Construction and validation of the "La Salle Instrument" to evaluate the ethical aspects in biomedical research on human beings

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Abstract

Introduction: *Research projects must demonstrate not only a rigorous scientific methodology, but also the ethical aspects that require profound reflection of the reviewers. Current regulations establish criteria for research projects on human health, but many of these aspects are subjective. How can the evaluation of such projects be standardized? This is the main subject of the current project.* **Materials and methods:** *This project comprises two phases. First, the design and construction of an instrument of evaluation based on the fundamental principles of bioethics, which are autonomy, beneficence, non-maleficence, and justice, and other aspects. The second phase consists of content validation through expert.* **Results:** *During the phase of reviewing the instrument, it was necessary to make changes by adding, removing, or changing the concepts or criteria, which lead to the construction of the second version of the format. This new instrument was reviewed and analyzed by using the AGREE II instrument, and this version was validated by experts by greater than 95%.* **Conclusions:** *There are some recommendations to analyze the ethical aspects in research protocols involving human subjects, but they define the concepts and criteria to be evaluated. By presenting the criteria to be evaluated individually, the "La Salle instrument" allows the evaluation to be more objective and standardized.*

KEY WORDS: *Ethics. Bioethics. Research. Research projects and instrument of measure.*

Introduction

Since late 19th century, mainly in hospitals, investigations are carried out in search for further information that impacts on knowledge. These investigations use individuals themselves as the research subject, primarily the most helpless and susceptible individuals, which is a situation that has contributed to consider new ethical problems that require profound reflection, not only by health professionals, but also by the entire society. The term "bioethics" is attributed to the German theologian, philosopher and educator Fritz Jahr, who in his 1927 article *Life sciences and the teaching of Ethics* defined it as the ethics of the relationships of humans with animals and nature. In 1970, Dr. Potter, a medical oncologist of the University of Wisconsin, in his work *Bioethics: the science of survival, perspectives in Biology and Medicine*[1], coined the word bioethics pointing at the danger survival of the entire ecosystem was in due to the rupture between two fields of knowledge, namely, scientific knowledge and humanistic knowledge.

The development of research and its ethical implications precedes bioethics. Events occurred in the 20th century and deriving from investigations conducted on human beings, especially on helpless groups, have given rise to bioethics.

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The atrocities perpetrated in Nazi concentration camps, as well as the outrageous investigations carried out in Europe and in the United States of America have definitely influenced on the doctor-patient relationship. Some examples are[2]:

- In 1920, an ethical problem was posed with mentally challenged individuals' sterilization in the United States for eugenesic purposes.
- In 1940, psychiatric patients' consent for psycho-surgical procedures was discussed, given the psycho-physical impairments that were produced.
- In World War II, scientists conducted experiments on freezing, where they used prisoners to find an effective treatment against hypothermia. They also used prisoners to test several methods for sea water purification. In the German concentration camps of Sachsenhausen, Dachau, Natzweiler, Buchenwald and Neuengamme, scientist tested immunization compounds and sera for the prevention and treatment of contagious diseases, including malaria, typhus, tuberculosis, typhoid fever, yellow fever and infectious hepatitis. In the Ravensbrueck camp, experiments were made with bone grafts and experiments to test the newly-developed sulfa drugs (sulfanilamide). In Natzweiler and Sachsenhausen, prisoners were exposed to phosgene and mustard gas in order to be able to test possible antidotes. The most infamous were the experiments of Josef Mengele in Auschwitz. Mengele carried out medical experiments with twins. He also conducted serologic experiments with Romani people (Gypsies), as Werner Fischer also did in Sachsenhausen, in order to establish how different "races" endured different contagious diseases. The research by August Hirt at the University of Strasbourg also attempted to establish "Jewish racial inferiority". Other studies that attempted to broaden racial objectives included a series of sterilization experiments carried out mainly in Auschwitz and Ravensbrueck. There, scientists tested several methods in an effort to develop an efficient and inexpensive method for total sterilization of Jews, Romani people and other groups regarded as racially or genetically undesirable.
- In 1963, experiments with tumor cells inoculation to elderly patients were discovered at Brooklyn Hospital.
- In 1969-1971, hepatitis viruses were inoculated to disabled children.
- Between 1932 and 1972, the Tuskegee experiment was carried out in Alabama by the Public Health Department of the United States. Back then, 600 African American farmers, mostly illiterate, were studied to observe the natural progression of syphilis is left untreated.

  From the above, the need to establish rules and regulate research involving human beings arose[2,3].
- In 1946, as a result of investigations carried out in World War II, the Nuremberg Code, which establishes the need for voluntary consent of subjects under investigation to undergo any kind of medical intervention, was formulated.
- In 1950 started the creation of committees in the United Stated to supervise clinical trials with drugs in patients.
- In 1962, Sir Austin Bradford Hill promoted the control of clinical trials with drugs in human beings by establishing the concepts of safety and efficacy.
- In 1964, the World Medical Association, through the Declaration of Helsinki, establishes the regulations for experiments in human beings. This declaration was later revised in Tokyo (1979), Venice (1983) and Hong Kong (1989).
- In 1978, the Department of Health, Education and Wellbeing of the United States, elaborated the Belmont Report, with the title *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*.
- In the decade of the 80's, the creation of research and research ethics committees was reinforced in different hospitals of the world.

In 1992, following an initiative of illustrious Mexican neurologist and neurosurgeon Dr. Manuel Velasco Suárez, Dr. Jesús Kumate Rodríguez started the creation of CONBIOETICA, which is currently a Ministry of Health-partially independent body with technical and operative autonomy and is a national and international bioethics model. CONBIOETICA promotes communication, dialogue and reflection between different social stakeholders, in order to analyze and discuss ethical, legal and social problems that translate into bioethical dilemmas that concern us as society[4].

As of 2002, CONBIOETICA focused on consolidating its administrative work towards the country's interior and contributed to the creation of the *Code of bioethics for health personnel*, in addition to strengthening the idea that each state should have a State Bioethics Commission.

The above events gave rise to the national and international set of rules that regulates ethical aspects in the conduction of research in human beings; the most relevant include the Nuremberg Code, the Declaration of Helsinki with its Tokyo, Venice and Hong Kong revisions, the Belmont Report, the Good Clinical Practice Guidelines, International Ethical Guidelines for Biomedical Research Involving Human Subjects, the UNESCO Universal Declaration on Bioethics and Human Rights, and the General Statute of Health Regulation in Matters of Research for Health, NOM-012-SSA3-2012, which establish the criteria for the execution of health research projects in human subjects, among other regulations and guidelines.

But, which are the ethical issues that stakeholders related to research in human beings have to observe? In the United States, mainly as a result of the history of the Tuskegee experiment, the National Research Act, which became a law on July 12, 1974 (Public Law 93-348), was created, giving rise to the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the purposes of the Commission was to determine the basic ethical principles that should govern biomedical and behavioral research involving human subjects, as well as to develop guidelines to guarantee that such research is carried out according to those principles. To achieve this, the Commission was asked to consider: 1) the distinction between biomedical and behavioral research and common and accepted medical practice; 2) the role played by risk-benefit assessment criteria to determine if the research including human subjects is appropriate; 3) adequate guidelines for the selection of human subjects that are to participate in the research; and 4) the nature and definition of a conscious consent in different investigational situations.

Thus was the Belmont Report born, which is named after the Belmont Conference Center, where the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research gathered to outline the first report[2,5,6]. This report explains the basic ethical principles for the use of human subjects in research, namely:

- Respect for persons: by protecting their autonomy; i.e., the capability they have to completely freely decide whether they want to participate or not in the study once all the risks, benefits and potential complications have been explained. This principle also implies the protection of subjects with higher risks, such as pregnant women or susceptible groups with limited autonomy, such as inmates, minors, mental patients or people with any type of impairment. Part of this principle entails obtaining an informed consent in every research, where the subject freely accepts in writing to participate in an investigation after a thorough explanation of it, and with all the right to withdraw from the study whenever the subject desires.
- Beneficence: this principle implies that increasing potential benefits to the maximum and decreasing the risks for subjects should be always be sought.
- Justice: the risks and benefits of a research study should be equally distributed between study subjects. Under every circumstance, the study of risky procedures exclusively in vulnerable populations for reasons of race, gender, mental health status, etc. should be avoided. The book by Dr. Tom L. Beauchamp, who participated in the Belmont Report, and Dr. James F. Childress, titled *Principles of biomedical ethics*[6], is the most influencing text of the North American bioethical movement, and is considered both in American and European bioethics circles as a reference text in the study of bioethics. In this text, these principles are reinforced by adding non-maleficence.
- Non-maleficence: trying not to harm the patient, which morally mandates investigators to seek the least possible risks for experimentation subjects.

After this initial proposal, other principles have been added up, which research ethics committees have to take into account when assessing research projects where the human being is the subject thereof, which include researchers' moral and academic authority, all aspects an informed consent should contain, research subjects' vulnerability context and relevance of the project in budget assignment, among many others[7,8].

There are several methods for research protocol assessment, which are criteria that are recommended to be assessed[9-12]; in our opinion, Gracia's methodology is the most thorough[2]. In some research ethics committees, project methodology and design are given more weight, and there are only few questions or aspects assessed from the ethical point of view. In addition, many of these aspects are subjective and difficult to evaluate, which makes it necessary for this process to be facilitated. How to achieve standardization in the evaluation of such projects? This is the purpose of the present work.

Methods

Design and construction of the evaluation instrument

To carry out this phase, members of the Research Unit of the La Salle University Mexican Faculty of Medicine had working meetings in order to integrate research projects' assessment criteria that encompassed the fundamental aspects from the ethical point of view. Once the instrument or matrix was designed, it was presented to the Local Research Ethics Committee members for assessment and consideration of changes, with the second version of it being generated.

The fundamental criteria that arose in the Belmont Report, where the bioethical principles of beneficence, autonomy and justice were first mentioned and that, together with the non-maleficence principle, became bioethics mainstays, were selected.

The proposed evaluation instrument (Table 1) consists of 5 categories:

1) General aspects.
2) Principle of autonomy (recognizing the capacity of freedom of choice, informed consent).
3) Principles of beneficence and non-maleficence (obligation to maximize benefits and minimize risks).
4) Principle of justice (impartiality and equity in selection, resources and benefits).
5) Other.

For each one of the categories, items or additions corresponding to each are proposed.

Validation of contents by means of an expert meeting

For validation of the *Evaluation guideline* content, the instrument was turned to 5 bioethics experts for its assessment according to the following aspects:

- Instrument presentation: it refers to the way it is exposed, to the appearance of the evaluation instrument.
- Clarity of content: it refers to the instrument being perfectly understandable.
- Relevance of each variable: it refers to the variable being a concrete proposal and being related to the things that are wanted to be assessed.
- Relevance of the variable: it refers to it being important and useful.
- Feasibility of application: it refers to the fact that the evaluation instrument is susceptible to be applied or concretized.

To answer each item, a Likert-type scale was used with 5 scoring categories, from 1 (total disagreement) to 5 (total agreement) (Table 2).

Table 1. "La Salle" form for biomedical research projects with human beings ethical aspects evaluation

Project title		
Responsible investigator	Name: (attach brief information on research training and experience)	Institution:
Associate investigators	Name: (attach brief information on research training and experience)	Institution:
Assessor name		**Date:**
Instructions: Dear assessor, please indicate with a mark according to your criterion		

Criteria	**Evaluation criterion**		**Observations**
	YES	**NO**	
I. General aspects			
1. Does the main investigator meet the requirements to be the author?			
2. Do the investigators have academic authority to be able to carry out the project?			
3. Is there adherence to national and international standards and regulations?			
4. Are the research dates established?			

(Continue)

Table 1. "La Salle" form for biomedical research projects with human beings ethical aspects evaluation (*Continued*)

Criteria	Evaluation criterion		Observations
	YES	NO	
5. If it is an original study, is the fact that there is higher possibility of error and risk taken into account?			
6. Where appropriate, is the use of placebo justified?			
7. Where appropriate, does it require an insurance policy? Is it adequate and valid?			
8. In pharmacological research, is Tx continuity at the conclusion of the project warranted?			
9. Is there any kind of funding? If so, is there a conflict of interest (s) statement?			
10. Where appropriate, is there a documented contract?			
II. Principle of autonomy (Recognizing the capacity of freedom of choice – Informed consent)			
1. Is self-determination respected? (see glossary)			
2. If the participant is legally incompetent, does he/she agree to a legal representative?			
3. Are conditions that generate vulnerability prevented?			
3. Is there an informed consent?			
3.1. Is it made evident that the explanation is made both verbally and written?			
3.2. Is it clearly mentioned what the project consists of?			
3.3 Is the language clear and simple?			
3.4. Is respect of confidentiality and privacy of provided data ensured?			
3.6. Are risks, benefits, advantages, disadvantages and the freedom of the patient to withdraw from the project anytime without prejudice to his/her care, human rights and wellbeing mentioned?			
3.7. Is it clearly stated that the patient has understood and signed it?			
3.8. In pharmacological research, is toxicology mentioned to the patient?			
3.9. In the case of subjects under legal age, is there informed consent granted by the parent or legal guardian? Is there approval of the minor?			
III. Principles of beneficence – non-maleficence (obligation to maximize benefits and minimize risks)			
1. Are benefits and risks identified?			
2. Are the means to be used to minimize risks and maximize benefits identified?			
3. Is it warranted that weighed risks are not greater than expected benefits?			
IV. Principle of justice (Impartiality and equity in selection, resources and benefits)			
1. Is there impartiality in participants' selection, resources and benefits?			
2. Is there equity in selection criteria, in resources and in benefits?			
V. Other			
1. The design methodology, is it rigorous?			
2. Are there precautions to supervise, assess and react in case of eventualities?			

(Continue)

Table 1. "La Salle" form for biomedical research projects with human beings ethical aspects evaluation (*Continued*)

Criteria	Evaluation criterion		Observations
	YES	NO	
3. If there is an incentive, is it fair and does not induce participation?			
4. Are the facilities where research is going to take place adequate and sufficient?			
5. Is the project feasible and pertinent?			
IF THEREIS ONE NEGATIVE ANSWER CONSIDER THE REJECTION OF THE RESEARCH PROJECT RULING: _____ Approved, Pending approval (requires modifications) or Rejected (warrants restructuration)			

For validity, the AGREE II* instrument was used, with a score of 80% being regarded as valid:

$$\text{Scale} = \frac{\text{Obtained score} - \text{Minimum possible}}{\text{Maximum possible} - \text{Minimum possible}} \times 100$$

Maximum possible = (5 is the maximum) x no. of criteria x no. of reviewers

Minimum possible = (1 is the minimum) x no. of criteria x no. of reviewers

This scale is for each one of the 32 items to be evaluated.

Results

The study was approved by the Research and Research Ethics Committee of the Mexican Faculty of Medicine of the La Salle University, which is recognized by CONBIOETICA (09 CEI 035 2013 05 16) and CONACyT (13 CEI 09 012 112).

An initial instrument that included the 4 fundamental principles of bioethics was designed and constructed, with other aspects related to research projects being added and included in other criteria, which yielded this assessment form with the following evaluation aspects: *I. General aspects*, where aspects of the group of investigators and context of the research project are taken into account; *II. Principle of autonomy*, the items of which explore things related to freedom of choice and, most strictly, aspects related to the informed consent; *III. Principle of beneficence and non-maleficence*, which assesses things related to risks and benefits of the intervention on the study subjects; *IV Principle of justice*, which evaluates things related to equity and impartiality in subject selection, resources and benefits; and *V. Other*, which explores and inquires about non-principialist aspects.

The instrument was reviewed by the members of the Research and Research Ethics Committee of the La Salle University Mexican School of Medicine, which is comprised by eight members, out of which five are physicians, one is a lawyer and two are bioethicists who, in work meetings, made suggestions for changes or additions, which were considered and incorporated to the instrument for its final version (Table 1).

To carry out the instrument's final version content validation, it was reviewed by five bioethics experts taking into account the above-mentioned criteria and their weighing according to the AGREE II instrument evaluation system, as described in detail in table 3. Of note, the evaluation instrument is accepted by more than 95% in all assessed criteria.

Discussion

Owing to the historical backgrounds already discussed in this work's introduction about the widely spread cruelty and excesses in research, especially in those assays that involved human beings as research subjects, there has been growing concern in taking into consideration the ethical aspects in scientific research.

As a result of different meetings of medical associations in the world, the ethical aspects that ought to be taken into account in biomedical investigations are concluded, with the fundamental principles of autonomy, beneficence-non-maleficence ratio and justice being the pillars to respect the human rights of the individual who participates as research subject. However, other aspects also fundamentally important have been

*The Appraisal of Guidelines for Research & Evaluation (AGREE)[19] instrument was developed to examine the issue of variability in guideline quality. To that end, the AGREE instrument is a tool that assesses the methodological rigor and transparency in which a guideline is developed. The AGREE instrument has been updated (AGREE II).The purpose of AGREE II is to offer a frame to assess the quality of guidelines, to provide a methodological strategy for the development of guidelines and to inform what information and how information ought to be presented in guidelines.

Table 2. Assessment: AGREE II instrument

For each criterion, please choose the answer that best characterizes it:					
	1. Total disagreement	**2. Disagreement**	**3. Indifferent**	**4. Agreement**	**5. Total agreement**
Instrument presentation	**1**	**2**	**3**	**4**	**5**
Regarding clarity of content					
I. General aspects					
1. Does the main investigator meet the requirements to be the author?	1	2	3	4	5
2. Do the investigators have academic authority to be able to carry out the project?	1	2	3	4	5
And so on with each item with regard to clarity of content, pertinence, relevance and application feasibility.					

Table 3. Results of the evaluation by experts according to the AGREE II instrument

Instrument presentation	**Score 75**	**Highest 75**	**Lowest 15**	**% 100**
With regard to clarity of content				
I. General aspects				
	Score 247	Highest 250	Lowest 50	% 98
II. Principle of autonomy (Recognizing the capacity of freedom of choice – Informed consent)				
	Score 72	Highest 75	Lowest 15	% 95
3. Is there informed consent?				
	Score 248	Highest 250	Lowest 50	% 99
III. Principles of beneficence-non-maleficence (Obligation to maximize benefits and minimize risks)				
	Score 75	Highest 75	Lowest 15	% 100
IV. Principle of justice (Impartiality and equity in selection, resources and benefits)				
	Score 50	Highest 50	Lowest 10	% 100
V. Other				
	Score 123	Highest 125	Lowest 25	% 98
With regard to pertinence of each criterion				
I. General Aspects				
	Score 249	Highest 250	Lowest 50	% 99
II. Principle of autonomy (Recognizing the capacity of freedom of choice – Informed consent)				
	Score 73	Highest 75	Lowest 15	% 96
3. Is there informed consent?				

(Continue)

Table 3. Results of the evaluation by experts according to the AGREE II instrument (Continued)

Instrument presentation	**Score 75**	**Highest 75**	**Lowest 15**	**% 100**
	Score 250	Highest 250	Lowest 50	% 100
III. Principles of beneficence-non-maleficence (Obligation to maximize benefits and minimize risks)				
	Score 75	Highest 75	Lowest 15	% 100
IV. Principle of justice (Impartiality and equity in selection, resources and benefits)				
	Score 49	Highest 50	Lowest 10	% 97
V. Other				
	Score 124	Highest 125	Lowest 25	% 99
With regard to relevance of content				
I. General Aspects				
	Score 248	Highest 250	Lowest 50	% 99
II. Principle of autonomy (Recognizing the capacity of freedom of choice – Informed consent)				
	Score 75	Highest 75	Lowest 15	% 100
3. Is there informed consent?				
	Score 250	**Highest 250**	**Lowest 50**	**% 100**
III. Principles of beneficence-non-maleficence (Obligation to maximize benefits and minimize risks)				
	Score 75	Highest 75	Lowest 15	% 100
IV. Principle of justice (Impartiality and equity in selection, resources and benefits)				
	Score 50	Highest 50	Lowest 10	% 100
V. Other				
	Score 124	Highest 125	Lowest 25	% 99
With regard to application feasibility				
I. General aspects				
	Score 250	Highest 250	Lowest 50	% 100
II. Principle of autonomy (Recognizing the capacity of freedom of choice – Informed consent)				
	Score 75	Highest 75	Lowest 15	% 100
3. Is there informed consent?				
	Score 250	Highest 250	Lowest 50	% 100

(Continue)

Table 3. Results of the evaluation by experts according to the AGREE II instrument (*Continued*)

Instrument presentation	**Score 75**	**Highest 75**	**Lowest 15**	**% 100**
III. Principles of beneficence-non-maleficence (Obligation to maximize benefits and minimize risks)				
	Score 75	Highest 75	Lowest 15	% 100
IV. Principle of justice (Impartiality and equity in selection, resources and benefits)				
	Score 50	Highest 50	Lowest 10	% 100
V. Other				
	Score 125	Highest 125	Lowest 25	% 100

added, such as those related to the investigator or group of investigators, to more detailed aspects about what should the informed consent contain and its written application and detailed explanation, among others. Controversies with regard to which scientific fields should be funded and which scientific problems should be prioritized are added up.

There are some recommendations for the analysis of ethical aspects in protocols of research in human subjects. Emanuel et al.[9] have proposed seven ethical requirements for clinical investigation:

1) Social or scientific value.
2) Scientific validity.
3) Equitable selection of research subjects.
4) Favorable risk/benefit ratio.
5) Independent evaluation.
6) Informed consent.
7) Respect for included subjects.

On the other hand, Diego Gracia[10], a Spanish expert and world authority in bioethics, recommends the following methodology:

I. On protocol scientific analysis:
   1) Trial objectives analysis.
   2) Design analysis.
   3) Assessment process analysis.
   4) Methodology analysis.
   5) Research team analysis.

II. On protocol ethical analysis:
   1) Informed consent analysis.
   2) Risk/benefit ratio analysis.
   3) Sample equitable selection analysis.

In our opinion, Gracia's methodology is the most comprehensive.

As we can see, the criteria and ethical aspects to be evaluated are well identified; however, the mo ment a research ethics committee has the project in its hands, it allows for the discussion to get lost in details.

The guideline we propose addresses the fundamental ethical aspects that have to be taken into account and that should exist in a biomedical research project, and assessment is made easier by answering "yes or no" and by suggesting non-acceptance if one of the criteria is missing.

The methodological aspects are assessed in a single line ("The methodology, is it rigorous?"), strongly considering ethical aspects, since the design and scientific method have already been assessed by the research committee.

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