF, [1 (week)] in medical chart * [Nil] in CRF, [Presence] in medical chart
	Character of nasal discharge	1	* [Nil] is marked in CRF, but [watery] is entered in original document (diary)

(5) Laboratory examinations

Inaccurate entry in CRF (transcription error)	Laboratory test values (blood)	16	* Incorrect posting from test slips to CRF
	Urine test	7	* Qualitative protein (after administration) [–] in CRF, [+] in medical chart * Incorrect posting of urobilinogen value * Urinary sediment, erythrocyte [–] in CRF, [+] in medical chart
	Judgment of normal or abnormal	16	* Normal hematocrit is entered as abnormal * Incorrect judgement of normal or abnormal in CRF * Total cholesterol level [abnormal] in CRF, [normal] in medical chart * Erythrocyte count and hemoglobin level on the following day of withdrawal are inconsistent between CRF and medical chart
	The date of follow-up examination	2	* K, Cl data on 12/16 in CRF are found to be data on 12/3 (incorrect posting)
	Allergy test	18	* Because the unit of specific IgE antibody measurement was changed due to the change of measurement method, the unit originally entered in CRF is corrected * Value of specific IgE antibody (cedar) is inconsistent between CRF and medical chart * Result of provocation test, lymphocyte count and basophil count are inconsistent between CRF and medical chart. (incorrect posting)
	Numerical value	1	* Numerical values of ACTH and cortisol are inversely entered
Omission of entry	Follow-up values, follow-up examination, IP data	4	* Nothing is entered in CRF although they are entered in medical chart
	Implementation or non-implementation of test	2	* Implementation or non-implementation of blood collection and urine collection for centralized measurement is entered in medical chart but nothing is entered in CRF
	Unit of urine test	3	* No entry on urobilinogen in CRF

(6) Accompanying symptom

Inaccurate entry in CRF	Administration and dosage of concomitant drug	1	* Information in CRF is different from that in medical record
	The date of onset	1	* The date of onset of gustatory abnormality entered in CRF is incorrect
	Medical record	1	* [Cataract] and [anemia] are entered in medical chart besides information entered in CRF

Table 5 (continued)

(7) Adverse drug reactions or adverse events

Inaccurate entry in CRF	The date and time of onset	1	• [7/22/1999] in CRF, [7/21/1999] in medical chart
	Adverse event/abnormal fluctuation of adverse event	1	• [1 week] in CRF, [-48 days] in medical chart
Omission of entry	Presence or absence	4	• [Absence] in CRF, [Presence] in medical chart
	Drug used	20	* Doctor concluded that bleeding during operation caused anemia and no entry of side effect was made in CRF
	Symptom, severity, the date of onset, treatment/course, comment on treatment/course, the date of conclusion, outcome, cause and effect	16	* No entry is made in CRF. Entries such as fracture, common cold, anemia, moderate, mild, 8/9/1999 etc. and continue, fixation with plaster done by other hospital, 9/8 etc., disappeared, no relationship etc. are made in medical chart

(8) Discontinuance (nil)

(9) Items for evaluation

Inaccurate entry in CRF	Presence or absence of chest pain	1	• [Unknown] in worksheet, [Nil] in medical chart
	Hypotensive effect	1	• [2 (slightly dropped)] in CRF, [1 (dropped)] in medical chart

(10) Miscellaneous

Inaccurate entry in CRF	Imaging time	1	• Time from completion of contrast medium administration for T 1 enhanced image to starting imaging is [40 min.] in CRF and [50 min.] in medical chart
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Table 6 Details of Deviation

* shows a representative case of same kind of deviation observed

Matters for deviation	No.	Details of deviation
Visiting at unappropriate day	2	* Patient visited 4 days after taking drug even though the rule stated that the patient should visit between 8 and 15 days after taking drug
Examination not performed	4	• Blood pressure measurement before starting administration
	2	• Electrocardiogram after administration
	2	• Blood, biochemical, and urine test after administration
	1	• Forgetting measurement of residual urine at 4 weeks
	2	• Examination for allergic condition
	5	* Mistake of ordering test to central laboratory (Mistake of order slip marking) * Impossible to measure due to blood coagulation

Table 6 (countinued)

Matters for deviation	No.	Details of deviation
Examination not performed	16	* Hematological and biochemical test at beginning of observation or right before administration
	1	• A/G before and at the end of administration
	3	• Urine test before and after administration
	1	• Items required to measure after visit 8
	10	• Leukocyte fraction
Date of examination delayed	1	• Although protocol requires the last examination should be performed within 2~5 weeks after admission, actual examination was performed 6 weeks after admission
	1	• Urine test before administration was actually performed 7 days after starting administration
Frequency of the measurement	1	• Although 3 blood pressure measurements are required, only 1 or 2 measurements were performed
Missing evaluation	1	• Forgetting DAD measurement
Prescribed period	1	• (4 W → 7 W), the number of tablets
Delayed dosing	1	• Although protocol prescribes the 3rd administration of investigational drug must be done 16 hours after the first administration, actual administration was done 16 hours 10 minutes after the first administration due to the error in implementation
Incorrect dosing interval	3	* Investigational drug was taken later than 12 weeks from the stipulated date of prescription. The drug must be taken within 12 weeks from the stipulated date of prescription
Incorrect dose	1	• Incorrect dosage regimen
Contra concomitant drug employed	3	* It was found that patient was taking drug contraindicated within 4 weeks from starting control observation period
Incorrect escalation of dose	1	• Although escalation of investigational drug dose is not allowed later than 8 weeks, the dose was escalated at 10 weeks
Out of exclusion criteria	1	• Patient with history of drug allergy was enrolled
Out of incursion criteria	1	• Contraindicated site was selected
	1	• Conformed to the criteria after retesting → shifted to treatment period
Incorrect informed consent	1	• Because there was no informed consent of Nippon Medical School available, a form, copy of the informed consent text in the plan for implementation of clinical trial was used
	1	• Directly obtained informed consent
Total	68	

(5) In 126 cases of 33 clinical trials 68 deviations were found. The majority of the deviations were because laboratory tests had not been carried out (47, 69.1%). There were

4 (5.9%) timing and time of medication related deviations, and in 2 (2.9%) the date of the laboratory test relayed deviations (Table 6). Serious deviations observed were out of exclu-

sion/inclusion criteria, out of the timing of informed consent, and omission of evaluation.

Discussion

Nippon Medical School Hospital where this survey was carried out is a general hospital with 1,164 beds. The number of clinical trials conducted in this hospital was 189 in 1995, 178 in 1996, 111 in 1997, 82 in 1998, 53 in 1999, and 49 in 2000 as IRB (Institutional Review Board for Drugs) cases. This number of cases may represent the average level of trials at university hospitals in Japan. Therefore, we carried out this survey to determine the details of clinical trials in this hospital, intending that the state of clinical trials in this hospital may reflect the actual state of clinical trials in other university hospitals.

SDV is a basic requirement in ICH-GCP ; it is carried out by monitors. However, collecting the clinical data and completing CRF to sponsor are performed by the investigator team at the site. In order to conduct self evaluation of clinical trial data, 3 kinds of quality measurements : the verification rate ; the inconsistency rate of clinical trials and occurrence state of deviation were surveyed using SDV carried out in Nippon Medical School Hospital. The former 2 items evaluate the clinical trial data itself, and the latter can be a quality scale to evaluate the attitude toward the clinical trial.

1. Evaluation of verification rate

The verification rate in this survey carried out 2 years after the full enforcement of the new GCP was $97.5 \pm 4.0\%$ which was 11% higher than $86.4 \pm 12.9\%$ of the verification rate shown in the survey carried out from October to December in 1997. Two years have past since the new GCP went into effect. During that period, the awareness of the new GCP in

medical institutions has been greatly enhanced and many institutions have become used to conducting SDV to maintain the quality of clinical trial data. The rise in the verification rate seen during the past 2 years likely reflects an increase in the skill for clinical trials at medical institutions. Conversely, if we know the verification rate of a clinical trial in a medical institution, we can judge the level of clinical trials conducted at that medical institution. The possibility to verify the CRF data means that at least the medical institution keeps the original data that is the basis of CRF.

The verification rate showed differences depending on the kind of data in this survey (Table 3). Data items for evaluation gave the lowest verification rate, followed by miscellaneous and adverse drug reactions or adverse events. When analyzing the reason for impossibility of verification, a direct entry was made in the CRF without entering original data in medical charts in the vast majority of such cases. Because comments for evaluation items, adverse drug reactions or adverse events etc. were usually entered directly in CRF, the verification rate for these data was low (Table 4). In addition, in some cases, for example source data on items for a patient's background were impossible to verify from medical charts because information from other medical institutions was not usually posted. In contrast, monitors could not correctly read the medical records such as medical charts and thus in some cases they could not find the source data, which led to failure of verification. In any case, the key to reliability of a clinical trial is the presence of source data and the verifiability of that data. Therefore, the verification rate is a measurement of quality to confirm clinical trials conducted in a medical institution.

Analysis of the results of this survey suggest-

ed that there are 2 approaches to improve the verification rate. If the purpose is to improve only the verification rate, it can be achieved by stating in the protocol that data entered directly in the CRF are identified as source data as shown in ICH-GCP (6-4-9). The idea to regard CRF as a source document is welcomed by the clinical trial sponsor because the verification process becomes simple while doctors also welcome this idea without requiring entry in both CRF and medical charts because they can save time. This approach, however, has a big problem that there is little information recorded in the medical charts on patients who are enrolled the clinical trial.

Another approach is that investigational physicians fulfill their data management duty by writing on the medical charts. There is a responsibility for all physicians investigating or treating patients to document any relevant findings and changes to current therapy. The records on what they have done and what they found including the evaluation of the results must be kept together with the information of any other treatments the patient has received. Consequently, the official medical records must include core information on the diseases and treatments for all the patients. It is important that the information on the patient's enrollment in clinical trial is recorded as a part of the standard hospital documentation for patients. Schuyl and Engel³⁾ stated that it is necessary to record the fact that the patient is in a clinical trial, the dates of visits, all severe adverse events, any concomitant diseases, confirmation of diseases under treatment, and main items for evaluation of the effectiveness on the medical charts. We do not agree with the preparation of the medical chart for the clinical trial separately. We maintain the belief that the medical chart should be prepared including all the infor-

mation as an official patient document. Most of the information concerning the clinical trial can be included in the ordinary medical chart by using the worksheet. Preparing a separate medical chart for clinical trial makes the procedure more complicated. Ideally, 1 medical chart for 1 patient should be prepared. When the complete details are recorded accurately, the verification rate should be improved naturally.

2. Evaluation of inconsistency rate

Among the data (I + II) in which verification between source documents and CRF data was possible, $1.7 \pm 2.3\%$ of the data showed inconsistency. There has been no report of the basis in Japan to judge whether this result is good or bad. In the English language literature, Schuyl and Engel³⁾ suggest that the acceptable inconsistency rate should be less than 1% and it should be close to 0 for particularly important data. According to the survey⁴⁾ on the occurrence rate of error when entering CRF, errors caused by incomplete entry were found in 0.5% of data. "Critical data" are the key data for the purpose of the clinical trial and they must be accurate. For example, they are "primary endpoint", "serious adverse events" etc. In the present survey on important data, the following results were obtained :

- ① There was little inconsistency in the items for evaluation.
- ② Some discrepancies were found in the evaluation of side effects between doctors and monitors who conduct SDV. Although the doctor enters the possible side effects in the medical chart, they sometimes do not enter them in CRF. The typical example of such case was found in the drug administered during trials in surgical operation. In that case, the monitor thought that the postoperative decrease in hemoglobin level should be entered in CRF as

an adverse event while the doctor did not consider it as a side effect because he diagnosed it was due to anemia caused by hemorrhage during operation.

On the other hand, “non-critical data” should also be accurate but most of the data such as laboratory examination values have less influence on the result of the clinical trial. Numerous inconsistencies of such data were found in this survey data due to incorrect transcription.

During a clinical trial, a large amount of data is generated. To maintain the accuracy of the data, the most important thing is to eliminate incorrect data⁶⁾. For that, the possible sources of incorrect data must be identified, taking carelessness and even corrupt practice into consideration. Intentionally produced false data and faulty data produced by the wrong procedure must be distinguished from a simple minor error such as a transcription error. Since data are generated and they are entered in CRF in the medical institution, the prevention and correction of inconsistency among data should be done in the medical institution. In this survey, it was virtually impossible to identify whether or not the wrong data were produced intentionally. Prevention of errors is preferable to intervention. The best means to prevent inconsistency is to establish a system within the medical institution to confirm whether all the source documents are identified and kept and to ensure that all the relevant data are entered in CRF with accurate and complete form. If the clinical research coordinator (CRC) plays a role in such a data keeping system, it is possible to prevent the production of wrong data as described above.

There were some cases where data required in the protocol could not be entered because of faulty CRF design. For example, many doctors made an incomplete entry in items where the

proper blank had to be selected and checked and then the comments had to be entered. There were also many mistakes found in the form where the calculated amount of transfusion during operation had to be entered. The design of CRF must be as simple as possible.

3. Occurrence state of deviation

Deviation occurred in the following process⁶⁾ of the clinical trial.

- (1) Clinical trial must be conducted in accordance with GCP.
- (2) Data obtained from clinical trial must be conformed to the protocol.
- (3) CRF data must be obtained from the clinical trial.

In this survey, the over whelming majority of deviations were cases where the examinations were not performed yet, which falls into the above category (3). Many were due to the investigator's carelessness and they might not have occurred if CRC had made proper scheduling. Out of exclusion and inclusion criteria, omission of evaluation falling into the category (2) and violation of timing for informed consent falling into the category (1) are considered as serious deviations.

Important thing is to consider that some occurrence of deviation is inevitable and to take proper measures regarding the deviations that have already occurred. In ICH-GCP (1996), the description about measures taken for deviations made is as follows : “4.5.3 The investigator, or person designated by the investigator should document and explain any deviation from the approved protocol.” When the chief investigator fails to take proper action regarding deviation, he (she) violates GCP. In this survey, all the deviations were documented.

In multiple step data collection as shown in Fig. 1, several measurements of quality of data

that are associated with each step can be set. Clarke⁵⁾ listed two measurements of quality, were accuracy of raw data and complete information processing from CRF to database in the viewpoint of clinical data management. In view of the verification rate, inconsistency rate and occurrence state of deviation found in this survey, it was realized that the medical institution could check the quality of clinical trial data. On the whole, the data error observed in this survey was considered within the acceptable range. If this result represents the level of clinical trials implemented in Japanese university hospitals, it can be concluded that the current level of clinical trials in Japan at 3 years after enforcement of new GCP is an appropriate level. This survey was carried out based on the report of SDV results implemented by the monitor and inspection implemented by IRB office. It is expected that standardized collection and validation of clinical trial data will be carried out by the internal monitoring of the medical institution under the clinical trial system with well-trained CRC in the future.

Conclusion

(1) Verification rate, inconsistency rate and occurrence state of deviation were surveyed for the result of SDV from 33 clinical trials (126 cases) carried out in Nippon Medical School Hospital in order to evaluate the accuracy and completeness of the data collected in a medical institution.

(2) In the SDV of 126 cases, the verification rate was $97.5 \pm 4.0\%$ (range : 85.8~100%). The data with the lowest verification rate was on items for "evaluation (82.9%)".

(3) Among 26,628 data for which verification was possible, inconsistency was found between CRF and the source documents in 333 data [$1.7 \pm 2.3\%$ (range : 0~8.1%)].

(4) In 126 cases of 33 clinical trials 68 deviations were found. The following serious deviations were observed : out of exclusion/inclusion criteria, inappropriate timing of informed consent, and omission of evaluation.

(5) Data errors observed in this survey were considered to be within the acceptable range.

We conclude that by reviewing the verification rate, the inconsistency rate and occurrence state of deviation as measurements of quality of clinical trial data, a medical institution can achieve their own data management. It should be noted that the investigational physician has the responsibility of completing an official medical chart of each patient as the physician's own data management.

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