한국의료윤리학회지 제19권 제4호(통권 제49호) : 518–530 ⓒ한국의료윤리학회, 2016년 12월
Korean J Med Ethics 19(4) : 518-530 ⓒ The Korean Society for Medical Ethics, December 2016
pISSN 2005-8284 eISSN 2234-3598

투고일: 2016년 11월 17일, 심사일: 2016년 11월 28일, 게재확정일: 2016년 12월 10일

한국의 한 대학병원의 연구윤리심의위원회 심의에서 나타난 임상연구계획의 과학적, 윤리적 문제*

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요약

최근 한국에서는 임상연구가 급증하여 대학병원 등의 연구기관에서 연구가 활발히 이루어짐에 따라, 연구의 과학성과 윤리성을 심사하는 임상시험심사위원회(institutional review board, IRB)의 역할이 더욱 중요해지고 있다. 사람을 대상으로 하는 임상연구에서는 비과학적인 연구는 비윤리적이므로 IRB는 연구계획의 윤리성과 과학성을 모두 심의하며, "생명윤리 및 안전에 관한 법률"에서도 IRB가 연구계획의 과학성과 윤리성을 모두 심의하도록 규정하고 있다. 그러나 한국의 IRB 심의에 대한 연구는 부족한 실정이다. 본 연구에서는 임상연구의 심의과정에서 제기되는 임상연구의 과학적, 윤리적인 문제점을 알아보기 위해 서울의 한 대학병원 IRB에서 1,244건의 연구 심의내용을 분석하였다. 두 명의 연구자가 독립적으로 심의내용을 분석하였고, 의견 불일치 시에는 제3자의 저자와 함께 의견을 타협하였다. 분석에 포함된 1,244건(2004~2006년 심의: 752건, 2013년 심의: 492건) 중 22.7%만이 초기 심의에서 승인되었고, 64.2%는 수정 후 신속심의, 12.6%는 보완 후 재심의로 결정되었다. 전체 연구의 62.2%에서 과학적 문제, 47.0%에서 윤리적 문제가 제기되었다. 과학적 문제 중 '불확실한 연구대상자 수'가 가장 많았고, 윤리적 문제 중 '피험자의 선정제외기준' 문제가 가장 많았다. 연구동의서 문제를 가진 연구는 전체 연구의 67.0%, 증례기록서 문제를 가진 연구는 41.3%로 나타났다. 2004~2006년에 비해 2013년에 '불확실한 연구디자인', '사생활 및 개인 정보', 동의서 문제가 있는 연구 비율이 증가하였다. 시험자 주도 임상시험에서는 과학적 문제가 가장 많았던 데에 비해, 의뢰자 주도 임상시험에서는 동의서 문제가 가장 많았다. 모든 문제점이 연구 승인 여부와 유의한 관련성이 있었으나, 윤리적 문제가 있는 연구의 승인비율이 가장 낮았다. 본 연구는 연구계획서에서 흔히 나타나는 과학적, 윤리적 문제를 규명함으로써 향후 연구자들의 연구윤리지침과 연구자들의 교육내용의 기초를 제공하였다.

색인어

임상시험심사위원회, 연구윤리심의위원회, 임상연구계획서, 임상시험, 생명윤리

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I. INTRODUCTION

The review and monitoring of clinical trials through an Institutional Review Board (IRB) is implemented internationally for ethical and safe clinical trials. In human studies, unscientific research is unethical because these studies could harm the patients and impair their quality of life. Therefore, regulations such as the 'Bioethics and Safety Act' advise that the IRB should review not only the ethical but also the scientific issues of protocols and that is why IRB approval is essential in clinical studies now. Even though several studies have shown the regulation about IRB review process [1-3], research into criteria and issues of IRB review, such as factors affecting the decision of IRB or factors IRB members are focusing, is lacking in Korea.

To arrive at a valid decision, the IRB must examine whether they review scientific issues as well as ethical issues. In addition, the IRB needs to monitor the criteria by which they do not approve a protocol. A recent systematic review of empirical studies of IRBs reported inconsistencies within the review process [4]. Additionally, previous studies indicated IRB review variability between institutions, even when using the same protocol [5-8].

Factors related to IRB decisions have not yet been clearly identified. Previous studies have reported various issues influencing the decision of an IRB to approve a protocol. A 12-year review of an IRB identified only 8% of studies that gained full ethical approval and 20% of protocols where approval was deferred due to inadequate research design, insufficient drug data and problems with informed consent forms [9]. Poorly-designed consent forms, inadequate study design, unacceptable risk to subjects and ethical or legal reasons have also been reported as common reasons for proposal rejection [10]. Rodriguez et al. [11] reported that 66% of clinical studies submitted to IRBs were approved, and the approval rate was higher in basic research and studies with fellowship involvement. Based on a recent survey of IRB members, perceived uncertainty about the potential benefit or harm of a proposed intervention influenced the approval decision [12].

Protocol issues examined during the IRB review process and the approval criteria for those issues could be changed by more rigorous regulations and guidelines for clinical studies. For example, in Korea, following the revision of the Korean Good Clinical Practice in 1995 [13], institutions conducting clinical trials have had to be registered with the Korean Ministry of Food and Drug Safety, and the Institutional Ethics Committee was established in 2005 to enforce the Bioethics and Safety Act. The Bioethics and Safety Act was revised in 2013 and now requires all institutions to register their IRBs. Since review criteria of IRBs for study approvals could have been changed by these new regulations, studies investigating changes in these criteria over time are needed. In this study, protocol issues were identified during initial IRB review to determine what IRB boards examine and to identify common protocol issues. Protocol issues from before and after accreditation were compared to assess a change in the IRB review process. Additionally, the relationship between identified issues and the approval of clinical studies was analyzed to

assess the effect of each issue on IRB approval.

II. METHOD AND MATERIAL

This research was only conducted for clinical trials, applying the same criteria for a consistent assessment. A total of 1,244 clinical trials, subject to regular review by Seoul National University Hospital's IRB (Seoul, Korea), were included. Of those, 752 studies were submitted from October 2004 to October 2006, and 492 were submitted in 2013. Seoul National University Hospital's IRB gained accreditation from the Forum for Ethical Review Committees in Asia and the Western Pacific (FERCAP) in 2006, and the Associations for the Accreditation of Human Research Protection Programs (AAHRPP) in 2012. To compare review processes of the IRB before and after accreditation, studies from 2004~2006 and 2013 were selected.

Two independent researchers having experience more than 2 years as full time IRB administrators, documented issues raised at the initial IRB review based on the recorded minutes. They assessed which issues were identified at initial review for each protocol and whether the protocol was approved or not. Disagreement between two researchers was discussed with a third researcher.

Issues were categorized into four types; scientific, ethical, consent and case report form (CRF). All issues in protocol were divided into scientific or ethical issues. Consents or CRF issues were considered when the additional information or the form of those documents had a problem.

Scientific issues included cases in which the title or purpose of the study was not clear (unclear study title/purpose) or the study design was not clear or inappropriate for the research objective (unclear study design); where outcome measurements were unclear or the primary and secondary outcomes were not clearly separated (unclear outcome assessment); where sample size calculations were not presented or not appropriate (unclear sample size calculation); and where methods of statistical analysis were not presented or were inadequate (unclear statistical analysis methods). Ethical issues included protocols in which subjects' recruitment plan or inclusion criteria were not clear (subjects' recruitment/inclusion criteria); where the protocol potentially collected personal data which was not essential for research purposes (privacy/personal data); where benefits and risks to subjects were not described properly or the risks outweighed the benefits (benefits/risks); and where additional costs or compensation for subjects were not described or were unclear (additional costs/compensation). When each scientific or ethical issue was not described in protocol, it was also considered as unclear issue.

Consent issues involved cases in which the contents of consent were inappropriate or inconsistent with the study protocol (contents of consent); where appropriate consent forms (e.g., consent for a gene study) was not used or administration information (e.g., contact person) was missing (consent form). CRF issues included cases for which the CRF was not submitted or was inconsistent with the study protocol. If more than one issue was identified in a clinical study, each issue was recorded, respectively.

The percentage of study protocols with relevant

issues were identified overall, and for each study type; investigator-initiated trials (IIT) and sponsor-initiated trials (SIT). To analyze the difference between the number of studies with issues and the number of issues per study between 2004~2006 and 2013, chi-square tests for categorical variables and T-tests for numerical variables were used. Each issue was also verified to determine whether it had a significant relationship with the study approval using chi-square test. IBM SPSS Statistics (version 19.0; IBM Co., Armonk, NY, USA) was used to analyze the data. Statistical significance was set at a value of $p<0.05$.

III. RESULTS

1. Analysis of the IRB decision

Of the 1,244 studies, 732 (58.8%) were IIT and 512 (41.2%) were SIT studies. Only 282 (22.7%) of the total studies were approved in the initial review. There was no difference in the number of approved studies between 2004~2006 and 2013, with 22.2% and 23.4% being approved, respectively (p=0.63). Approval rate for IIT studies decreased from 19.4% in 2004~2006 to 7.6% in 2013, whereas SIT study approval increased from 26.8% to 41.6%, over the same period.

Minor revisions were the most common decision for both IIT and SIT studies. Total 799 studies (64.2%) were identified that underwent minor revisions, and 157 studies (12.6%) underwent major revisions. Protocols with minor revisions were reviewed again by two expedite reviewers after re-submission, whereas protocols with major

<Table 1> The Institutional Review Board Decision after Initial Review

	2004~2006						2013						Total					
	IIT		SIT		Total		IIT		SIT		Total		IIT		SIT		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Approval	91	19.4	76	26.8	167	22.2	20	7.6	95	41.6	115	23.4	111	15.2	171	33.4	282	22.7
Minor revision	297	63.5	181	63.7	478	63.6	204	77.3	117	51.3	321	65.2	501	68.4	298	58.2	799	64.2
Major revision	78	16.7	25	8.8	103	13.7	40	15.2	14	6.1	54	11.0	118	16.1	39	7.6	157	12.6
Withholding	0	0	1	0.4	1	0.1	0	0	0	0	0	0	0	0	1	0.2	1	0.1
Rejection	2	0.4	1	0.4	3	0.4	0	0	2	0.9	2	0.4	2	0.3	3	0.6	5	0.4
Total	468	100	284	100	752	100	264	100	228	100	492	100	732	100	512	100	1,244	100

p-value of difference in approval rate between 2006 and 2013: 0.631.

IIT : investigator-initiated trial, SIT : sponsor-initiated trial.

revisions had to be re-reviewed at the full board meeting following re-submission. Only one study (0.1%) was withheld and five (0.4%) were rejected <Table 1>.

2. Scientific issues

Overall, 62.2% of studies had one or more scientific issue; 47.0% had ethical issues; 67.0% had consent issues and 41.3% had a CRF issue. Among the scientific issues, unclear sample size calculations occurred most frequently (41.4%). The second most frequent issue was unclear study design (31.9%), followed by unclear statistical analysis methods (31.5%). Excluding unclear study design, fewer studies had other scientific issues in 2013 compared with 2004~2006. Additionally, the number of studies with one or more issue (67.3% in 2004~2006 and 54.5% in 2013) and the mean number of issues per study (1.66 in 2004~2006 and 1.38 in 2013) decreased significantly ($p<0.001$).

3. Ethical issues

The most frequently occurring ethical issues were the subjects' recruitment/inclusion criteria (31.5%), privacy/personal data (17.3%), and additional costs and compensation (9.6%). Overall, the number of studies with other ethical issues decreased, however privacy/personal data issues significantly increased in 2013 with a frequency of 28.3% compared with 10.1% in 2004~2006 ($p<0.001$).

4. Consent and CRF issues

Regarding consent, issues related to the contents of consent (60.9%) occurred more often than issues related to consent forms (37.5%). Between 2004~2006 and 2013, both of these issues increased significantly, from 49.5% to 78.5% ($p<0.001$) for contents of consent, and from 35.0% to 41.3% ($p=0.025$) for consent forms. Of the issues related to consent forms, the most frequent was missing contact information.

In total, the number of studies with CRF issues was 41.3%. The number of studies with CRF issues decreased from 48.8% in 2004~2006 to 29.9% in 2013 ($p<0.001$). In studies with one or more issue, consent issues were the most frequent, followed by scientific and ethical issues and CRF issues were the least frequent <Table 2>.

5. IIT vs SIT studies

When comparing IIT with SIT studies, scientific issues were more frequent in IIT studies, with 73.1% of studies being identified as having one or more scientific issues, compared with 46.7% of SIT studies. The mean number of scientific issues per protocol was 1.96 for IIT and 0.97 for SIT trials. In IIT studies, the percentage of studies with scientific issues increased from 69.2% in 2004~2006 to 79.9% in 2013 ($p=0.002$) and the number of scientific issues per study increased from 1.85 in 2004~2006 to 2.15 in 2013 ($p=0.011$). Conversely, scientific issues in SIT studies reduced, with the frequency of studies with scientific issues decreasing from 64.1% in 2004~2006 to 25.0%

in 2013 (p<0.001) and the number of scientific issues per study falling from 1.34 in 2004~2006 to 0.5 in 2013 (p<0.001). In SIT studies, all scientific issues decreased between 2004~2006 and 2013 from 18.3% to 10.1% for unclear study title/purpose; 26.8% to 13.6% for unclear study design; 35.6% to 5.7% for unclear outcome assessment; 31.7% to 12.7% for unclear sample size calculation and 21.8% to 7.9% for unclear statistical analysis methods (p<0.001). Conversely, in IIT studies, several scientific issues increased in frequency between the two time periods, including unclear study design (32.9% to 51.5%, p<0.001), unclear sample size calculation (49.8% to 61.7%, p=0.002) and unclear statistical analysis methods (38.9% to 49.2%, p=0.007).

In IIT studies, the most frequent ethical issue was recruitment/inclusion criteria (35.5%), followed by privacy/personal data issues (24.5%). Similarly, the most frequent issue identified in SIT studies was recruitment/inclusion criteria (25.8%); however, the second most frequent issue in SIT

<Table 2> Frequency of Clinical Research Protocols with Each Issue in 2004~2006 and 2013

		Year, N (%)		Total, N (%)	p-value
		2004~2006	2013		
Scientific issues	Unclear study title/purpose	184 (24.5)	77 (15.7)	261 (21.0)	<0.001
	Unclear study design	230 (30.6)	167 (33.9)	397 (31.9)	0.214
	Unclear outcome assessment	268 (35.6)	97 (19.7)	365 (29.3)	<0.001
	Unclear sample size calculation	323 (43.0)	192 (39.0)	515 (41.4)	0.169
	Unclear statistical analysis methods	244 (32.4)	148 (30.1)	392 (31.5)	0.380
	Number of studies with issue	506 (67.3)	268 (54.5)	774 (62.2)	<0.001
	Number of issues per study (mean±SD)	1.66±1.56	1.38±1.55	1.55±1.56	<0.001
Ethical issues	Subjects' recruitment/inclusion criteria	274 (36.4)	118 (24.0)	392 (31.5)	<0.001
	Privacy/personal data	76 (10.1)	139 (28.3)	215 (17.3)	<0.001
	Benefits/risks	64 (8.5)	33 (6.7)	97 (7.8)	0.246
	Additional cost and compensation	74 (9.8)	45 (9.1)	119 (9.6)	0.684
	Number of studies with issue	354 (47.1)	231 (47.0)	585 (47.0)	0.966
	Number of issues per study (mean±SD)	0.65±0.81	0.68±0.84	0.66±0.82	0.633
Consent issues	Contents of consent	372 (49.5)	386 (78.5)	758 (60.9)	<0.001
	Consent form	263 (35.0)	203 (41.3)	466 (37.5)	0.025
	Number of studies with issue	415 (55.2)	418 (85.0)	833 (67.0)	<0.001
Case report form issues		367 (48.8)	147 (29.9)	514 (41.3)	<0.001
Total		752 (100)	492 (100)	1,244 (100)	

SD : standard deviation.

studies was benefits/risks (7.4%). Ethical issues were identified in 55.9% of IIT and 34.4% of SIT studies. In both IIT and SIT studies, privacy/personal data were the only issue that increased in 2013 compared with 2004~2006. The number of studies with ethical issues increased in IIT studies between 2004~2006 and 2013, from 50.0% to 66.3% ($p<0.001$) and the mean number of issues per study increased from 0.7 to 0.97 ($p<0.001$). In SIT studies, the number of studies with ethical issues decreased from 42.3% to 24.6% ($p<0.001$) and the mean number of issues per study decreased from 0.57 to 0.35 ($p<0.001$) between 2004~2006 and 2013.

In IIT studies, frequency of issues related to contents of consent and consent forms were 65.6% and 40.0%, respectively, whereas in SIT studies the frequency of these issues was 54.3% and 33.8%, respectively. Additionally, the percentage of studies with one or more consent issue was 69.3% in IIT studies and 63.7% in SIT studies. The percentage of studies with issues related to consent

<Table 3> Frequency of Investigator-Initiated Trials with Each Issue in 2004~2006 and 2013

		Year, N (%)		Total, N (%)	p-value
		2004~2006	2013		
Scientific issues	Unclear study title/purpose	132 (28.2)	54 (20.5)	186 (25.4)	0.021
	Unclear study design	154 (32.9)	136 (51.5)	290 (39.6)	<0.001
	Unclear outcome assessment	167 (35.7)	84 (31.8)	251 (34.3)	0.290
	Unclear sample size calculation	233 (49.8)	163 (61.7)	396 (54.1)	0.002
	Unclear statistical analysis methods	182 (38.9)	130 (49.2)	312 (42.6)	0.007
	Number of studies with issues	324 (69.2)	211 (79.9)	535 (73.1)	0.002
	Number of issues per study (mean±SD)	1.85±1.63	2.15±1.54	1.96±1.60	0.011
Ethical issues	Subjects' recruitment/inclusion criteria	172 (36.8)	88 (33.3)	260 (35.5)	0.353
	Privacy/personal data	65 (13.9)	114 (43.2)	179 (24.5)	<0.001
	Benefits/risks	39 (8.3)	20 (7.6)	59 (8.1)	0.718
	Additional cost and compensation	51 (10.9)	34 (12.9)	85 (11.6)	0.422
	Number of studies with issues	234 (50.0)	175 (66.3)	409 (55.9)	<0.001
	Number of issues per study (mean±SD)	0.70±0.84	0.97±0.86	0.80±0.86	<0.001
Consent issues	Contents of consent	247 (52.8)	233 (88.3)	480 (65.6)	<0.001
	Consent form	173 (37.0)	120 (45.5)	293 (40.0)	0.024
	Number of studies with issue	264 (56.4)	243 (92.0)	507 (69.3)	<0.001
Case report form issues		245 (52.4)	127 (48.1)	372 (50.8)	0.270
Total		468 (100)	264 (100)	732 (100)	

SD : standard deviation.

<Table 4> Frequency of Sponsor-Initiated Trials with Each Issue in 2004~2006 and 2013

		Year, N (%)		Total	
		2004~2006	2013	N (%)	p-value
Scientific issues	Unclear study title/purpose	52 (18.3)	23 (10.1)	75 (14.6)	0.009
	Unclear study design	76 (26.8)	31 (13.6)	107 (20.9)	<0.001
	Unclear outcome assessment	101 (35.6)	13 (5.7)	114 (22.3)	<0.001
	Unclear sample size calculation	90 (31.7)	29 (12.7)	119 (23.2)	<0.001
	Unclear statistical analysis methods	62 (21.8)	18 (7.9)	80 (15.6)	<0.001
	Number of studies with issue	182 (64.1)	57 (25.0)	239 (46.7)	<0.001
	Number of issues per study (mean±SD)	1.34±1.37	0.50±1.0	0.97±1.29	<0.001
Ethical issues	Subjects' recruitment/inclusion criteria	102 (35.9)	30 (13.2)	132 (25.8)	<0.001
	Privacy/personal data	11 (3.9)	25 (11.0)	36 (7.0)	0.002
	Benefits/risks	25 (8.8)	13 (5.7)	38 (7.4)	0.183
	Additional cost and compensation	23 (8.1)	11 (4.8)	34 (6.6)	0.139
	Number of studies with issue	120 (42.3)	56 (24.6)	176 (34.4)	<0.001
	Number of issues per study (mean±SD)	0.57±0.76	0.35±0.68	0.47±0.73	<0.001
Consent issues	Contents of consent	125 (44.0)	153 (67.1)	278 (54.3)	<0.001
	Consent form	90 (31.7)	83 (36.4)	173 (33.8)	0.262
	Number of studies with issue	151 (53.2)	175 (76.8)	326 (63.7)	<0.001
Case report form issues		122 (43.0)	20 (8.8)	142 (27.7)	<0.001
Total		284 (100)	228 (100)	512 (100)	

SD : standard deviation.

was significantly higher in 2013 compared with 2004~2006 in both IIT (56.4% in 2004~2006 and 92.0% in 2013, p<0.001) and SIT studies (53.2% in 2004~2006 and 76.8% in 2013, p<0.001). CRF issues were identified in 50.8% of IIT and 27.7% of SIT studies. The frequency of studies with CRF issues decreased in both IIT (52.4% in 2004~2006 and 48.1% in 2013, p=0.27) and SIT studies (43% in 2004~2006 and 8.8% in 2013, p<0.001), but the difference was only significant in SIT studies. Based the number of studies with one or more issue, scientific issues were most frequent in IIT studies, and consent issues were most frequent in SIT studies <Table 3, 4>.

6. Analysis of the approval decision

Studies with issues relating to all scientific issues including unclear study title/purpose, unclear study design, unclear outcome assessment, unclear sample size calculation and unclear statistical analysis methods were significantly less likely

<Table 5> Approval Rate of Study Protocols with Each Issue in 2004~2006 and 2013

			2004~2006		2013		Total (%)
			Approval rate (%)	p-value	Approval rate (%)	p-value	
Scientific issues	Unclear study title/purpose	Yes	8.7	<0.001	0.0	<0.001	6.1
		No	26.6		27.7		27.1
	Unclear study design	Yes	6.1	<0.001	1.2	<0.001	4.0
		No	29.3		34.8		31.4
	Unclear outcome assessment	Yes	9.3	<0.001	0.0	<0.001	6.8
		No	29.3		29.1		29.2
	Unclear sample size calculation	Yes	7.7	<0.001	2.6	<0.001	5.8
		No	33.1		36.7		34.6
	Unclear statistical analysis methods	Yes	9.8	<0.001	1.4	<0.001	6.6
		No	28.1		32.8		30.0
	Number of studies with issue	Yes	10.7	<0.001	2.6	<0.001	7.9
		No	45.9		48.2		47.0
	Number of issues per study (mean±SD)	Approved	0.62±1.13	<0.001	0.08±0.33	<0.001	0.40±0.93
		Rejected	1.96±1.54		1.78±1.56		1.89±1.55
Ethical issues	Subjects' recruitment/ inclusion criteria	Yes	0.0	<0.001	2.5	<0.001	0.8
		No	34.9		29.9		32.7
	Privacy/personal data	Yes	0.0	<0.001	1.4	<0.001	0.9
		No	24.7		32.0		27.2
	Benefits/risks	Yes	0.0	<0.001	0.0	0.001	0.0
		No	24.3		25.1		24.6
	Additional cost and compensation	Yes	0.0	<0.001	4.4	0.002	1.7
		No	24.5		25.3		24.9
	Number of studies with issue	Yes	0.0	<0.001	2.6	<0.001	1.0
		No	42.0		41.8		41.9
	Number of issues per study (mean±SD)	Approved	0.0±0.0	<0.001	0.06±0.27	<0.001	0.02±0.18
		Rejected	0.83±0.84		0.87±0.87		0.85±0.85
Consent issues	Contents of consent	Yes	0.0	<0.001	14.0	<0.001	7.1
		No	43.9		29.8		46.9
	Consent form	Yes	0.0	<0.001	14.3	<0.001	6.2
		No	34.2		57.5		32.5
Case report form issues		Yes	6.3	<0.001	1.4	<0.001	4.9
		No	37.4		32.8		35.2

SD : standard deviation.

to gain approval in both 2004~2006 and 2013 ($p<0.001$). Among scientific issues, studies with unclear study design had the lowest mean approval rate of 4%.

Studies with ethical issues also had significantly lower approval rates compared with studies without ethical issues including subjects' recruitment/inclusion criteria ($p<0.001$ in 2004~2006 and 2013), privacy/personal data ($p<0.001$ in 2004~2006 and 2013), benefits/risks ($p<0.001$ in 2004~2006, $p=0.001$ in 2013) and additional costs and compensation ($p<0.001$ in 2004~2006, $p=0.002$ in 2013). Notably, studies with benefits/risks issues were rarely approved. Approval rate of studies with scientific issues was 7.9%; however, the approval rate of studies with ethical issues was only 1.0%.

The approval rates of studies with contents of consent issues and consent form issues were 7.1% and 6.2%, respectively. Among studies with CRF issues, 4.9% were approved after initial review. Contents of consent ($p<0.001$), consent form ($p<0.001$), and CRF issues ($p<0.001$) were highly related to study approval in both 2004~2006 and 2013 <Table 5>.

IV. DISCUSSION

In a previous study conducted in the United States, inadequate consent was the most significant factor associated with non-approval [10], and another study reported inappropriate study design was the main reason for deferral [9]. In the current study, the approval rate of studies with ethical issues was the lowest in all four categories. However, all issues had a significant relationship with the study approval in IRB review. This indicates the IRB considers both ethical and scientific issues important in clinical trials.

Seoul National University Hospital's IRB gained FERCAP accreditation in 2006 and AAHRPP accreditation in 2012. During this process, standard operating procedures for the IRBs were amended and became more rigorous compared with 2006, to fulfill the accreditation standard. The increase in approval rate of studies with ethical and consent issues in this study might be because every detail related to ethical issues were highlighted at the initial IRB review through these strengthened regulations, rather than because of alleviated approval criteria. Additionally, rules dealing with personal data from participants in clinical trials have been reinforced since the Personal Information Protection Act was enforced in 2011. This could be one reason why frequency of privacy/personal issues increased in 2013 compared with 2004~2006.

Several studies have reported that perceived uncertainty [12] or risk perception [14] as a factors affecting IRB decision. However, many studies have shown that scientific issues as well as ethical issues including study design [11], inadequate or insufficient data [9], consent form [10] were obstacles of IRB approval. In this study, analysis of the IRB decision revealed that the proportion of studies approved during initial review was only 22.7%, and most other studies underwent minor or major revisions. Additionally, a large proportion of studies had problems in each of the scientific (62.2%), ethical (47.0%), consent (67.0%), and CRF categories (41.3%). Scientific or consent

issues were more frequent compared with ethical issues, indicating researchers were not fully aware of the prerequisite knowledge or adequate description associated with clinical research protocols. These issues could be improved by targeted education programs for clinical researchers and improved guidelines.

Approval rate and frequency of protocol issues varied according to the type of study. IIT studies had a higher percentage of studies with each issue compared with SIT studies, for all categories. Additionally, changes in the percentage of studies with issues from 2004~2006 compared with 2013, were identified between IIT and SIT studies. In 2013, the number of studies with unclear study design, unclear sample size calculation, unclear statistical analysis methods, privacy/personal data issues and consent issues increased in IIT studies, whereas only privacy/personal data and consent issues increased in SIT studies. In South Korean, the number of SIT has increased from 340 in 2010 to 505 in 2014 [15]. Researchers of SIT might have more chance to work with assistance from various expertise like statisticians, and those differences could be contributed to the change in approval rate for SIT studies. Researchers should consider the importance of scientific knowledge and statistical proficiency especially when they conduct IIT, and additionally, there is a need to advise clinical researchers on ethical and consent issues.

A study carried out in the United States has revealed study approvals granted by IRBs varies significantly depending on unexperienced researchers' inclusion in clinical studies or the presence of funding [16]. However, this study is limited by a lack of in-depth assessment of issues such as researchers' conflicts of interest. It is essential to investigate the impact of study's external characteristics on IRB approval, independently of problems related to study design.

IRB review and approval is becoming essential in clinical trials, however in a survey conducted for Korean clinical researchers, more than 50% of IRBs did not offer in-house training [17]. Also, many IRB administrators in America reported that 20% or less of members on their IRBs had ethical expertise [18], and another study reported that 47% of IRB members identified lack of education and training as a problem [19]. There a need for education programs for researchers and IRB members, and by identifying commonly occurring issues in protocols, this study can be used to form the basis of an education program. In addition, the results of this study can be used for consistent and efficient IRB reviews through IRB members are aware of criteria on which they approve studies.

The result of this study has a limitation since this study analyzed only the IRB's data of one institution. The issues of clinical studies could be different depending on various factors of IRB. For more valid and reliable conclusion, further studies regarding another IRBs of Korea are needed.

In conclusion, a large proportion of the studies assessed by this research had some issues with scientific, ethical, consent, and CRF categories. Among these, consent issues were most frequent, and studies with ethical issues had the lowest approval rates. All categories were significantly related to study approval in the IRB review. This study will help improve the quality of protocols and the

IRB review process. Future studies should address ways to ensure the quality of clinical studies and improve study ethics.

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한국의료윤리학회지 제19권 제4호(통권 제49호) : 518–530 ⓒ한국의료윤리학회, 2016년 12월
Korean J Med Ethics 19(4) : 518-530 ⓒ The Korean Society for Medical Ethics, December 2016
pISSN 2005-8284 eISSN 2234-3598

Scientific and Ethical Issues with an Institutional Review Board (IRB)'s Clinical Research Protocols in the IRB Review in a Teaching Hospital in South Korea*

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Abstract

With the increased number of clinical trials being conducted in South Korea, Institutional Review Boards (IRBs) have acquired greater significance. In human clinical trials, unscientific studies may be unethical in light of their potential for causing harm to participants. Therefore, IRBs should review both the scientific and the ethical issues of any research protocol. However, research into the IRB review process is lacking in Korea. This study examined the protocols for clinical trials under the review of the IRB at Seoul National University Hospital. In total 1,244 protocols (752 between 2004 and 2006; 492 in 2013) were analyzed. Of these 22.7% were approved, 64.2% underwent minor revision, and 12.6% underwent major revision. In total, 62.2% of these protocols raised scientific issues, and 47.0% raised ethical issues. Among the scientific issues, "unclear sample size calculation" occurred most frequently. "Subjects' recruitment/inclusion criteria" was the most frequently cited ethical issue. A total of 67.0% had consent issues and 41.3% raised questions about the case report form. Compared to the period from 2004 to 2006, the prevalence of protocols with "unclear study design" and those that raised questions about "privacy/personal data" increased in 2013. While scientific issues were the most frequent among investigator-initiated trials, consent issues were the most frequent in sponsor-initiated trials. Although all issues were significantly associated with the approval decision, the approval rate of studies with ethical issues was lowest. These results provide a basis for the development of guidelines for researchers by identifying common issues in clinical protocols.

Keywords

Institutional Review Board, IRB, clinical protocol, clinical trials, bioethical issues

** This study was supported by research grants of the Seoul National University Hospital and the SNUBH Incentive for Education and Research. We extend our gratitude to Jeonghee Cha and Myung Jik Han for their support and advice.*
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