

Principles and regulations for the evaluation of clinical research funded by the pharmaceutical industry in Ethics Research Committees in Panama

Principios y regulaciones que orientan la evaluación de ensayos clínicos patrocinados por la industria farmacéutica en Comités de Ética de Investigación en Panamá

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Abstract

The results of a multicenter research evaluation of the Research Ethics Committees (CEI) in Panama are presented, which seeks mechanisms that help strengthen their capacity to evaluate, from a bioethics and human rights approach, the protocols of the trials clinics financed by the pharmaceutical industry or foreign research centers, as well as monitoring the implementation of approved

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protocols. Sufficient documentation was reviewed and interviews were conducted with members of four CIS. From there, it is concluded that in Panama the CIS respect the international standards of operation and protocol review, and that the problems encountered are related to their experience, the social context and the evolution of the interests of pharmaceutical companies.

Keywords: Bioethics Research Committees, financed clinical protocols, clinical trials.

Introduction

In October 2016, a group of researchers met under the name of Ethics and Medicines Research Group, sponsored by the Department of Bioethics of El Bosque University, Bogotá, Colombia, to agree on a research project entitled «Research Ethics Committees and the protection of participants in biomedical research residing in Latin America». Its objective was «to seek mechanisms that help strengthen the capacity of Latin American CEIS to evaluate clinical trial protocols financed by the pharmaceutical industry or by foreign research centers, and to monitor the implementation of approved protocols from a bioethics and human rights approach» (1). Eight countries were present: Argentina, Brazil, Chile, Colombia, Mexico, Panama, Dominican Republic and Peru.¹ This analysis of the situation in Panama is part of the multinational project.²

1. Clinical research funded by pharmaceutical companies

Clinical research is an essential requirement for biomedical research and for the commercialization of new medicines, because it ensures that they are effective and safe for society (2). However, history has revealed numerous examples of abuses that gave rise to inter-

national and national standards. Among them are the Declaration of Helsinki, the recommendations of the Pan American Health Organization (PAHO) and the Organization for Science, Education and Culture (UNESCO), which have systematized the requirements for the formation of RECs, whose function is to protect participants (until now called «subjects») in clinical research (3).

Panama's development is based on its capacity for trade and services, and on the fiscal advantages it offers for international investment (4). In this framework, clinical research financed by pharmaceutical companies has had a progressive increase since 1990, recruiting local researchers in the medical body with an absence of national research laws until 2019,³ but with CBI recognized by law since 2003 (5).

2. Purpose

The purpose of the study has been to evaluate the criteria, principles and regulations that guide the members of the IBC in the evaluation of clinical pharmacological and/or pharmacogenetics research sponsored by the pharmaceutical industry in Panama.

3. Method

Within the framework of the National Meeting on Research Ethics at El Bosque University in 2016 (1), discussion workshops were held to carry out this proposal. This is a qualitative research, and the following instruments were used: a self-evaluation form, review of official IWC documents, their information on web pages, and semi-structured interviews that were tested prior to application.

At the time the research began in Panama, there were eight IWCs accredited by the National Bioethics Committee (CNBI). Three committees were eliminated because they did not evaluate clinical trials, and another one because it was being reorganized at

that time. Letters of invitation to participate were sent to the presidents of four committees evaluating funded clinical trials: three from the public health sector⁴ and one from the private sector, and to the directors of the three public institutions for acceptance of the study. The CNBI was added, due to the relevance of its regulatory and supervisory role of the IWCs in Panama.

The necessary documentation to obtain the registration of the research in the General Directorate of the Ministry of Health and for the endorsement of the Bioethics Committee of the Social Security Fund (which did not review funded clinical studies) was submitted and obtained in October 2017. During 2017 the maximum amount of data was collected and the first results were presented in a second multicenter workshop in 2018. During 2018-2019 the field study was carried out: collection of more documentation, self-evaluation forms made to the participating CBIs and 13 interviews in the selected Committees.

The interviewees were chosen according to the established selection criteria. The interviews met the criteria of privacy, consent and confidentiality; they were recorded, transcribed, reviewed, corrected and coded. The recording, processing and analysis of the data collected followed the steps agreed upon in the general multinational protocol.

The coordinators of the multinational project reviewed all the results collected and completed the information provided at a second meeting in May 2019.⁵ All original documentation and recordings will be kept for five years after the publication of the multicountry analysis and then destroyed.

4. Results

a) Historical evolution and legal framework of the IWC

The creation of the IWCs in Panama has been linked to the development of funded clinical research and has followed the guidelines

of the World Health Organization, through the advice and supervision of the PAHO Regional Bioethics Program (6). Although they belong to a public or private institution that assures them the necessary resources for their operation, they are autonomous in the recruitment of their members and in their decisions on the protocols submitted for review.

Before 1990, clinical research at the Hospital del Niño, Dr. José Renán Esquivel (HDNDJRE), was essentially of a descriptive nature, and was carried out by resident physicians and specialists within the framework of medical teaching. With the change of direction, the first applications for funded clinical research arrived. The first CBI was installed by memorandum DM-M-0041 of January 25, 1991, replacing the existing Commission of Investigation, and it said: «its main function is to protect the welfare and rights of persons participating as subjects in an investigation» (7).

The Gorgas Memorial Institute for Health Studies (ICGES) is the pioneer of health research in Panama, and is attached to the Ministry of Health (MINSA). This role of leader of health research was formalized in Resolution No. 201 of August 6, 1999 (Official Gazette-GO 23,872 of July 26, 1999), which established the policies, priorities and basic norms of health research, and attributed to the IWC of ICGES the responsibility of the ethical evaluation of the clinical research studies that were carried out in the facilities and regions of the National Health System, as well as the specialized interpretation of the guidelines recommended by the documents of the WHO and the Council of International Organizations of Medical Sciences (CIOMS). This Committee was known as the National Gorgas Bioethics Committee. In Resolution No. 390, of November 6, 2003 (OG No. 24,938 of November 28, 2003), the Operational Guidelines on Bioethics in Research were adopted. With the entry into force of Executive Decree 1,110, of June 6, 2012 (OG No. 27,056-A of June 14, 2012), reforms were made to the composition of the members of the National Committee on Bioethics in Research, and it was moved from the Gorgas Memo-

rial Institute to its current headquarters in the National Secretariat of Science and Technology (SENACYT). Through Resolution 013 of July 5, 2012 of the ICGES Board of Directors (OG No. 27,090 of August 1, 2012), the Research Bioethics Committee of this institution was created, with the purpose of ensuring the ethical, legal and methodological revision of all research protocols that were submitted to this committee (8).

As of 2012, and with Executive Decree 1,110 of June 6, 2012 (OG No. 27,056-A of June 14, 2012), reforms were made to the composition of the members of the National Committee on Research Bioethics (CNBI), their origin and the number of members. The scope of their functions to accredit, supervise and audit local and institutional Research Bioethics Committees was detailed, and the evaluation of protocols with indigenous populations and stem cell research protocols was defined within their competencies. With Executive Decree 1317 of July 25, 2012 (OG No. 27,089-A, July 31, 2012) changes were again made, both in the number and nature of the composition of the CNBI: the number of members was increased from nine to eleven (representing government institutions, research centers, hospitals, universities and civil society, which are ratified by the Ministry of Health. Between the years 2011-2014 the image of the CNBI was tarnished, due to conflicts of interest that endangered the safety of patients. The local institutional committees tried to make a difference, by putting the requirements for ethical review to an extreme. As a result of this situation, the CNBI underwent further changes in Executive Decree No. 1,843 of December 16, 2014. It is currently regulated by Law No. 84 of May 14, 2019. It is attached to the Superior Office of the Ministry of Health, with independence and autonomy in its functions, and receives logistical support from the National Secretariat of Science, Technology and Innovation (SENACYT). «It is in charge of guiding public research policies, guaranteeing the quality of the clinical research system, through the accreditation of the institutional Bioethics or Research Ethics Committees, and evaluating clinical

studies on stem cells» (9). According to the CNBI website, both public and private institutions can apply for IWC accreditation and, from 2018 to the date of presentation of this report, five new IWCs have been accredited, two of them from private universities.

According to its website, Hospital Punta Pacífica, currently Pacífica Salud, is a private hospital affiliated with Johns Hopkins Medicine International and has a high technology. The medical and nursing staff has a continuous education program with relevant topics, through real-time video conferences and refresher symposia in various branches of medicine. The hospital develops research studies on diseases. The Research Bioethics Committee (CBI-PP) has been restructured in 2017 and has been recertified in 2019 (10).

b) Composition of Research Bioethics Committees and training of members

Panama's IWCs have tried to follow PAHO's recommendations on their composition and functioning. The minimum number of members is five and the total may reach thirteen. UNESCO's recommendations (2005) on the formation and functioning of IWCs emphasize the importance of multidisciplinary (11, 12, and 13). However, physicians represent between 50% and 75% of the members in the committees studied. The other members are from the health team: nurses, pharmacists, physiotherapists, health workers, social workers. To participate in a CBI, scientific knowledge in health and research methodology is required.⁶ Some members are or have been clinical researchers, which allows them to contribute their experience to the evaluation of the feasibility and relevance of some modalities of a protocol under review.

The representation of members external to the institution does not exceed one member, with the exception of CBI-ICGES, which has four external members (25%), which compensate for the presence of three department directors of the institution. These members are selected by invitation, on the recommendation of one of the CNBI members and patient support organizations (CBI-

PP, interviews), or an advocacy body from a particular sector, such as the Children's Secretariat at CBI-HDNDRJRE. Community members have the same duties and rights as other members and participate actively in the review of the protocols, after three months of their integration into the committee. This period varies according to the dynamics of each committee, the professional background, personality and security of the external member. It often happens that they only evaluate whether the form of consent can be understood by the experimental subject. But they do not know if the subject has understood or not, because no committee has spoken with the participants.

The interviewees recognize that the lack of participation of external members is a weakness, but they relate it to their functioning: *ad honorem* and in hours that can be conflictive for the work of these people; therefore, the active search of some IWCs is directed towards the liberal professions and retirees, with relative success, since it can take months to find a volunteer.

Until 2016, Good Clinical Practices (GCP) courses offered by pharmaceutical companies were accepted, in addition to the IITC PROGRAM or the United States Institute of Health (NIH) online courses. As of 2018, the CNBI stipulated to standardize the preparation of IWC members in Panama and to avoid possible biases and conflicts of interest by offering free refresher courses. The mandatory courses are those of Participant Protection and GCP, given by any of the accredited committees and valid for three years.

c) Resources of the Research Bioethics Committees

Public IWCs must submit to the administrative rules of this sector. All institutions must make available their own office and the necessary equipment to meet the requirements of their functions, as well as a technical secretariat.⁷ It is mandatory that they maintain all information regarding their operation on their own website and in an updated manner.

The IWCs surveyed charge for the review of the protocols, according to a fee published on their website (IWC-HDNDRJRE, IWC-ICGES) or informed during the review application process (IWC-PP). In the case of public IWCs, this fee goes to the institution's common fund, and its use is subject to the requirements of activity execution. Private IWCs manage their budget, which allows them to provide a per diem to members to attend meetings and to review a research protocol. For both public and private IWCs, payment for review does not imply rapid or automatic approval of the protocol under review by the principal investigator.⁸

IWCs do not have the resources to carry out some of the responsibilities they have acquired: systematic monitoring of research sites and interviews with patients to ensure that they have truly understood informed consent and that they do not take unnecessary risks or compromise the integrity of the information. However, they are aware of this and, in 2017 and 2018, three committees carried out four supervisions of research centers.

d) Working Methodology of Research Bioethics Committees

When a clinical research protocol funded by a pharmaceutical company is entered, it undergoes the same process of registration, distribution to reviewers, and scheduling for discussion at a regular meeting as other non-funded clinical research.

At CBI-HDNDRJRE, documentation is distributed to all members for review, because of the perceived particular vulnerability of participants (under 15 years of age) and because of the volume of protocols submitted for review. In all other IWCs, two reviewers are appointed sequentially, and they have fifteen days to present their report to the plenary at a regular meeting, where the questions are discussed.

When the reviewers have previously agreed and one is unexpectedly absent, the member present speaks on behalf of both. If both are absent, then the discussion is rescheduled. After exchanging

considerations on questionable points or clarifying scientific or ethical updates, the members make the decision unanimously. A voting system is provided for in the event that no agreement is reached, but it has not been used in any of the committees surveyed.

e) Conflicts of interest

All IWCs have approved a Standard Operating Procedure (SOP) for the management of potential conflicts of interest of their members. This SOP requires the withdrawal of discussions on a particular protocol when the member is a member of the research team for that protocol, works in the same department, or has a relationship with one of the researchers. This provision is fulfilled without conflict, because it is in the interest of the CBI that the research not be questioned by the scientific, institutional and general community.

f) Research centers and principal investigators

Apart from ICGES, which is an institute solely dedicated to basic, clinical and epidemiological research in health, the other research centers are in public hospitals as part of medical education or as an autonomous service and in private clinics: individual practices or centers dedicated to research. There is no specific legislation on research centers. Since 2015, the CBI-ICGES has asked clinical trial investigators for a minimum of requirements to deal with possible emergencies, such as resuscitation equipment at the participants' place of care and to be as close as possible to an emergency room.

In recent years, several investigators belonging to public institutions have created their own research center outside the institution where they work, but in some cases they submit the protocol for review in the committee of the public institution of which they are part. There is no legal impediment to this; however, this fact can represent an ethical dilemma and a conflict of interest.

95% of the clinical trials financed and registered in the IWCs considered are carried out by a team of three or more researchers, most of whom are doctors specialized in the pathology under study. Panama, a country of few inhabitants, and with few medical specialists, a recurrence of the teams is observed on a regular basis (for example Infectology and Oncology).

g) Registration of information on clinical trials

CBI-HDNDRJRE and CBI-ICGES publish on their website the annual report of all research reviewed by them since 2008. As HDNDRJRE is a hospital that trains physicians, most of the research corresponds to the theses of the resident physicians.

As of 2015, all accredited IWCs in Panama must submit a monthly report and an annual report to the CNBI, which publishes them on its website. This report contains: the title of the study and its reference number; the dates of admission for review, request for corrections and approval, the sponsor, names of the principal investigators and their category and site of study.

h) Role of the Regulatory Agency

Until 2015, the role of the regulatory agency had been delegated to the CNBI. As of that year, MINSAs published Executive Decree number 6, of February 3, 2015,⁹ with which it was created the Department of Research in charge of reviewing whether the investigations affected MINSAs's health policies and programs, and installed a registration platform on its website. It also promoted the participatory drafting of Law 84 on health research for the years 2018-2019. This law took into account the following: the protection of participants; the priorities of MINSAs's lines of research and the appointment of a research advisory committee; the regulatory and oversight roles of MINSAs and the CNBI; the evaluation of protocols; education on research ethics for the CNBI and the IWCs;

human, financial and physical resources for the functioning of the IWCs; the financing of research; and the duties and rights of researchers (14).

i) Clinical trials: design, phases and types of drugs

Of the research protocol reports reviewed by the IWC in this study between 2012 and 2017,¹⁰ 90% of the clinical investigations are phase III on the efficacy, dose and safety of the drugs studied. Most of the protocols use the methodology of randomized groups, single or double blind, with detailed inclusion and exclusion criteria related to the pathology under study and the expected risks.

These studies are designed in two stages, so that the control group receives the study drug after collecting the data from the first group. The new antibiotics are compared with a standard antibiotic in double-blind studies. The drugs studied were, in decreasing order: antibiotics, anti-RSV, anti-HIV,¹¹ montelukast, inhaled dexamethasone, poloxamer, antibiotic cream, monoclonal antibodies.¹² On the other hand, several antibiotics studied, as well as inhaled drugs and certain monoclonal antibodies, can be considered *me too* drugs.

Some IWC members consider that the social impact of *me too* trials does not represent a major risk, and that they do not have legal backing that would allow them to not approve this type of trial when the other criteria are met. Others consider that the social value should be taken into account: price increase without obvious benefit and economic burden for patients and the health system. This situation requires a debate on the social impact: on the group? On society as a whole? So far this has not happened in the IWCs, and we consider that it requires the participation of organized society.

About 5% of the studies are phase IV follow-up studies of the treatment of a disease. These protocols arise from a lack of offi-

cial records from the region's health ministries and the need to design programs for these diseases. In addition to this problem of the state's social responsibility, there is an alliance between a pharmaceutical company and a medical association that shares personal data in the registries (privacy problem) and would allow this company to have a monopoly on this data.¹³

About another 5% of the studies are phase I, with trials of vaccines in pediatrics by infectious diseases, of intraocular devices for glaucoma in ophthalmology and of urethral catheters in urology.

j) Evaluation of clinical trial proposals

1. Required documentation

In order to review a protocol, the IBC requires the submission of a series of documents, such as data from the research team, the operation of the investigation, the protocol, process descriptions, and about the drug under study.

Some committees do not have a pharmacology specialist, which makes it difficult to review the investigator's brochure and the risks to participants. Most of the committees are faced with opposition from the pharmaceutical companies to modify their protocol, arguing that they are multi-center and that it is not possible to make changes for only one country.¹⁴

2. Recruitment of participants

It is mandatory to include the participant recruitment plan in the research protocol. CBI believes that medical researchers cannot recruit their patients, but must make a statement that an investigation will be initiated and that people can approach a team member at the appropriate address.¹⁵ The investigator may also ask other physicians to recruit volunteers for the research.¹⁶ These provisions comply with the principle of autonomy and transparency. However, the question arises about the subjective influence of the

doctor-patient relationship in the case of referring physicians and the notoriety of some researchers.

The selection of participants is determined by their pathology and their willingness to participate. The majority of participants are exclusively from the poorest and least educated sectors that depend on public health services, relying exclusively on the individual factor of age, gender or illness, without taking into account these external factors of vulnerability.¹⁷ This «biological» vision reflects a lack of knowledge about the social factors that can increase risks and that will be important when implementing them in the care, and to evaluate their impact in the control of this pathology. From the bioethical point of view, this practice clashes with equality, justice and non-maleficence (15).

Monetary and participant care incentives are not allowed in Panama (14), and the IWCs are vigilant about compliance with this provision (SOP).¹⁸ Pharmaceutical companies pay researchers to administer research and this includes the recruitment of participants. There have been occasional claims of incentives for peripheral physicians to recruit participants; however, there is no official evidence of this.¹⁹

3. Process of reviewing clinical trial protocols

The steps for the revision of a protocol have been defined in an SOP and the differences between IWCs are minimal, since the indicators follow PAHO guidelines adapted by the CNBI. Currently, the SOPs of all IWCs consider the maximum time for review of an investigation protocol to be 60 days, but it is generally reviewed in 30 days. Most CBI members interviewed consider this time to be sufficient.

4. Review of the informed consent (IC) process

This step is considered the most important by all the committees. Some request that the procedure for the IC be detailed in the protocol, as it is customary to provide the written form for the poten-

tial participant to read and sign. The related SOPs detail the points of written consent, both for adults and for children under 18 and those with disabilities, according to GCP guidance. It is mandatory to include that there are alternative treatments; to define randomization and placebo and the possibility of being in the group not receiving the experimental treatment; to indicate what the direct and indirect benefits of this research are, the risks and the measures foreseen to prevent or mitigate them. Also indicate where the care of the damages will be carried out, and it must be stated that there will be no cost for the participant or his or her family member.²¹

Biomedical research protocols indicate that they are funded by the pharmaceutical company, whose name is listed on the header page, and that the researchers are paid for their performance. The amount of this benefit and whether the institution where the research is conducted also receives a financial benefit is not indicated, because current laws do not require this.²²

The IWCs review the technical language, asking for clarification and more understandable wording in the context of the detailed information. It must be recognized that the IBC forms have become very complicated, are too long (more than 20 pages) and seem to be written to avoid legal problems rather than to inform patients. IWCs are requesting clarifying changes to the technical language on virtually all IQ forms and adjustments to the process itself on some, especially to ensure confidentiality and privacy. These change requests are honored by the investigators with the agreement of the funding pharmaceutical companies.

About five years ago, one of the CBIs faced a problem with a request for collection of what was left of biological samples, or for a new collection for future studies (*broad consent*) on the IC form for a research study. After reviewing the international literature and internal discussions, it was decided to require a separate form, which would allow the participant to participate in the main research, accept or refuse to submit their samples for future research independently. There was resistance from the funding company, but the

committee stood by its decision and eventually accepted the submission of two independent informed consents.

5. *Adverse Events (EA)*

The CBI has defined how and when investigators should report adverse events according to their level of severity, as well as deviations and amendments.²³ The CBI may request more information about a particular event until it is considered that it has been satisfactorily resolved. On occasion, the sponsoring financial institution has wanted to impose that information be provided to it so that it would report to the CBI (and to health authorities if appropriate). For this reason, the endorsement of the investigation has been conditioned on the information to be given to the CBI as a priority or in parallel with the sponsoring financial entity.

Another problem, results in the attention of the ADs that occur during the investigation. The IWC has been attentive to protocols that specify that participants will be compensated for this care; however, some protocols specify that this amount will be «reasonable» and that it concerns only «study-related» adverse events and not «in study». Often the care of AEs is left to the public institutions that provide the necessary care, or to the participant who must use his or her private insurance. In Panama there are two rates: the public health sector rate, which is subsidized by the State so that it is a minimum cost for users after a socioeconomic assessment of the family and its ability to pay. On the other hand, health insurance and care costs in the private sector have shown a significant increase in recent years.²⁴ The monitoring of the rights of participants and sponsoring institutions depends on the experience and consensus achieved by each IWC on these issues, since there is no specific legislation. The CBIs interviewed have imposed the change of the term «reasonable» to «compensation according to the official rates in the country»; this rate can be found on the websites of the Ministry of Economy and Finance and the Comptroller General of the Republic.

Another ethical problem results from the verification of the relationship of the AEs with the medicines in the study. Unless it is evident, which has been relatively rare, this relationship is left to the principal investigator or the sponsoring financial entity. None of the CBI members interviewed have mentioned any case in which this relationship was established. Nor did they recall the actual use of insurance taken out by the sponsoring financial institution. These two facts highlight the limits that CBIs have in verifying the intended compensation.²⁵

6. Monitoring and Supervision, Data Integrity and Reporting

The IWCs in Panama do not have a budget to carry out their functions, and this has been an impediment to adequate supervision. The CNBI asked accredited IWCs to conduct supervisions when they received questions or complaints from participants or observed inconsistencies in reports, or at the request of the investigators themselves. Some members of the surveyed CBIs have participated in these inspections which follow an established operating procedure.

The CBI technical secretariat agrees on a date for the inspection to ensure the presence of the principal investigator and the study manager. CBI appoints a three-member commission, with no conflict of interest with this site or the researchers, to conduct the inspection according to a question and document review form. This commission should have access to all research documents, respecting the principle of data confidentiality. The inspection report with the observations is signed by the commission members and those responsible for the investigation at the end of the visit, and is presented for discussion at the next regular meeting of the IWC. No IWC has overseen the implementation of a clinical trial through observation during a participant visit; nor is there capacity to oversee the recruitment and consent processes. This situation represents a problem that IWCs must address. A regular schedule of research site inspections is still lacking, due to the lack of financial and

transportation resources, and the multiple occupations of IWC members, who are not recognized as having this specific burden by their institutions. The perception of the institutional management authorities regarding research in general, and clinical research funded in particular, demands even greater conviction about its importance and, at the same time, clinical research funded is perceived as a private source of income.

During the implementation of approved clinical trials, the principal investigator must send progress reports, according to the periodicity set by the CBI that approved it. For low risk clinical trials, this report is sent every six months and annually. For higher risk trials, monthly or quarterly reports can be requested, in addition to the annual report.

5. Discussion

The right to life and health implies that the medicines used must be effective, safe and accessible. To this end, the medicines made available to patients, doctors and pharmacists must comply with a series of research stages before being marketed, without ignoring the stage of permanent pharmacovigilance after consumption (16). The history of drug research has been plagued by violations of participants' human rights, which have led to the establishment of international laws, standards, and guidelines that have served as models for local laws and regulations (3). Despite these legal standards, the media report corruption scandals in clinical research, which impact on the safety of participants and then on the sick (17).

Indeed, the production of medicines is an important economic industry (18), which finds a positive echo among Panama's economic decision makers. The Panamanian economic vision insists on the advantages of its geographical position and fiscal incentives (Cabinet Resolution No. 1, January 7, 2020). Within this framework, the installation of pharmaceutical companies in Panama

«towards the position of a pharmaceutical *pole*» is attractive, both for the ease of distribution of medicines in the region and for «the State's agenda for attracting direct foreign investment; for the country's labor conditions and the good receptivity of Panamanian governments».²⁶ This facility has been preceded and accompanied by the realization of clinical trials with medicines and vaccines whose results have changed some public policies,²⁷ and have consolidated the conviction in the treating physicians, researchers and general public of the absolute benefits of clinical research. However, it is important to consider the institutional position and the social influence of researchers linked to pharmaceutical companies for the IWCs when making decisions.

On the other hand, the current epidemiological profile in Panama is that of a society in transition. The first ten causes of death include cancers, cardiovascular diseases, hematological diseases and diabetes. Childhood and re-emerging infectious diseases are also a public health problem. Faced with this situation, health authorities have supported medical associations and international guidelines (19).²⁸ Funded research on medicines is part of the Panamanian epidemiological profile; the ethical problem lies in the State's ability to negotiate access to medicines that have proven to be beneficial. The IWC has approved research extensions for the direct benefit of participants, but the ethics of equity and justice, as well as the right to access to medicines, go beyond the functions of these committees. Other ethical problems result from *me too* medicines, and from social and pharmaceutical pressure on doctors to use them as «new», violating the principles of beneficence/non-maleficence, transparency and justice.

In Panama, the State has delegated to the institutional CBIs the role of monitoring clinical research, and to the CNBI its accreditation. Therefore, the criteria and their periodicity allow «harmonizing the scientific standards and rationalizing the documentary and administrative procedures used in the conduct of clinical trials with medicines for human use», and are accompanied by an accounta-

bility of the IWCs regarding the protocols reviewed, accepted and rejected, in addition to the registration and publication on the website of MINSA. However, the difference in experience between the older and newer IWCs highlights more the importance of initial accompaniment and ongoing advice on rare issues (20).²⁹

The collection of documents from the CBIs surveyed and from the interviews shows the conformity with current guidelines and the relative uniformity of the work and decision-making process of these committees. Each aspect of the review of a funded clinical protocol may represent a conflict of interest between different obligations: responding to the research and the funding company, and ensuring the protection of participants and society.

The transfer of knowledge and technology for the development of local and national capacities in research and health care is part of the social impact of research, and represents the expression of solidarity in international cooperation embodied in the DUBDH (UNESCO, 2005). The specialized tests are carried out in a laboratory outside the country that is linked to the pharmaceutical company, leaving the common tests for the local laboratories. National and international standards and IWC regulations do not mention this point as part of the review they are required to conduct; therefore, no SOPs were found on this topic.

On the other hand, most international protocols do not present the research budget, invoking their multi-center character and the confidentiality of these data in the face of market competition.³⁰ This situation may lend itself to institutional and researcher corruption practices (21), and should be discussed.³¹

The IWCs require, as proof of transparency, that the IWC form indicate whether the research team receives fees, but they do not request the amount of these fees or the amount of compensation from the institution hosting the research. Weissman and colleagues (22) report that more than half of CBI members believe that relationships with the pharmaceutical industry affect the integrity of research.³²

These situations were analyzed during the discussions for the drafting of Law 84 of 2019, which regulates research.³³ It is an important step and it is necessary to include the ethical values of equity and justice among the participants in the elaboration, analysis and publication of the research. The regulation of the law should take into account these principles in order to address the specific aspects of these possible agreements. Both in the case of technology transfer and in the transparency of research funding and management, the IWCs could act as facilitators between researchers and institutional managers within the framework of ethical principles of social responsibility.

Respect for the dignity of individuals implies respect for and protection of their privacy and the confidentiality of their data. IWCs have inscribed in their SOPs the monitoring of the confidential handling of participants' data. Provisions to preserve this confidentiality (collection, retention and destruction) should be included in both the protocol and the informed consent form; this obligation has not been questioned so far by the financial sponsors.³⁴

Regarding the handling of biological samples, SOPs require that it be specified how and for how long the samples will be kept, who will have access to them, and how they will be destroyed. This same information should be included in the informed consent. However, it is common for IWCs to require their inclusion after reviewing the documentation provided. The General Law 3 on Anatomical Components Transplants of 2010, establishes the conditions for import and export of biological samples. Despite this, pharmaceutical companies use the possibility given by the law to carry out studies outside when they do not exist in Panama. Lately, the companies condition the participation in the research of a medicine to the consent to keep the samples for future research, which represents a coercion of the participant, who has the perception that this research represents a hope to prolong his life or to diminish his suffering.

CBI members should have knowledge of clinical research methodologies until scientific review committees are operational. Some articles postulate that it is the responsibility of members to review the investigator's manual on the type of drug being studied, the methodology chosen, and possible biases (23, 24). However, these manuals are increasingly complicated, and the critical sensitivity of CBI members is very important in suspecting possible injury to participant safety.³⁵ It is important that at least one of the committee members is a pharmacist, and that the advice of a veterinarian can be sought on the types of animals used and the interpretation of the results in them, applying the risk-benefit, non-maleficence, prudence and benefit ratio.

Most of the researchers in these clinical trials are physicians who conduct research at research centers or at their private and sometimes public care facility. It is difficult for participants to separate care from research, even though all the documents mention that it is research, because the research physician has the title of the specialty that is treating your disease or will be treating it in the future. Even though he has been recruited by another doctor, it represents a bias that is difficult to resolve due to the size of the Panamanian population and the number of medical specialists.

The DUBDH, the Declaration of Helsinki and the CIOMS guidelines insist on the evaluation of the risk/benefit ratio as a criterion for the protection of the participant, and the application of these will depend on the knowledge and values of the members of the IWC. Evoking «reasonable risk» will depend on several factors, including the underlying disease, the research context, and ultimately the drug under study. We agree with Rudra and Lenk (25) that risk assessment should be progressive and permanent from the design of the research to establish mitigation measures, and that it is necessary to put an absolute limit on risk, particularly in extremely vulnerable patients. An important aspect is the possible psychological effect of the drugs under investigation on participants. If

these side effects have not been anticipated, it is difficult for participants themselves to associate them with the study medication (16).³⁶

On the other hand, previous rules on the renewal of IWC members every four years represented a handicap for the accumulation of experience in the management of clinical protocols and the inclusion of new members.³⁷ The lack of interest in bioethics until the last two years has meant that some IWC members have remained members who have administrative functions in their own institution. Therefore, some members remain in committees for several years and only now can they be progressively replaced, due to a greater interest in bioethics and the formation of new members.³⁸ To resolve this cause of conflict of interest, one IWC recently decided not to review the protocols in which the institution's leadership is involved. The CNBI and society in general must address these conflicts of interest in order to propose ethical solutions for a better quality of the work of the institutional IWCs (26). The continuing education programs of IWC members, and particularly IWC meetings and case studies, represent tools for improving the quality of their work. (27) In no case can these issues be invoked in favor of the development of «independent» committees outside of the institutions, whose financial relationships with the pharmaceutical industry represent conflicts of interest (28).

The participation of external members is important for the transparency of the discussions and the protection of the participants. The current IWCs have integrated people from outside the institution, with different results, due to the honorary nature of the members and the elitist image of science and scientists. The IWCs surveyed all have external members, but their capacity to intervene in discussions on the methodological and ethical quality of drug research is very uneven, despite their participation in the trainings.³⁹ Law 84 of May 2019 requires that IWCs have a minimum of 20% external members, and provides that they will be compensated for expenses incurred to attend meetings and trainings. What

should be the profile of these external members to strengthen the protection of participants against possible institutional interests?

The IWC's monthly reports allow for the recording of health research conducted in the country, reflecting the IWC's desire for transparency and constituting an important source of information for researchers, health decision-makers and the general public, so as not to duplicate research and to be alert to unapproved research.⁴⁰ But they do not allow for the evaluation of the quality of research or the protection of participants, researchers and institutions. These complex issues of complete safety in drug research have yet to be addressed.

Public sector administrative and financial rules are intended to present an image of transparency and accountability. However, they constitute a handicap for the continuity of previously programmed activities; in particular for educational activities, and represent a serious obstacle for the continuous supervision of ongoing research. This lack of oversight is the most serious problem perceived by the CBIs, as internal difficulties can be progressively resolved.⁴¹ One of the ethical problems of the current situation is that the IWCs have no alternative but to rely on the ethical sense of the researcher and his/her team in the development of the research. Therefore, IWCs must insist on the ethical education of researchers and on the development of a climate of mutual trust, as a basis for working together to protect participants and without hindering research. At the same time, the establishment of clear standards that are mandatory for the pharmaceutical industry means that the IWCs must be able to enforce them.

The hope of a treatment, even if it is still under investigation, is in itself an incentive to participate in it, when there is no evidence-based treatment yet. This situation represents a bioethical dilemma between beneficence (of a possibly effective treatment) and non-maleficence (not subjecting participants to unknown risks), which IWCs resolve according to their sensitivity. Is the ethics of individual and social responsibility a utopia?

6. Conclusions

Regulation of clinical research in Panama has progressed in favor of participants, as reflected in national laws and regulations adopted since 2003. However, two unresolved problems have been encountered:

1. The guarantee of health benefits and protection against adverse situations that depend, in addition to the ethical vigilance of the IWCs, on public policies in health and research. The weight of national and international companies in trade relations suggests that the resolution of this problem will be slow. In this sense, the role of the IWCs, academies, and researchers in educating patients' associations and the general public about their rights is important.

2. The bureaucratization of IWCs and the transformation of debates on research ethics into debates on compliance with existing laws and regulations in this area. IWCs should incorporate different disciplines and pluralistic thinking in order to encourage deliberation about the implications of pharmaceutical industry funded research in the Panamanian context of extreme social inequalities, and measures to contain this risk. The multiplication of CBI and the time needed to acquire the experience and moral strength to request the correction of some protocols or to reject them, represent a threat to the effective protection of the participants. In this sense, it is worth analyzing the possibility of segregating Bioethics Committees from Research with Medicines, specializing those functions as in the Spanish example (Royal Decree 1090/2015, December 4) (29).

Respect for life and human rights; health, safety and equality, as well as the protection of vulnerable persons and groups (Art. 3 and 15 of the UDHR); social responsibility and health (Art. 14); the sharing of benefits (Art. 15), as well as on ethical transnational practices (Art. 21) affirmed in the UDHR, and the ethical principles of autonomy, beneficence/non-maleficence and justice, should

constitute the ethical references for the discussion and the search for solutions to these problems.

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Bibliographic notes

¹ Chile withdrew and Costa Rica and El Salvador joined.

² To be consistent with the definition of Panamanian laws on this subject, we will use the term Research Bioethics Committees (RBC) instead of RECS, as this is the official name of these committees in Panama.

³ While the article was being prepared for publication, the National Assembly passed Research Law 84 in 2019.

⁴ One of them was not included in the analysis because of the little public information available.

⁵ The coordinators conducted in-depth interviews with six CBI members who had participated in the first stage and chosen at random and a new member. The objective was to clarify doubts and test whether some proposals being discussed in other countries would be acceptable in Panama.

⁶ Community members must participate in a course on research ethics and good clinical practice within the first six months of joining a CBI.

⁷ The CBI-ICGES also has two administrative secretariats, due to the volume of protocols under review.

⁸ Some years ago, there was an attempt to lobby which met with clear opposition. According to the IWC members interviewed, it has not been repeated since the last five years.

⁹ It modifies Executive Decree 1843 of December 16, 2014, which regulated the CNBI of Panama (OG No. 27,716), and made mandatory the registration of all health research.

¹⁰ In total, 165 protocols were approved for the four committees studied from 2007 to 2018, according to information on their websites.

¹¹ The anti-HIV studies are extensions of previous studies that allow participants to receive them; MINSA ensures the treatment of HIV/AIDS to the pediatric population

and adult volunteers. However, there is an empirical observation that the adult group is more compliant with a research protocol than the corresponding care clinics; this is an observation that deserves a psycho-social study that has not been conducted.

¹² Trials with vaccines were excluded because they are not considered medicines.

¹³ Some committees require that these data be shared with the Ministry of Health.

¹⁴ One of the committees requested major changes in a protocol based on the data found, which ended with the withdrawal of the research project from Panama.

¹⁵ There are no regulations on this point and it is up to each IWC to decide.

¹⁶ Researchers must report who will perform this function; they cannot be residents or interns.

¹⁷ Oncology research, which includes people from the public and private sectors, should be highlighted.

¹⁸ It is necessary to investigate whether problems of access to health services influence participation in clinical research.

¹⁹ As there is no law allowing the IWC to request this information, which is considered confidential by researchers and institutions, it is not possible to confirm these data.

²⁰ Placebo research without medication has been rare: for respiratory syncytial virus or new vaccines, and IWCs require that the participant or their guardian be informed of this possibility.

²¹ Research with possibly teratogenic drugs includes offering tested contraceptives and following the desired pregnancy until birth.

²² Funding institutions and researchers have relied on the absence of the legal framework not to respond to IWCs that have requested this information, and the IWCs themselves have not insisted.

²³ The CBI must ensure that the rules are met: sending the information in the established time to the General Directorate of the Ministry of Health and to the pharmaceutical companies; report of causality between the investigated drug and the adverse event. The report of adverse events and deviations must specify the measures taken to respond to them.

²⁴ These fees are not subject to review and control by the Ministry of Health.

²⁵ Law 84 of 2019 opens a possibility, by requiring a prior contract between the principal investigator, the sponsoring institution and the sponsoring financial entity to develop an investigation. Little by little the legal framework replaces ethical doubts.

²⁶ Martes Financiero magazine, which exposes the vision of the sector in Panama, has insisted on these advantages. Hernández K. 2020. [Accessed January 8, 2020]. Available at: <https://www.martesfinanciero.com/portada/multinacional-britanica-comprueba-ventajas-del-hub-farmaceutico/>

²⁷ Inclusion of antiretroviral treatment for pregnant women and vaccines against pneumococcus, rotavirus, papilloma virus in the National Immunization Program.

²⁸ The possible conflicts of interest of these groups are not known.

²⁹ This accompaniment is in the CNBI's accreditation SOP, and it is hoped that discussions for the regulation of Law 84 on research will address several of the concerns presented in this paper.

³⁰ Nor do they present the detailed local budget, because there are no regulations on this matter.

³¹ International reports on the subject are the subject of much discussion in the Panamanian media. The Star of Panama; January 23, 2020. Available at: <https://www.laestrella.com.pa/nacional/200123/panama-ocupa-posicion-numero-101-180-paises-indice-corrupcion>

³² The CBI members surveyed had no opinion on this issue and no specific SOP was found. The general opinion is that it is a function of national administrative and institutional authorities.

³³ Article 46: *Any proposal for international research to be carried out in the national territory must have the responsible counterpart in the country and with the support and endorsement duly formalized. Prior to the start of the research project, the respective agreement should be established between the funding sources, the information institution and the principal researcher, for the management of data that may be of importance for public health decision-making, economic aspects and other rights and obligations of the parties.*

³⁴ Law 81 on Personal Data Protection (2019) sets the legal framework for the collection, handling and storage of personal data in the Big Data era, and its implementation will begin in 2021. Because of its importance, IWCs will need training to apply it to clinical trials.

³⁵ All CBI respondents have requested the support of an external expert on a rare topic with good response.

³⁶ Both the design and duration of clinical trials (usually between six months and a year) make it difficult to observe these changes. Only oncology research provides for a follow-up period of at least five years.

³⁷ Law 84 attempts to respond to this situation by increasing the period of participation of members to six years, renewable only once

³⁸ According to Carla Sáenz, PAHO advisor on Bioethics, this permanence does not represent a problem, since it brings with it accumulated experience (Skype interview with CNBI).

³⁹ The interview of these external members was not foreseen in the design of this work, and it remains as a pending task.

⁴⁰ Registry of protocols, MINSA web version available at: <https://cnbi.senacyt.gob.pa/comites-acreditados/> and Reports of accredited Bioethics Committees available at: <https://cnbi.senacyt.gob.pa/informes-de-comites-de-bioetica-institucionales/> Accessed July 23, 2020. Both are publicly available.

⁴¹ CBIs need to develop expertise in protecting participants by detecting possible alterations, falsifications and omissions of data (particularly adverse events) during their own audits.

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