Study characteristics affecting clinical trial quality: investigation using subjects excluded from the efficacy analysis or those deviating from the protocol as indicators

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Abstract

Background: The concept of risk-based approach has been introduced as an effort to secure the quality of clinical trials. In the risk-based approach, identification and evaluation of risks in advance are considered important. The purpose of this research was to objectively identify the quality related risks in clinical trials by investigating the correlation between the study characteristics and the protocol deviations from completed clinical trials. The result is expected to support identifying quality risks in new clinical trials in advance.

Methods: In Research 1, new drugs approved in Japan in fiscal 2014 and 2015 were investigated. For 102 trials, the reasons for excluding subjects from the PPS efficacy analysis were described in the new drug application documents, which were publicly disclosed after the drugôs regulatory approval. In Research 2, new drugs for which Pfizer Japan Inc. obtained approval in Japan in fiscal 2007 to 2016 were investigated. The reasons for excluding subjects from the Per Protocol Set (PPS) efficacy analysis and for protocol deviations were available for 84 trials and 105 trials, respectively. Number of trials with information on both the reasons for excluding subjects from the PPS efficacy analysis and for protocol deviations was 52. I extracted the reasons with the number of cases in each clinical trial and the information on the study characteristics.

Then, direct comparison, univariate and multivariate regression analysis were carried out based on the exclusion rate or the deviation rate to find out study characteristics influencing the exclusion/deviation.

Result: In the multivariate regression analysis for the research based on published data, inhalant, ñRespiratory systemò and ñDermatologicalsò were selected as study characteristics leading to a higher exclusion rate. In the research based on the Pfizer internal data, ñNervous systemsò and ñwithin 31 days of drug administrationò was selected as study characteristics leading to a higher exclusion rate. ñAntineoplastic and immunomodulating agentsò was selected as a study characteristic leading to a higher deviation rate. In ñAntineoplastic and immunomodulating agentsò, many deviations were observed, but the exclusion rate compared with the deviation rate was low; on the other hand, that for ñAntiinfectives for systemic useò was high.

Conclusions: Some characteristics of clinical trials which are likely to cause protocol deviations were suggested. These trials should be considered for specific attention and priority observation in the trial protocol or the monitoring plan and its execution, such as a clear description of inclusion/exclusion criteria in the protocol, development of training materials to site staff and/or trial subjects, as specific risk alleviating measures. I believe that by taking a risk-based approach for monitoring, it becomes possible to

make efficient monitoring activities while maintaining quality of clinical trials.

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Abbreviations

AIC	Akaike Information Criteria
ATC Classification	Anatomical Therapeutic Chemical Classification
CAPA	Corrective Action and Preventive Action
CONSORT	Consolidated Standards for Reporting of Trials
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	US Food and Drug Administration
MRCT	Multi Regional Clinical Trial
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per Protocol Set
QMS	Quality Management System
RBM	Risk-Based Monitoring
RCT	Randomized Controlled Trial

1. Introduction

The monitoring activity of clinical trials is to confirm proper implementation of the trial at the medical institutions and to ensure accuracy of the data to be reported from the original source documents such as medical records. How to implement this monitoring activity more efficiently while maintaining the quality level is a challenge we are facing today. Quality risk in clinical trials is defined as the risk affecting human subject protection and data reliability. In order to secure the quality of clinical trials, the concept of quality management system (QMS), consisting of risk-based approach handling risks as a preliminary action and corrective action and preventive action (CAPA) handling several issues as a post action, has been introduced in clinical trials.

The risk-based monitoring (RBM) method is used in the monitoring activities for many clinical trials today. In RBM, it is necessary to have a focused quality system that adapts to the characteristics of clinical trials instead of conventional monitoring procedure. In RBM, identification and evaluation of risks in the clinical trial prior to the study start are considered important [1, 2, 3]. Based on this background, it was considered whether any useful information with regard to quality can be obtained from the record of protocol deviations [4, 5] in past clinical trials to estimate quality risks such

as protocol deviations that are likely to occur in future clinical trials.

In a previous study, reporting of protocol violations in 80 clinical trials published in four major medical journals was studied, and correlation between the study characteristics and the following categories of protocol violations was examined: enrolment, randomization, study intervention, patient compliance, and data collection errors. The result concerning the correlation was inconclusive due to the under-reporting of protocol violations in the publications, though larger trials were more likely to report violations [6]. Based on this study, I thought more tangible information could be obtained to support identifying quality risks related to clinical trials through collecting more information on the study characteristics.

Recently, qualification of investigators has been assessed by sponsors of clinical trials prior to commissioning trials, and training for the protocol requirement is carried out. Since clinical trials are a form of research targeted to human subjects, some protocol deviations are unavoidable. Nevertheless, it is important to take preventive measures in advance to reduce the deviation as much as possible.

The purpose of this research was to objectively identify the quality related risks in clinical trials by investigating the correlation between the study characteristics and the protocol deviations from completed clinical trials. Identification of the risks which

may affect the quality of clinical trials is expected to be used for preliminary quality control in clinical trials, especially for identifying risks to be considered in RBM.

2. Method

2.1. Data source and collection

I investigated the results of clinical trials that were used for efficacy evaluation for new drug approval in Japan from two sources of regulatory documents. One was those that were published by the regulatory agency (Research 1) and the other was internal data of Pfizer Japan Inc. (Research 2).

Subjects with protocol deviation mean study subjects who have deviated from the protocol regardless of whether they are adopted to the efficacy analysis among the randomized subjects. Subjects with exclusion of efficacy analysis mean study subjects who have been excluded from the efficacy analysis among the randomized subjects (Figure 1).

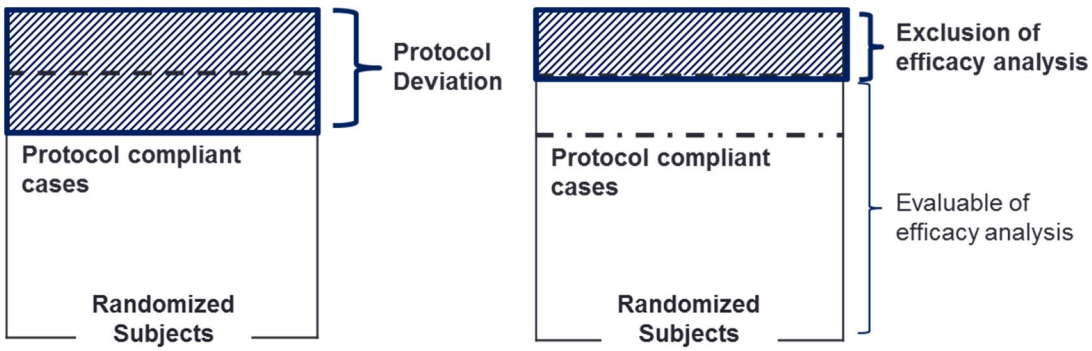

Figure 1. Subjects excluded from efficacy analysis and those with protocol deviation

2.1.1. Research 1: Investigation on published data

The information source of Research 1 was the summary documents of new drug approval applications in Japan placed on the website of Pharmaceuticals and Medical Devices Agency (PMDA)

[https://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0019.html]. A total of 234 newly approved pharmaceutical products in Japan in fiscal 2014 and 2015 were the subjects of the present research.

In Research 1, since all the information on protocol deviations in each clinical trial was not available in the summary documents, I used instead the information on protocol deviations that led to the exclusion from the Per Protocol Set (PPS) for efficacy analysis. Information about cases excluded from the PPS contains a wider range of facts on protocol deviations compared to those for Full Analysis Set (FAS), and I used the cases excluded from the PPS as an index of quality risk.

I also collected information of the study characteristics: study phase, study design, study region, administration route, target diseases, duration of drug administration, number of trial sites, number of subjects, and starting year. With regard to target diseases, Anatomical Therapeutic Chemical (ATC) Classification information of the drug was used (Table 1).

Table 1. Study characteristics and methods of categorization

Study phase	Phase 1, Phase 2, Phase 3, Phase 4
Study design	Randomized Controlled Trial (RCT), Non-randomized Trial (Open)
Study region	Japan domestic trial, Multi regional Clinical Trial (MRCT)
Administration route	Oral administration, Injection, Inhalant, External use
Target diseases	Anatomical Therapeutic Chemical (ATC) classification
Duration of drug administration	Categorized as 1-31 days, 32-182 days, 183-365 days, 366 days or more
Number of trial sites	(numerical)
Number of subjects	(numerical)
Starting year	Categorized as 2000 or before, 2001-2005, 2006-2010, 2011 or after

2.1.2. Research 2: Investigation on Pfizer Internal data

The information source of Research 2 was internal data of Pfizer Japan Inc. that was used for new drug approval applications in Japan. A total of 61 newly approved pharmaceutical products in Japan in fiscal 2007 to 2016 were the subjects of the present research.

In Research 2, I collected information of cases excluded from the efficacy analysis using the same criteria as Research 1 (Research 2.1), those with protocol deviation (Research 2.2), and those excluded from the efficacy analysis and those with protocol deviation in the same clinical trials (Research 2.3). Then, I collected information of

the study characteristics in the same manner as Research 1.

2.2. Data calculation and analysis (both Research 1 and 2)

First, for each of the clinical trials, I calculated the overall exclusion/deviation rate by dividing the total number of the exclusion cases or that of the protocol deviation cases by the number of randomized subjects, and then calculated their median and range across the trials. I also calculated the exclusion/deviation rate by the study characteristics.

Second, I classified the reasons of the exclusion or those of the protocol deviation into 5 categories: deviation concerning inclusion/exclusion criteria, deviation concerning investigational drugs, deviation concerning concomitant treatment, deviation concerning study procedures, and other inappropriate cases such as inappropriate informed consent, randomization errors, or inappropriate unblinding process (Table 2). Then, the exclusion/deviation rate by the 5 reasons was calculated.

Table 2. Classification of reasons of protocol deviation

Classifications	Major cause of exclusion
Deviation concerning inclusion/exclusion criteria	Deviation from the inclusion/exclusion criteria of study subjects
Deviation concerning investigational drugs	Deviation from the dosage and administration for investigational drugs
Deviation concerning concomitant treatment	Deviation from the provisions of concomitant treatment
Deviation concerning study procedures	Deviation concerning study procedures such as no data available on specific visit date
Other inappropriate cases	Randomization errors, inappropriate unblinding process, and inappropriate informed consent

Third, I conducted regression analysis to investigate the relationship between the exclusion/deviation rate and the study characteristics.

Univariate regression analysis was conducted to examine the relationships between the exclusion/deviation rate (overall rate and the rate by the 5 reasons) and each of the study characteristics. Phase 3 in study phase, randomized controlled trial (RCT) in study design, Japan in study region, oral in administration route, A ñAlimentary tract and metabolismò in the ATC classification, 1 to 31 days in duration of drug administration, and year 2005 or before in study starting year were the reference classification for comparisons in this variable group for the analysis of Research 1. Considering the number of studies falling into each classification of characteristics, in Research 2, I changed the reference classification in the ATC classification to C ñCardiovascular

systemò for Research 2.1 and 2,2, to J ñAntiinfectives for systemic useò for Research 2.3, and in study starting year to 2000 or before for all the analyses in Research 2.

Multivariate regression analysis was done using the exclusion/deviation rate as a response variable and the study characteristics as explanatory variables with stepwise variable selection based on AIC (Akaike Information Criteria). Variables were selected by stepwise method based on AIC and the estimates of regression coefficient in the final models were presented. The analyses were conducted with ñR version 3.1.0ò [7] and values of $p<0.05$ were considered statistically significant. In the regression analysis, small clinical trials with less than 20 subjects were excluded. When the number of target diseases of clinical trials falling into a class of the same ATC classification was less than 5, I combined them as class Z to get more reliable estimates of regression models. Because there were a lot of missing data for starting year on published data, this variable was excluded from the multivariate regression analysis in Research 1.

In addition to the above analysis, comparison of the results of exclusion of efficacy analysis and those of protocol deviation were done in Research 2.3.

3. Result

3.1. Research 1: Investigation on published data

1) Exclusion rates by study characteristics

The median of the overall exclusion rate among 102 clinical trials investigated was 8.3%. When I looked into it by the study characteristics, an exclusion rate of 15% or more was found in inhalant (25.6%) in the administration route, J ñAntiinfectives for systemic useò (27.7%), R ñRespiratory systemò (25.6%) and D ñDermatologicalsò (18.3%) in the ATC classification, and 2005 or earlier (19.8%) and 2006 to 2010 (16.3%) in the starting year (Table 3). The data set of the inhalant in the administration route was same as that of R ñRespiratory systemò in the ATC classification.

2) Exclusion rates by the classification of reasons of exclusion

The median exclusion rate for the reason of deviation concerning investigational drugs such as a deviation from dosage and administration was the highest (1.6%), followed by deviation concerning study procedures (0.9%) such as no data available on specific visit date, and deviation concerning concomitant treatment (0.5%).

3) Univariate regression analysis

The results of the univariate regression analysis with the exclusion rate (overall rate and

the rate by the 5 reasons) as a response variable are shown in Table 4. For the overall exclusion, inhalant showed a higher exclusion rate than oral administration ($p<0.001$) as administration route, and R ñRespiratory systemò showed a higher exclusion rate than A ñAlimentary tract and metabolismò ($p<0.001$) as target diseases. As for the deviation concerning inclusion/exclusion criteria, the exclusion rates of injection and inhalant were higher than that of oral administration ($p=0.024$ and $p=0.006$, respectively). As for the deviation concerning investigational drugs, Multi regional Clinical Trial (MRCT) showed a higher exclusion rate than Japan domestic trial ($p=0.038$) as study region, inhalant showed a higher exclusion rate than oral administration ($p<0.001$), and R ñRespiratory systemò showed a higher exclusion rate than A ñAlimentary tract and metabolismò ($p<0.001$). Also, as starting year, the exclusion rate of clinical trials started 2005 or before was higher than that started 2011 or after ($p=0.009$). As for the deviation concerning concomitant treatment, the exclusion rate of non-randomized trial (Open) was higher than that of RCT ($p=0.006$) as study design. Also, the exclusion rate of Japan domestic trials was higher than that of MRCT ($p=0.039$). For the deviation concerning study procedures, RCT showed a higher exclusion rate than Open trial ($p=0.0496$), MRCT showed a higher exclusion rate than Japan domestic trials ($p=0.039$). Also, D ñDermatologicalsò, R ñRespiratory systemò, and V ñVariousò

showed a higher exclusion rate than A ñAlimentary tract and metabolismò ($p<0.001$, $p=0.013$, and $p=0.002$, respectively). For other inappropriate cases, the exclusion rate of MRCT was higher than that of Japan domestic trials ($p=0.006$).

4) Multivariate regression analysis

The results of the 6 multivariate regression analyses with the exclusion rate (overall rate and the rate by the 5 reasons) as a response variable are shown in Table 5.

For the overall exclusion, administration route was selected as an explanatory variable, and inhalant was related to a higher exclusion rate. Also both for the deviation concerning inclusion/exclusion criteria and deviation concerning investigational drugs, administration routes were selected as an explanatory variable, and inhalant was related to a higher exclusion rate. As for the deviation concerning concomitant treatment, study design and study region were selected as explanatory variables, and Open trial was related to higher exclusion rates. For the deviation concerning study procedures, ATC classification and number of trial sites were selected as explanatory variables, and ATC classifications D ñDermatologicalsò, R ñRespiratory systemò and V ñVariousò were related to higher exclusion rates. For the other inappropriate cases, study design, ATC classification, duration of drug administration, number of trial sites, and number of patients were selected as explanatory variables, and RCT, 366 days or more drug

administration, and number of trial sites were related to higher exclusion rates.

Table 3. Exclusion rates by study characteristics (published data)

Study Characteristics		Number of studies	Exclusion rate (%) [Median, Range]
Total number of studies		102	8.3 [0.6 ï 83.3]
Phase	3	72	8.1 [0.6 ï 83.3]
	2	30	8.8 [1.1 ï 45.5]
Study design	RCT	65	8.2 [0.6 ï 47.0]
	Open	37	10.3 [0.8 ï 83.3]
Study region	Japan domestic trial	64	7.8 [0.6 ï 83.3]
	MRCT	38	13.3 [0.7 ï 47.0]
Administration route	Oral administration	47	7.6 [0.6 ï 47.0]
	Injection	34	7.9 [1.1 ï 83.3]
	Inhalant	8	25.6 [8.4 ï 34.2]
	External use	13	12.5 [2.4 ï 25.6]
Target disease: ATC Classification; A: Alimentary tract and metabolism		19	8.2 [0.6 ï 45.5]
B: Blood and blood forming organs		10	6.9 [1.2 ï 17.1]
C: Cardiovascular system		2	9.9 [3.3 ï 16.4]
D: Dermatologicals		6	18.3 [2.4 ï 25.6]
G: Genitourinary system and sex hormones		2	0.7 [0.7 ï 0.8]
J: Antiinfectives for systemic use		6	27.7 [2.0 ï 83.3]
L: Antineoplastic and immunomodulating agents		13	2.9 [1.1 ï 31.4]
M: Musculo-skeletal system		9	4.9 [3.0 ï 18.3]
N: Nervous system		17	10.4 [3.2 ï 52.8]
R: Respiratory system		8	25.6 [8.4 ï 34.2]
S: Sensory organs		4	10.7 [5.7 ï 16.3]
V: Various		6	10.4 [2.5 ï 47.0]
Duration of drug administration (days) 1 ï 31		29	8.1 [1.1 ï 83.3]
32 ï 182		37	8.4 [0.6 ï 32.0]
183 ï 365		25	10.3 [0.8 ï 47.0]
366 -		11	12.9 [2.3 ï 45.5]
Starting year -2005		3	19.8 [2.0 ï 21.7]
2006-2010		21	16.3 [0.7 ï 47.0]
2011-		24	4.7 [0.6 ï 31.6]

Table 4. Summary results of the univariate regression analysis with the exclusion rate (published data) [1)]

	Overall		Inclusion/exclusion criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Phase (reference classification for comparison : Phase 3)												
2	0.002	p=0.889	-0.002	p=0.691	0.006	p=0.238	-0.006	p=0.216	0.006	p=0.363	-0.002	p=0.436
Intercept	0.118		0.017		0.032		0.025		0.034		0.009	
Study design (reference classification for comparison : RCT)												
Open	0.002	p=0.927	0.014	p=0.083	-0.007	p=0.435	0.025	p=0.006**	-0.024	p=0.0496*	-0.007	p=0.222
Intercept	0.118		0.011		0.038		0.013		0.046		0.010	
Study region (reference classification for comparison : Japan)												
MRCT	0.042	p=0.051	0.004	p=0.634	0.019	p=0.038*	-0.019	p=0.039*	0.024	p=0.039*	0.014	p=0.006**
Intercept	0.103		0.015		0.028		0.029		0.029		0.003	
Administration route (reference classification for comparison : Oral)												
Injection	0.022	p=0.324	0.020	p=0.024*	-0.422×10^{-3}	p=0.964	0.017	p=0.095	-0.019	p=0.136	0.005	p=0.426
Inhalant	0.156	p<0.001***	0.040	p=0.006**	0.073	p<0.001***	0.005	p=0.771	0.036	p=0.079	0.003	p=0.786
External	0.044	p=0.145	0.003	p=0.828	0.145×10^{-3}	p=0.991	0.011	p=0.426	0.030	p=0.077	0.001	p=0.940
Intercept	0.093		0.007		0.029		0.015		0.036		0.006	
Target disease: ATC Classification (reference classification for comparison : A)												
B	-0.004	p=0.910	-0.010	p=0.490	-0.002	p=0.918	-0.014	p=0.436	0.022	p=0.266	-0.001	p=0.933
D	0.077	p=0.091	-0.006	p=0.745	0.002	p=0.910	-0.011	p=0.596	0.092	p<0.001***	-0.001	p=0.955
L	-0.237×10^{-3}	p=0.995	-0.015	p=0.282	-0.004	p=0.775	0.025	p=0.128	-0.011	p=0.541	0.005	p=0.540
M	-0.014	p=0.717	-0.010	p=0.522	-0.004	p=0.828	-0.011	p=0.535	0.007	p=0.744	0.004	p=0.686
N	0.065	p=0.050	0.005	p=0.675	0.024	p=0.080	0.018	p=0.226	0.014	p=0.403	0.002	p=0.781

	Overall		Inclusion/exclusion criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
R	0.168	p<0.001***	0.031	p=0.058	0.076	p<0.001***	0.001	p=0.966	0.054	p=0.013*	0.007	p=0.484
V	0.081	p=0.073	-0.008	p=0.645	0.017	p=0.354	-0.005	p=0.805	0.077	p=0.002**	$0.026x10^{-3}$	p=0.998
Z [2)]	0.039	p=0.280	0.018	p=0.208	-0.013	p=0.370	-0.002	p=0.927	0.002	p=0.921	0.034	p<0.001***
Intercept	0.080		0.015		0.026		0.019		0.019		0.001	
Duration of drug administration (days) (reference classification for comparison : 1-31 days)												
32-182	-0.002	p=0.948	-0.014	p=0.146	0.021	p=0.054	-0.025	p=0.021*	0.014	p=0.314	0.002	p=0.691
183-365	0.013	p=0.659	-0.018	p=0.094	0.015	p=0.231	-0.022	p=0.071	0.035	p=0.021*	0.002	p=0.714
366-	$-0.167x10^{-3}$	p=0.997	-0.006	p=0.706	-0.014	p=0.435	0.005	p=0.764	-0.017	p=0.440	0.031	p=0.001**
Intercept	0.116		0.027		0.024		0.036		0.025		0.004	
Number of sites												
	$0.031x10^{-3}$	p=0.887	$-0.011x10^{-3}$	p=0.866	$0.167x10^{-3}$	p=0.086	$-0.091x10^{-3}$	p=0.338	$-0.010x10^{-3}$	p=0.446	$0.062x10^{-3}$	p=0.268
Intercept	0.114		0.014		0.026		0.026		0.043		0.004	
Number of patients												
	$-0.003x10^{-3}$	p=0.838	$-0.005x10^{-3}$	p=0.464	$0.009x10^{-3}$	p=0.208	$-0.008x10^{-3}$	p=0.281	$0.001x10^{-3}$	p=0.931	$-0.001x10^{-3}$	p=0.793
Intercept	0.120		0.018		0.032		0.025		0.037		0.008	
Starting year (reference classification for comparison : 2005 or before)												
2006ï 2010	0.024	p=0.733	0.008	p=0.748	-0.027	p=0.357	0.002	p=0.938	0.035	p=0.299	0.007	p=0.680
2011-	-0.061	p=0.386	-0.001	p=0.982	-0.079	p=0.009**	0.014	p=0.576	-0.003	p=0.918	0.008	p=0.632
Intercept	0.145		0.016		0.096		0.008		0.024		0.002	

1) No adjustment for multiple comparisons

2) In case a category of the ATC classification is less than 5 trials, analysis was carried out by combining them as class Z.

Table 5. Summary results of the multivariate regression analysis with the exclusion rate (published data) [1)]

	Overall		Selection criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Phase (reference classification for comparison : Phase 3)												
2												
Study design (reference classification for comparison : RCT)												
Open							0.020	p=0.035*			-0.012	p=0.047*
Study region (reference classification for comparison : Japan)												
MRCT							-0.014	p=0.109				
Administration route (reference classification for comparison : Oral)												
Injection	0.007	p=0.753	0.012	p=0.759	-0.005	p=0.624						
Inhalant	0.155	p<0.001***	0.040	p<0.001***	0.071	p<0.001***						
External	0.043	p=0.117	0.003	p=0.739	-0.001	p=0.926						
Target disease: ATC Classification (reference classification for comparison : A)												
B									0.029	p=0.157	0.006	p=0.539
D									0.088	p<0.001***	0.006	p=0.581
L									-0.016	p=0.382	0.009	p=0.315
M									0.256×10^{-3}	p=0.990	0.014	p=0.131
N									0.010	p=0.571	0.004	p=0.634
R									0.056	p=0.0097**	0.005	p=0.597
V									0.075	p=0.002**	0.004	p=0.687
Z [2)]									-0.002	p=0.921	0.042	p<0.001***
Duration of drug administration (days) (reference classification for comparison : 1-31 days)												

	Overall		Selection criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
32-182											0.002	p=0.713
183-365											0.004	p=0.572
366-											0.028	p=0.002**
Number of sites												
									-0.186×10^{-3}	p=0.132	0.217×10^{-3}	p=0.020*
Number of patients												
											-0.012×10^{-3}	p=0.065
Intercept												
	0.094		0.006		0.031		0.020		0.030		-0.009	

1) Variables were selected by stepwise method based on AIC (Akaike Information Criteria) to construct final models.

2) In case a category of the ATC classification is less than 5 trials, analysis was carried out by combining them as class Z.

3.2. Research 2: Investigation on Pfizer Internal data

3.2.1. Investigation on cases of exclusion from efficacy analysis

1) Exclusion rates by study characteristics

The median of the overall exclusion rate among 84 clinical trials investigated was 8.1%. When I looked into it by the study characteristics, an exclusion rate of 15% or more was found in Open trial (16.3%) in the study design, J ñAntiinfectives for systemic useò (17.7%) in the ATC classification, and 1-31 days (15.3%) in the durations of drug administration (Table 6).

2) Exclusion rates by the classification of reasons of exclusion

The median exclusion rate for the reason of deviation concerning study procedures was the highest (0.73%), followed by deviation concerning inclusion/exclusion criteria (0.66%).

3) Univariate regression analysis

The results of the univariate regression analysis with the exclusion rate (overall rate and the rate by the 5 reasons) as a response variable are shown in Table 7.

Phase 3 in study phase, RCT in study design, Japan in study region, oral in administration route, C ñCardiovascular systemò in the ATC classification, 1 to 31 days in duration of drug administration, and year 2000 or before in study starting year were

the reference classification for comparisons in this variable group.

For the overall exclusion, Open trial showed a higher exclusion rate than RCT (p=0.049). As for the deviation concerning inclusion/exclusion criteria, the exclusion rates of injection and others (injection to oral) were higher than that of oral administration (p=0.015 and p=0.010, respectively), J ñAntiinfectives for systemic useò was higher than C ñCardiovascular systemò (p=0.008), 32-182 days, 183-365 days and more than 366 days in duration of drug administration were lower than that of 1-31 days (p=0.005, 0.006 and <0.001, respectively). As for the deviation concerning investigational drugs, N ñNervous systemò showed a higher exclusion rate than C ñCardiovascular systemò (p=0.003). Also, as starting year, the exclusion rate of clinical trials started 2001 to 2005 was higher than that started 2000 or before (p=0.031). As for the deviation concerning concomitant treatment, the exclusion rate of J ñAntiinfectives for systemic useò was higher than C ñCardiovascular systemò (p=0.004), 32-182 days, 183-365 days and more than 366 days in duration of drug administration were lower than that of 1-31 days (p=0.009, 0.012 and 0.002, respectively). As for the deviation concerning study procedures, N ñNervous systemò and S ñSensory organsò showed a lower exclusion rate than C ñCardiovascular systemò (p=0.007 and 0.037, respectively). As for other inappropriate cases, the exclusion rate of MRCT was

higher than that of Japan domestic trials (p=0.032), others (injection to oral) were higher than that of oral administration (p<0.001).

4) Multivariate regression analysis

The results of the 6 multivariate regression analysis with the exclusion rate (overall rate and the rate by the 5 reasons) as a response variable are shown in Table 8.

For the overall exclusion, study design was selected as an explanatory variable and Open trial was related to a higher exclusion rate. As for the deviation concerning inclusion/exclusion criteria, ATC classification and starting year were selected as an explanatory variable, and the clinical trials started in 2001-2005, 2006-2010 were related to a higher exclusion rate. As for the deviation concerning investigational drugs, study design, study region, ATC classification and duration of drug administration were selected as an explanatory variable, and Open trials, N ñNervous systemò and less than 183 days in duration of drug administration were related to a higher exclusion rate. As for the deviation concerning concomitant treatment, study region, duration of drug administration and starting year were selected as explanatory variables, and 1-31 days in duration of drug administration and clinical trials started in 2000 or before were related to higher exclusion rate. As for the deviation concerning study procedures, study region was selected as explanatory variables, but there were no

specific characteristics that were related to higher exclusion rates. As for the other inappropriate cases, study region, administration route and duration of drug administration were selected as explanatory variables, and external use, others (Injection to oral) and 366 days or more in duration of drug administration were related to higher exclusion rates.

Table 6. Exclusion rates by study characteristics (Pfizer internal data)

Study Characteristics		Number of studies	Exclusion rate (%) [Median, Range]
Total number of studies		84	8.1 [0.2 ï 73.8]
Phase	3	64	7.9 [0.2 ï 73.8]
	2	20	10.5 [0.5 ï 45.1]
Study design	RCT	53	6.7 [0.5 ï 73.8]
	Open	31	16.3 [0.2 ï 45.1]
Study region	Japan domestic trial	31	9.8 [0.5 ï 40.0]
	MRCT	53	6.7 [0.2 ï 73.8]
Administration route	Oral administration	53	8.0 [0.2 ï 73.8]
	Injection	20	11.0 [1.4 ï 45.1]
	External use	9	7.4 [1.0 ï 12.9]
	Others (Injection to Oral)	2	25.2 [21.5 - 28.9]
Target disease: ATC Classification; B: Blood and blood forming organs		2	12.6 [7.5 ï 17.6]
C: Cardiovascular system		19	2.8 [0.5 ï 73.8]
G: Genitourinary system and sex hormones		3	8.5 [2.0 ï 9.8]
J: Antiinfectives for systemic use		18	17.7 [2.2 ï 45.1]
L: Antineoplastic and immunomodulating agents		11	4.3 [0.2 ï 37.3]
N: Nervous system		21	11.5 [0.7 ï 40.0]
S: Sensory organs		10	7.4 [1.0 ï 12.9]
Duration of drug administration (days) 1 ï 31		18	15.3 [2.2 ï 45.1]
32 ï 182		43	7.9 [0.5 ï 73.8]
183 ï 365		8	6.8 [1.0 ï 26.7]
366 -		15	7.4 [0.2 ï 37.3]
Starting year -2000		25	4.2 [0.5 ï 45.1]
2001-2005		32	9.3 [7.3 ï 73.8]
2006-2010		25	9.1 [0.2 ï 27.0]
2011-		2	12.1 [3.2 ï 21.1]

Table 7. Summary results of the univariate regression analysis with the exclusion rate (Pfizer internal data) [1)]

	Overall		Inclusion/exclusion criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Phase (reference classification for comparison : Phase 3)												
2	0.022	p=0.543	-0.031	p=0.106	0.030	p=0.073	0.007	p=0.456	0.019	p=0.302	-0.003	p=0.431
Intercept	0.120		0.047		0.024		0.013		0.030		0.005	
Study design (reference classification for comparison : RCT)												
Open	0.062	p=0.049*	0.025	p=0.138	0.028	p=0.063	0.011	p=0.156	-0.006	p=0.713	0.004	p=0.241
Intercept	0.102		0.030		0.021		0.011		0.037		0.003	
Study region (reference classification for comparison : Japan)												
MRCT	-0.005	p=0.864	0.002	p=0.901	-0.027	p=0.070	-0.011	p=0.161	0.024	p=0.148	0.007	p=0.032*
Intercept	0.129		0.038		0.049		0.022		0.020		0.262×10^{-3}	
Administration route (reference classification for comparison : Oral)												
Injection	0.016	p=0.658	0.047	p=0.015*	-0.017	p=0.332	0.011	p=0.233	-0.026	p=0.169	0.002	p=0.605
External	-0.053	p=0.296	0.003	p=0.899	-0.034	p=0.156	-0.007	p=0.559	-0.023	p=0.381	0.008	p=0.076
Others	0.128	p=0.208	0.136	p=0.010*	-0.006	p=0.897	-0.013	p=0.602	-0.033	p=0.523	0.044	p<0.001***
Intercept	0.124		0.025		0.040		0.013		0.044		0.002	
Target disease: ATC Classification (reference classification for comparison : C)												
J	0.059	p=0.203	0.062	p=0.008**	0.016	p=0.438	0.033	p=0.004**	-0.057	p=0.015*	0.005	p=0.309
L	-0.027	p=0.612	-0.034	p=0.203	0.046	p=0.054	-0.003	p=0.821	-0.043	p=0.107	0.006	p=0.241
N	-0.015	p=0.728	-0.030	p=0.173	0.060	p=0.003**	0.014	p=0.183	-0.062	p=0.007**	0.002	p=0.696
S	-0.058	p=0.289	-0.012	p=0.644	0.003	p=0.900	0.431×10^{-3}	p=0.974	-0.058	p=0.037*	0.009	p=0.107

	Overall		Inclusion/exclusion criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Z [2)]	-0.039	p=0.581	-0.004	p=0.899	-0.006	p=0.858	-0.005	p=0.774	-0.038	p=0.279	0.015	p=0.046*
Intercept	0.129		0.040		0.007		0.005		0.077		0.386×10^{-3}	
Duration of drug administration (days) (reference classification for comparison : 1-31 days)												
32-182	-0.050	p=0.207	-0.056	p=0.005**	0.013	p=0.485	-0.025	p=0.009**	0.015	p=0.472	0.004	p=0.691
183-365	-0.089	p=0.137	-0.085	p=0.006**	0.009	p=0.765	-0.036	p=0.012*	0.024	p=0.435	-0.001	p=0.874
366-	-0.080	p=0.104	-0.090	p<0.001***	0.022	p=0.351	-0.038	p=0.002**	0.017	p=0.497	0.008	p=0.110
Intercept	0.174		0.092		0.020		0.038		0.022		0.001	
Number of sites												
	-0.314×10^{-3}	p=0.377	0.070×10^{-3}	p=0.717	-0.243×10^{-3}	p=0.147	-0.078×10^{-3}	p=0.382	0.058×10^{-3}	p=0.753	0.018×10^{-3}	p=0.617
Intercept	0.138		0.042		0.042		0.018		0.033		0.004	
Number of patients												
	-0.019×10^{-3}	p=0.241	-0.011×10^{-3}	p=0.212	-0.005×10^{-3}	p=0.542	-0.004×10^{-3}	p=0.341	0.001×10^{-3}	p=0.904	-0.001×10^{-3}	p=0.754
Intercept	0.134		0.044		0.034		0.016		0.035		0.005	
Starting year (reference classification for comparison : 2000 or before)												
2001-2005	0.045	p=0.233	0.039	p=0.056	0.038	p=0.031*	-0.017	p=0.063	-0.016	p=0.403	0.002	p=0.642
2006ï 2010	0.001	p=0.985	0.026	p=0.221	-0.003	p=0.890	0.004	p=0.689	-0.030	p=0.141	0.004	p=0.398
2011-	0.013	p=0.897	0.037	p=0.507	0.023	p=0.631	0.006	p=0.802	-0.049	p=0.353	-0.003	p=0.781
Intercept	0.108		0.016		0.017		0.020		0.051		0.003	

1) No adjustment for multiple comparisons

2) In case a category of the ATC classification is less than 5 trials, analysis was carried out by combining them as class Z.

Table 8. Summary results of the multivariate regression analysis with the exclusion rate (Pfizer internal data) [1)]

	Overall		Selection criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Phase (reference classification for comparison : Phase 3)												
2												
Study design (reference classification for comparison : RCT)												
Open	0.062	0.049*			0.037	p=0.032*						
Study region (reference classification for comparison : Japan)												
MRCT					-0.025	p=0.115	-0.011	p=0.171	0.024	p=0.148	0.005	p=0.090
Administration route (reference classification for comparison : Oral)												
Injection											0.004	p=0.293
External											0.010	p=0.028*
Others											0.043	p<0.001***
Target disease: ATC Classification (reference classification for comparison : C)												
J			0.025	p=0.333	0.008	p=0.743						
L			-0.080	p=0.011*	0.054	p=0.061						
N			-0.072	p=0.005**	0.060	p=0.008*						
S			-0.037	p=0.170	0.003	p=0.899						
Z [2)]			-0.042	p=0.241	-0.013	p=0.682						
Duration of drug administration (days) (reference classification for comparison : 1-31 days)												
32-182					0.010	p=0.606	-0.025	p=0.006**			0.004	p=0.327
183-365					-0.061	p=0.008**	-0.041	p=0.004**			-0.001	p=0.931

	Overall		Selection criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
366-					-0.038	p=0.418	-0.037	p=0.002**			0.012	p=0.020*
Number of sites												
Number of patients												
Starting year (reference classification for comparison : 2000 or before)												
2001-2005			0.065	p=0.003**			-0.022	p=0.016*				
2006-2010			0.058	p=0.019*			-0.003	p=0.745				
2011-			0.050	p=0.330			-0.016	p=0.515				
Intercept												
	0.102		0.026		0.026		0.055		0.020		-0.006	

1) Variables were selected by stepwise method based on AIC (Akaike Information Criteria) to construct final models.

2) In case a category of the ATC classification is less than 5 trials, analysis was carried out by combining them as class Z.

3.2.2. Investigation on cases of protocol deviation

1) Deviation rates by study characteristics

The median of the overall deviation rate among 105 clinical trials investigated was 27.8%. When I looked into it by the study characteristics, a deviation rate of 40% or more was found in phase 2 (42.3%) and L ñAntineoplastic and immunomodulating agentsò (60.1%) (Table 9).

2) Deviation rates by the classification of reasons of protocol deviation

The median deviation rate for the reason of deviation concerning study procedures was the highest (7.84%), followed by deviation concerning inclusion/exclusion criteria (3.17%), and deviation concerning concomitant treatment (2.71%).

3) Univariate regression analysis

The results of the univariate regression analysis with the deviation rate (overall rate and the rate by the 5 reasons) as a response variable are shown in Table 10.

For the overall deviation, phase 2 showed a higher deviation rate than phase 3 ($p=0.043$), the deviation rate of L ñAntineoplastic and immunomodulating agentsò was higher than that of C ñCardiovascular systemò ($p=0.002$). As for the deviation concerning inclusion/exclusion criteria, the deviation rates of MRCT was higher than that of Japan domestic trial ($p<0.001$), the clinical trials started in 2001-2005 and 2006-2010 were

lower that of the study started in 2000 or before (p=0.007 and 0.005, respectively). As for the deviation concerning investigational drugs, phase 2 showed a higher deviation rate than phase 3 (p=0.023), the deviation rate of L ñAntineoplastic and immunomodulating agentsò was higher than that of C ñCardiovascular systemò (p=0.027). As for the deviation concerning concomitant treatment, the clinical trials started in 2011 or after showed a higher deviation rate than that in 2000 or before (p=0.004), the clinical trials started in 2001-2005 showed a lower deviation rate than that in 2000 or before (p=0.017). As for the deviation concerning study procedures, the deviation rate of L ñAntineoplastic and immunomodulating agentsò was higher than that of C ñCardiovascular systemò (p=0.005), the clinical trials started in 2006-2010 showed a higher deviation rate than that in 2000 or before (p=0.043). As for other inappropriate cases, the deviation rate of Open trials was higher than that of RCT (p=0.015), MRCT was higher than that of Japan domestic trials (p=0.004), L ñAntineoplastic and immunomodulating agentsò was higher than that of C ñCardiovascular systemò (p=0.038).

4) Multivariate regression analysis

The results of the 6 multivariate regression analysis with the deviation rate (overall rate and the rate by the 5 reasons) as a response variable are shown in Table 11.

For the overall deviation, ATC classification was selected as an explanatory variable, and L ñAntineoplastic and immunomodulating agentsò was related to a higher deviation rate. As for the deviation concerning inclusion/exclusion criteria, study region, number of patients and starting year were selected as an explanatory variable, and MRCT and the clinical trials started in 2000 or before were related to a higher deviation rate. As for the deviation concerning investigational drugs, study region and ATC classification were selected as an explanatory variable, and L ñAntineoplastic and immunomodulating agentsò was related to a higher deviation rate. As for the deviation concerning concomitant treatment, number of patients and starting year were selected as explanatory variables, and the clinical trials started in 2000 or before were related to higher deviation rate. As for the deviation concerning study procedures, ATC classification was selected as explanatory variables, and L ñAntineoplastic and immunomodulating agentsò was related to a higher deviation rate. As for the other inappropriate cases, study design, study region and starting year were selected as explanatory variables, and RCT and MRCT were related to higher deviation rates.

Table 9. Deviation rates by study characteristics (Pfizer internal data)

Study Characteristics		Number of studies	Deviation rate (%) [Median, Range]
Total number of studies		105	27.8 [0.6 ï 206.3]
Phase	4	1	29.0
	3	70	26.1 [0.6 ï 161.5]
	2	33	42.3 [5.7 ï 206.3]
	1	1	90.6
Study design	RCT	49	22.0 [0.6 ï 161.7]
	Open	56	31.1 [0.7 ï 206.3]
Study region	Japan domestic trial	46	31.1 [1.5 ï 206.3]
	MRCT	59	26.7 [0.6 ï 161.7]
Administration route	Oral administration	77	26.3 [0.6 ï 166.7]
	Injection	26	29.9 [3.0 ï 206.3]
	Others (Injection to Oral)	2	77.2 [26.7 ï 127.8]
Target disease: ATC Classification; B: Blood and blood forming organs		1	26.1
C: Cardiovascular system		15	13.7 [2.2 ï 79.2]
G: Genitourinary system and sex hormones		4	19.7 [0.6 ï 27.7]
J: Antiinfectives for systemic use		18	29.9 [5.1 ï 127.8]
L: Antineoplastic and immunomodulating agents		34	60.1 [3.0 ï 206.3]
N: Nervous system		32	22.9 [0.7 ï 105.7]
S: Sensory organs		1	49.5
Duration of drug administration (days) 1 ï 31		16	29.9 [5.1 ï 63.8]
32 ï 182		41	26.7 [1.5 ï 161.7]
183 ï 365		12	23.2 [4.7 ï 108.9]
366 -		36	38.8 [0.6 ï 206.3]
Starting year -2000		13	40.7 [2.2 ï 118.9]
2001-2005		44	18.7 [0.6 ï 206.3]
2006-2010		46	34.9 [2.4 ï 166.7]
2011-		2	79.2 [68.4 ï 90.0]

Table 10. Summary results of the univariate regression analysis with the deviation rate (Pfizer internal data) [1)]

	Overall		Inclusion/exclusion criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Phase (reference classification for comparison : Phase 3)												
2	0.179	p=0.043*	-0.003	p=0.903	0.056	p=0.023*	0.009	p=0.540	0.120	p=0.067	-0.002	p=0.847
1	0.547	p=0.183	0.050	p=0.651	-0.030	p=0.791	-0.045	p=0.494	0.572	p=0.060	-0.001	p=0.990
4	-0.068	p=0.868	0.034	p=0.760	0.021	p=0.851	0.034	p=0.604	-0.138	p=0.648	-0.019	p=0.664
Intercept	0.358		0.072		0.054		0.049		0.164		0.019	
Study design (reference classification for comparison : RCT)												
Open	0.050	p=0.544	-0.033	p=0.125	0.022	p=0.326	0.009	p=0.471	0.072	p=0.233	-0.021	p=0.015*
Intercept	0.391		0.090		0.059		0.047		0.166		0.030	
Study region (reference classification for comparison : Japan)												
MRCT	0.056	p=0.496	0.079	p<0.001***	-0.036	p=0.112	-0.018	p=0.163	0.006	p=0.916	0.025	p=0.004**
Intercept	0.385		0.026		0.091		0.062		0.201		0.004	
Administration route (reference classification for comparison : Oral)												
Injection	0.069	p=0.469	0.013	p=0.619	0.029	p=0.278	0.025	p=0.097	0.006	p=0.936	-0.003	p=0.797
Others	0.379	p=0.200	0.106	p=0.176	0.072	p=0.381	-0.033	p=0.475	0.254	p=0.250	-0.020	p=0.533
Intercept	0.393		0.067		0.062		0.047		0.198		0.020	
Target disease: ATC Classification (reference classification for comparison : C)												
J	0.113	p=0.401	0.019	p=0.619	0.036	p=0.353	0.023	p=0.319	0.032	p=0.752	0.003	p=0.833
L	0.376	p=0.002**	0.013	p=0.706	0.079	p=0.027*	0.002	p=0.940	0.255	p=0.005**	0.028	p=0.038*
N	0.007	p=0.951	-0.028	p=0.413	0.038	p=0.286	0.014	p=0.477	-0.023	p=0.802	0.006	p=0.651

	Overall		Inclusion/exclusion criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Z [2)]	-0.041	p=0.824	-0.028	p=0.592	-0.023	p=0.668	0.035	p=0.263	-0.017	p=0.902	-0.008	p=0.710
Intercept	0.280		0.075		0.029		0.041		0.127		0.008	
Duration of drug administration (days) (reference classification for comparison : 1-31 days)												
32-182	0.039	p=0.747	-0.012	p=0.711	0.011	p=0.750	-0.013	p=0.479	0.048	p=0.589	0.006	p=0.658
183-365	-0.013	p=0.932	-0.014	p=0.733	-0.011	p=0.802	-0.028	p=0.253	0.030	p=0.793	0.010	p=0.559
366-	0.176	p=0.161	-0.017	p=0.622	0.031	p=0.373	-0.028	p=0.157	0.181	p=0.051	0.008	p=0.530
Intercept	0.345		0.084		0.057		0.070		0.122		0.012	
Number of sites												
	-0.001	p=0.326	-0.012×10^{-3}	p=0.928	-0.145×10^{-3}	p=0.303	-0.093×10^{-3}	p=0.245	-0.324×10^{-3}	p=0.393	-0.073×10^{-3}	p=0.178
Intercept	0.445		0.073		0.078		0.057		0.222		0.015	
Number of patients												
	-0.071×10^{-3}	p=0.075	-0.008×10^{-3}	p=0.436	-0.014×10^{-3}	p=0.198	-0.009×10^{-3}	p=0.149	-0.039×10^{-3}	p=0.186	-0.156×10^{-6}	p=0.971
Intercept	0.450		0.076		0.077		0.056		0.222		0.019	
Starting year (reference classification for comparison : 2000 or before)												
2001-2005	-0.077	p=0.554	-0.092	p=0.007**	-0.009	p=0.793	-0.046	p=0.017*	0.081	p=0.397	-0.011	p=0.440
2006ï 2010	0.078	p=0.544	-0.096	p=0.005**	-0.005	p=0.889	-0.025	p=0.181	0.194	p=0.043*	0.011	p=0.436
2011-	0.271	p=0.524	-0.076	p=0.495	0.188	p=0.113	0.183	p=0.004**	-0.006	p=0.985	-0.019	p=0.678
Intercept	0.413		0.154		0.075		0.081		0.085		0.019	

1) No adjustment for multiple comparisons

2) In case a category of the ATC classification is less than 5 trials, analysis was carried out by combining them as class Z.

Table 11. Summary results of the multivariate regression analysis with the deviation rate (Pfizer internal data) [1)]

	Overall		Selection criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Phase (reference classification for comparison : Phase 3)												
2												
1												
4												
Study design (reference classification for comparison : RCT)												
Open											-0.017	p=0.038*
Study region (reference classification for comparison : Japan)												
MRCT			0.085	p<0.001***	-0.041	p=0.072					0.030	p<0.001***
Administration route (reference classification for comparison : Oral)												
Injection												
Others												
Target disease: ATC Classification (reference classification for comparison : C)												
J	0.113	p=0.401			0.034	p=0.378			0.032	p=0.752		
L	0.376	p=0.002**			0.078	p=0.026*			0.255	p=0.005*		
N	0.007	p=0.951			0.029	p=0.412			-0.023	p=0.802		
Z [2)]	-0.041	p=0.824			-0.030	p=0.575			-0.017	p=0.902		
Duration of drug administration (days) (reference classification for comparison : 1-31 days)												
32-182												
183-365												

	Overall		Selection criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
366-												
Number of sites												
Number of patients												
			-0.019 x10^{-3}	p=0.057			-0.008x10^{-3}	p=0.155				
Starting year (reference classification for comparison : 2000 or before)												
2001-2005			-0.089	p=0.005**			-0.047	p=0.014*			-0.005	p=0.720
2006-2010			-0.073	p=0.024*			-0.028	p=0.136			0.026	p=0.051
2011-			-0.022	p=0.834			-0.177	p=0.005*			0.016	p=0.703
Intercept												
	0.280		0.101		0.057		0.086		0.127		0.001	

1) Variables were selected by stepwise method based on AIC (Akaike Information Criteria) to construct final models.

2) In case a category of the ATC classification is less than 5 trials, analysis was carried out by combining them as class Z.

3.2.3. Comparison between cases of exclusion from efficacy analysis and those of the protocol deviation in the same trial

The median of the overall exclusion rate and deviation rate among 52 clinical trials investigated were 11.5% and 29.9%, respectively. In the comparison between the median of the exclusion rates and the median deviation rates, the exclusion rate was about 30 to 40% of the deviation rates for the overall, phase, study design, study region, and administration route (Table 12). In the ATC classification, the proportion of the exclusion rate against the deviation rate of L ñAntineoplastic and immunomodulating agentsò was as low as 18.2%. On the other hand, that of J ñAntiinfectives for systemic useò was 59.2% of the deviation rate and the ratio of the exclusion rate to the deviation rate was high (Figure 2).

The higher median exclusion rate and deviation rate by the classification of reasons of protocol deviation were shown in both deviation concerning inclusion/exclusion criteria (1.24% and 2.15%, respectively) and deviation concerning study procedures (0.12% and 7.87%, respectively).

The results of univariate regression analysis and multivariate regression analysis of the exclusion rate and the deviation rate for this data set were shown in Table 13-16. In the multivariate regression analysis, the features of the trials suggested that both the

higher exclusion rate and the higher deviation rate were Phase 3 in deviation concerning inclusion/exclusion criteria, Open trial in deviation concerning investigational drugs, and clinical trials that started 2000 or before in deviation concerning concomitant treatment.

Table 12. Exclusion rates and deviation rates by study characteristics on the data set of same studies (Pfizer internal data)

Study Characteristics		Number of studies	Exclusion rate (%) [Median]	Deviation rate (%) [Median]
Total number of studies		52	11.5	29.9
Phase	3	38	10.5	27.6
	2	14	11.6	43.7
Study design	RCT	26	7.7	20.5
	Open	26	16.9	40.1
Study region	Japan domestic trial	26	13.2	32.6
	MRCT	26	8.8	27.6
Administration route	Oral administration	32	10.5	24.9
	Injection	18	10.9	35.4
	Others (Injection to Oral)	2	25.2	77.2
Target disease: ATC Classification; C: Cardiovascular system		3	70.9	46.4
G: Genitourinary system and sex hormones		3	8.5	13.3
J: Antiinfectives for systemic use		18	17.7	29.9
L: Antineoplastic and immunomodulating agents		9	4.3	23.6
N: Nervous system		18	10.5	34.9
S: Sensory organs		1	7.4	49.5
Duration of drug administration (days) 1 ï 31		16	16.4	29.9
32 ï 182		22	12.0	34.9
183 ï 365		3	6.9	6.9
366 -		11	7.4	45.1
Starting year -2000		6	20.0	43.7
2001-2005		24	9.1	15.5
2006-2010		21	9.1	33.7
2011-		1	21.1	68.4

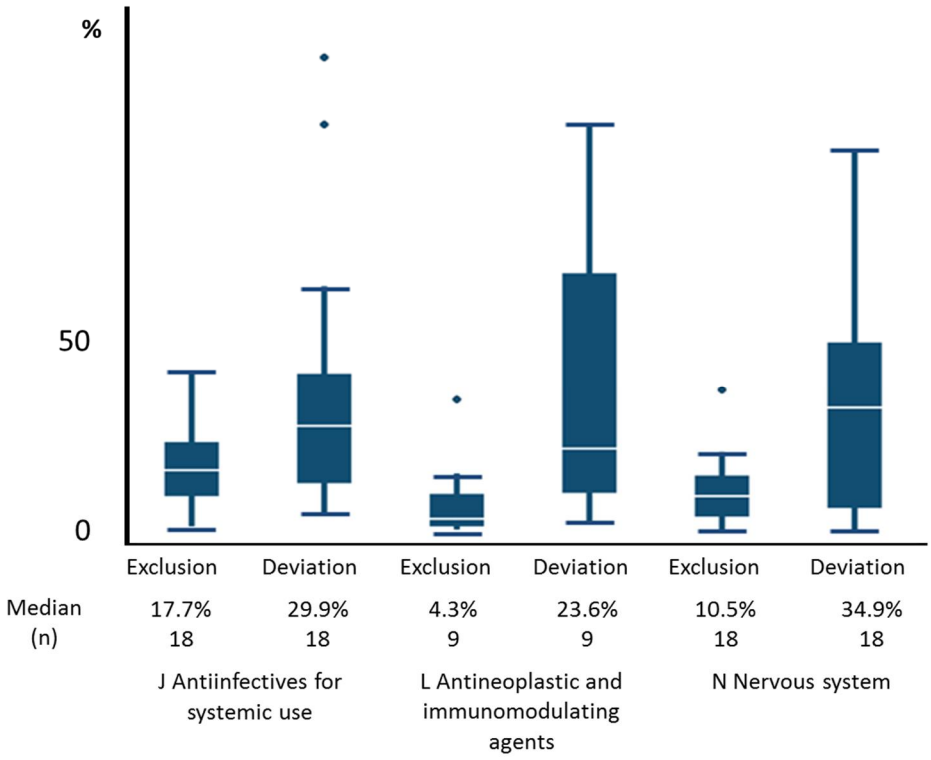

Figure 2. Exclusion rate and deviation rate by ATC classification on the data set of the same studies (Pfizer internal data)

Table 13. Summary results of the univariate regression analysis with the exclusion rate on the data set of same studies (Pfizer internal data) [1)]

	Overall		Inclusion/exclusion criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Phase (reference classification for comparison : Phase 3)												
2	0.020	p=0.699	-0.052	p=0.059	0.048	p=0.047*	0.009	p=0.522	0.020	p=0.409	-0.004	p=0.209
Intercept	0.150		0.068		0.029		0.020		0.028		0.004	
Study design (reference classification for comparison : RCT)												
Open	0.054	p=0.231	0.024	p=0.339	0.033	p=0.130	0.008	p=0.510	-0.011	p=0.600	0.001	p=0.792
Intercept	0.129		0.042		0.026		0.018		0.039		0.003	
Study region (reference classification for comparison : Japan)												
MRCT	0.020	p=0.655	0.019	p=0.450	-0.029	p=0.180	-0.002	p=0.871	0.026	p=0.220	0.006	p=0.043*
Intercept	0.145		0.045		0.057		0.023		0.020		0.313×10^{-3}	
Administration route (reference classification for comparison : Oral)												
Injection	-0.015	p=0.758	0.031	p=0.233	-0.028	p=0.234	0.006	p=0.626	-0.022	p=0.331	-0.002	p=0.300
Others	0.095	p=0.426	0.122	p=0.059	-0.019	p=0.735	-0.021	p=0.508	-0.031	p=0.579	0.044	p<0.001***
Intercept	0.157		0.039		0.053		0.021		0.042		0.002	
Target disease: ATC Classification (reference classification for comparison : J)												
L	-0.093	p=0.153	-0.094	p=0.005**	0.042	p=0.179	-0.035	p=0.042*	-0.003	p=0.901	-0.002	p=0.632
N	-0.071	p=0.182	-0.090	p=0.001**	0.040	p=0.120	-0.016	p=0.264	-0.002	p=0.923	-0.003	p=0.472
Z [2)]	0.059	p=0.403	-0.075×10^{-3}	p=0.998	-0.015	p=0.667	-0.030	p=0.113	0.107	p<0.001***	-0.004	p=0.404
Intercept	0.188		0.102		0.023		0.038		0.020		0.005	

	Overall		Inclusion/exclusion criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Duration of drug administration (days) (reference classification for comparison : 1-31 days)												
32-182	-0.003	p=0.957	-0.037	p=0.184	0.024	p=0.360	-0.021	p=0.123	0.025	p=0.337	0.007	p=0.061
183-365	-0.096	p=0.345	-0.091	p=0.090	0.051	p=0.304	-0.042	p=0.101	-0.015	p=0.763	0.001	p=0.858
366-	-0.085	p=0.185	-0.091	p=0.008**	0.036	p=0.249	-0.042	p=0.010**	0.011	p=0.716	0.002	p=0.648
Intercept	0.180		0.094		0.022		0.042		0.022		0.000	
Number of sites												
	-0.317×10^{-3}	p=0.626	0.065×10^{-3}	p=0.857	-0.435×10^{-3}	p=0.161	-0.133×10^{-3}	p=0.437	0.154×10^{-3}	p=0.618	0.033×10^{-3}	p=0.455
Intercept	0.168		0.052		0.059		0.027		0.028		0.002	
Number of patients												
	-0.018×10^{-3}	p=0.400	-0.011×10^{-3}	p=0.353	-0.007×10^{-3}	p=0.478	-0.004×10^{-3}	p=0.434	0.005×10^{-3}	p=0.626	-0.257×10^{-6}	p=0.861
Intercept	0.163		0.059		0.045		0.024		0.031		0.003	
Starting year (reference classification for comparison : 2000 or before)												
2001-2005	-0.626	p=0.390	0.026	p=0.528	0.016	p=0.638	-0.077	p<0.001***	-0.030	p=0.376	0.002	p=0.626
2006ï	-0.123	p=0.096	0.018	p=0.666	-0.027	p=0.439	-0.055	p=0.002**	-0.065	p=0.065	0.005	p=0.303
Intercept	0.236		0.034		0.046		0.081		0.075		0.000	

1) No adjustment for multiple comparisons

2) In case a category of the ATC classification is less than 5 trials, analysis was carried out by combining them as class Z.

Table 14. Summary results of the multivariate regression analysis with the exclusion rate on the data set of same studies (Pfizer internal data) [1)]

	Overall		Selection criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Phase (reference classification for comparison : Phase 3)												
2			-0.059	p=0.024*	0.036	p=0.163						
Study design (reference classification for comparison : RCT)												
Open			0.039	p=0.126	0.063	p=0.006**					-0.003	p=0.141
Study region (reference classification for comparison : Japan)												
MRCT											0.004	p=0.055
Administration route (reference classification for comparison : Oral)												
Injection											-0.002	p=0.303
Others											0.044	p<0.001***
Target disease: ATC Classification (reference classification for comparison : J)												
L			-0.059	p=0.343	0.037	p=0.249			-0.003	p=0.901		
N			-0.091	p=0.113	0.054	p=0.029*			-0.002	p=0.923		
Z [2)]			0.063	p=0.343	-0.011	p=0.744			0.107	p<0.001***		
Duration of drug administration (days) (reference classification for comparison : 1-31 days)												
32-182			0.046	p=0.387			-0.015	p=0.182				
183-365			-0.082	p=0.286			-0.043	p=0.064				
366-			-0.015	p=0.812			-0.027	p=0.055				
Number of sites												

	Overall		Selection criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Number of patients												
			-0.018×10^{-3}	p=0.099								
Starting year (reference classification for comparison : 2000 or before)												
2001-2005					0.047	p=0.168	-0.070	p<0.001***			-0.001	p=0.820
2006-					-0.020	p=0.585	-0.046	p=0.007**			0.004	p=0.147
Intercept												
	0.155		0.080		-0.036		0.089		0.020		0.439×10^{-3}	

1) Variables were selected by stepwise method based on AIC (Akaike Information Criteria) to construct final models.

2) In case a category of the ATC classification is less than 5 trials, analysis was carried out by combining them as class Z.

Table 15. Summary results of the univariate regression analysis with the deviation rate on the data set of same studies (Pfizer internal data) [1)]

	Overall		Inclusion/exclusion criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Phase (reference classification for comparison : Phase 3)												
2	0.087	p=0.399	-0.037	p=0.231	0.038	p=0.275	0.026	p=0.252	0.064	p=0.360	-0.003	p=0.802
Intercept	0.343		0.074		0.056		0.050		0.144		0.018	
Study design (reference classification for comparison : RCT)												
Open	0.151	p=0.096	-0.012	p=0.659	0.076	p=0.012*	0.027	p=0.174	0.080	p=0.196	-0.019	p=0.110
Intercept	0.291		0.071		0.029		0.043		0.122		0.027	
Study region (reference classification for comparison : Japan)												
MRCT	0.032	p=0.726	0.081	p=0.002**	-0.051	p=0.093	-0.040	p=0.045*	0.018	p=0.771	0.024	p=0.050*
Intercept	0.350		0.024		0.092		0.076		0.153		0.005	
Administration route (reference classification for comparison : Oral)												
Injection	0.035	p=0.714	0.038	p=0.189	-0.009	p=0.795	0.010	p=0.640	-0.002	p=0.972	-0.002	p=0.890
Others	0.435	p=0.070	0.127	p=0.076	0.067	p=0.412	-0.041	p=0.447	0.301	p=0.064	-0.019	p=0.571
Intercept	0.337		0.047		0.067		0.055		0.151		0.019	
Target disease: ATC Classification (reference classification for comparison : J)												
L	0.040	p=0.772	-0.074	p=0.069	0.008	p=0.858	-0.019	p=0.521	0.106	p=0.247	0.018	p=0.313
N	-0.048	p=0.667	-0.042	p=0.200	0.020	p=0.597	0.002	p=0.940	-0.039	p=0.602	0.011	p=0.441
Z [2)]	-0.124	p=0.408	-0.016	p=0.706	-0.055	p=0.264	-0.032	p=0.325	-0.012	p=0.901	-0.007	p=0.707
Intercept	0.393		0.094		0.066		0.064		0.158		0.011	

	Overall		Inclusion/exclusion criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Duration of drug administration (days) (reference classification for comparison : 1-31 days)												
32-182	0.033	p=0.762	-0.009	p=0.772	0.004	p=0.914	-0.010	p=0.670	0.041	p=0.574	0.008	p=0.609
183-365	-0.220	p=0.295	-0.063	p=0.313	-0.035	p=0.620	-0.033	p=0.479	-0.078	p=0.578	-0.011	p=0.692
366-	0.093	p=0.474	-0.057	p=0.145	0.045	p=0.305	-0.033	p=0.251	0.128	p=0.147	0.010	p=0.553
Intercept	0.345		0.084		0.057		0.070		0.122		0.012	
Number of sites												
	-0.302×10^{-3}	p=0.820	0.213×10^{-3}	p=0.592	-0.428×10^{-3}	p=0.334	-0.389×10^{-3}	p=0.179	0.054×10^{-3}	p=0.953	0.249×10^{-3}	p=0.158
Intercept	0.378		0.056		0.083		0.072		0.160		0.008	
Number of patients												
	-0.060×10^{-3}	p=0.170	-0.007×10^{-3}	p=0.587	-0.014×10^{-3}	p=0.347	-0.011×10^{-3}	p=0.277	-0.028×10^{-3}	p=0.355	-0.001×10^{-3}	p=0.868
Intercept	0.392		0.067		0.072		0.061		0.173		0.018	
Starting year (reference classification for comparison : 2000 or before)												
2001-2005	-0.200	p=0.180	-0.104	p=0.014*	-0.029	p=0.573	-0.071	p=0.024*	0.007	p=0.943	-0.002	p=0.908
2006ï	-0.039	p=0.796	-0.142	p=0.001**	-0.028	p=0.587	-0.017	p=0.574	0.140	p=0.164	0.009	p=0.646
Intercept	0.475		0.173		0.092		0.097		0.099		0.014	

1) No adjustment for multiple comparisons

2) In case a category of the ATC classification is less than 5 trials, analysis was carried out by combining them as class Z.

Table 16. Summary results of the multivariate regression analysis with the deviation rate on the data set of same studies (Pfizer internal data) [1)]

	Overall		Selection criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Phase (reference classification for comparison : Phase 3)												
2			-0.066	p=0.030*					0.176	p=0.023*		
Study design (reference classification for comparison : RCT)												
Open	0.151	p=0.096			0.076	p=0.012*						
Study region (reference classification for comparison : Japan)												
MRCT			0.052	p=0.050			-0.032	p=0.104	0.126	p=0.059	0.024	p=0.050*
Administration route (reference classification for comparison : Oral)												
Injection												
Others												
Target disease: ATC Classification (reference classification for comparison : J)												
L												
N												
Z [2)]												
Duration of drug administration (days) (reference classification for comparison : 1-31 days)												
32-182												
183-365												
366-												
Number of sites												

	Overall		Selection criteria		Investigational drugs		Concomitant treatment		Study procedures		Other inappropriate cases	
	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value	Regression coefficient	p value
Number of patients												
			-0.016×10^{-3}	p=0.151								
Starting year (reference classification for comparison : 2000 or before)												
2001-2005			-0.119	p=0.004**			-0.073	p=0.019*	0.078	p=0.429		
2006-			-0.159	p<0.001***			-0.029	p=0.362	0.277	p=0.014*		
Intercept												
	0.291		0.185		0.029		0.118		-0.102		0.005	

1) Variables were selected by stepwise method based on AIC (Akaike Information Criteria) to construct final models.

2) In case a category of the ATC classification is less than 5 trials, analysis was carried out by combining them as class Z.

4. Discussion

In the present research, in order to assess a wider range of quality risks of clinical trials, cases of protocol deviations or exclusion of subjects from the PPS efficacy analysis were used as an indicator, though efficacy analysis is usually focused on the FAS analysis. I believe this was the first research to examine the relationship between protocol deviations and study characteristics based on regulatory documents for new drug application.

In the research on published data (Research 1), the result of multivariate regression analysis suggested that clinical trials of inhalant were related to a higher exclusion rate for overall exclusion as well as for deviation concerning inclusion/exclusion criteria and for deviation concerning investigational drugs. Clinical trials for ñDermatologicalsò and ñRespiratory systemò as target diseases (ATC classification) were related to higher exclusion rates for deviation concerning study procedures. The present research suggested that there were some study characteristics that could lead to more frequent exclusion of study subjects from efficacy analysis.

In order to reduce protocol deviations in clinical trials of inhalant, for which more frequent exclusion concerning inclusion/exclusion criteria and investigational drugs was suggested, it is important to prepare a monitoring plan to execute monitoring activity

more carefully in compliance with the trial protocol than other therapeutic areas. It could be recommended that inclusion and exclusion criteria for study subjects are clearly set in the protocol and that investigators are trained properly prior to the trial start. In general, medication adherence for inhalant medications has become an issue in medical practice [8]. There are several types of medication instructions by medical doctors and pharmacists or by other co-medical staff, and explanatory materials for patients available. It is also recommended that thorough guidance to the subjects to help understand the way of administering the inhalants should be given, and drug compliance should be monitored in a timely manner. In clinical trials for dermatological and respiratory drugs, frequent exclusion of subjects due to deviation concerning study procedures such as non-availability of trial data on specific visit date was shown. It might be owing to the nature of the target diseases which are often non-life-threatening; psoriasis vulgaris, acne vulgaris and onychomycosis were included in the dermatological classification, and maintenance therapy for mild to severe asthma was included in the respiratory classification in the present research. In order to reduce such deviations, it is recommended that a preliminary feasibility assessment of the protocol requirement concerning the examination schedule should be conducted and that study subjects be thoroughly informed about the visit schedule by the investigators.

In the research on Pfizer internal data (Research 2), in the investigation on cases excluded from efficacy analysis, the median of exclusion rate was 8.1%, which was similar to the result of published data (8.3%). In the study region, the exclusion rate of the Japan local study was lower than that of the MRCT in published data, but Pfizer internal data showed higher exclusion rate in the Japan local study compare to the result of MRCT. No clear reason was identified for this difference.

The result of multivariate regression analysis suggested that clinical trials of ñNervous systemò were related to a higher exclusion rate for deviation concerning investigational drugs, and 1-31 days in duration of drug administration was related to a higher exclusion rate for deviation concerning concomitant treatment. In order to reduce protocol deviations in clinical trials, efforts to improve medication compliance should be considered, such as preparing supportive materials to the patients, when conducting clinical trials targeted for ñNervous systemò area. The clinical trial with a short administration period seemed to be attributed to the large influence of the concomitant treatment given to the efficacy evaluation of the clinical trial, and it was considered that attention to concomitant treatment was required for the clinical trials with shorter duration of drug administration. The multivariate regression analysis showed different results to those obtained by investigation on published data (Research 1) in the

characteristics of the clinical trial with a high exclusion rate. The reason may be attributable, in particular, to the difference in the distribution of ATC classifications of investigational products. Especially, clinical trials for inhalants, ñDermatologicalsò, and ñRespiratory systemò that suggested a higher exclusion rate in the investigation on published data were not included in the Pfizer internal data.

In the investigation on cases of protocol deviation, the result of multivariate regression analysis suggested that clinical trials of ñAntineoplastic and immnomodulating agentsò was related to a higher exclusion rate for overall deviation, deviation concerning investigational drugs, and deviation concerning study procedures. In ñAntineoplastic and immnomodulating agentsò, it was thought that there were some opportunities for protocol deviations to occur depending on the patient's condition. It was reported that about 10% of all protocol deviation in oncology clinical trials were due to the condition of the disease [9]. However, because information of the reason behind the protocol deviation was not available, I could not mention about that in the present research.

In the comparison between the exclusion rate and the deviation rate in the same clinical trials, 30 to 40% of protocol deviation cases were generally excluded from the efficacy analysis. In ñAntineoplastic and immunomodulating agentò, there were many protocol deviations in investigational drugs, concomitant treatment or study procedure, but the

percentage of exclusion from the efficacy analysis was low. It seemed that the criteria for evaluating efficacy analysis are not affected greatly by mild protocol deviation. Meanwhile, with regard to ñAntiinfectives for systemic useò, the percentage of exclusion of protocol deviation cases was high. The infectious disease is usually an acute disease and protocol deviation has a large influence on the efficacy evaluation. Therefore, prevention of protocol deviations in clinical trials of ñAntiinfectives for systemic useò was considered to be important.

Protocol deviations in clinical trials may cause disadvantages to the patients and possibly lead to inaccurate results. There are recommendations or toolkits for the management of protocol deviations to minimize their adverse impact on the results [10), 11)]. Some investigators, who actually conducted clinical trials, reported based on their experience that there are two types of protocol deviations ï preventable deviation and unpreventable deviation because it is based on patientsô condition [9, 12)]. Thus, taking preventive measures of protocol deviation in advance, and management of protocol deviations, such as early discovery and mitigation, are very important to maintain the quality of the clinical trial. I believe that the risk-based approach is applicable for the prevention of protocol deviations at the planning stage.

In the present research, I used the information on protocol deviations that led to the

exclusion from the dataset for efficacy analysis based on the published summary documents of new drug approval applications in Japan as available quality information of clinical trials. From the viewpoint of predicting the overall quality risk of clinical trials, it is preferable to consider all the protocol deviations. In addition to the features of study characteristics investigated in the present research, investigators and site staff who conduct clinical trials and monitors who conduct monitoring activity may also affect the quality risk of clinical trials. Additionally, criteria of protocol deviations and that of exclusions from efficacy analysis are not the same in all the clinical trials. Such information is available only for those involved in the trial and I think this is the limitation of this research.

Also, detailed information on the number of study subjects excluded from the PPS and the reasons thereof was not available for many trials. If we can obtain such information from more clinical trials, it would be possible to estimate the risk with higher accuracy. It is expected that information on the protocol deviation and the exclusion from the efficacy analysis will be disclosed more positively. In the consolidated standards for reporting of trials (CONSORT) statement, for the purpose of increasing the report quality of randomized control trials, a description of the exclusion reason along with the number of exclusions from the analysis is recommended to be

reported [13]. Furthermore, a broader risk prediction becomes possible by reporting not only the exclusion of efficacy analysis but also all the protocol deviations, including those not excluded from the analysis.

Risk-based approach in clinical trials is to consider in advance the measures for minimizing the occurrence of protocol deviation and for early discovery of the problem and the response at the time of occurrence. It is important to give weight to feasibility assessment of trial protocol, monitoring plan, investigator training and supportive documents, etc. based on the quality risks by characteristics of each clinical trial. Especially in the monitoring activity, it is necessary to build a focused quality system, such as concentrating resources on items that are important for patient safety and efficacy evaluation, and on items in which protocol deviations are likely to occur; other areas will be checked by sampling. In clinical trials with characteristics in which protocol deviations and/or exclusion from efficacy analysis are likely to occur, as suggested in the present research, effective preventive measures should be taken.

I believe that the present research would provide more accurate information on quality risk of clinical trials by increasing the information on protocol deviations and the number of trials, and that it could be used for preliminary risk identification in RBM. Also, it is worthwhile to extend this approach to the FDA (US Food and Drug

Administration) and EMA (European Medicines Agency) repositories of clinical trials in the future.

5. Conclusion

As a result of correlation analysis between the cases of protocol deviation or the exclusion cases of the efficacy analysis and study characteristics based on past clinical trials, the characteristics of the clinical trial which is likely to cause protocol deviations were suggested. The findings are expected to be used for prior notice, priority observation or mitigation measures in the study protocol and in the monitoring plan with regard to quality risk, which leads to securing patientsô safety and quality of clinical trials.

References

1. Food and Drug Administration. Guidance for Industry: Oversight of Clinical Investigations ï A Risk-Based Approach to Monitoring, Aug 2013. https://www.fda.gov/downloads/Drugs/Guidances/UCM269919.pdf. Accessed July 6, 2017.

2. European Medicines Agency. Reflection paper on risk based quality management in clinical trials, November 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500155491.pdf. Accessed July 6, 2017.

3. TransCelerate Biopharma Inc. Position paper: Risk-Based Monitoring Methodology, May 2013. http://www.transceleratebiopharmainc.com/wp-content/uploads/2016/01/TransCelerate-RBM-Position-Paper-FINAL-30MAY2013.pdf.pdf. Accessed July 6. 2017.

4. Bhatt A. Protocol deviation and violation. *Perspectives in Clinical Research*. 2012; 3:117.

5. Ghooi RB, Bhosale N, Wadhwani R, Divate P, Divate U. Assessment and classification of protocol deviations. *Perspectives in Clinical Research.* 2016;7: 132-136.

6. Sweetman EA, Doig GS. Failure to report protocol violations in clinical trials: a threat to internal validity? *Trials* 2011;12:214.

7. R Core Team. R: A Language and Environment for Statistical Computing. 2014. https//www.R-project.org

8. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JL, Ownby DR, Johnson CC. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol, 2004;114:1288-1293

9. Sasada S, Ushirozawa N, Kobayashi N, et al. Surveillance of protocol deviations in Japanese oncology registration trials: a single institute experience. *Invest New Drugs.* 2017; 35:392-396.

10. Mehra M, Kurpanek K, Petrizzo M, et al. The Life Cycle and Management of Protocol Deviations. *Therapeutic Innovation and Regulatory Science.* 2014;48 (6):762-777.

11. Mohan S, Mehra M, Petrizzo M, Katz T. A Toolkit for the Management of Protocol Deviations. *Therapeutic Innovation and Regulatory Science.* 2016;50 (6):791-800.

12. Jalgaonkar SV, Bhide SS, Tripathi RK, Fujiwara Y, Tamura K, Yamamoto N. An Audit of Protocol Deviations Submitted to an Institutional Ethics Committee of a Tertiary Care Hospital [Published online January 6, 2016] . *PLOS One.* doi:10.1371/jounal.pone.0146334

13. Uetani K, Nakayama T, Ikai H, Yonemoto N, Moher D. Quality of Reports on Randomized Controlled Trials Conducted in Japan: Evaluation of Adherence to the CONSORT Statement. *Internal Medicine.* 2009;48(5):307-313

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