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RESEARCH ARTICLE

ANALYSIS OF CLINICAL TRIALS INFORMED CONSENT COMPLIANCE WITH SAUDI FDA AND ICH-GCP GUIDELINES

***Isamme N. AlFayyad and Pendo Ntinika**

Research Center, King Fahad Medical City, Saudi Arabia

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ABSTRACT

Background: the purpose of the informed consent document in clinical trials is to inform research participants about the nature of a clinical trial, its risks, benefits, underlying procedures, and alternative treatments.
Objective: to assess the quality of the information provided in informed consent document during clinical trials.
Methods: A cross-sectional retrospective study was performed at our institution. In total, 55 informed consent document that accompanied research proposals submitted to the institutional review board from January 2012 to August 2016 were reviewed. Descriptive and inferential statistical analyses were performed to assess overall mean compliance.
Results: overall compliance with the essential elements of the informed consent document was 90.8%. The elements of unforeseeable risk, termination of a subject's participation by the investigator, and disclosure of new findings during the study were highly related to the source of the study ($p < 0.001$, 0.002, and 0.003, respectively).
Conclusion: the results indicate high-quality information in the reviewed informed consent document and a high compliance rate with International Conference on Harmonization-Good Clinical Practice guidelines and Saudi law.

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INTRODUCTION

Clinical trials have become an essential step in the development of new knowledge. Informed consent (IC) is an ethical obligation and a legal requirement in the conduct of clinical trials. The ultimate goals of IC are to protect research participants from harm and to promote their rights, safety, and well-being. Informed consent document (ICD) plays an integral part in the process of obtaining IC. Participants gain a better understanding of the trial through the ICD (Padhy, 2011). The purpose of IC is to inform research participants about the nature of a clinical trial, its risks, benefits, underlying procedures, and alternative treatments. International Conference on Harmonization (ICH)-Good Clinical Practices (GCP) and the Code of Federal Regulations have sections dedicated to the content of ICs. These requirements state that ICDs shall be prepared with understandable language, allowing patients/participants to become familiar with their content and meaning.

****Corresponding author: Isamme N. AlFayyad.,***
Research Center, King Fahad Medical City, Saudi Arabia

The consent document must be written in a clear and logical manner that can be understood by a reasonable person (Baer, 2011), in practice, this is often assessed as grade levels 6–8 (Bloswick, 2015). The Saudi Food and Drug Authority (SFDA) emphasizes following the ethical principles stated in ICH-GCP guidelines and Declaration of Helsinki for fulfilling the requirements of ICDs (Saudi Food and Drug Authority, 2013). Several pharmaceutical companies are currently considering Saudi Arabia as a potential site for clinical studies (Journal for Clinical Studies, 2013). The current number of clinical trials in Saudi Arabia with a known status (data from clinicaltrials.gov) is 379 (ClinicalTrials.gov, 2015). However, despite rigorous guidelines, studies suggest that institutional review board (IRB) review may not ensure compliance with IC requirements and may not protect subjects adequately (Nair, 2015); moreover, trial participants remain inadequately informed despite strict guidelines (Padhy, 2011). IC challenges for clinical trials in the Middle East and North Africa exist with regard to language, culture, and social and health literacy issues, similar to other emerging regions (Nair, 2015). Stryker concluded that participants who enrolled in clinical trials rapidly might not completely understand the implications of trial participation, which may lead to regret the decision to

participate (Stryker, 2006). Alahmad et al explored ten "national codes, regulations, and guidelines concerning research ethics" documents from eight Arab countries (Alahmad, 2012). Interestingly, all of the national documents had deficiencies in their stated protections; indeed, the many deficiencies observed in these guidelines leave a question mark as to their adequacy in fulfilling the necessary protections for research subjects in the region. Comprehension of IC is a vital part of clinical trials. Every effort should be made to keep the content of the ICD simple. The comprehension of patients in clinical studies performed in developing countries can be practically sufficient if the investigators explain the consent form in simple language to the participants (Bhansali, 2006). Readability and difficulty testing for ICDs in English are widely accessible through many software packages. The aim of this study was to assess the compliance of ICDs with the national and international ethical guidelines of IC.

MATERIALS AND METHODS

A retrospective, cross-sectional review of ICDs was conducted at a single tertiary hospital in Riyadh, Saudi Arabia. The retrospective analysis was performed on ICDs that accompanied research proposals that were submitted to the IRB from January 2012 to August 2016 and that met the inclusion criteria. Research proposals for observational and interventional trials for the evaluation of drugs, medical devices, stem cells, new techniques, and epidemiological studies submitted for initial IRB review were considered eligible and included in the study. Research proposals submitted for subsequent review and amendment were excluded. In total, 55 ICDs met the eligibility criteria. Each ICD was compared and examined independently by a clinical research coordinator, a native Arabic speaker, based on universally accepted GCP guidelines and SFDA requirements for basic and additional elements of ICDs (see Appendix 1). The basic and additional elements of ICDs that were in accordance with SFDA and GCP requirements, identified in the study protocol and described in Arabic, were coded as "essential information element present" and scored as +1. If an item was partially or completely absent or did not fulfil all criteria, it was coded as "essential information element absent" and scored as 0. Study characteristics, including the source, year, and type, were examined. A minimum score of 0 points and a maximum of 13 points were possible for the basic elements for each ICD. A minimum score of 0 points and a maximum of 6 points were possible for the additional elements for each ICD. IRB approval was obtained before the study commenced. SPSS software 21.0 (SPSS, Chicago, IL, USA) was used for all data analyses. The analyses included descriptive statistics: means, medians, and standard deviations. The χ^2 test was used to compare variables; p-values < 0.05 were considered to indicate statistical significance.

RESULTS

Approved IC forms from 2012 to 2016 for interventional and non-interventional studies were reviewed. In total, 55 ICDs were eligible for inclusion in this study. (Table.1). Of the reviewed studies, 26 (47.3%) were academic proposals, and 29 (52.7%) were industry-sponsored proposals. 26 (47.3%) were for academic proposals and 29 (52.7%) for industrially sponsored proposals. The majorities of the ICDs were for epidemiological studies 33 (60%) and drug trials 15 (27.3%). The difference between the source and type of the study proposals was not significant. Moreover, the majority of ICDs were submitted during the period 2014-aug-2016, with a statistically significant difference between the source and year of the study (p-value= 0.036). (Table.1) Table 2 shows the percentages of compliance with GCP and SFDA requirements for the ICDs. Overall compliance with the basic elements of the mandated GCP and SFDA requirements was 90.8%. However, overall compliance with the additional elements mentioned in GCP and SFDA guidelines was 70%. In both study types, there was 100% compliance with the statement that participation is voluntary (refusal to participate will involve no penalty or loss of benefits) and an explanation of the purposes of the research. Regarding a statement that the study involves research, 100% of industry studies were compliant, as were 88.5% of academic studies. Industry studies were 100% compliant with a statement on the research methods, while academic studies were 96.2% compliant (i.e., 3.8% of academic studies did not explain this). Regarding a statement about who to contact for answers to pertinent questions, academic studies were 100% compliant and industry studies were 93.1% compliant. About equal compliance was seen in terms of a description of any benefit to the subject (92.3% in academic studies and 96.6% in industry studies). Regarding an explanation as to whether any medical treatment was available if an injury occurred, compliance in academic studies was 73.9% compared to 80.8% in industry studies. For research involving more than minimal risk, an explanation as to whether any compensation was available was included in 75% of academic studies and 90% of industry studies. Regarding a statement that the subject may discontinue participation at any time, compliance in academic studies was 92.3% and 96.8% in industry studies. (Table.2) Low compliance was observed regarding a statement about the termination of a subject's participation by the investigator (44.9%) and the disclosure of new findings resulting from the study (50%). (Table.2).

Table 1. Characteristics of the studies

		Study source		Total	p-value
		Academic 26 (47.3%)	Industry 29 (52.7%)		
Type of study	Device trial	0	2 (6.9%)	2 (3.6%)	0.172
	Drug trial	5 (19.2%)	10 (34.5%)	15 (27.3%)	
	Epidemiological studies	16 (61.5)	17 (58.6%)	33 (60%)	
	Interventional psychological studies	5 (19.2%)	0	5 (9.1%)	
	Total	26 (100%)	29 (100%)	55 (100%)	
Year of study	2012	0	3 (10.3%)	3 (5.5%)	0.036*
	2013	3 (11.5%)	1 (3.4%)	4 (7.3%)	
	2014	6 (23.1)	10 (34.5%)	16 (29.1%)	
	2015	9 (34.6%)	11 (37.9%)	20 (36.4%)	
	2016	8 (30.8%)	4 (13.8%)	12 (21.8%)	
	Total	26 (100%)	29 (100%)	55 (100%)	
Translation	Yes	26 (100%)	29 (100%)	55 (100%)	

Table 2. Compliance assessment of the ICD elements from industry and academic studies with GCP and SFDA guidelines

		Study source		Total
		Academic	Industry	
Basic elements				
A statement that the study involves research	Yes	23 (88.5%)	29 (100%)	52 (94.5%)
	No	3 (11.5%)	0	3 (5.5%)
Explanation of the purposes of the research	Yes	26 (100%)	29 (100%)	55 (100%)
Methods of the research	Yes	25 (96.2%)	29 (100%)	54 (98.2%)
	No	1 (3.8%)	0	1 (1.8%)
Expected duration of the subject's participation	Yes	17 (65.4%)	24 (82.8%)	41 (74.5%)
	No	9 (34.6%)	5 (17.2%)	14 (25.5%)
A disclosure of appropriate alternative procedures	Yes	17 (77.3%)	23 (88.5%)	40 (83.3%)
	No	5 (22.7%)	3 (11.5%)	8 (6.7%)
An explanation of whom to contact for answers to pertinent questions	Yes	26 (100%)	27 (93.1%)	53 (96.4%)
	No	0	2 (6.9%)	2 (3.6%)
A description of any benefits to the subject	Yes	24 (92.3%)	28 (96.6%)	52 (94.5%)
	No	2 (7.7%)	1 (3.4%)	3 (5.5%)
A description of any reasonably foreseeable risks	Yes	21 (84%)	26 (89.7%)	47 (87%)
	No	4 (16%)	3 (10.3%)	7 (13%)
An explanation as to whether any medical treatments are available if injury occurs	Yes	17(73.9%)	21 (80.8%)	38 (77.6%)
	No	6 (26.1%)	5 (19.2%)	11 (22.4%)
For research involving more than minimal risk, an explanation as to whether there is any compensation	Yes	12 (75%)	18 (90%)	30 (83.3%)
	No	4 (25%)	2 (10%)	6 (16.7%)
A statement describing the extent, if any, of the confidentiality of records	Yes	25 (96.2%)	27 (96.4%)	52(96.3%)
	No	1(3.8%)	1 (3.6%)	2 (3.7%)
A statement that participation is voluntary (that refusal to participate will involve no penalty or loss of benefits)	Yes	26 (100%)	29 (100%)	55 (100%)
A statement that the subject may discontinue participation at any time	Yes	24(92.3%)	28(96.8%)	52(94.5%)
	No	2 (7.7%)	1 (3.4%)	3(5.5%)
Overall mean compliance		87.8%	93.4%	90.8%
Additional elements:				
A statement that the particular treatment or procedure may involve risks to the subject that are currently unforeseeable	Yes	7(50%)	24(85.7%)	31(73.8%)
	No	7(50%)	4(14.3%)	11(26.2%)
Anticipated circumstances under which the subject's participation may be terminated by the investigator	Yes	4(18.2%)	18(66.7%)	22(44.9%)
	No	18 (81.8%)	9 (33.3%)	27(55.1%)
Any additional costs to the subject	Yes	18 (69.2%)	22 (81.5%)	40 (75.5%)
	No	8 (30.8%)	5 (18.5%)	13 (24.5%)
The consequences of a subject's decision to withdraw from the research	Yes	21 (91.3%)	28(96.6%)	49 (94.2%)
	No	2 (8.7%)	1 (3.4%)	3 (5.8%)
A statement regarding significant new findings developed during the course of the research	Yes	7 (26.9%)	20 (71.4%)	27 (50%)
	No	19 (73.1%)	8 (28.6%)	27 (50%)
The approximate number of subjects involved in the study	Yes	18 (69.2%)	26 (92.9%)	44 (81.5%)
	No	8 (30.8%)	2 (7.1%)	10 (18.5%)
Overall mean compliance		54.1%	82.5%	70%

Table 3. Stratification of informed consent elements by study characteristics

	Study source	Study type	Study year
Basics and additional elements	*p-value*	*p-value*	*p-value*
Expected duration of the subject's participation	0.140	0.003	0.928
Disclosure of appropriate alternative procedures	0.501	0.029	0.477
An explanation as to whether any medical treatments are available if injury occurs	0.840	0.017	0.701
For research involving more than minimal risk, an explanation as to whether any compensation is available	0.415	0.015	0.654
A statement that the particular treatment or procedure may involve risks to the subject that are currently unforeseeable	< 0.001	0.005	0.556
Anticipated circumstances under which the subject's participation may be terminated by the investigator	0.002	0.153	0.088
A statement about significant new findings developed during the course of the research	0.003	0.025	0.340
The approximate number of subjects involved in the study	0.052	0.316	0.016

Table 3 present a stratification of the basic elements presented in the reviewed ICDs with the studies' characteristics. Most of the elements were statistically significant with the study type, except for the elements of termination of subject's participation by the investigator ($p = 0.088$) and the number of subjects involved in the study ($p = 0.016$). Moreover, the elements of unforeseeable risk, termination of a subject's participation by the investigator, and disclosure of new findings during the study were significant with regard to the source of the study ($p < 0.001$, 0.002, and 0.003, respectively).

DISCUSSION

The safety, integrity, and welfare of clinical trial participants, as set out in the ICH-GCP, Declaration of Helsinki, and SFDA (http://www.sfda.gov.sa/en/drug/Clinical_Trials/Pages/default.aspx), regulations should be major elements of investigator concern. However, they are also the responsibility of other parties involved in the conduct of clinical trials and the evaluation of clinical trial protocols. Moreover, as the number of clinical trials is increasing in Saudi Arabia, it is ethically essential to ensure that ICDs and the explanation process are adequate. Our results support international and local ethical guidelines in protecting research subjects' rights and well-being by using a comprehensive and well-structured ICD. The overall compliance rate for the ICDs was 90.8%, generally indicating high-quality documents and the strict adoption of ethical standards. The results reveal a marginal difference in the compliance rate between industry and academic studies. It was found that the overall compliance rate for industry studies (93.4%) was slightly higher than that for academic studies (87.8%); a similar result was reported by Nair and Ibrahim

(Alahmad, 2012). The non-compliance score for ICDs from industry-sponsored studies was 9.7±0.7, significantly lower than the 12.2±1.3 for non-sponsored studies; this could be explained by the rigorous role of the local IRB. A substantial difference between the drug industry and academic ICDs was detected in the presentation of additional elements. The overall compliance for additional elements was 70%: 82.5% in industry ICDs and 54.1% in academic ICDs. This difference could be due to prolonged drug industry experience in clinical trials and the resources they possess. A significant number of ICDs from academic studies had incomplete or missing information precluding proper IC. This could be explained by the different background of the investigators and various training systems available at the institution. GCP training and adherence to the ICD format are important for improving the quality of IC in clinical trials (Nair, 2015). Although a well-structured and full ICD protects the rights and well-being of research subjects, comprehension by subjects of the content is a crucial step in securing IC. Giving an opportunity for research subjects to read and understand all of the elements of IC is necessary for a valid IC process. Although analyses of the readability and difficulty of ICDs are feasible and applicable to ICDs written in English using various software programs (e.g., those using Flesch-Kincaid reading and grade levels), such software is not yet available in Arabic.

Limitations

Low sample size is major limitation in the current study; however, this could be contributed to the functional age of the study site in research activity (less than 10 years). Moreover, lack of software programs to assess readability and difficulty of ICDs is another challenge and limitation. This warrants the need for such programs to enable evaluating participants understanding of the content of ICDs. To attain a systemic transformation in the ICDs lay language, institutional review board needs to enhance the available ICDs sample format for researchers.

Conclusions

Our study showed ICDs accompanied with research proposal concord with basic elements of IC, which reflects Saudi research institutions' compliance with the local and international ethical and regulatory guidelines of IC. Given the lower compliance with 'additional' elements; especially for academic ICDs, more robust scrutinizing and improvement in the additional elements is necessary to ensure the protection of human research subjects.

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