



TECHNICAL NORM N° 57

REGULATION OF THE CLINICAL TRIAL PRACTICE ON PHARMACEUTICAL PRODUCTS INVOLVING HUMAN SUBJECTS

Prepared by: Ad-Hoc Working Group, Ministry of Health

Coordinated by: Department of People Programs

With the collaboration of: Regional Program on Bioethics for Latin America and The Caribbean , PAHO/WHO

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Ministry of Health
Dep. of Legal Consulting
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APPROVAL OF NEW TECHNICAL
NORM FOR THE REGULATION OF
CLINICAL TRIALS WHICH USE
PHARMACEUTICAL PRODUCTS IN
HUMAN SUBJECTS

EXENT N° 952

Santiago, 04th June of 2001

WHEREAS: the provisions of the article 102, second section of the Statutory Decree N° 725 of 1968 from the Ministry of Health, which approved the Health Code; the article 16, section c) of the Executive Decree N° 1876 of 1995 from the Ministry of Health, which approved the Regulations of the National System for the Control of Pharmaceutical Products, Food for Medical Use, and Cosmetics; the article 92 bis of the Executive Decree N° 42 of 1986, which approved the General Regulations of the Health Services; the Resolution N° 520 of 1996, of the Office of the Comptroller General of the Republic;

WHEREAS: as requested by the Division of People Health in its Memorandum N° 4C/467 on 14th May of 2001, and

WHEREAS: the faculties conferred me by the articles 4° and 6° of the Decree-Law N° 2763 of 1979, I issue the following

RESOLUTION:

1°. The text of the General Technical Norm N° 57 on the Regulation of Clinical Trials On Pharmaceutical Products in Human Subjects is approved.

2°. The norm approved in this action is contained in a document titled "Technical Norm: Regulation of Clinical Trials On Pharmaceutical Products in Human Subjects", text composed of 29 pages and 5 attachments, of which the original document, properly signed by the Undersecretary of Health, will be kept in custody in the Division of People Health, organization which will be responsible that all the copies issued are strictly exact to such original document.

3°. A copy of this norm is sent to all the premises of the Ministry of Health and the rest of organizations of the National System of Health Services which are forced to carry out such a norm.

REGISTER AND LET IT BE KNOWN



MICHELLE BACHELLET JERIA
MINISTER OF HEALTH

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FOREWORD

The Ministry of Health is very pleased to give the present norm to the professional institutions and investigators of health area. Such a norm is intended for the Regulation of the Clinical Trial Practice on Pharmaceutical Products in Human Subjects.

The satisfaction is mainly the result of the fulfillment of a responsibility which it is very difficult to meet due the few regulation existing in both, our country and the rest of Latin America, regarding to this field of unquestionable scientific and ethical significance.

The document presented below is the result of the investigation and thinking deployed by outstanding professionals of different areas who composed, from August of 1997 and as an answer to the requirement expressed by this Ministry, a work commission where they have given all their competence. It is worth to mention and thank for the important support received from the Regional Program on Bioethics for Latin America and The Caribbean, Panamerican Health Organization, and World Health Organization.

The issue has, undoubtedly, a very big complexity. Who should decide which experiments are ethical and safe? Which are the proper considerations, the valid criteria, and the suitable institutions to carry out such task? These and other questions put in evidence the necessity of the performed task in order to have explicit principles and a clear regulatory frame which guides the investigative praxis.

It has been considered the national and international experience, and assumed the big bioethical principles of autonomy, charity, and justice as articulating criteria, all of that in order to contribute with the yearned connection between scientific development and promotion of people rights.

This kind of norms only try to put in practice that great ethical conquest of our civilization which is the recognition of the person as the carrier of an inalienable dignity. Such dignity demands in all kind of fields, including that of the scientific research, to be estimated as a goal itself and never be treated only as a means which is part of a instrumental logic, despite of the value of the results pursued. Since it is an ethical conquest, and in order to state and ensure such dignity, is needed the active expression of our freedom and all the legal and institutional frames available.

Our times are complexes, characterized by phenomena and processes which cross each other, triggering effects whose diversity and rapidity demand to increase the extent of our lucidity and dialogue. The globalization, a decisive event of our time, also involves challenges. It means, for instance, the occurrence of favourable conditions for the communication and solidarity of the ethical and scientific impulses, but also involves the tendency to functional and impersonal practices, typical of an excessive and utilitarian pragmatism.

It is important to prevent and avoid any kind of economic, political, or instrumental opportunism, which may produce typical risks of colonial outlines already overcome, which

occurs now in a concealed way under a technical and scientific modulation. The regulatory frames in so sensitive areas like this should contribute to an exchange of culture and science among the countries of the world which is based on a strong and unnegotiable estimation of the human dignity as a value which must rule any aim and any means, any tactics and strategy.

This norm is opened to any possible improvement and is, finally, the result of a constant and inalienable wish to look for a deep unity between science and ethics. The Ministry of Health indicates its commitment in such improvement and invite to perform this task to all the groups and institutions related to people care and scientific research into the health field.

Dr. Michelle Bachelet Jeria
Minister of Health

Santiago, May of 2001

GENERAL BACKGROUND

Because the shortage of regulations and legislation on the subject, in August of 1997 the Minister of Health, Dr. Alex Figueroa Muñoz, called to a multiprofessional work group for preparing a proposal to that effect ⁽¹⁾, which finally gave way to the norm whose general contents are given below.

It has been taken into account the historical evolution experienced by the international regulations on research in humans, from the days after the Second World War (The Nuremberg Code) to the agreements recently achieved by the World Health Organization, the Council of Europe, and the World Medical Association.

The situation in Chile is very similar to that of the majority of the South America's countries, where exists a very minimal specific regulation, with only general references to the people's rights and intellectual property, both emanated from the Political Constitution. Regarding to the regulation, it is important to emphasize that it exclusively resides in the Director of the Instituto de Salud Pública (Public Health Institute), who would need the suitable and constant support, both technical and ethical support, allowing to give a basis for his(her) decisions about the approval or rejection to the importation of drugs and biological products intended to be used in humans for purposes of experimentation.

The Executive Decree N° 494 of 1999 from the Ministry of Health, creates an organization named *Scientific Ethics Evaluation Committee*, which will deal with the revision of the protocols of clinical trials. Because its composition and procedures of functioning, they are clearly different of the current Hospital Ethics Committees ⁽²⁾. The implementation of the norm transfers to the former the functions assigned to the latter respect to the clinical research.

The Ministry of Health will have a register with all the Committees which are working. If a Health Service does not have an active Committee, the director of such Service will define a Reference Committee. Finally, this norm establishes a procedure for the receipt, study and conclusions on the clinical trial projects submitted to the Committees, as well for the follow-up of the results from the investigation.

⁽¹⁾ Exent Resolution N° 2085 of 31th December 1997, from the Ministry of Health, where the Ad-Hoc Commission is composed.

⁽²⁾ Exent Resolution N° 134 of 11th February 1994 on the Ethics Committees of Health Services, and modified by exent resolution N° 1586 of 19th November 1999.

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REGULATION OF THE CLINICAL TRIALS PRACTICE USING PHARMACEUTICAL PRODUCTS IN HUMAN SUBJECTS

I. INTRODUCTION

The advancement of the biomedical science and technology, and its use in the medical practice is producing some of public concern since it confronts the society with new ethical problems. The concern is expressed respect to the necessity to enhance the development of the biomedical technology through a high level scientific research, and avoiding, at the same time, potential excesses derived from the methodology which is necessary to use for achieving valid results.

Indeed, the standard scientific method in the clinical research begins with the elaboration of hypothesis, which are further subjected to laboratory tests and experimental tests with animals. Finally, in order to the conclusions are clinically useful, the experiments should be performed in human subjects.

Therefore, such kind of research, even if it is designed very carefully, entails a risk for the people. “Such a risk is justified in human subjects because the participants will be favoured rather than for a personal benefit to the investigator or the research institution, and for its potential contribution to human knowledge, suffering relief, and life extension”.⁽³⁾

HISTORICAL ANTECEDENTS

In order to protect itself from potential excesses, the society has adopted different measures. The first International Code of Ethics for the research involving human subjects was the Nuremberg Code, as a reply to the atrocities committed by the medical investigators of the German Nazism and carried out by physicians. From that, it occurs the ethics of the research involving human subjects, oriented to prevent any repetition, by the doctors, of violations to the rights and wellness of people.

The Nuremberg Code, published in 1947, established the regulations to carry out experiments on human subjects, emphasizing particularly the voluntary consent of person. Completing such initiative, in 1964, the World Medical Association adopted the Declaration of Helsinki, whose more recent revision occurred in October 2000, where are established ethical guidelines for research involving human subjects.⁽⁴⁾

⁽³⁾ International Ethical Guidelines for Biomedical Research Involving Human Subjects, prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), Geneva, 1993.

⁽⁴⁾ World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects, adopted by the 18th World Medical Assembly (Helsinki, June 1964) and as revised by the 29th World Medical Assembly (Tokyo, October 1975), the 35th World Medical Assembly (Venice, October 1983), the 41st World Medical Assembly (Hong Kong, September 1989), and the 52th World Medical Assembly (Edinburgh, October 2000).

In 1966, the General Assembly of United Nations adopted the International Covenant on Civil and Political Rights, which came into force in 1976, and stipulate in its article 7 the following: “No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation.” It is through of this declaration that the society expresses the fundamental human value which should rule any research involving human subjects: protection of the rights and wellness of all human subjects who are subjected to scientific experimentation.⁽⁵⁾

In the International Covenant on Economic, Social, and Cultural Rights (article 15, number 3), also during 1966, is established: “the State undertakes to respect the freedom indispensable for scientific research and creative activity”. Thus, it is tried to preserve the scientific initiative, which may be restricted by all the agreements previously adopted.⁽⁶⁾

Regarding the special circumstances of the developing countries respect to the suitability of the Nuremberg Code and the Declaration of Helsinki, in the late of 1970s the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) carried out a new examination of this matter and published in 1982 the International Ethical Guidelines for Biomedical Research Involving Human Subjects. The purpose of such guidelines was to indicate “how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the Declaration of Helsinki, could be effectively applied, particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and executive and administrative arrangements”.⁽⁷⁾

It is also relevant to mention the Convention on Human Rights and Biomedicine, Council of Europe (Oviedo 1997), and the Universal Declaration on the Human Genome and Human Rights, UNESCO (Paris 1997).

SITUATION IN CHILE

In the Political Constitution of the Republic of Chile, the State recognizes the different rights of people related to this subject, as well the duty assigned to the State to protect such rights.⁽⁸⁾

⁽⁵⁾ International Covenant on Civil and Political Rights, adopted by the General Assembly of the United Nations, 1966.

⁽⁶⁾ International Covenant on Economic, Social, and Cultural Rights, adopted by the General Assembly of the United Nations, 1966.

⁽⁷⁾ International Ethical Guidelines for Biomedical Research Involving Human Subjects, prepared by the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO), Geneva 1993.

⁽⁸⁾ See in Attachment 2, N°1, Outstanding articles from the Political Constitution of the Republic of Chile, 1980.

According to the Health Code and the Regulations of the National System for the Control of Pharmaceutical Products, Food for Medical Use, and Cosmetics, approved by Executive Decree N° 1876 of 1995, Ministry of Health, the Director of the Instituto de Salud Pública is responsible to grant the provisional authorization for using pharmaceutical products in scientific research or clinical trials, without a previous registration, and with a founded resolution. However, it has not be established the procedure to be followed in order to give to such resolution the technical and ethical basis about the protection required by the people who will be used as volunteers in clinical trials. ⁽⁹⁾

Regarding to the existing regulations in the clinical field, the Executive Decree N° 42 of 1986, Ministry of Health, which approved the General Regulations of Health Services, and its amendment approved by Executive Decree N° 1935 of 24th November 1993, grants to the hospital's directors the faculty to authorize research projects in their institutions. Furthermore, it gives to the directors of Health Services and hospitals the faculty to designate Ethics Committes for supervising such investigations.

In the same way, according to the exent resolution N° 134 of 11th February 1994, Ministry of Health, which approved the General Technical Norm N° 2, the Medical Ethics Committees existing in the Health Services and their dependent institutions, will deal with the situations where are involved “decisions on diagnostic and therapeutic procedures which have a high cost or a controversial nature”, and also know in a periodical way “the research protocols submitted to its consideration”.

As time goes by, it was possible to include into the General Regulations of Health Services, the Scientific Ethical Evaluation Committees, which are responsible to declare its opinion on the investigations to be carried out involving subjects who are using pharmaceutical products. ⁽¹⁰⁾

In January of 2001, it was set up the National Council of Health Research, a permanent organization responsible to give advise to Minister of Health about the management of a national policy on health scientific research.

During the 2001, it is started the process of accreditation of the Scientific Ethical Evaluation Committees in the Health Services, in order to constitute a national network of committees entitled to evaluate and follow up of clinical trials. This process is coordinated by the Unit of Bioethics from the People Health Division, Ministry of Health, also including the Ethics Committees in hospitals which are responsible of clinical ethics issues.

The country should have, at medium term, a law which rules the investigation involving human subjects, and establishes the creation of a National Comission on Bioethics. ⁽¹¹⁾

⁽⁹⁾ See the Attachment 2, N° 2, references to the Chilean Health Code, Edition of 1996, and the Executive Decree N° 1876 of 1995.

⁽¹⁰⁾ See the Attachment 2, N° 3, the respective articles of the General Regulations of Health Services, approved by Executive Decree N° 42 of 1986, Ministry of Health, and its amendment approved by Executive Decree N° 494 of 19th July of 1999, where the Scientific Ethical Evaluation Committees are created.

⁽¹¹⁾ See Initiative from the Senate, Gazette 1993-11.

II. GENERAL ETHICAL PRINCIPLES

All research involving human subjects should be conducted in accordance with three basic ethical principles, namely *respect for persons (principle of autonomy)*, *beneficence (principle of beneficence and of nonmaleficence)*, and *justice*. It is generally agreed that these principles, which in the abstract have equal moral force, guide the conscientious preparation of proposals for scientific studies. In varying circumstances they may be expressed differently and given different moral weight, and their application may lead to different decisions or courses of action.

Respect for persons⁽¹²⁾ incorporates at least two fundamental ethical considerations, namely:

- a) respect for autonomy, which requires that those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination; and
- b) protection of persons with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse.

The controlled clinical trials involving human subjects should primarily respect the principle of autonomy of the human being through the application of the consent based on a wide and deep information on his(her) participation in the investigation, considering his(her) ability, and respecting the vulnerable groups.

Beneficence⁽¹³⁾ refers to the ethical obligation to maximize benefits and to minimize harms. This principle gives rise to norms requiring that the risks of research be reasonable in the light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to safeguard the welfare of the research subjects.

Beneficence further proscribes the deliberate infliction of harm on persons; this aspect of beneficence is sometimes expressed as a separate principle, nonmaleficence (do no harm).⁽¹⁴⁾

⁽¹²⁾ See Attachment 2, N° 4, Exent Resolution N° 134 of 13th February of 1994, Ministry of Health, which approved the General Technical Norm N° 2 ruling the constitution and functioning of the Ethics Committees in Hospitals and Health Services.

⁽¹³⁾ See Attachment 3, N° 1 for a more detailed description of the principle of autonomy.

⁽¹⁴⁾ See Attachment 3, N° 2 for a more detailed description of the principle of beneficence and nonmaleficence.

Justice ⁽¹⁵⁾ refers to the ethical obligation to treat each person in accordance with what is morally right and proper, to give each person what is due to him or her.

In the ethics of research involving human subjects the principle refers primarily to *distributive justice*, which requires the equitable distribution of both the burdens and the benefits of participation in research. Differences in distribution of burdens and benefits are justifiable only if they are based on morally relevant distinctions between persons; one such distinction is *vulnerability*.

Therefore, it is relevant the existence of equity and the distribution of resources which make efficient the experimentation in human subjects seeking benefits for people. Furthermore, it is not allowed any kind of arbitrary discrimination during the process of enrollment.

Among the four principles enunciated, beneficence, nonmaleficence, autonomy, and justice, in the ethics of research using human subjects are particularly relevant those of *nonmaleficence and autonomy*. The most important is the principle of nonmaleficence, “do no harm”, which is considered former to any other and its observance as absolutely obligatory for all people involved in an investigation.

There is other basic ethical principle, the principle of *prudence*. The clinical trials should be carried out based on updated scientific knowledge. The investigators should meet the requirements of experience and competence.

III. REQUISITES TO BE MET BY CLINICAL TRIALS ON PHARMACEUTICAL AGENTS INVOLVING HUMAN SUBJECTS. ⁽¹⁶⁾

1. REQUISITES FOR PHASE I CLINICAL TRIALS ⁽¹⁷⁾

- 1.1 *Informed Consent* from the person who will participate in the study. In order to obtain the consent, it will be necessary to follow the guideline indicated in the attachment 1, which does not exclude any other information the investigator considers relevant to give for a better understanding and voluntary collaboration of the person.
- 1.2 *Commitment* of the responsible investigator with the *ethical guidelines* indicated in the attachment 1.
- 1.3 *Appropriate insurance or guarantee* against those adverse effects directly derived from the investigation, such an insurance should meet the principle of proportionality, and may be subjected to an impartial arbitration, if any doubt occurs.
- 1.4 *Report on potential benefits* to the volunteer participants.

⁽¹²⁾ See Attachment 3, N° 3, other antecedents about the principle of justice.

⁽¹³⁾ The necessary requisites shown in this Norm are intended to phase I to IV clinical trials involving human subjects. Pre-clinical studies are not considered, since they are conducted in animals, even though the information obtained from such studies are very useful to support studies in human subjects.

⁽¹⁴⁾ Phase I Studies: they are studies on safety and pharmacokinetics, and are primarily conducted in healthy subjects. See a more detailed description in Attachment 4, N° 1.

- 1.5 *Protocol* including basic criteria which defines *healthy subject* or, in case of an exception, states clearly a *situation of compasive use*.
- 1.6 A detailed *Protocol of research*, including:
- i) Purpose of the study.
 - ii) Number of subjects to be studied.
 - iii) Inclusion and exclusion criteria.
 - iv) Design (blind, unblinded, etc.).
 - v) Duration
 - vi) Endpoints (e.g., pharmacokinetic analysis, clinical and biochemical safety parameters, etc.).
 - vii) Statistical analysis to be used.
- 1.7 *Previous study of toxicity* in animals, including carcinogenicity and teratogenicity.
- 1.8 *Investigational Drug Brochure*, including any information available about the product to be evaluated.
- 1.9 *Report on the number of patients* in who the product has been previously used, and the countries where such clinical trials have been conducted, indicating if one of them is the country of origen of the drug. It is also advisable to have information regarding to the age, gender, and race of such patients, indicating the age in months for children under two years.
- 1.10 *Existence of an institution* with the facilities and personnel appropriate to meeting the basic requisites for carrying out Phase I Studies.
- 1.11 *A well-based report from the respective Scientific Ethical Evaluation Committee*, which approved the study after the revision the above mentioned antecedents.

2. REQUISITES FOR PHASE II (IIA AND IIB) CLINICAL TRIALS ⁽¹⁸⁾

- 2.1 *Informed Consent* from the person who will participate in the study. In order to obtain the consent, it will be necessary to follow the guideline indicated in the attachment 1, which does not exclude any other information the investigator considers relevant to give for a better understanding and voluntary colaboration of the person.

⁽¹⁵⁾ Phase IIA Studies are pilot studies of efficacy and safety conducted in selected populations of patients: See a more detailed description in Attachment 4, N° 2.
Phase IIB Studies are pilot studies which represent the most rigorous demonstration of the efficacy and safety of a drug: See a more detailed description in Attachment 4, N° 3.

- 2.2 *Commitment* of the responsible investigator with the ethical guidelines indicated in the attachment 1.
- 2.3 *Appropriate insurance or guarantee* against those adverse effects directly derived from the investigation, such an insurance should meet the principle of proportionality, and may be subjected to an impartial arbitration, if any doubt occurs.
- 2.4 *Report on potential benefits* to the volunteer participants.
- 2.5 A detailed *Protocol of research*, including:
- i) Purpose of the study
 - ii) Number of subjects to be studied.
 - iii) Inclusion and exclusion criteria.
 - iv) Design (blind, unblinded, etc.).
 - v) Duration.
 - vi) Endpoints (e.g., pharmacokinetic analysis, clinical and biochemical safety parameters, etc.).
 - vii) Statistical analysis to be used.
- 2.6 *Previous study of toxicity* in animals, including carcinogenicity and teratogenicity.
- 2.7 *Results of Phase I Studies*.
- 2.8 *Investigational Drug Brochure*, including any information available about the product to be evaluated.
- 2.9 *Report on the number of patients* in who the product has been previously used, and the countries where such clinical trials have been conducted, indicating if one of them is the country of origin of the drug. It is also advisable to have information regarding to the age, gender, and race of such patients, indicating the age in months for children under two years.
- 2.10 *Existence of an institution* with the facilities and personnel appropriate to meeting the basic requisites for carrying out Phase II Studies.
- 2.11 *A well-based report from the respective Scientific Ethical Evaluation Committee*, which approved the study after the revision the above mentioned antecedents.

3. REQUISITES FOR PHASE III (IIIA AND IIIB) CLINICAL TRIALS ⁽¹⁹⁾
- 3.1 *Informed Consent* from the person who will participate in the study. In order to obtain the consent, it will be necessary to follow the guideline indicated in the attachment 1, which does not exclude any other information the investigator considers relevant to give for a better understanding and voluntary collaboration of the person.
- 3.2 *Commitment* of the responsible investigator with the ethical guidelines indicated in the attachment 1.
- 3.3 *Appropriate insurance or guarantee* against those adverse effects directly derived from the investigation, such an insurance should meet the principle of proportionality, and may be subjected to an impartial arbitration, if any doubt occurs.
- 3.4 *Report on potential benefits* to the volunteer participants.
- 3.5 A detailed *Protocol of research*, including:
- i) Purpose of the study.
 - ii) Number of subjects to be studied.
 - iii) Inclusion and exclusion criteria.
 - iv) Design (blind, unblinded, etc.).
 - v) Endpoints (e.g., pharmacokinetic analysis, clinical and biochemical safety parameters, etc.).
 - vi) Statistical analysis to be used, and statistical evaluation of the minimal sample size necessary in order to achieve conclusive results. Pharmacoeconomics and/or quality of life analysis, if applicable.
- 3.6 *Previous study of toxicity* in animals, including carcinogenicity and teratogenicity.
- 3.7 *Results of Phase I, II, and IIIA studies*, if applicable.
- 3.8 *Investigational Drug Brochure*, including any information available about the product to be evaluated.
- 3.9 *Accumulative report of adverse effects*, related or non related.
- 3.10 *Report from the respective Scientific Ethical Evaluation Committee*, which approved the study after the revision the above mentioned antecedents.

⁽¹⁹⁾ Phase IIIA Studies: they are studies conducted after the therapeutic efficacy of drug has been demonstrated: See Attachment 4, N° 4.

Phase IIIB Studies: they are studies conducted during the period of approval of drug, on the population to who the drug is intended for. See Attachment 4, N° 5.

4. REQUISITES FOR PHASE IV CLINICAL TRIALS ⁽²⁰⁾
- 4.1 *Informed Consent* from the person who will participate in the study. In order to obtain the consent, it will be necessary to follow the guideline indicated in the attachment 1, which does not exclude any other information the investigator considers relevant to give for a better understanding and voluntary collaboration of the person.
- 4.2 *Commitment* of the responsible investigator with the ethical guidelines indicated in the attachment 1.
- 4.3 *Appropriate insurance or guarantee* against those adverse effects directly derived from the investigation, such an insurance should meet the principle of proportionality, and may be subjected to an impartial arbitration, if any doubt occurs.
- 4.4 *Report on potential benefits* to the volunteer participants.
- 4.5 A detailed *Protocol of research*, including:
- i) Purpose of the study.
 - ii) Number of subjects to be studied.
 - iii) Inclusion and exclusion criteria.
 - iv) Design (blind, unblinded, etc.).
 - v) Duration.
 - vi) Statistical analysis to be used, and statistical evaluation of the minimal sample size necessary in order to achieve conclusive results. Pharmacoeconomics and/or quality of life analysis, if applicable.
- 4.6 *Previous study of toxicity* in animals, including carcinogenicity and teratogenicity.
- 4.7 *Results* of Phase I, II, and III studies, if applicable.
- 4.8 *Investigational Drug Brochure*, including any information available about the product to be evaluated.
- 4.9 *Accumulative report of adverse effects*, related or non related.
- 4.10 *A favourable and well-based report from the respective Scientific Ethical Evaluation Committee*, after the revision the above mentioned antecedents.

⁽²⁰⁾ Phase IV Studies: they are those conducted after the drug or biological agent has been approved for sale. See a more detailed description in Attachment 4, N° 6.

IV. REQUISITES TO BE MET BY THE INVESTIGATORS OF CLINICAL TRIALS ON PHARMACOLOGICAL AGENTS INVOLVING HUMAN SUBJECTS

1. REQUISITES OF THE RESPONSIBLE INVESTIGATOR OF A CLINICAL TRIAL:

1.1 Definition of Investigator: A person responsible for the performing of the clinical trial in the study center. If the study is conducted by a team, the team leader is named *principal investigator*.

1.2 Professional accreditation: Because the studies are carried out in human subjects, it is a requisite of the principal investigator to have a medical doctor degree, valid in Chile. Such a degree ensures a certain kind of competence in the administration of biological agents in humans, and confers him(her) the “medical” responsibility over the participants.

In special cases where the professionals have other degree into the biological field (dentist, veterinarian, biologist, nurse, etc.), and meet the requisites of experience into the area of the drug under investigation, it will be necessary an university qualification of not less than 5 years.

For this purpose, postgrade studies related to the subject matter of the proposed investigation are included here. Such studies should accredit the Investigator is highly prepared on the topic under investigation. In this case, it will be required the participation of a medical doctor responsible for the medical care of participants.

1.3 *Accreditation of experience in the subject matter* in which the investigation is focused: it is considered as highly desirable to have previous experience in clinical research or otherwise have the support of people qualified in clinical research.

1.4 *Accreditation of membership* in one of the following institutions, or evidence of explicit support for developing the clinical study: public hospital, an university with state recognition, a private clinic properly qualified for this effect, and/or a clinical work group who has a formal recognition in clinical research, basically endorsed by previous works spreaded in the formal scientific literature.

1.5 An annual updated *Curriculum vitae*.

2. REQUISITES OF THE CO-INVESTIGATOR OF A CLINICAL TRIAL:

2.1 *Professional accreditation*: university degree with no less of five years of education (including postgrade studies).

- 2.2 An annual updated *Curriculum vitae*.
- 2.3 A supporting letter from the investigator responsible of the study proposed.
3. RESPONSIBILITIES OF PRINCIPAL INVESTIGATOR:
- 3.1 *In general terms*, the investigator should conduct the study according to the protocol approved by the respective Scientific Ethical Evaluation Committee. The sponsor of the study shall ensure the investigator may take his(her) medical, ethical, and legal responsibility in despite of the provisions which can be demanded in the fulfillment of the protocol and development of the investigation.
- 3.2 *Responsibilities in the fulfillment of protocol:*
- i) Do not make amendments to protocol without the approval of the respective Scientific Ethical Evaluation Committee, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject. In such case, the Committee shall be informed as soon as possible. In turn, the Committee will inform to the Ministry of health in a period no longer than 15 days.
 - ii) To start the study only when it has been obtained the written and dated approval from the Committee, and the authorization of importation and use of the product under investigation granted by resolution of the Instituto de Salud Pública.
 - iii) To inform to the sponsor if the Committee cancels its approval to the study.
- 3.3 *Responsibilities with the Scientific Ethical Evaluation Committee:*
- i) To inform periodically to the Committee respect to the progress of the study. The frequency of the reports will be set according to each protocol, but not less than once a year.
 - ii) To submit to the Committte a copy of the final report of the study.
- 3.4 *Responsibilities related to the product under investigation:*
- i) To safeguard the integrity and preseervation of the products used in the investigation.
 - ii) To explain to each patient the proper use of the product, and verify, during the study, the fulfillment of the instructions.

3.5 *Responsibilities in the notification of adverse events:*

- i) To inform the adverse events, occurred during the investigation, to the National Center of Drug Information and Pharmacosurveillance, Instituto de Salud Pública, to the sponsor and the Scientific Ethical Evaluation Committee.
- ii) The Committee will report those serious adverse events probably related with the study, to the Ministry of Health in a period no longer than 15 days.

3.6 *Responsibilities before the persons involving in the study:*

- i) To meet the provisions included in the present norm, regarding to the informed consent which must enclose any clinical trial involving human subjects.
- ii) To inform to the patients involved in the study the completion of the study or any eventual withdrawal, ensuring the patients receive an appropriate treatment, if applicable.

4. *Requisites of the associate or supervisor of a clinical trial:*

- i) *Professional accreditation:* university degree with no less of five years of education (including postgrade studies) in the biological area or health sciences.
- ii) Approved course on good clinical practices.
- iii) Annual updated Curriculum vitae.

V. REQUISITES TO BE MET BY THE INSTITUTIONS WHERE THE CLINICAL TRIALS ON PHARMACOLOGICAL AGENTS INVOLVING HUMAN SUBJECTS WILL BE CARRIED OUT

1. *To demonstrate previous experience* in the care of persons and/or patients similar to the subjects to be enrolled into the clinical trial proposed.
2. *Letter of proposal from the responsible investigator* and a letter of acceptance from the “authority” of the institution.⁽²¹⁾

⁽²¹⁾ It is considered “authority” of the institution that person who has the highest hierarchical level. Such authority should be the final responsible of the wellness of the subjects into the institution during the study proposed.

3. *Letter-Description* of the site where the clinical trial will be carried out, including a description of the facilities, human resources, and material resources. This description should allow to certify the institution meets the basic requirements for developing the investigation proposed.

VI. REQUISITES TO BE MET BY THE SPONSORS OF CLINICAL TRIALS ON PHARMACOLOGICAL AGENTS INVOLVING HUMAN SUBJECTS

1. *To propose a clinical trial* which meets the basic requisites indicated in the section II of the present norm.
2. *To identify and propose an investigator responsible* for the clinical trial who meets the basic requisites indicated in the section III of the present norm.
3. *To ensure* that the clinical field where the study will be carried out, meets the requisites indicated in the section IV of the present norm.
4. *To supply to the principal investigator* all the chemical, pharmaceutical, toxicological, and pharmacological information which guarantees the safety of the drug and necessary to be submitted to the respective committees, as well all the information necessary to conduct the clinical trial.
5. *To ensure the immediate communication* to both the responsible investigator and the Scientific Ethical Evaluation Committees, institutional authorities, and Ministry of Health, of any significant adverse effect related to the study drug, occurred in Chile and abroad, previously or during the conduction of the clinical trial.
6. *To grant an insurance (or other appropriate guarantee) which covers the medical care required due to adverse effects* directly derived from the use of the drug or the procedures directly related to the performing of the clinical protocol.
7. *To ensure the correct performing of the study*, by means of a constant monitoring and the presentation of periodical and final reports to be submitted to the respective Scientific Ethical Evaluation Committees, and to the ministerial technical units in those cases mentioned by this norm.
8. Payment of the respective fees corresponding to the expenses for the protocol evaluation, and set by the authority.

VII. ROLE OF THE INSTITUTO DE SALUD PÚBLICA IN CLINICAL TRIALS ON PHARMACEUTICAL AGENTS INVOLVING HUMAN SUBJECTS.

The legal health norms in force allow to the director of the Instituto de Salud Pública to declare his(her) opinion respect to the import application of a pharmaceutical product or drug intended to be used for research purposes. In such a case, he(she) will issue a resolution which authorizes or rejects the use and disposition of the respective product.

The present norm regulates the scientific and ethical aspects of the research and experimentation of pharmaceutical and/or biological products involving human subjects in Chile. This norm is applicable to the pharmacoclinical investigation performed with pharmaceutical products which are not registered in the country, both those manufactured in Chile and those imported products.

Furthermore, it allows the director of the Instituto de Salud Pública has all the scientific-technical and ethical evidence supported by expert people in the field and, on such a basis, bases his(her) approval or rejection to the importing application of any pharmaceutical product or drug to be used for research purposes.

Therefore, he(she) can grant the importing authorization of a pharmaceutical product or drug to be used in the carrying out of a clinical trial into the Chilean territory, which will be exclusively used as the provisions of the study protocol, and according to a favourable evaluation from the respective Scientific Ethical Evaluation Committee.

In the cases where the director of the Instituto de Salud Pública does not receive the report about any investigation protocol evaluated by a Scientific Ethical Evaluation Committee, he(she) will propose to the Ministry of Health the rejection of such a protocol. The Ministry will summon to an ad-hoc committee for making a decision on the protocol, reporting to the Instituto about the resolution in a period no longer than 30 days.

VIII. CONSTITUTION OF THE SCIENTIFIC ETHICAL EVALUATION COMMITTEE

1. GENERAL ASPECTS:

- 1.1 *Any institution where is carried out an investigation protocol involving human subjects who will receive a drug under investigation, must ask to a local Scientific Ethical Evaluation Committee the revision the scientific-ethical aspects of the investigation protocol, the investigators, the site where the investigation will be carried out, and the sponsoring institution, according to the sections II, III, IV, and V of the present norm.*

- 1.2 Those Health Services which do not have a Scientific Ethical Evaluation Committee, the Direction of the Health Service shall design a *Reference Scientific Ethical Evaluation Committee*. The Investigators shall turn to this Committee when the studies are in the jurisdictional area of the respective Health Service.
- 1.3 Locally, there will be ad-hoc Scientific Ethical Evaluation Committees which will be in charged of the revision of multicentric studies which exceed the field of three or more Health Services, or those which may have a strategic importance for the general health policies of the nation, even if they have not a big extension.
- 1.4 The Ministry of Health will have a register of the functioning Committees, the protocols which are carrying out, and make periodical revisions of their progressing. Also, it will have at its disposal a system of accreditation of the functioning Committees. ⁽²²⁾

2. CHARACTERISTICS AND OPERATION OF THE COMMITTEE:

2.1 *Objectives:*

- * To evaluate the ethical aspects of the project.
- * To evaluate the scientific-ethical aspects.
- * To audit the carrying out of the clinical trial as the protocol approved.

2.2 *Composition:*

- The Committee will be composed for at least 8 members.
- All members will be of a permanent nature, and one of them will practise the functions of *Chairman*, and other as *Secretary* of Committee.
- Members will be nominated each four years by the respective authority of the corresponding level, either the Director of the Institution or the Director of the respective Health Service, based, in general terms, on their knowledge and recognized scientific expertise and ethics.
- It will be possible to designate a member once again only.
- The Chairman of Committe will be able to call to experts, if necessary.

2.3 *Selection of the members:*

- * The respective authority who must design the members of the Committee will have the possibility to choose among trained professionals of his(her) institution, or ask for support to the faculties of Medicine and/or Scientific Societies accredited in the Chilean Medical Society and/or organizations which depend on the Ministry of Health, for proposing a trained professional.

⁽²²⁾ See Attachment 5 for Guidelines on Accreditation of Scientific Ethical Committees

- * In the nomination of the members of these Committees should be considered the inclusion of representatives of both genders, together with the participation of jurists and health professionals other than physicians. At least one of the members must have knowledge on researching methodology, and furthermore, it must have a representative of any organization with an extrainstitutional base acting as representative of community.
- * Each nominated must accept in writing his(her) incorporation to Committee, promising to meet his(her) task properly.
- * None of members of Committee should be directly or indirectly related to the sponsor or investigators respect to the proposed investigation protocol. In the case that one of the members who compose the Committee has a conflict of interest with the investigation, he(she) will have to declare him(her)self disqualified, and will be replaced specifically for this evaluation.
- * The members of the Committee will have to receive, from the respective institutional authority, the support necessary for the best fulfillment of their roles. Also, they will have to receive the equipment and secretary support during the development of his(her) task.

2.4 *Operation*

- * All investigation project which include a clinical trial with pharmacological agents involving human subjects will have to be submitted to the Chairman of the respective Scientific Ethical Evaluation Committee by the responsible investigator, according to the center where the study will be carried out. It will be necessary to attach information respect to ethical declarations regarding to the investigation project or the product, whatever is applicable.
- * All the documentation shall be submitted in its original language and in Spanish, if applicable. In any case, the patient information document and the consent form will be always in Spanish.
- * The Chairman of the Committee will check, *in a period of 10 (ten) calendar days*, if it has been attached enough antecedents for performing the evaluation of the project, according to the requisites above mentioned. If it is so, he will acknowledge receipt as conform, starting from this date the terms established for the evaluation. If any antecedent is missing, the documentation will be given back to the investigator, giving evidence of the missed elements.

- * In order to approve or reject the investigation, it will be only necessary the report of a Committee. In case of multicentric studies, the institutional authorities involved will formally delegate the evaluation of the project in only one Committee.
- * Once the Scientific Ethical Evaluation Committee is called and composed in the established terms and according to the previously indicated, will be able to approve or reject the study proposed, as scientific-technical and/or ethical criteria, and in well-based way, *in a period no longer than 60 (sixty) calendar days*, from the date of conform receipt.
- * It will be possible to ask the consultancy of other specialist in order to base in a better way its decision, giving evidence of that.

2.5 *Approval or rejection of the studies*

- * The clinical trial shall be approved or rejected by consensus of the members of the Committee, accepting up to one minority vote. The approval or rejection shall be always explicit and well-based, and each of the members will have to sign the document, despite of the fact if they agree or disagree with the study.
- * If the study is approved, the Committee will inform in writing to the responsible investigator.
- * If it is a study which corresponds to the importing application of a pharmaceutical product or drug under investigation which does not have a health registration, the Committee will submit immediately the notification and all the respective antecedents to the director of the Instituto de Salud Pública, according to the provisions of the section VII of the present norm. This authority will have *a period no longer than 20 (twenty) calendar days* from the receipt of the report by the Office of Documentation Receipt in the Instituto.
- * If the study is approved or rejected, the Committee will inform in writing to the responsible investigador. Such investigator will be able to refuse in writing the objections and, if necessary, orally before the Committee, in a period no longer than 15 (fifteen) calendar days from the date of notification of the rejection. Afterwards, the Committee will have 30 (thirty) calendar days for making a final decision.
- * If the investigator does not submit, in the established period, new information after his(her) project has been objected or rejected, the study will be considered as definitely rejected. The same will occur if the final decision, after to evaluate the new information submitted, is to reject the project.

- * If the proposed study is definitely rejected due to any of the causes expounded, the Committee will inform in writing to the responsible investigator and the Ministry of Health.
- * The Committee will meet *at least once a year* for evaluating the running of the protocol. It will meet in an extraordinary way for approving or rejecting the amendments of such protocol and/or evaluating the adverse effects occurred during the carrying out of the study.
- * If during the conduction of the study, the Committee considers compulsory to stop the study, the responsible investigator will be required to evaluate the situation. After the analysis of the problem which may exist, the Committee will recommend to the authority where the study is performed: to maintain the authorization, to maintain the authorization with modifications, or to cancel the authorization to carry out of protocol. The respective authority will have a period of 15 (fifteen) calendar days, from the date of receipt the objections, to give an opinion about the subject. The Committee shall inform to the Ministry of Health, in a period no longer than 15 days, the decision adopted respect to the investigation.

2.6 *Reports and documentation:*

- * The reports on the running of the investigation protocol, the amendments of it, and of the *final results*, as well of any other matter which can be relevant for the normal development of the study, will be timely submitted to the Ministry of Health by the Scientific Ethical Evaluation Committee.
- * All the procedures, antecedents, reports, and results related to the investigation and investigators, will have to be protected by the norms of confidentiality and discretion in force, according to the ethical and legal rules which are applicable to this kind of subject.
- * Each Committee must have a file with the documents considered as relevant, for a period of three years after the completion of the study. It will have at least the following files:
 - procedures in writing
 - list of identification and activity of its members
 - documents submitted by the investigator
 - minutes of meeting
 - correspondence

2.7 *Commitment of the Committee:*

All the members of the Committee shall bear in mind the fulfillment of the terms established for the revision of investigation antecedents in order to avoid delays in a decision which may affect the interest of investigators and sponsors, and for your eventual clinical benefit: the interests of all the community.

IX. TRAINING OF PROFESSIONALS ON MATTERS OF BIOETHICS AND METHODOLOGY OF INVESTIGATION.

1. It will be necessary to form a critical mass of professionals qualified in matters of Bioethics and Methodology of Investigation, to be nominated in the Committees of the different Regions of the country.
2. For such effect, every year is established, by ministerial initiative, a Program of Continuing Training in subjects of Bioethics and Methodology of Investigation, to which can have access the professionals who show interest for training in such areas, and which will also have as a support for those who are members of Hospital Ethics Committee.

X. FINAL COMMENT:

The application of this Norm will allow to solve, on the one hand, the problem of the lack of protection in which our population is respect of the clinical research with drugs. On the other hand, it will give to the investigators and institutions an ethical guidance and an order of technical requirements which allow them to meet appropriately with their interest in helping to society through the advancement of science.

According to the established terms, the total processing of an investigation protocol of a pharmaceutical product or drug for which an importing application for research purposes has been submitted, will take a period no longer than one hundred and twenty (120) calendar days, from the time of its conform receipt by the Committee to the time the Director of the Instituto de Salud Pública grants or not the importing authorization of the product. Such a term falls into the group of internationally accepted standards, and is inconvenient to extend it since the excessive *delay* in decisions on this subject may deeply affect the interests of investigators and sponsors, as well those of the community, due its possible subsequent clinical benefits.

This norm is a matrix from which may emanate other provisions allowing the scientific and ethical control of areas such as the research and experimentation involving human subjects in a wide sense, and with the use of those pharmaceutical products named “generics” and also those included in the “alternative medicine”.

Finally, it is emphasized that all the provisions contained in this norm will be possible to carry out only if there are Scientific Ethical Evaluation Committees, as described in Chapter VIII. The experience shows these Committees will be composed and work appropriately provided that the respective authorities support their tasks, make the things easy, and give the encouragement necessary to fulfill their functions in a responsible and involved way.

In this sense, the pecuniary encouragements are not the best alternative, because the characteristics required to members and the matters to be discussed, but there is not a doubt regarding to the necessity to give them time availability and non economic incentives (e.g. a commendable note in the worker file), as well training on bioethics, and methodology and access to bibliographical information and casuistic data. All these incentives and facilities should be clearly established in the norm and in the resolution which gives rise to such Committees.

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ATTACHMENT 1

ESSENTIAL INFORMATION FOR THE PROSPECTIVE RESEARCH SUBJECTS.⁽²³⁾

1. *Before requesting an individual's consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand.*
 - a) that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary;
 - b) the expected duration of the individual's participation;
 - c) the benefits which reasonably may be expected to result to the participants or other people, as a result of the research;
 - d) any foreseeable risks, pain or discomfort, or inconvenience to the individual, associated with participation in the research;
 - e) any other procedure or treatment which may be as useful for the participant as the procedure or treatment under investigation.
 - f) the provisions that will be made to ensure respect for the confidentiality of records in which subjects are identified;
 - g) the extent of the investigator's responsibility to provide medical services to the participant, and the recommendation that it will be a third party.
 - h) that will be offered a free therapy, in case of adverse events derived from the use of the drug or procedures directly related to the carrying out of the research;
 - i) that the participant, his(her) family, or the people who depend on him(her) will be indemnified in case of disability or death as a result of adverse events derived from the use of the drug or procedures directly related to the carrying out of the research;
 - j) that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled;

⁽²³⁾ Based on the International Ethical Guidelines for Biomedical Research and Experimentation involving Human Subjects. Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), Geneva, 1993.

2. *Regarding to the informed consent, the investigator has the duty to:*
- a) communicate to the potential participant, all the information necessary for obtaining a consent appropriately informed;
 - b) give to the potential participant, a full opportunity to make questions and enhance to do it;
 - c) refrain from unjustified deception, undue influence, or intimidation;
 - d) seek consent only after ascertaining that the prospective subject has adequate understanding of the relevant facts and of the consequences of participation and has had sufficient opportunity to consider whether to participate;
 - e) obtain from each potential participant or legal representative, a signed document which accredit his(her) informed consent;
 - f) renew the informed consent of each subject if there are significant changes in the conditions or procedures of the research. This amended consent should be submitted to the Scientific Ethical Evaluation Committee to get its approval;
 - g) give to the patient or legal representative, any new information which could affect his(her) willingness to participate in the study;
 - h) the informed consent should be drawn up using a simple and untechnical language, understandable for the patient or his(her) legal representative;
 - i) the information given, including the consent, should not give to understand that the participation of the patient means a renounce of his(her) rights, or excuses to the investigator or sponsor from responsibility in case of a medical negligence;
 - j) the investigator will give to patient or legal representative, the time necessary to decide his(her) participation in the study, and the opportunity to make questions;
 - k) if the patient or his(her) legal representative do not know to read, during the discussing of the written consent will have to be present an impartial witness, who will have to sign the consent after the patient or his(her) legal representative have orally given their assent;
 - l) the patient should receive a copy, signed and dated, of the written consent.

3. *Before to conduct a research where children will be involved, the investigator should be sure about the following:*
- a) it will not participate children in a research which may be carried out in adults;
 - b) the purpose of the research should be to get knowledge relevant to the needs of the children health;
 - c) one of the parents or the legal tutor of each child has granted his(her) consent as tutor;
 - d) the consent of each child has been obtained according to his(her) ability;
 - e) the refusal of the child to participate in research activities should be always respected, except that, as the investigation protocol, the child receives a therapy for which there is not an acceptable alternative from a medical point;
 - f) the risk of the interventions of which the purpose is not to benefit to the child, is low and proportional to the importance of the knowledge to be obtained, and
 - g) it is possible the procedures, of which the purpose is to give a therapeutic benefit, are as favourable for the child as any other alternative available.
4. *Before to carry out a research where is considered the participation of persons with mental or behaviour disorders who, therefore, are not able to give a consent appropriately informed, the investigator should be sure about the following:*
- a) these people will not participate in research activities which could be also conducted in persons who have full mental faculties;
 - b) the purpose of the research is to get knowledge relevant to the needs of health of people with mental or behaviour disorder;
 - c) it has been obtained the consent of each participant in the extent of his(her) ability, and always respecting the refusal of a potential participant to be included in a non clinical trial;
 - d) in the case of legally incompetent participants, it is obtained the informed consent from the legal tutor or any other person properly authorized;

- e) the extent of the risk of the interventions of which the purpose is not to benefit to the child, is low and proportional to the importance of the knowledge to be obtained, and
- f) it is possible the procedures, of which the purpose is to give a therapeutic benefit, are as favourable for the child as any other alternative available.

TEMPLATE OF INFORMED CONSENT FOR A CLINICAL TRIAL⁽²²⁾

RESPONSIBLE INVESTIGATOR: (full personal and professional data)

TITLE OF PROTOCOL: (identification of the research project)

TITLE OF THE ACT OF CONSENT: (this title is written if it has a name different to that of protocol).

I have been invited to participate in a research project which are studying (describes the purpose of study). If I take part of this study, I agree to (short description using general terms, of the procedures of which the individual is agreed).

I understand that:

- a) The potential risks of this procedure include (it is prepared a list of the known risks or side effects; if such risks do not exist, it should be established).
- b) The alternative treatments include (a list is prepared, describing briefly the advantages and disadvantages of each; if there are not exist, it should be established).
- c) The potential benefits which will have in this study are (enumerate it; if there are not benefits, it should be established).
- d) Any question I want to make related to my participation in this study will have to be answered by (it will be prepared a list with the names and positions of the persons who will have to answer the questions).
- e) I am free to discontinue my participation in this study at anytime, and I am not obligated to give reasons, and such a decision will not affect my quality of patient and/or user.
- f) The results of this study may be published, but my identity will not be revealed, and my clinical and experimental data will kept confidential, except that my identity is asked by law enforcement.
- g) My consent has been voluntary given, with no obligation or in a forced way.
- h) In the event that I resulted physically injured from this study, the medical care and treatment will be given preferently by this institution and, in any case, under the medical and legal responsibility of the responsible investigator or doctor who signs this consent.

SIGNATURE OF THE RESPONSIBLE
INVESTIGATOR OR DOCTOR

SIGNATURE OF PATIENT
OR LEGAL REPRESENTATIVE

DATE

⁽²²⁾ Purtillo R. Ethical Dimension in the Profession. Section Threep. 134. 0. SOunders Company Second Edition, 1993. Translation C. Quintana and M. Lavados.

ATTACHMENT 2 REFERENCE TO LEGAL PROVISIONS

1. Political Constitution of Chile, in its Articles 1°, 5°, and 19°, establishes:
 - a) the State recognizes:
 - the freedom and equality of dignity and rights of people
 - the family as the key core of society, and
 - as limitation of the exertion of sovereignty, respect to the essential rights emanated from the human nature, are those guaranteed by the Constitution or by international treaties ratified by Chile.
 - b) the duty of the State to:
 - act to the service of the human person, where its goal is the promotion of general wellness,
 - give protection to population,
 - promote the harmonical integration of all the sectors of Nation, and
 - ensure the rights of people to participate with equality of chances in the national matters.
 - c) among the constitutional rights and duties:
 - the right to live and the physical and mental integrity of person,
 - the protection of that who has to be born,
 - the same legal protection in the exertion of the people rights,
 - the respect and protection of the private and public life, and of the personal dignity of his(her) relatives,
 - the right to personal freedom and individual safety,
 - the right to health protection,
 - the right of ownership in its different types, particularly on any sort of goods, corporal and uncorporal (respect to the subject under investigation, and the investigator), and
 - the authorship rights (investigator) on his(her) intellectual creations.
2. Provisions from the Health Code and the Executive Decree N° 1876:

The Chilean Health Code, Ed. 9th of 1996, in its Article 102°, and the Regulations of the National System of Control of Pharmaceutical Products, Food for Medical Use, and Cosmetics, approved by Executive Decree N° 1876 of 1995, Chilean Ministry of Health, in its Article 16°, section c), and its amendment approved by executive decree N° 494 of July 19th 1999, grant to the director of the Instituto de Salud Publica, the faculty to authorize provisionally the sale or use, without a previous health registration, of pharmaceutical products to be used for purposes of scientific research or clinical trials, provided the availability of a previous report from the Scientific Ethical Evaluation Committee of the Health Service or Hospital, conforms to the current ministerial regulations.

3. General Regulations of Health Services:

The General Regulations of Health Services, approved by Executive Decree N° 42 of 1986, Ministry of Health, and its amendment approved by executive decree N° 494 of July 19th 1999, grant to the Hospital Directos the faculty to designate the Scientific Ethical Evaluation Committee.

The responsibility of Committee is to inform respect to the investigations to be carried out involving patients of public and private hospitals, located into the territory of its competence, in which are using drugs not registered yet in the country.

ATTACHMENT 3

REFERENCE TO CONCEPTS AND DEFINITIONS INCLUDED IN THE NORM

1. *Respect for persons. Principle of Autonomy:*

It is based on the fact that the individual has the ability to choose his(her) way to act as person, i.e., determine his(her) own rule. He(she) has the autonomy to choose, freely, applying his(her) own reasoning, and according to the analysis of the positive and negative aspects, determine what will be his(her) behaviour before a determined situation. As Kant, the man is person because has the ability “to give himself the categorical imperative of the moral law”¹¹, a goal which allow him to behaviour as an autonomous moral individual. He indicates that to be autonomous is to be self-directed, not influenced by other persons nor other circumstances. The autonomy can be considered operatively as an act of autonomous choice, which, as Faden and Beauchamp, should have three conditions: intentionality, knowledge, and absence of control.

- * *The intentionality* is or not; it has not grades; it exists when is wanted or wished according to a plan, conforming wanted acts.
- * *The knowledge* refers to the extent of understanding or comprehension of the action, when its nature is understood, and its outcomes are foreseen. The comprehension of the acts should be suitable and complete. Such characteristic of the action has different grades.
- * *The absence* of external control has grades: coercion, manipulation, and persuasion.
 - + Coercion refers to the intentional and effective influence on a person under threat to suffer unwanted and avoidable damages.
 - + Manipulation is the intentional and effective influence on a person by non coercitive means, by non persuasive means on the perception of such choices by the individual.
 - + Persuasion is the intentional influence to induce to freely accept believes, attitudes, and values of the persuader.

The autonomous actions should be authentical, and based on deliberation, in order to achieve an authentical decision. The common wellness should limit the free decisions in order to avoid the anarchism, always considering the principle of beneficence.

2. *The searching of good: Principles of Beneficence and Nonmaleficence.*

They refer to the concept to maximize benefits and minimize harms. Therefore, it should be known the risks, implying to define clearly when and in what conditions are justified to know the benefits, despite the risks of potential or predicted harms.

The paternalism, although it is less common in our days, for the supremacy and respect of persons, has varied in a remarkable way, from an autoritary position, as an order, to a position of refusal-acceptance or to get the wishes, options, and actions of other person, for the single benefit of such a person.

It is necessary to distinguish the principle of “nonmaleficence” from that of “beneficence”. The former “obligates to everybody in a primary way and, therefore, is previous to any kind of information or consent” (Diego García). On the other hand, the principle of beneficence is related to the consent.

Regarding to the principle of beneficence, it is aesthetically relevant respect to the research involving human subjects, the validity on the fact the subject accepts his(her) participation knowing the predicted risks which should not be greater than the minimal risk. Here it is introduced the concept of power of decision who has the patient in the choice from his(her) own benefit, accepting or refusing to be part of the investigation, and related to his(her) ability as competent patient.

In order to understand completely the relative importance of the principles of nonmaleficence and beneficence, it has been indicated that “to make the good” is an aspiration, and “do not harm” is an obligation.

3. *Principle of Justice:*

According to Ulpiano, a Roman jurist of III. Century, “justice is the constant and permanent willingness to give to each one his(her) own right”. The fair one is identified with the right one and the good one. The justice begins like a general virtue, “the justification”, and from that the “fair” value, and “to try to everyone and anyone in such a way to allow them to perform their own perfection”. The justification would have several moments: the contractual freedom, the justice as social equality, and justice as public usefulness.

In the doctor-patient relationship, it is possible to find the *Distributive injustice*. a complex virtue which conforms a particular case of moral justification, given by the State and the responsible institutions of the people health. In the experimentation involving human subjects, the principle of justice refers to consider to any group of people who benefits of its results; that such experimentation is performed in the groups in which is necessary to study the phenomenon, and only to exclude the vulnerable groups, avoiding to committ an injustice, depriving them of the benefits of the outcomes.

4. *The vulnerability:*

It refers to the emphasized unability of a person to protect his(her) own interests because to impediments such as impossibility to grant an informed consent, it cannot resort to any other way to get medical care or satisfy other expensive necessities, or to be a member of a lower level or subordinated to a hialarchical group. Therefore, it is necessary to establish special provisions in order to protect the rights and wellness of vulnerable people (see Attachment 1).

ATTACHMENT 4

CHARACTERISTICS OF CLINICAL TRIAL AS ITS PHASE

Phase I Studies:

These are safety and pharmacokinetics studies, and are carried out primarily in healthy subjects. Its principal purpose is to establish the range of dose tolerated by the subject. The Phase I studies has a short term duration, and include a small number of subjects (10-100 subjects)

The Phase I studies may, in exceptional cases, be carried out in *severely ill subjects*, in who the use of the drug and/or biological agent will not modify extensively the prognosis, or, if it is considered as an act of compassion where the severity of disease and the absence of a known effective treatment for it supports an informed decision from the patient to evaluate a new drug of uncertain result (for instance: terminal cancer or patients with advanced HIV which not respond to known therapies).

It is also possible to perform Phase I studies in patients with a not so severe disease, in order to evaluate the pharmacokinetics of the drug (for instance: metabolism of drug in patients with previous induction of microsomal enzymes, using related medications).

Phase IIa Studies:

These are pilot studies on efficacy and safety, in selected populations of patients with the condition or disease to be treated, diagnosed, or prevented. Its purpose is directed to determine the optimal dose of drug, the type and severity of the pathology where it is intended to be used, and objectively define its safety and efficacy by means of appropriate design and methods. Generally, the number of subjects is lesser than 100.

Phase IIb Studies:

These are pilot studies which represent the most rigorous demonstration of the efficacy and safety of a drug, in selected populations of patients with the condition or disease to be treated. They are also known as pivotal or essential clinical trials, and generally the number of subjects studied is between 100 to 500.

Phase IIIa Studies:

These are studies which are carried out after the demonstration of therapeutic efficacy of medication, in populations of patients for which the drug was designed. They are used to get the approval of the drug by the health regulating organizations. They produce efficacy and safety data in populations relatively big of patients (500 or more patients). These studies produce the most part of the information used in the marketing dossier of the medication (for example: adverse effects, dose, route of administration, use intended).

Phase IIIb Studies:

These are the studies carried out during the period of approval of medication, for the population intended to use it. They supplement or complete the information of previous studies, or can be directed to evaluate other aspects, such as: quality of life, pharmaceutical-economical analysis, etc. Generally, they include among 100 to 500 or more patients.

Phase IV Studies:

These are studies performed before the drug or biological agent has been approved for sale. These studies give primarily further information on the efficacy and safety profile of drug, after its use in big populations during a extended period of time.

They are particularly useful for detecting and definition of adverse effects previously unknown, and also additional unknown risk factors. These studies reevaluate formulations, dosages, duration of treatments, drug-drug interactions, comparison with other drug of similar clinical and/or phamacological action.

ATTACHMENT 5

Guidelines for Scientific Ethical Evaluation Committees Accreditation (CEC)

The CEC must comply 2 main functions: evaluation of protocols, and follow up of authorized trials.

A) THE CEC PREPARE A GUIDE FOR EVALUATION OF PROTOCOLS WHICH CONSIDERS THE FOLLOWING ITEMS:¹

Note: The CEC ask to the responsible investigators of the studies the needed number of issues, drawn up in Spanish, including: protocol, investigator's brochure, informed consent form, *curriculum vitae* of the investigators (sponsors) responsible of the study.

1. Technical and scientific aspects:

- 1.1 Type of protocol
 - 1.1.1 Phase of the study. Double blind or not, randomized or not.
 - 1.1.2 Risk/favourable benefit Ratio.
 - 1.1.3 With or without direct benefit for people (it cannot be carried out studies without direct benefit involving people under legal age, legally incompetent, or arrested.
 - 1.1.4 With healthy persons or ill people
 - 1.1.5 Number of patients to be studied
 - 1.1.6 Duration of the study

- 1.2 Scientific validity
 - 1.2.1 Sponsor and principal investigator(s) clearly identified and qualified to carry out the study.
 - 1.2.2 Enrollment of the work team and a clear way to hire the team of co-investigators.
 - 1.2.3 Objectives, hypothesis, inclusion and exclusion criteria of patients without arbitrary discrimination, and considering updated knowledge.
 - 1.2.4 A clearly formulated protocol (control group; it will be examined with special attention the placebo group, method of randomization).
 - 1.2.5 Relevant clinical and laboratory techniques.
 - 1.2.6 A clearly established method of data analysis, guaranteeing confidentiality.
 - 1.2.7 An established modality to notify the adverse events.

2. Legal aspects:

- 2.1 Insurance of the sponsor of study: considers the expenses related with secondary adverse events related, and compensation in case of severe events; it defines the method of payment.

- 2.2 Insurance of the investigators before a report of malpractice related to the study (as a matter of information).
- 2.3 The necessity (or not) to establish an agreement between the sponsor of the study and the Health Service, clinical enviromental of the study.
- 2.4 Sources of financing of the study.

3. Ethical aspects:

- 3.1 Informed consent
 - 3.1.1 A clear, understable, and complete information on: purposes, hypothesis, potential benefits, potential discomforts and adverse events, duration of the study.
 - 3.1.2 Explicit right of person to refuse the participation or to withdraw the study at anytime, without any kind of damage.
 - 3.1.3 The participation is free of charge (modality of compensation for healthy people who participate in a study without a direct benefit)
 - 3.1.4 Identification of the responsible investigator(s), and persons to contact, if is necessary.
 - 3.1.5 Signature of person or his(her) legal tutor, and signature of the responsible investigator. In the case of children or incompetent people, it is advisable to have the further signature of a witness.
 - 3.1.6 Stamp of CEC and the date of approval.
- 3.2 Confidentiality of personal data has to be explicity guaranteed.
- 3.3 Absence of arbitrary discrimination (protection of populations vulnerable for many reasons, particularly persons under legal age, pregnant women, elderly adults, patients who went into a coma or into an emergency condition, patients with mental disorders, patients socially vulnerable, arrested people)
- 3.4 Absence of coercion or incentives for participating.
- 3.5 Aspects of health justice:
 - 3.5.1 Possibility of a compasive extension of the use of the drug, when it is effective.
 - 3.5.2 Possibility to implement, in a reasonable period of time, the method or the product under investigation in the population.

Note: This kind of evaluation corresponds to protocols involving the intervention of human subjects. Protocols of investigation without direct intervention of human subjects such as epidemiological studies, cost-effectiviness studies, or protocols conducted in animals, do not need the same type of evaluation. At any case, it is advisable the investigators inform to CEC, which evaluates the scientific significance of the study and the confidentiality at the management of personal data conforms the Law 19,628.

B) THE CEC MUST HAVE GUIDELINES FOR FOLLOWING UP OF PROTOCOLS, INCLUDING THE FOLLOWING ITEMS:

1. Monitoring of severe events associated (ESA) with or not related to the study.

The ESA will be reported to CEC in a period no longer than 5 days. The ESA with a possible relation with the study will be reported by the CEC to the Unit on Bioethics from MINSAL in a period no longer than 15 days. The ESA may require of further information from the CEC or MINSAL.

2. Evidence of benefit

It could imply the incorporation of a control group to the experimental group, and the subsequent withdrawal of the study (notification to the Unit on Bioethics from MINSAL).

3. Evidence of an unfavourable benefit/risk ratio

It could imply the withdrawal of the study (notification to the Unit on Bioethics from MINSAL).

4. Refusal to participate, patients who withdrew the study

They will be anonymously reported to CEC.

The MINSAL may stop the carrying out of a study if:

- > **it has not been respected the ministerial norm,**
- > **there is an negative evaluation by the CEC,**
- > **there is a risk for the public health.**

¹ See Technical Norm, chapters III to V