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Research Article

Informed Consent in Human Subjects Research: A Comparison of International and Saudi Arabian Guidelines

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ABSTRACT

Objective: Informed Consent (IC) is an essential requirement for the conduct of medical research involving human subjects. Since the Nuremberg Code was adopted in the aftermath of the Second World War, various international guidelines have specified the conditions for a valid IC for medical research. Among the most relevant guidelines are the World Medical Association's Declaration of Helsinki, the guidelines of the Council of International Organization of Medical Sciences (CIOMS), and the Good Clinical Practice Guidelines of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP). This paper aims to compare the above-mentioned international guidelines with Saudi Arabia's Law of Ethics of Research on Living Creatures regarding the requirements for IC. The comparison also includes some relevant regional and domestic laws. The objective of the study is to determine whether the compared regulations coincide regarding the requirements for a valid IC or whether they show significant differences, and to what extent such requirements are also present in Saudi Arabia's regulations.

Methods: We conducted a content comparative analysis of the above-mentioned guidelines regarding five elements of IC: Disclosure, comprehension, voluntariness, competence, and form of consent. These five topics were subdivided into 44 subtopics. Then we compared and critically analyzed their similarities and differences.

Results: The similarities and differences observed in the seven guidelines are summarized under the five components of IC mentioned above and regarding 44 selected subtopics.

Conclusion: The analysis of the above-mentioned guidelines shows that while the most basic components of IC are present in all the compared documents, there are some differences between them. Specifically, the study found that the Saudi Arabian regulations include 26 of the 44 subtopics considered and that most of the elements that are missing relate to the disclosure of information to participants.

Keywords: Informed consent; Medical research; Disclosure; Comprehension; Voluntariness; Competence; International guidelines

ABBREVIATIONS

IC: Informed Consent; WMA: World Medical Association; DoH: Declaration of Helsinki; CIOMS: Council for International Organizations of Medical Sciences; WHO: World Health Organization; ICH: International Council for Harmonization; GCP: Guideline for Good Clinical Practice; ICH-GCP: International Conference on Harmonization Good Clinical Practice; HRA: Swiss Human Research Act; CFR: Code of Federal Regulations; CHRB: Council of Europe's Convention on Human Rights and Biomedicine; KSA: Kingdom of Saudi Arabia; NCBE: National Committee of Bioethics

INTRODUCTION

Obtaining Informed Consent (IC) from participants is an absolute requirement when conducting clinical research, as mandated by all major guidelines. The aim of IC is to ensure that individuals

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make a free and informed decision about participating in a research study. This process involves providing potential subjects with clear and understandable details about the study, such as its purpose, procedures, risks, benefits, and alternatives to participation. This requirement arises from the ethical principle of respect for individual autonomy and is formally recognized in international human rights law [1,2].

Informed consent has been an axiom of clinical research and practice since the end of the Second World War II. In 1947, the military tribunal that sentenced the Nazi doctors who conducted brutal experiments in concentration camps developed a set of ten ethical principles for medical research, which is known since then as the "Nuremberg Code". In its first principle, the Nuremberg Code provides that

- "The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision".

Since then, it has been widely accepted that obtaining research participants' consent encompasses criteria of disclosure, comprehension, voluntariness, and competence [3]. However, because of its association with Nazi war crimes, the Nuremberg Code had relatively little effect on the practice of medical research. In 1964, the World Medical Association (WMA) decided to develop a new set of ethical principles more directly focused on clinical research than the Nuremberg Code. The outcome of those efforts is the Declaration of Helsinki (DoH), which has been revised seven times since its adoption in 1964, most recently in 2013 [4].

An entire section of the DoH (Paragraphs 25 to 32) is devoted to informed consent, which clearly is one of the key components of the document. According to Paragraph 26, potential subjects must be adequately informed of the "aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study". In addition, potential subjects must be informed of their "right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal".

The Council for International Organizations of Medical Sciences (CIOMS), which is a non-governmental body associated with the World Health Organization (WHO), is another important organization in this field. Since 1982, it has been involved in the development of international guidelines for medical research. In 2016, CIOMS replaced previous guidelines with the "International Ethical Guidelines for Health-related Research Involving Humans" [5]. This document includes 25 Guidelines on various aspects of biomedical research. Informed consent is specifically addressed in Guidelines 9 and 10.

Another international body involved in this area is the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), which brings together regulatory authorities and representatives of the pharmaceutical industry and developed the Guideline for Good Clinical Practice (GCP) in 1996. This guideline aims to ensure ethical and scientific quality in designing, recording, and reporting trials that involve human subjects, and that trial data are credible and reliable, regardless of where in the world the trials have been conducted. In 2016, the GCP was updated by means of an addendum that provides additional guidance [6]. The informed consent requirement of is addressed in Paragraph 4.8 among the researcher's responsibilities.

In parallel with the international organizations mentioned above, several countries and regional organizations have adopted regulations on biomedical research over the past few decades. This paper examines three of them: The Swiss Human Research Act (HRA) (2011); The US Code of Federal Regulations (CFR) (Title 21, Section 50, and Title 45, Section 46); and the Council of Europe's Convention on Human Rights and Biomedicine (CHRB) (1997), also known as "Oviedo Convention". The inclusion of the Swiss Human Research Act in the present analysis can be explained by the circumstance that the study was conducted in Switzerland.

This study aims to compare the above-mentioned international, regional, and national regulations with the Kingdom of Saudi Arabia (KSA) Law of Ethics of Research on Living Creatures (2010) (hereafter, "The Law") with regard to the requirements for informed consent for medical research. It must be noted that The Law was established to monitor studies involving genetic material, human parts, and living creatures without contravening Islamic laws. A supplemental document, called "Implementing Regulations of the Law of Ethics of Research on Living Creatures" (hereafter, the Implementing Regulations), was later approved in 2011. The two are used concurrently to protect research subjects from unethical conduct. Besides, the KSA has a National Committee of Bioethics (NCBE) that focuses specifically on the involvement of human subjects in clinical trials [7]. Ultimately, the goal of this study is to consider whether the Saudi guidelines provide sufficient protection for the rights of research subjects regarding the informed consent requirement.

To our knowledge, this is the first study to systematically compare the requirements for informed consent in Saudi Arabia and international and national regulations. In 2017, a study by the bioethicist Ghiath Alahmad analyzed 10 guidelines on medical research, including the ICH-GCP, CIOMS, and DoH's, as well as the guidelines from eight Arabic counties, including Saudi Arabia. However, it was not focused on the specific elements of informed consent [8]. Another comparative study by Alahmad et al. concluded, in general, that the requirement of informed consent is the only item mentioned in all the compared guidelines [9].

It must also be mentioned that, in order to ensure a truly informed consent, it is vital to facilitate content comprehension by participants. This explains the need for simplified versions of informed consent documents. In some settings, such as in developing countries with low levels of literacy, researchers may be particularly required to explain the content of the IC form to participants. However, the importance of such an explanation is critical for all participants around the world, regardless of their educational achievements. Interestingly, a study has shown that there is no direct correlation between the educational achievements of research participants and their comprehension abilities regarding the planned research [10]. In any case, guidelines for medical research have always had the difficult task of adapting basic ethical concepts to varied cultural and social contexts and promoting education in research ethics. Obviously, ethical research violations may occur in spite of policy statements and guidelines on clinical trials [11].

METHODOLOGY

In this study, the content analysis focused on five major components of IC:

1. Disclosure
2. Comprehension
3. Voluntariness
4. Competence
5. Consent

The international standards selected for the analysis were the DoH, CIOMS, and ICH-GCP [4-6]. The CHRB, the CFR, and the HRA were chosen as the legal standards regulating human participant research in developed countries, while the Implementing Regulations are the national guidelines used in Saudi Arabia [7, 12-14]. Table 1 shows which issuing bodies in which countries provide guidelines.

As a first step, we identified the provisions dealing with IC in the DoH, CIOMS, ICH-GCP, CHRB, CFR, HRA, and the Saudi Implementing Regulations [4-7, 12-14]. Each standard was identified through a direct online search using their respective titles and initials. The search websites (PubMed, and Google Scholar) with detailed information about a standard were used for further analysis. Governmental websites, bioethics sites, and other reputable sources were preferred for the identification of the right content.

The next stage was to compare these seven guidelines and critically analyze the similarities and differences between them regarding the above-mentioned five components. The analysis focused on a particular theme in one guideline and crosschecked its presence or absence in the other guidelines. After completing one document, the same process was repeated with the other regulations. Therefore, there was no specific standard used as a baseline or a reference point for the comparison analysis. This ensured that all common and unique themes across all the guidelines were equally analyzed. The critical analysis and evaluation of the highlighted components were comprehensively displayed in a Table 2. The comparison (Table 2), was filled out by two researchers (MM and MF). The meaning of "not explicitly" is used to indicate that a broad or common notion is referred to but not with the exact term. The Declaration of Helsinki, for example, says that participants "must be adequately informed of the methods" (Paragraph 26) [4]. However, the term "methods" is too broad and would need more explanation. If during the analysis the two researchers extracting the data disagreed on a particular term, the original text was reviewed again, and the dispute was resolved through discussion Table 2.

Table 1: Selected issuing bodies and their guidelines.

Country/ International	Issuing year	Last update year	Guideline(s)	Issuing body
International	1964	2013	Declaration of Helsinki (DoH)	World Medical Association (WMA)
International	1982	2016	International Ethical Guidelines for Biomedical Research Involving Human Subjects	Council for International Organizations of Medical Sciences (CIOMS)
International	1995	2016	International Conference of Harmonization Guidelines for Good Clinical Practice (ICH–GCP)	International Conference on Harmonization (ICH)
International/ Council of Europe	1997	2005	Convention on Human Rights and Biomedicine (CHRB), Council of Europe	Council of Europe
United States	2006	2023	Code of Federal Regulations (CFR)	Federal Agencies
Switzerland	2011	2014	Human Research Act (HRA)	The Federal Assembly of the Swiss Confederation
Kingdom of Saudi Arabia	2011	2022	Implementing Regulations of the Law of Ethics of Research on Living Creatures.	National Committee of Bioethics (NCBE)

Table 2: Comparison of informed consent elements from different ethical guidelines.

IC Components	Informed consent elements	DoH	CIOMS	GCP	CHRB	CFR	HRA	The Implementing Regulations
Disclosure to participants	The fact that this is scientific research	+	+	+	+	+	+	+
	Aims of the study	+	+	+	+	+	+	+
	Possible benefits and risks of the study intervention	+	+	+	+	+	+	+
	Trial–related injury treatment and/or compensation	+	+	+	+	+	+	+
	Right of the participant to withdraw the consent at any time without receiving any drawbacks	+	+	+	+	+	+	+
	Record confidentiality for identifying information	+	+	+	+	+	+	+
	Research participation invitation	–	+	–	+	+	–	+
	Research title	–	+	–	–	–	–	+
	Methods of the study, e.g., randomization	–	+	+	–	–	–	–
	Duties and functions of the participants connected to the study, including follow–up appointments	+	+	+	–	–	–	+
	Possible discomfort or burden	+	+	+	+	+	+	–
	Alternative interventions that are available outside the research and their benefits and risks	–	+	+	–	+	–	+
	Different interventions of the study arms	–	+	+	–	–	–	–
	Trial participation payment as prorated (if any)	–	+	+	–	–	–	–
	The chance to receive a placebo intervention or no intervention	–	–	–	–	–	–	–
	Blinding of the participant or the physician	–	+	–	–	–	–	–
	Ethics committee approval	–	+	–	–	–	–	–
	The existence of another study group that may receive a seemingly more attractive intervention in the case the participant was allocated to the control group	–	–	+	–	–	–	–
	The fact that a new treatment can cause unwanted effects that one cannot reliably predict, and which can harm the participant	–	–	–	–	+	–	–
	Sources of funding for the study	+	+	–	+	–	–	–
	Potential conflicts of interest	+	+	–	–	–	–	–
	Researchers' institutional affiliations	+	+	–	–	–	–	–
	The name of the institution approving the research	–	–	–	–	–	–	+
	The contact person(s) for further information	–	–	+	–	+	–	+
	Informing participants of new findings that might affect their willingness to participate in the research	–	+	+	+	+	–	+
	Receiving the results of the study	+	+	–	+	+	+	–
	Termination of participation without the subject's consent for foreseeable reasons and/ or circumstances	–	+	+	–	+	–	–
	The approximate number of subjects involved in the trial	–	–	+	–	+	–	–
	The trial participation duration	–	+	+	+	+	+	+
	The need for further details in the case of genetic research and the possible future use of biological materials collected during the research	+	+	–	+	–	+	–
Comprehension	The information should be given in a language and at a level of understanding appropriate to the research subject (The informed consent document should be simplified as much as possible)	+	+	+	–	–	–	+
	Comprehension verification through questions and clarifications	+	+	–	–	–	–	+

Voluntariness	Voluntariness of the participation/right of the participant to refuse participation	+	+	+	+	+	–	+
	The physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress	+	+	+	–	–	–	+
Competence	Potential research subjects who are incapable of giving informed consent (incompetent/vulnerable subjects and minors): the physician must seek informed consent from the legally authorized representative	+	+	+	+	–	+	+
Formal requirements of consent	The informed consent in written format	+	+	+	+	+	+	+
	Signature of the human subject	–	+	+	–	+	–	+
	Before a decision on consent is made by the persons concerned, they must be allowed an appropriate period for reflection	–	+	+	–	–	+	+
	Reassurance by the physician that the participant understood the information	+	+	–	–	–	+	+
	Providing a copy of the IC forms and explanations about the study	–	–	+	–	+	–	+
	Date and place of the "Informed Consent"	–	–	–	–	–	–	+
	The study is conducted by experts according to ethics guidelines	–	–	–	–	–	+	–
	The principal investigator obtains the consent or assigns a delegate	+	+	+	–	–	–	+
	Consent renewal when needed	–	+	+	+	–	–	–
Total items	44	21	35	28	17	20	15	26

RESULTS

The similarities and differences observed in the seven guidelines with regard to the five selected components of informed consent were highlighted in Table 2. Each guideline contains at least 15 or more items of the 44 viewed items to be disclosed to potential participants in research studies when their IC is obtained. The CIOMS guidelines have the highest number of items relating to IC 35, followed by ICH-GCP 28 and then the Implementing Regulations 26 elements. The DoH, CFR, CHRB, and HRA come at the end of the list with only 21, 20, 17, and 15 elements of IC, respectively.

Disclosure to participants

All seven guidelines concur on information disclosure. The essential content to inform the participants includes the fact that this is a scientific study (research), the aims of the research, the risks and benefits, trial-related injury compensations and/or treatment, freedom to withdraw from the research without victimization, and confidentiality of participant identification information.

An invitation to participate in research is mentioned in CIOMS (Guideline 9), CHRB (Article 13), the CFR (Sec. 50.25), and the Implementing Regulations (Article 11.2) but not in the DoH, ICH-GCP, or HRA. Only CIOMS and the Implementing Regulations (Article 11.2) mention the title of the research study. While the study methods, e.g., randomization, are mentioned in CIOMS (Guideline 9) and ICH-GCP (Paragraph 4.8.10), they are not included in the DoH, the CHRB, the CFR, the HRA, or the Implementing Regulations. The duties and functions of the participants connected to the study, including follow-up appointments, are referred to in the DoH (Paragraph 26), CIOMS (Guideline 9), ICH-GCP (Paragraph 4.8.10), and the Implementing Regulations (Article 11.2) but not in the CHRB, the CFR, or the HRA.

Except for the Implementing Regulations, all ethical guidelines mention potential discomfort or burdens. Alternative interventions beyond the research and their potential risks and benefits are referred to in CIOMS (Guidelines 4 and 9) and ICH-GCP (Paragraph 4.8.10), the CFR (Sec. 50.25), and the Implementing Regulations (Article 11.2) but not in the DoH, the CHRB, or HRA. Researchers' institutional affiliations and potential conflicts of interest are mentioned only in the DoH (Paragraph 26) and CIOMS (Guideline 9). CIOMS (Guidelines 13 and 5) and ICH-GCP (Paragraph 4.8.10) mention participants' payment (if any) and the use of different interventions. The chance to receive a placebo intervention or no intervention is not included in any of the seven guidelines. There are two IC elements (the blinding of the participant or the physician, and the requirement of an ethics committee approval) that are mentioned only in the CIOMS guidelines (Guideline 6 and Guideline 23). Only the ICH-GCP guidelines (Paragraph 4.8.10) mentions the existence of another study group that may receive a seemingly more appealing intervention if the research allocated a participant to the control group. The CFR guidelines (Sec. 50.25) is the only stating that a new treatment can cause unwanted effects that one cannot reliably predict and that these can harm the participant.

The source of funding for the study is mentioned in the DoH (Paragraph 26), the CIOMS guidelines (Guidelines 9 and 25), and the CHRB (Article 13), but not in ICH-GCP, the CFR, the HRA, or the Implementing Regulations. While the name of the institution approving the research (that is, the IRB) is only included in the Implementing Regulations (Article 11.2), the emphasis on the contact person(s) can be found in the ICH-GCP (Paragraph

4.8.10), the CFR (Sec. 50.25), and the Implementing Regulations (Article 11.2).

The provision on informing the participants of findings that might affect their willingness to participate in the research is mentioned in the CIOMS guidelines (Guideline 9), the ICH-GCP (Paragraph 4.8.10), the CHRB (Article 24), the CFR (Sec. 50.25), and the Implementing Regulations (Article 11.2), but not in the DoH or the HRA. Receiving study results is mentioned in the DoH (Paragraph 26), CIOMS (Guideline 9), CHRB (Article 13), CFR (Sec. 50.25), and HRA (Art. 8), but not in the ICH-GCP and in the Implementing Regulations.

The possible termination of participation without the subject's consent due to foreseeable reasons and/or circumstances is only included in CIOMS guidelines (Guideline 4), ICH-GCP (Paragraph 4.8.10), and the CFR (Sec. 50.25). Two of the seven guidelines (ICH-GCP, Paragraph 4.8.10, and CFR, Sec. 50.25) require disclosure of the approximate number of participants. All six guidelines, except the DoH, mention the expected research duration. The DoH (Paragraph 32), the CIOMS (Guideline 11), the CHRB (Article 13), and the HRA (Art. 32) discuss the need for further details in the case of genetic research and the possible future use of biological materials collected during the research (see Additional file 1).

Comprehension

The DoH (Paragraph 26), CIOMS (Guideline 9), the ICH-GCP (Paragraph 4.8.6), and the Implementing Regulations (Article 12.1) agree that the ICD should be simplified as much as possible, and the information should be designed in an easily understandable language for all subjects. However, this requirement is absent from the CHRB, the CFR, and the HRA. The verification of information comprehension through questions and clarifications is only stated in the DoH (Paragraph 26), CIOMS (Guideline 9), and the Implementing Regulations (Article 12.1), (see Additional file 1).

Voluntariness

With the only exception of the HRA, all other guidelines refer explicitly to the need to indicate voluntariness as part of IC, which is understood as a voluntary participation or the right of the participant to refuse participation. Taking preventive measures for dependent relationships and consent under duress are only listed in DoH (Paragraph 27), CIOMS (Guideline 9), ICH-GCP (Paragraph 1.61), and the Implementing Regulations (Article 12.1), (see Additional file 1).

Competence

All guidelines, with the exception of the CFR, require the physician to consult a legally authorized person when participants are unable to give informed consent (incompetent or vulnerable subjects and minors), (see Additional file 1).

Consent (Formal requirements of informed consent)

The seven guidelines recommend that the documentation of IC be made in written form. While the signature of the human subject is mentioned by CIOMS guidelines (Guideline 9), the ICH-GCP (Paragraph 4.8.11), the CFR (Sec. 50.27), and the Implementing Regulations (Article 11.2), it is not mentioned by the DoH, the CHRB, and the HRA. Some ICs allow a reflection period for the subjects before they sign the consent. Although this is included in the CIOMS guidelines (Guidelines 9 and 25), the ICH-GCP (Paragraph 4.8.7), the HRA (Article 16), and the Implementing Regulations (Article 12.1), it is not mentioned by the DoH, the CHRB, or the CFR. The requirement that consent should only be sought after the physician has ensured that the participant understands the information is mentioned by the DoH (Paragraph 26), CIOMS (Guideline 9), HRA (Article 7), and the Implementing Regulations (Article 12.1). This is not mentioned in the ICH-GCP, the CHRB, or the CFR.

Providing a copy of the IC form and explaining the study to subjects are required by the ICH-GCP (Paragraph 4.8.11), the CFR (Sec. 50.27), and the Implementing Regulations (Article 13.4), but they are not mentioned in the remaining four guidelines. The date and place of the IC are specified in the Implementing Regulations (Article 11.2). Conducting a study by experts according to ethical guidelines is mentioned only in the HRA (Article 10). Obtaining "informed consent" shall be done by the principal investigator or their delegated assistant, as specified in the DoH (Article 26), CIOMS (Guideline 9), ICH-GCP (Paragraphs 4.1.5 and 4.8.5), and the Implementing Regulations (Article 13.3). However, this is not included in the CHRB, the CFR, or the HRA. Consent renewal was only mentioned in CIOMS (Guideline 9), ICH-GCP (Paragraph 4.8.2), and the CHRB guidelines (Article 24), (see Additional file 1).

DISCUSSION

The analysis of various IC standards shows significant variation in most parameters regarding the five facets under consideration: disclosure, comprehension, voluntariness, competence, and consent. However, it is also evident that there are several similarities between the KSA and international standards.

Areas of consensus

The disclosure facet highlights several similarities between the KSA and the international standards. Disclosure is the first factor to consider while analyzing IC standards. This element has the highest number of parameters, which allows researchers to obtain full disclosure [15]. The Implementing Regulations and the international standards agree on the basic information about participants. Therefore, researchers using either standard have the mandate to maintain high confidentiality levels for entrusted information and should also develop strategies to respect the confidentiality promise given in ICs [16]. Although not in all international standards, the analysis noted important areas of consensus in the invitation to participate, the presentation of the research title (only in the Implementing Regulations and CIOMS), and the institution approving the research. These parameters are essential in research. For instance, Nesom et al. explained that most standards require approval by Institutional Review Boards. The researchers also noted that IRBs use standardized variables and therefore there are no major variations across institutions [17]. The regulations ensure that the research adheres to institutional guidelines and does not violate the affiliate's domestic or international standards.

The analysis also highlights several similarities between the international and KSA ethical laws on the comprehension component. International standards such as CIOMS, ICH-GCP, and the DoH acknowledge the need for ICD simplification, which is also evident in the Implementing Regulations. The Implementing Regulations and most international standards also allow the participants to seek clarification and question the IC for more clarity. The use of clear and non-technical language in

the IC form is essential to facilitate participants' understanding, especially when participants have low educational backgrounds. For such populations, researchers need to develop and use better communication strategies to improve their understanding of the clinical trial [18]. Seeking clarification depends on the participant's ability to understand the consent content. Lack of questioning or clarification from the participants often indicates a lack of understanding. Lack of understanding and inability to seek clarity may pose a great risk, especially for high-risk studies. Current studies have shown that only 50% of participants have a good understanding of the planned research, including blinding, voluntary participation, and freedom to withdraw from a study [19]. Therefore, it is vital to ensure that the IC form is written in a language understandable by a layperson.

Voluntariness and competence are other essential components of IC. In this regard, several similarities can be found between the international and KSA ethical standards. Indeed, all the international standards and the Implementing Regulations express the need to promote voluntariness. The concept of voluntariness also includes the freedom to refuse to participate in research. Also, the KSA research ethics and several international standards concur on the dependent relationship of consenting under duress. The concept of voluntariness aligns with the principle of autonomy in research. All researchers must ensure participant autonomy [20]. In some instances, researchers may require the input of incompetent participants, minors, and particularly vulnerable subjects. In such instances, the international standards and KSA ethical standards emphasize the need for the consent of the authorized legal representatives. The researchers should always be in contact with participants' representatives. The concept of legal representatives extends to vulnerable populations and illiterate participants [21]. In bioethics research where participants are pregnant women, researchers may need to seek approval from the fathers, who are considered legally competent parties in this case [22].

All the standards recommend that consent be in written format. In addition, the Implementing Regulations, and several international standards (CIOMS, ICH-GCP, and the Code of Federal Regulations) allow participants to confirm that they have understood the consent and are ready to participate in research. Both sets of standards (KSA and International) allow a reflection period and require the provision of a copy of the IC to participants. Bioethics standards consider written formats to be the most basic principle of IC [19]. This explains why most ethical standards concur with providing this format to all participants.

Areas of disagreement

The wide variability in the elements required by the guidelines is shown by two figures: Only 7 of the 44 elements considered are found in all the guidelines, and 19 of the 44 elements considered are found in three or less of the seven guidelines.

The two sets of ethical guidelines have several variations in many components of the IC. On disclosure, two international standards, CIOMS and ICH-GCP highlight the methods used in research, which are absent in the Implementing Regulations. Also, all the international laws mention the burden and discomfort of the research study, which is lacking in the Implementing Regulations. The Implementing Regulations do not mention conflicts of interest in a study, in contrast to the DoH and CIOMS ICs. In addition, international standards, such as CIOMS, require approval by the ethics committee, while several international standards include the source of funding and termination of participation by the researchers. The KSA standards do not include these components in their IC. Some of the highlighted factors can significantly affect the outcomes of a researcher. For instance, a conflict of interest from research funders (such as funding by drug companies or the government), might affect the research direction [23].

Furthermore, the study method enables participants to understand the course of the study and decide whether to participate or not. It is important to inform them before the start of a randomized placebo-controlled trial that they may receive a placebo. Participants have the right to receive all information about the study that is relevant to their decision to participate or not. This specifically includes knowing about the possibility of receiving a placebo instead of an active treatment. Potential participants may feel that a placebo cannot help them and prefer to choose another therapy that is more promising in their eyes, outside of the trial. Therefore, it should be mandatory in ethics guidelines to inform about the possible receipt of a placebo. There is also a debate among scientists as to whether exceptions to the strict requirement of individual patient consent are permissible or even necessary in certain circumstances in order not to falsify the study results [24,25].

Regarding the information about the expertise of researchers, the KSA ethical standards do not state that the IC form should mention that circumstance, in contrast with the HRA, which requires the IC to include such information. Nor do the KSA guidelines specify the need for consent renewal, as it is stipulated in the CIOMS standards. It must be mentioned that re-consenting is common in many studies and requires participants to sign informed consent forms in order to participate in the study again. However, it is important to note that re-consent is different from reaffirming a willingness to continue in a study after reconsidering various factors and the research progress [26].

Best methodological practice recommendation

The analysis reveals numerous similarities between the KSA and international standards. Not all international standards have similar components in their ICs. All the proposed standards are effective in guiding researchers about the information to be provided to participants. Most of these recommendations are based on studies on areas that might breach ethics in research such as a lack of detailed information about the risks resulting from study participation [27]. Another essential factor is the participants' understanding of IC and related ethics. This suggests that it is vital for principal investigators and other researchers to ensure that participants understand the research process and risks associated with various research procedures. In addition, studies on IC and medical research ethics have revealed variations in institutional guidelines, but with similar weaknesses [28]. The differences and weaknesses of institutional ethics mechanisms suggest a need to regulate institutional ethical review boards. The recommendation is also essential for the KSA standards.

Two very concrete items are particularly important for the protection of participants' rights: The first is the name of a contact person for further information. In times of service, which is provided by an artificial intelligence system, it is a special protection for study participants if they are given a contact person for further questions about the study. The second item is the handing out of a copy of the consent form to the study participant. Even though there are illiterate people who cannot read the provided information, the IC in written format should always be provided to participants

so that they can discuss it with others later or inform the primary care physician. The KSA guidelines included both items as well as CIOMS and CFR.

Areas of future research

The analysis of the IC concepts exposed several gaps that might need detailed research. One of the factors of interest was the variation of standards in different regions. For instance, the highlighted differences between ethics in KSA and federal standards in the USA. Researchers have shown that cultures could influence the differences in the guidelines [29]. Due to this, the researcher needs to assess the extent to which culture affects the formulation of the standards. The second factor needing detailed investigation is variation in understanding the IC guidelines. Researchers should focus on assessing whether participants might have varying comprehension abilities for different concepts, as highlighted in different standards. The research should also highlight which standards the participants comprehend best.

Strengths and limitations of the study

The strength of this paper lies in its comprehensive analysis and comparison of the informed consent guidelines both internationally and in Saudi Arabia. This paper provides a thorough examination of the quality of informed consent in Saudi Arabia and highlights the need for improvements. The study was unable to address several factors related to the topic. These include the applicability of the international standards in Saudi Arabia, factors influencing preferential use of the international standards in various regions, and the variation in participants' (doctors' and patients') perceptions of the informed consent standards. Additionally, the study did not completely analyze the whole content of the bioethics standards, which is a complex and broad topic requiring the input of multiple researchers. Future studies should also focus on these limitations.

Challenges

During the process of data extraction, we encountered several challenges. We faced a challenge of inconsistency in the terminology used by different guidelines, which caused disagreements between researchers about certain elements of informed consent. To resolve these disagreements, we held a meeting to discuss the issues and analyze the content thoroughly to make sure the data was accurate and consistent. Another challenge we encountered in our data extraction process was subjective judgment, as researchers may interpret the importance of certain provisions differently. To address this challenge, we provided clear criteria that reflect the foundational principles of informed consent, which were used for critical analysis. A single researcher handled data collection and initial analysis, which raised the possibility of bias and subjectivity on their part. Then preliminary data were presented to the full research team for peer review and reflection on potential researcher bias. Furthermore, a second researcher reviewed the analysis outputs to validate the findings. Finally, a full research team critically examines these biases and ensures they do not influence the data collection and analysis process. The authors addressed these challenges explicitly within the paper through the transparency and reliability of their methodology, to provide a clearer understanding of the above-mentioned study's limitations and strengths.

CONCLUSION

Ethical standards are important in medical research, as they aim to protect participants and minimize negative outcomes. This analysis has compared six different international, regional, and national standards with the informed consent guidelines in Saudi Arabia. The analysis has focused on the basic information requirements and variations in the five components of informed consent. From this analysis, it can be concluded that some essential concepts present in other standards are missing in the KSA regulations. Moreover, the research has noted that there are significant differences among the six standards, which may reflect cultural or contextual variations rather than deficiencies. Furthermore, these variations in regulations may also reflect the evolution of ethical considerations and the incorporation of new principles over time. It is important to consider that the participants' comprehension ability may vary depending on the variations in these standards, which could potentially affect their informed consent decisions. Therefore, it is essential for researchers and healthcare professionals to take these variations into account and make an effort to ensure that all participants have a clear understanding of the study and receive accurate and comprehensive information before making informed consent decisions, regardless of the standard used to obtain informed consent.

The study's main contributions lie in providing policymakers and healthcare providers with valuable insights into the ethical considerations surrounding informed consent in Saudi Arabia, helping them develop more effective guidelines that align with the country's cultural and legal context. Overall, upholding ethical standards in research studies in Saudi Arabia benefits not only the participants but also researchers, who can add valuable insights within the research ethics field. This can contribute to the advancement of knowledge and ethical practices in the field of ethics. Also, contribute to the development of guidelines and protocols that can be implemented in future medical research studies.

SUPPLEMENTARY INFORMATION

Additional file 1

Comparison of 44 informed consent elements from different ethical guidelines

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Consent for publication

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Not applicable

Authors' contribution

MM contributed to the study design, data collection, data analysis, and interpretation, and drafted the initial manuscript.

RA contributed to the legal aspects of the paper and reviewed the manuscript. MF was involved in the study design, data analysis, and interpretation and reviewed the manuscript. All authors read and approved the final manuscript.

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