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The use of placebos in phase III clinical trials in Brazil

El uso de placebo en ensayos clínicos de fase III en Brasil

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ABSTRACT In 2008, Brazil's Federal Council of Medicine [*Conselho Federal de Medicina*] (CFM) – regulatory and supervisory agency on the ethical practice of medicine – banned the participation of Brazilian doctors in studies using placebos for diseases with efficient and effective treatment. This position differs with the Helsinki Declaration, which allows the use of placebos in methodologically justified conditions. To ascertain whether the CMF's ethical regulation modified the use of placebos in phase III clinical trials in Brazil, characteristics of the records in *ClinicalTrials.gov* were researched in the periods from 2003 to 2007 and from 2009 to 2013. The conclusions reached were: a) the regulations issued by the CFM in 2008 were ineffective and the position adopted by the Helsinki Declaration prevails; b) there was significant sponsorship by the multinational pharmaceutical industry of trials with placebos; c) the research was predominantly on new drugs for chronic diseases, with little study done of the neglected diseases which are of great importance to Brazil.

KEY WORDS Ethics, Research; Ethics, Medical; Clinical Trial; Placebos; Helsinki Declaration.

RESUMEN El Consejo Federal de Medicina de Brasil (CFM) –órgano normativo y fiscalizador del ejercicio ético de la medicina– prohibió, en 2008, la participación de médicos brasileños en investigaciones que utilizaran placebo para enfermedades con tratamiento eficaz y efectivo, en contraposición a la Declaración de Helsinki, que permite su uso en condiciones metodológicamente justificadas. Con el objetivo de verificar si la normativa ética del CFM modificó el uso de placebo en ensayos clínicos de fase III en Brasil, se analizaron varias características de sus registros en el ClinicalTrials.gov, en los períodos de 2003 a 2007 y de 2009 a 2013. Se concluye que: a) la normativa promulgada por el CFM en 2008 fue ineficaz y prevaleció la posición adoptada por la Declaración de Helsinki; b) el patrocinio de ensayos con placebo por parte de la industria farmacéutica multinacional fue significativo; c) predominaron las investigaciones de fármacos para enfermedades crónicas, y fueron poco significativas para las enfermedades postergadas, de importancia para Brasil.

PALABRAS CLAVES Ética en Investigación; Ética Médica; Ensayo Clínico; Placebos; Declaración de Helsinki.

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INTRODUCTION

While dating several centuries back when it was used by doctors and medicine traders, the use of placebo in therapy has been discussed in debates about medical ethics up to the present.[1-3] Similarly, the use of placebo as a comparator in clinical studies started after the Second World War.[4] Although the immorality of the medical studies precedes the atrocities of the Nazi concentration camps,[5] it was the International Military Tribunal and the trial of the main war criminals that gave rise, in 1947, to the first set of international ethical principles for research studies of human beings known as the Nuremberg Code. In the same year, the World Medical Association (WMA) was re-established with the sole purpose of sharing the common problems of doctors around the world and restoring the image of medicine. As a consequence, in 1954 at the 8th General Assembly in Rome, the WMA adopted the "Resolution on human experimentation and the principles for those in research and experimentation," a document that was precursor to the Declaration of Helsinki.[6] Although the subject was a matter of debate at that time, neither of these two documents addressed the use of placebo in medical research. Even in the 1st Declaration of Helsinki in 1964 and in its first revision in 1975, the term "placebo" was still absent, although in this revision, the term "best current" was coined for the diagnoses and methods of therapy used as a comparator in the studies, assuring the best treatment for all research participants. Therefore, although at that time the term "placebo" was not explicit, everybody assumed that when there was an existing known therapy for the disease under study, the use of an inert procedure or substance as a comparator in the control group would be regarded as an ethical fault. Around the 1970s, for the first time, Sissela Bok observed the deceptive use of placebo in clinical treatments and clinical trials, where on several occasions the patient was not informed of its use.[7] According to this author, apart from frequently causing unforeseeable risks, the use of placebo would contribute towards compromising the prestige of the institution and losing trust in the medical team. Therefore, from that time onward, the discussion over placebo use has become more intense and frequent, and it is being held with new evaluation parameters. At the end of the 1980s and in the beginning of the next decade, multiple reports of studies using placebo for diseases with existing therapy were published in highly prestigious scientific journals,[8,9] which led the WMA to pass a revision of the Declaration of Helsinki in 1996, reaffirming that the use of placebos would only be ethical when no other known therapy existed.

In October 2000, the 52nd General Assembly of the WMA, held in Edinburgh, Scotland, adopted the 5th revision of the Declaration of Helsinki that stated that using a placebo in a group control was ethical only in cases where no known intervention existed. The text that was passed at that time arose so much controversy around the world that, in 2002, the WMA attempted to clarify the doubts about placebo use, which is available for reading in paragraph 29 of such revision. It was then, at the 53rd General Assembly held in Washington, that the use of placebo in control groups of clinical trials was expanded, enabling its use even for diseases with known therapy available, in cases where there are scientifically sound reasons or when the patient is not subject to serious risks or irreversible harm. However, instead of providing clear guidance, the note of clarification increased the controversies over placebo use.[10]

Thus, the most discussed topic in the Declaration of Helsinki, due to its ethical, methodological, scientific, and economic implications, is still the use of placebo in multicenter clinical trials, especially those conducted in developing countries with extremely limited resources.

In relation to the debate over placebo use in clinical research studies, Brazil – through the Federal Council of Medicine (CFM) [*Conselho Federal de Medicina*], the National Commission for Ethics in Research [*Comissão Nacional de* Ética *em Pesquisa*], the National Health Council (CNS) *[Conselho Nacional de Saúde*], and the Brazilian Society of Bioethics [*Sociedade Brasileira de Bioética*] – has attracted international attention due to its countless actions to defend the ethics of clinical studies, taking into account participants' safety and placebo use exclusively for disease studies without known therapy available.[11,12] In this scenario, 2008 was an important year for this discussion due to three reasons: first, due to the 59th General Assembly of the WMA in Seoul, in which the greatest amount of flexibility in the

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Declaration of Helsinki was passed and such flexibility was included in paragraph 32.[13] Second, since this revision could have led to reducing participants' protection and increasing the benefits of the sponsors,[14] the CFM, immediately after the meeting in Seoul, issued CFM's Resolution 1885/2008, which categorically banned Brazilian doctors from engaging in any trial using placebo where there are efficient and effective treatments available.[15] Third, in 2008 as well, the CNS, the highest institution for deliberation on the human health domain, urged by the National Commission for Ethics in Research (CONEP) *[Comissão Nacional de* Ética *em Pesquisa*], passed an ethical regulation on the control of placebo use (CNS's Resolution 404/2008) restricting it to situations where no proven prophylactic, diagnostic and therapeutic methods existed.[16] Completing and reinforcing this orientation, CFM kept, in the new Code of Medical Ethics[17] passed in 2009, in the chapter on Medical Research and Teaching (Article 106), the same spirit of CFM's Resolution 1885/2008.

Therefore, the aim of this study is to learn the actual frequency of placebo use in phase III clinical trials conducted in Brazil, considering the year 2008 as the turning point, and identifying a few of its features, such as the role of Brazil in clinical trials, its primary sponsors, the most researched diseases, its use in diseases with known therapy (type 1 diabetes, type 2 diabetes and hypertension) and the introduction of the word "placebo" in titles of trials registered in *ClinicalTrials.gov*.

METHODOLOGY

The research study was carried out between January and March, 2014, and it was about the clinical trials included on the ClinicalTrials.gov web site that were registered between January 1, 2003 and December 31, 2007, and between January 1, 2009 and December 31, 2013. The aim was to compare the drug clinical trials conducted in the five years before and after 2008, when CFM's Resolution 1858/2008 and the 2008 Declaration of Helsinki were passed. The data was analyzed by reading the official titles and the methodology of the projects registered in the periods mentioned above.

ClinicalTrials.gov is a web-based public resource that provides information on clinical studies that are testing the efficacy of experimental drugs for a wide range of diseases. The site, created as a result of the Food and Drug Administration (FDA) Modernization Act of 1997, was at the public's disposal in February, 2000, and it has been maintained and updated by the *National Library of Medicine* (NLM), which reports to the National Institutes of Health (NIH).[18]

Hence, in the first stage, with the purpose of establishing the total annual number of clinical drug trials, the following search fields and descriptors were used under the "Advanced search" option:

ADVANCED SEARCH:

Search terms: "*Drug*"
Recruitment: "*All studies*"; "*Exclude Unknown Status*"
Study Results: *"All studies"*
Study Type: *"Interventional Studies"*

TARGETED SEARCH:

Interventions: *"Drug"*

LOCATIONS:

Country 1: "*Brazil*"

ADDITIONAL CRITERIA:

Gender: *"All Studies"*
Age Group: *"Child"; "Adult"; "Senior"*
Phase: *"Phase 3"*
Funder Type: *"NHI"; "Other US Federal Agency"; "Industry"; All others (Individual, University, Organization,...)*
First Received: *From 01/01/2003 to 12/31/2003.*

The same procedure was repeated for all the years under study.

In the second stage, in order to establish the number of trials using placebo, the word drug was changed to placebo on the Interventions search field; and for the different variables of the studies, as an example, the name of the disease taken from the International Classification of Diseases of the World Health Organization (WHO) was entered on the Conditions search field below TARGETED SEARCH. In order to identify the sponsors of the trials, in the Funder Type item, the options

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Industry; NHI; Other US Federal Agency; All others (Individuals, Universities, Organizations...) were separately checked, integrating research institutes, hospitals and foundations, both Brazilian and foreign as well as public or private.

In order to verify the frequency of the use of placebo in phase III studies of diseases with countless therapy alternatives, the same procedures were followed on ClinicalTrials.gov to study type 2 diabetes and hypertension trials, and a search was launched on October 12, 2014 with and without the word "placebo" in the "Interventions" field. Finally, to identify if the use of placebo in trials registered in ClinicalTrials.gov in the mentioned ten years expressed that information in the brief title and in the official title, on January 10, 2014, a thorough reading was carried out over the study design of the group of treated patients and of the control group (placebo) and it was compared with the two types of trial titles. The brief title is determined by the research study team and it may be omitted if the researchers so desire. However, the official title is compulsory, must be detailed, and must include the name of the intervention, the condition under study and the outcome.[19] Currently, ClinicalTrials.gov, apart from gathering studies from the 50 states in US, also stores information on clinical trials conducted in more than 180 countries.

For the statistical analysis, Fisher's exact test was used.

RESULTS

In the periods under review there was an increase in the number of trials (Table 1), going from 392 in the five years before 2008 to 615 in the subsequent five-year period. Another observation is that out of the total 1007 clinical trials registered in the 10 years under study, placebo was used in 438 clinical trials (43.5%). There was no difference regarding statistics between the proportions of the clinical tests that used placebo and the tests that did not use placebo in relation to the periods before and after 2008 ($p = 0.696$), considering all types of sponsors.

When selecting only the studies sponsored exclusively by the pharmaceutical industry (Table

Table 1. Phase III clinical trials with drug intervention, conducted in Brazil with and without placebo use, registered in ClinicalTrials.gov between 2003 and 2007, and between 2009 and 2013.

Years	Clinical trials with placebo		Clinical trials without placebo		Total clinical trials	
	n	%	n	%	n	%
2003	12	1.2	10	1.0	22	2.2
2004	10	1.0	25	2.5	35	3.5
2005	43	4.3	67	6.6	110	10.9
2006	53	5.2	75	7.4	128	12.6
2007	49	4.9	48	4.8	97	9.7
Subtotal	167	16.6	225	22.3	392	38.9
2009[a]	53	5.2	88	8.7	141	13.9
2010[a]	87	8.6	70	6.9	157	15.5
2011[a]	41	4.1	82	8.2	123	12.3
2012[a]	45	4.5	59	5.9	104	10.4
2013[a]	45	4.5	45	4.5	90	9.0
Subtotal	271	26.9	344	34.2	615	61.1
Total	438	43.5	569	56.5	1,007	100.0

Source: Own Elaboration.
[a]Years after implementing CFM's Resolution 1885/2008 and after the revision of the Declaration of Helsinki, Seoul, 2008.

2), the same proportion of trials before and after 2008 with placebo use was maintained ($p = 0.944$). However, in the trials sponsored by other organizations (Brazilian and foreign universities, National Institutes of Health in US and other national organizations), there is a significant increase in the period under review, going from 16.1% (5/31) in the years before 2008, to 43.1% (44/102) in the subsequent five-year period ($p = 0.006$). As shown in Table 2, the pharmaceutical industry funded 92.1% (361/392) of clinical trials between 2003 and 2007 and 83.4% (513/615) in the subsequent five-year period, reaching 86.8% (874/1007) in the 10 years under study.

When identifying sponsors, evidence confirms that seven pharmaceutical industries funded 47% (206/438) of studies with placebo in Brazil: Sanofi-Aventis, 37 trials; Hoffmann-La Roche, 35; Novartis, 32; Bristol-Myers Squibb, 29; Eli Lilly, 28; AstraZeneca, 24; and Janssen, 21 trials (Figure 1).

Regarding the diseases being studied with placebo use (Table 3), the largest percentage belongs to neoplasms with 23.1% of the 438 trials, followed by circulatory system diseases (12.8%), endocrine, nutritional and metabolic diseases (12.3%) and certain immune system-related disorders (11.0%). Certain infectious and parasitic diseases account for less than 10% of the clinical trials.

In regards to phase III clinical trials on type 2 diabetes, for those conducted between 2003 and 2013 and funded by any type of sponsor, evidence confirms that placebos were used in 49 out of the 93 registrations (52.7%) with *ClinicalTrials.gov*; out of this total number, 92 (98.9%) were funded by the pharmaceutical industry. When comparing the prevalence of placebo use on studies of type 2 diabetes in the five years before 2008 with the five years after 2008, excluding 2008 itself, an important, although not significant, increase occurred in the last five-year period, going from

Table 2. Sponsors of phase III clinical trials with drug intervention conducted in Brazil with placebo use, registered in ClinicalTrials.gov between 2003 and 2007, and between 2009 and 2013.

Years	Total clinical trials (Phase III)			Trials sponsored by the pharmaceutical industry			Trials sponsored by other institutions[a]		
	Total	With placebo		Total	With placebo		Total	With placebo	
	N	n	%	N	n	%	N	n	%
2003	22	12	54.5	19	12	63.1	3	0	0.0
2004	35	10	28.6	31	9	29.0	4	1	25.0
2005	110	43	39.1	101	41	40.6	9	2	22.2
2006	128	53	41.0	122	53	43.4	6	0	0.0
2007	97	49	50.5	88	47	53.4	9	2	22.2
Subtotal	392	167	42.6	361	162	44.9	31	5	16.1
2009[b]	141	53	37.6	118	43	36.4	23	10	43.4
2010[b]	157	87	55.4	141	79	56.2	16	8	50.0
2011[b]	123	41	33.3	103	31	30.1	20	10	50.0
2012[b]	104	45	44.2	79	38	48.1	25	7	32.0
2013[b]	90	45	50.0	72	37	51.4	18	8	44.4
Subtotal	615	271	44.2	513	228	44.4	102	44	43.1
Total	1,007	438	43.6	874	390	44.6	133	48	33.8

Source: Own elaboration.
[a]National Institutes of Health (NIH) in US, other US federal agencies, individuals, universities, Brazilian laboratories, organizations, among others.
[b]Years after implementing CFM's Resolution 1885/2008 and after the revision of the Declaration of Helsinki, Seoul, 2008.

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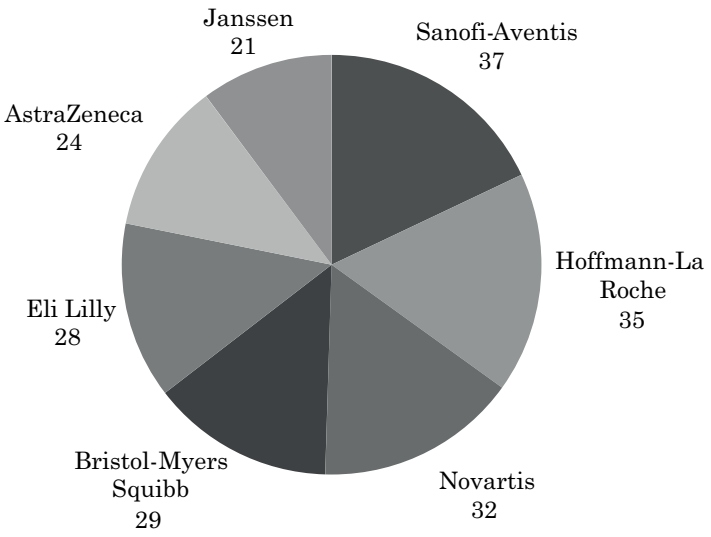

Figure 1. Pharmaceutical industries sponsoring 47% (206/438) of phase III clinical trials with drug intervention and placebo use, conducted in Brazil and registered in ClinicalTrials.gov between 2003 and 2007, and between 2009 and 2013.

Source: Own elaboration

Table 3. Diseases under study in phase III clinical trials with drug intervention conducted in Brazil with placebo use, registered in ClinicalTrials.gov between 2003 and 2007, and between 2009 and 2013.

Diseases[a]	Before 2008		After 2008[b]		Total	
	n	%	n	%	n	%
Tumors (neoplasms)	39	8.9	62	14.2	101	23.1
Circulatory system diseases	28	6.4	28	6.4	56	12.8
Endocrine, nutritional and metabolic diseases	28	6.4	26	5.9	54	12.3
Certain immune system-related disorders	14	3.2	34	7.8	48	11.0
Certain infectious and parasitic diseases	9	2.0	31	7.1	40	9.1
Nervous system diseases	8	1.8	19	4.3	27	6.1
Digestive system diseases	11	2.5	15	3.4	26	5.9
Blood diseases	1	0.3	5	1.1	6	1.4
Others	21	4.8	44	10.1	65	14.9
Total	167	38.1	271	61.9	438	100.0

Source: Own elaboration.
[a]Designation according to the 2010 International Classification of Diseases of the World Health Organization (WHO).
[b]After implementing CFM's Resolution 1885/2008 and after the revision of the Declaration of Helsinki, Seoul, 2008.

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44.5% (20/45) to 64.2% (25/39) ($p = 0.05645$). In the study about hypertension, in the period between 2003 and 2013, in phase III trials, 15 trials out of a total of 36 (41.7%) were conducted with placebos, and 31 out of that total 36 (86.1%) were sponsored by multinational pharmaceutical companies. In the comparative stratification before 2008 (2003-2007) and the comparative stratification after 2008 (2009-2013), the percentage figures were 40.0% (6/15) and 31.2% (5/16), respectively; their difference attains no statistical significance ($p = 0.4467$).

In this research study, placebo in the control group is highlighted for having been possibly used as a complement to any other – active or inactive – drug, or as a sole (pure) drug in the control group of an experimental drug.

In relation to the presence of the word "placebo" in the official title of trials using placebo, out of the 438 trials studied on January 25, 2014, the word "placebo" was present in 290 of them (66.2%). Therefore, nearly a third of these studies did not contain any information about them being placebo-controlled. Regarding brief titles, out of the 391 registered trials, 342 (88.5%) did not include the term "placebo."

DISCUSSION

There was a significant increase in the number of phase III clinical trials with recruitment from Brazil that were registered with ClinicalTrials.gov in the periods under study, going from 392 before 2008 to 615 after that year (Table 1). With regard to that increase, between 2003 and 2005, that number became five times larger and rose from 22 to 110. Such increase might be a result of the International Committee of Medical Journal Editors (ICMJE)[20] starting to demand, from 2005 onward, that only articles with their trial results registered on a public platform should be accepted. Although there was a significant increase in the year mentioned above in accordance with such demand,[21] data for that year in Brazil is the result of an increase in the number of projects analyzed by the Brazilian Health Surveillance Agency (ANVISA), which had approved 198 clinical trials, 107 of which (54%) were phase III.[22] That means that even if there was a possible limitation in the registration of clinical trials before 2008, the increase in trials in Brazil in the period being studied could be considered real.

Compared with other countries in South America, Brazil is the leader, as verified by the current registrations with *ClinicalTrials.gov*. So, on the map displayed on this platform that compiles figures for all types of clinical studies (interventional and observational) registered around the world through its years of operation, out of the 6050 studies conducted in this region up to October 12, 2014, 4115 of them were conducted in Brazil and 1808 in Argentina. Such figures registered for Brazil are similar to the figures for the whole African continent (4121).[23] Brazil has been in 15th place on the worldwide scale for clinical trial conduction since 1990,[24] estimating that, only in the last 10 years, more than 100,000 volunteers participated in clinical studies.[25] This yields an estimation of a rough average of 100 participants per trial, when considering the 1007 trials registered in this study in 10 years. This reality is partly the result of the growing globalization of clinical trials in the worldwide scenario, in search of recruiting participants for the studies,[26] which might give rise to ethical consequences.[27] Among the weaknesses of clinical research studies in the context of social vulnerability, the trial participants' instrumentalization derived from the pharmaceutical industries' necessities is highlighted, said industries tend to move to middle-income and low-income countries, as is exemplified by the Brazilian scenario.[28] The developing countries joined the route of investments of the pharmaceutical companies since cost reduction is one of the principal stimuli to expand their presence in peripheral countries.[29] This phenomenon is the result of reducing the number of trials in developed countries due to the delay in the conduction of trials by those in charge of the academic centers and the subsequent use of the contract research organizations (CRO) to accelerate the development of clinical research studies.[30] As a consequence, there has been a progressive increase in clinical research studies in Brazil and an increased participation from the multinational pharmaceutical industry.[31] This study served to confirm that foreign participation in clinical trials conducted in Brazil was 86.8% (874/1007) in the 10 years under study and that 47% (206/438) of these clinical research

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studies using placebos in Brazil were sponsored by only seven companies (Figure 1), out of which, five (Sanofi-Aventis, Hoffman-La Roche, Novartis, Eli Lilly and AstraZeneca) constitute the Big Pharma group, which includes the global top 10 companies, based on revenue in 2014.[32] Other studies report similar outcomes, specifically that 75% and 80% of clinical trials in Brazil are sponsored by the pharmaceutical industry.[24,33] The second percentage figure is reported by the Brazilian Health Surveillance Agency. The mentioned figures show an increase in clinical drug trials conducted in Brazil that are sponsored by foreign companies. This increase is in direct opposition to the visions that the ban imposed by the Federal Council of Medicine on the unethical use of placebo expected, which should have decreased the research studies in the country.[34]

Hence, drug research studies in Brazil are regarded as multicenter, international studies led by the companies' headquarters and, therefore, are conducted with little interference from the developing countries' professionals, who are devoted to start and monitor the data generating process, according to a pre-established methodological design.[24] This is the case despite the fact that Brazilian professionals are highly qualified to conduct phase III clinical trials, reasonably qualified for phase II and IV trials, and extremely unqualified for phase I research studies.[35]

As for the diseases researched in the clinical trials conducted in Brazil with placebo use in the ten years under study, neoplasms were the most researched diseases, with 23.1% out of the 438 clinical trials, with a growing global presence and the constant search in laboratories for the discovery of active drugs. The other most researched diseases also present with prolonged clinical behavior, such as circulatory system-related diseases, endocrine, nutritional and metabolic diseases and certain immune system-related disorders. However, this is just a part of the Brazilian necessities, since the country is still affected by really important endemic diseases in its nosological framework, namely: malaria, dengue, Chagas disease, leishmaniasis, schistosomiasis, leprosy, viral hepatitis, among others.[36] Historically, pharmaceutical companies have conducted relatively fewer research studies for new drugs to treat neglected diseases since these diseases mostly affect people with very low incomes; for that reason, investment is of no interest to the pharmaceutical companies. An example of this is that, between 1975 and 1999, out of 1393 drugs, only 16 new drugs were commercialized for tropical diseases and tuberculosis.[37] In this study, in relation to Brazil, the treatment for neglected diseases, which are of great interest to the country, was hardly studied, with less than 10% of research studies with drug intervention (Table 3).

The outcomes of this study show that research studies of drugs are controlled by a small number of big multinational companies and that their research studies follow the market laws more than the medical priorities or the social necessities of the place in which they are conducted.[38] For this reason, since drug development for neglected diseases will not be performed by the pharmaceutical industry, it should be fostered by the public organizations in the region.[39] This economic interest in drugs that are used continuously has led the industries to nearly abandon the research study of acute disease drugs; the most conclusive and dramatic example is the identification of new antibiotics, which is pushed into the background despite the serious and growing problem of antimicrobial resistance. Antimicrobial resistance results in deaths all over the world in alarming numbers and opens the malevolent perspective of threats of bioterrorism and irreparable economic losses.[40]

As for placebo use in clinical studies, the latest news on the ethics of research studies reveals the contradictions of the deceptive use of placebo in clinical treatment and clinical trials. Several times placebos were used without informing patients of their use, since, apart from frequently causing unforeseeable risks, it compromises the prestige of the institution and causes a loss of trust in the medical team.[7] Unbelievably, after nearly half a century, questions about the use of placebo are still generating discussions and controversies, envisaging the existence of powerful forces that are able to push for endless years in order to justify what cannot be justified about the daily use of placebo in clinical trials for diseases with known treatment.

Clearly, there are opinions in favor of placebo-controlled trials for diseases with known treatment[41] and other opinions against this position.[9,12] The former opinions state that placebo

use reduces the number of participants in clinical trials, it is faster and cheaper for sponsors, and that it is justified, from a methodological viewpoint, because effectiveness and safety are better tested that way. Many of those justifying placebo use for methodological and scientific reasons, agree that testing a new drug on diseases with proven effective treatment is unethical.[42] On the contrary, those criticizing this position highlight essential ethical matters, such as the right to the best current treatment, taking into account that, in controlled trials, clinical equipoise no longer exists, since placebo does not treat diseases and, therefore, when clinical equipoise is lost, the study becomes ethically fragile.[10] Undeniably, in those trials, there is a reduction in protection due to placebo use because it substitutes an active drug that could be administered to control group participants for diseases with known treatment.

In this study, the achieved outcomes show an excess of placebo use, both before and after 2008, the year in which the new ethical regulation was passed by the CFM. Such excess can be observed by the 43.5% (438) of the total 1007 clinical trials that were registered in the ten years with the *ClinicalTrials.gov* platform, with no significant difference found between the two periods under study. Remarkably, unsuccessful efforts were made to find in the references other studies that have used a methodology akin to this research study. Nevertheless, a cross-sectional study on psoriasis detected placebo use in 38.5% of drug intervention trials, with a much higher frequency in industry-funded trials compared to those funded by other sponsors.[43] Such figures might be the result of a large number of placebo-controlled trials conducted by the pharmaceutical industry throughout history, independent of any national or international ethical regulation and, generally, supported by the US Food and Drug Administration.

However, one surprising piece of information revealed by this study is the significant increase in placebo use after 2008, compared with the previous period, in trials sponsored by non-industry sectors, such as universities and public organizations ($p = 0.006$). A possible explanation may be the flexibility permitted by the latest revisions of the Declaration of Helsinki, as opposed to CFM's Resolution 1885/2008 which restricts placebo use to diseases without known treatment. Complementing the observations in this study, the excess of placebo use in research studies for type 2 diabetes and hypertension is noteworthy; these are chronic diseases for which a reduction in frequency was expected, taking into account the multiple existing drugs for their treatments. In phase III clinical trials for type 2 diabetes, placebo use in almost 53% of clinical research studies in the period studied is ethically unjustifiable. Considering the high percentage of placebo use in the five years before and after 2008 in type 2 diabetes it was expressed that placebo use was a methodology permanently employed by the pharmaceutical industry and that it found no ethical support in any national regulation. The highest percentage after 2008, although there is no statistical significance in the last five-year period, represents an important increase that must be regarded and might be related to the increase in tolerance that exists in the revision of the 2008 Declaration of Helsinki. What kind of explanation can be given for the fact that, in more than half of those drug interventions in type 2 diabetes, the control group receives placebo even though there are several alternatives known for efficient treatment available? A similarly surprising and exaggerated situation arose as far as hypertension trials are regarded, since 4 out of 10 trials were placebo-controlled, presenting an equally high frequency when comparing the years before and after 2008, which proves that such methodology is constantly used throughout the years, similar to type 2 diabetes. Such placebo-controlled hypertension trials are deemed unethical, especially due to their lengthy duration; for that reason, placebo use is not advisable because of the risks that it poses to participants, as suggested by the US FDA.[44] Data on diabetes and hypertension trials reveal the disregard for the national ethical regulations since, when admitting that those companies' protocols are elaborated abroad and that more than 90.0% of those trials are sponsored by multinational pharmaceutical companies, Brazilian doctors are entitled to choose to not be part of the local teams of trials whose characteristics are repudiated by the national and Latin American medical entity and by the Brazilian organizations of bioethics and the system of Research Ethics Committees and the National Commission for Ethics in Research. A

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study on placebo clinical trials in Brazil showed that, although most of them respect the national ethical regulations, greater rigor is necessary for employing placebo control group and for participants' protection.[45]

As a result of these ethical abuses, these suggestions were offered for Latin America [46]: a) the absolute rejection of placebo use in clinical trials, in any type of study; b) the abandonment of the Declaration of Helsinki; c) the creation of an ethical document specifically for Latin America based on its regional reality.

These different opinions become more evident when comparing placebo-controlled trials in developed countries with those in developing countries. In the latter countries, the phenomenon called "double standard" is firmly rejected;[47,48] however, many believe that its use in low-income countries or communities with a poor health care and medical infrastructure is ethically justifiable.[49] The "placebo effect" is a mysterious causal agent of benefits, as claimed by the pharmaceutical industry, taking into account that a positive effect might equal spontaneous improvement or might be the result of the power of the participant's suggestion.[39]

Therefore, what explanation can be given for the fact that in more than 50% of the type 2 diabetes trials mentioned above and in almost 40% of hypertension clinical tests conducted in Brazil, the control group receives placebo when many existing known drugs are efficient for both diseases?

Surprisingly enough, in Brazil, where there is a system of ethical control with double evaluation for clinical trials that have foreign cooperation and funding – by one local committee and one national committee – so many unethical studies for diabetes and hypertension have been approved, using placebo in their control group. In clinical trials on cancer introduced in the Meeting of the American Society of Clinical Oncology, 65% of the 26 studies had no authorization from the ethical agencies[39] and, in addition, half of the studies registered with *ClinicalTrial.gov* were never published.[50] Another important fact is that, in 2005, a few clinical trials in Brazil were conducted without the relevant ethical authorization.[31] Despite this fact, it is hard to imagine that this might happen in Brazil in relation to several studies on type 2 diabetes and hypertension, or perhaps it might be the result of constant faults committed by the Research Ethics Committees and the National Commission for Ethics in Research on Humans. In addition, the well-known lack of control and monitoring of clinical trials of the Brazilian ethical system needs to be reviewed so that similar situations do not turn into a constant feature. Whatever the answer to these doubts may be, to ponder on the participation of the teams involved in these trials is important, particularly of physician-investigators, taking into account that medical action breaches the Hippocratic principle *primum non nocere*, or non-maleficence, whose participants are called therapeutic orphans.[51] Factors related to serious conflicts of interests are acknowledged to possibly lead Brazilian doctors to participate in the studies mentioned above and to leave aside CFM's Resolution 1885/2008, their Code of Medical Ethics and the bioethical principle of beneficence over a secondary interest. That attitude inverts the historical relation between doctor and patient, where the doctor meets the patient's necessities, while the physician-investigator might be motivated by other interests, such as seeking scientific prestige, participating in the management of the financial resources for the investigation project and increasing their scientific production.[52] The possibility that doctors induce their vulnerable patients to participate in trials motivated by big compensation for conducting them is also cited in the references.[53] Along the same lines, the authors of the classic piece *Principles of Biomedical Ethics* emphasize that the two roles of the physician-investigator and the clinician go in different directions and entail both obligations and conflicts of interests.[54] They even describe that research studies on human beings, although important to society, are also morally perilous, since individuals are exposed to a certain degree of risk for science's benefit, stating that: "placebos cannot be used if an effective treatment exists."[54 p.492] This seems to show that there is an ethical problem inherent to clinical research study in the country, considering regulations that oppose placebo use in clinical trials when proven interventions exist.

It is worth highlighting that, in 2008, in addition to the prohibitive regulations adopted by the Federal Council of Medicine, the Brazilian government, through the National Health Council

also objected to the revisions of the Declaration of Helsinki that allowed the release of placebo research studies when proven treatments existed, for which reason it issued CNS's Resolution 404/2008.[16] CNS's Resolution 466/12 does not ratify the 2008 Declaration of Helsinki but accepts only the Declaration passed in 2000 in Edinburgh, Scotland.[55] Similarly, the Brazilian Bioethics Society (SBB) [*Sociedade Brasileira de Bioética*] objected the use of placebo in clinical trials for interventions with already-existing treatment.[56]

In Latin America there is a strong movement against the indiscriminate use of placebo in clinical trials, led by the Medical Confederation of Latin America and the Caribbean (CONFEMEL) [*Confederación Médica Latinoamericana y del Caribe*],[57] an organization that gathers similar entities from the countries in the region and that has vehemently taken its position in such subject. The first public statement was given in 2012 with the Declaration of Bogota[58] that dealt with medical study on human beings in its XV Ordinary General Assembly when it stated that: a) it does not allow placebo use in diseases with efficient medicine; b) it objects to paragraphs 32 and 33 of the Declaration of Helsinki for contradicting the principles and values of the medical profession; c) poor and vulnerable populations in the region must have the same levels of safety as in the trials conducted in developed countries. The CONFEMEL passed in November 2013 the Declaration of Pachuca,[59] with severe and harsh criticism against the 2013 revision of the Declaration of Helsinki made in Brazil. The document suggests that governments should not allow trials with the ethical bias of using placebo in studies for diseases with known treatment available, and it proposes reporting such situations at all levels of the Executive Branch in order to prevent them from being applied in the territory. This seems to reflect the strong discontent of the supervisory agencies of the medical practice in Latin America and the Caribbean at the flexibility of placebo use introduced in the Declaration of Helsinki in 2013.

The use of placebo in a few types of clinical research studies, particularly in Brazil, might be related to other interests that are not especially research study subjects' protection, since the studies considered critical were expected to decrease their number from an ethical viewpoint. On the contrary, even after the CFM's Resolution 1885/2008, the medical behavior seems to have been insensitive to the position of restraining placebo use in these clinical trials, which might be considered a severe ethical breach. The necessity of acknowledging the risks of the participants in these trials seems to have been replaced by the marketing necessities of medicine production.

Regarding the most used databases for registration of clinical trials, the *ClinicalTrials.gov* platform was described as the only existing database that meets the criteria adopted by the International Committee of Medical Journal Editors,[19] although currently other registrations on international platforms are accepted. Two studies conducted about *ClinicalTrials.gov*[60,61] and one study conducted about the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization[62] concluded that they have large limitations, such as the high prevalence of clinical trials with insufficiently described methodology, which correlates with what was found in this study regarding difficulties to properly identify the type of intervention of the control group, which can result in a limitation that should be considered. It should be noted that, despite the fact that the three international studies mentioned above have addressed the interventions in the trials, they oddly included no assessment on placebo use, which seems to prove the prevalence of the technical-scientific interest over the most relevant and most debated ethical issues related to drug trials. Considering such flaws in registrations, it should be warned that various studies might get different outcomes. For that reason, it is suggested that international platforms be revised.[61,63]

A few objections to *ClinicalTrials*.gov mentioned in this study that could be expanded are:

a) Multicenter trials that do not specify the number of participants per country, although they inform the total worldwide number.
b) A significant percentage of registered trials with voluntary omission by investigators of the word "placebo" in the brief title, although it is their responsibility.
c) Equally important, although less frequent, the absence of the word "placebo" in the official title. In the identification of the study characteristics, whether it is a placebo-controlled study

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or not is relevant since the absence of that word masks and hides the use of this inert drug from the general public.

d) Study designs not being very clear, principally, in relation to the control group and the use of an active drug and/or placebo, which hinders the identification of the actual intervention to be performed.

As a conclusion, the ethical regulation passed by the Federal Council of Medicine in 2008 did not alter the big picture on trials with placebo use in the period under study considering all sponsors, among which the massive participation of the multinational pharmaceutical industry is highlighted. In the studies funded by these companies, placebo remained present in the control group with high and steady levels throughout the 10 years under study. The fact that these protocols are elaborated outside the country's boundaries without Brazilian doctors interfering is worth mentioning, and so, they do not depend on the national ethical legislation. Additionally, the outcome of trials funded by other Brazilian and foreign institutions (except multinational pharmaceutical industries) is also surprising. Moreover, no plausible explanation was found for the significant increase in placebo use in trials after the promulgation of the prohibitive regulation adopted by the Federal Council of Medicine in 2008. The high rates of placebo use in trials for diseases with effective and efficient treatment, such as type 2 diabetes and hypertension, serve as a situation deemed severe for a country with double approval at multicenter studies. The chronic diseases were the most studied diseases, probably because they require continuous therapy. This gives rise to an economic interest from the Big Pharma group and restrains drug research studies focusing on neglected diseases. Therefore, to conclude, the regulation promulgated in 2008 by the Federal Council of Medicine was ineffective, especially for Brazilian doctors participating in or elaborating clinical protocols during the time period of the study that breached the ethical regulations.

Clinical registration databases as well as data derived from those studies must be understood as a public asset. In doing so, this reaffirms the importance of increasing transparency in such databases, the classification of the assessments of research study protocols, and also the Brazilian ethical system's necessity to monitor clinical research studies in order to extend the safety mechanisms to participants in clinical trials.

CONFLICT OF INTERESTS

The authors declare to have no commitments with the funding sources or any other type of relationship that might be understood as conflict of interest.

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REFERENCES

1. Beecher HK. The powerful placebo. JAMA. 1955;159(17):1602-1606.

2. Shapiro AK. A contribution to a history of the placebo effect. Systems Research and Behavioral Science. 1960;5(2):109-135.

3. Marcus DM. Clinical and ethical aspects of placebos in clinical practice. JAMA Internal Medicine. 2013;173(8):711-712.

4. Pignarre P. O que é o medicamento?: Um objeto estranho entre ciência, mercado e sociedade. São Paulo: Editora 34; 1999.

5. Lederer SE. Subjected to science: human experimentation in America before the Second World War. Baltimore: Johns Hopkins University Press; 1995.

6. Human D, Fluss SS. The World Medical Association's Declaration of Helsinki: Historical and contemporary perspectives [Internet]. 2001 [cited18 Set 2014]. Available from: http://www.wma.net/en/20activities/10ethics/10helsinki/draft_historical_contemporary_perspectives.pdf.

7. Bok S. The ethics of giving placebos. Scientific American. 1974;231(5):17-23.

8. Angell M. Ethical imperialism?: Ethics in international collaborative clinical research. New England Journal of Medicine. 1988;319(16):1081-1083.

9. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. New England Journal of Medicine. 1994;331(6):394-398.

10. Malik AY, Ghafoor F. International collaborative trials, placebo controls and the Declaration of Helsinki: need for clarification in paragraph 32. Indian Journal of Medical Ethics. 2012;9(1):13-17.

11. Schlemper Junior BR. Historia del control ético de la investigación en seres humanos en Brasil. Boletín Fármacos [Internet]. 2008;11(5):9-10 [cited 20 Aug 2014). Available from: http://www.saludyfarmacos.org/wp-content/files//nov08.pdf.

12. Schlemper Junior BR, Hellmann F. Controvérsias em tempos de mudanças na Declaração de Helsinque e a experiência brasileira em Ética em Pesquisa. In: Caponi S, Verdi M, Brzozowski FS, Hellmann F, organizadores. Medicalização da vida: ética, saúde pública e indústria farmacêutica. 2a ed. Curitiba: Editora Prismas; 2013.

13. Associação Médica Mundial (AMM). Declaração de Helsinki VI [Internet]. [cited 12 Mar 2014]. Available from: http://www.wma.net/es/30publications/10policies/b3/17c_es.pdf.

14. Garrafa V, Lorenzo C. Helsinque 2008: redução de proteção e maximização de interesses privados. Revista da Associação Médica Brasileira. 2009;55(5):497-520.

15. Conselho Federal de Medicina (CFM). Resolução Nº 1885, de 23 de outubro de 2008 [Internet]. 2008 [cited 20 Aug 2014]. Available from: http://www.portalmedico.org.br/resolucoes/CFM/2008/1885_2008.htm.

16. Brasil, Ministério da Saúde, Conselho Nacional de Saúde (CNS). Resolução Nº 404, de 1º de agosto de 2008 [Internet]. 2008 [cited 25 Aug 2014]. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/cns/2008/res0404_01_08_2008.html.

SALUD COLECTIVA, Buenos Aires, 11(1):99-114, January - March, 2015

17. Conselho Federal de Medicina. Resolução Nº 1931, de 17 de setembro de 2009 [Internet]. 2009 [cited 20 Mar 2014]. Available from: http://www.portalmedico.org.br/resolucoes/CFM/2009/1931_2009.pdf.

18. National Institutes of Health. About this site [Internet]. 2014 [cited 25 Aug 2014]. Available from: https://www.clinicaltrials.gov/ct2/about-site.

19. De Angelis C, Drazen JM, Frizelle FA, Haug C, et al. Is this clinical trial fully registered? — A statement from the International Committee of Medical Journal Editors. New England Journal of Medicine. 2005;352(23):2436-2438.

20. International Committee of Medical Journal Editors (ICMJE). Update on trials registration [Internet]. 2004 [cited 15 Oct 2014]. Available from: http://www.icmje.org/news-and-editorials/trial_reg_oct2004.html.

21. Laine C, Horton R, DeAngelis CD, Godlee F, et al. Update on Trials Registration: Clinical Trial Registration: Looking Back and Moving Ahead [Internet]. International Committee of Medical Journal Editors (ICMJE); 2007 [cited 27 Sep 2014]. Available from: http://www.icmje.org/news-and-editorials/clincial_trial_reg_jun2007.html.

22. Scariot M, Pereira M. Ensaios clínicos aprovados pela Agência Nacional de Vigilância Sanitária. Brasília Médica [Internet]. 2011;48(3) [cited 9 Sep 2014]. Available from: http://www.ambr.org.br/ensaios-clinicos-aprovados-pela-agencia-nacional-de-vigilancia-sanitaria/.

23. National Institutes of Health. Map of all studies in ClinicalTrials.gov [Internet]. 2014 [cited 20 Sep 2014]. Available from: https://clinicaltrials.gov/ct2/search/map.

24. Gomes RP, Pimentel VP, Landim AB, Pieroni JP. Ensaios clínicos no Brasil: competitividade internacional e desafios. BNDES Setorial Complexo Industrial da Saúde [Internet]. 2012 [cited 9 Set 2014];36:45-84. Available from: http://www.bndes.gov.br/SiteBNDES/export/sites/default/bndes_pt/Galerias/Arquivos/conhecimento/bnset/set3602.pdf.

25. Zucchetti C, Morrone FB. Perfil da pesquisa clínica no Brasil. Revista do Hospital das Clínicas de Porto Alegre. 2012;32(3):340-347.

26. Shah S. Cazadores de cuerpos: la experimentación farmacéutica con los pobres del mundo. Madrid: 451 Editores; 2009.

27. Petryna A. When experiments travel: Clinical trials and the global search for human subjects. Princeton: Princeton University Press; 2009.

28. Petryna A. Experimentalidade: Ciência, capital e poder no mundo dos ensaios clínicos. Horizontes Antropológicos. 2011;17(35):127-160.

29. Associação da Indústria Farmacêutica de Pesquisa (Interfarma). Guia Interfarma [Internet]. 2014 [cited 16 Sep 2014]. Available from: http://www.interfarma.org.br/biblioteca.php? publicacao = &categoria = G.

30. Bodenheimer T. Uneasy alliance: Clinical investigators and the pharmaceutical industry. New England Journal of Medicine. 2000;342(20):1539-1544.

31. Freitas CBD, Schlemper Junior BR. Progress and challenges of clinical research with new medications in Brazil. In: Homedes N, Ugalde A, organizadores. Clinical trials in Latin America: Where ethics and business clash. London: Springer; 2014.

32. Statista. 2014 ranking of the global top 10 biotech and pharmaceutical companies based on revenue (in billion U.S. dollars) [Internet]. 2014 [cited 18 Sep 2014]. Available from: http://www.statista.com/statistics/272717/top-global-biotech-and-pharmaceutical-companies-based-on-revenue/.

33. Zucchetti C, Morrone FB. Perfil da pesquisa clínica no Brasil. Revista do Hospital das Clínicas de Porto Alegre. 2012;32(3):340-347.

34. Sousa MSA, Franco MAG, Massud Filho J. A nova declaração de Helsinque e o uso de placebo em estudos clínicos no Brasil: a polêmica continua. Revista Médica (São Paulo). 2012;91(3):178-188.

35. Quental C, Salles Filho S. Ensaios clínicos: capacitação nacional para avaliação de medicamentos e vacinas. Revista Brasileira de Epidemiologia. 2006;9(4):408-424.

36. Zago MA. A pesquisa clínica no Brasil. Ciência & Saúde Coletiva. 2004;9(2):363-374.

37. Trouiller P, Olliaro P, Torreele E, Orbinski J, Laing R, Ford N. Drug development for neglected diseases: a deficient market and a public-health policy failure. The Lancet. 2002;359(9324):2188-2194.

38. Moreno RP. La investigación de la industria farmacéutica: ¿condicionada por los intereses del mercado? Acta Bioethica. 2011;17(2):237-246.

39. Ugalde A, Homedes N. Four words regarding clinical trials: science/profit, risks/benefits. Salud Colectiva. 2011;17(2):135-148.

40. Spellberg B, Martin B, Guidos RJ, Boucher HW, Bradley JS, Eisenstein BI, Gerding D, Lynfield R, Reller LB, Rex J, Schwartz D, Septimus E, Tenover FC, Gilbert DN. Combating antimicrobial resistance: policy recommendations to save lives. Clinical Infectious Disease. 2011;52(Suppl 5):S397-S428.

41. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: Ethical and scientific issues. Annals of Internal Medicine. 2000;133(6):455-463.

42. Miller FG, Brod H. What makes placebo-controlled trials unethical? The American Journal of Bioethics. 2002;2(2):3-9.

43. Katz KA, Karlawish JH, Chiang DS, Bognet RA, Propert KJ, Margolis DJ. Prevalence and factors associated with use of placebo control groups in randomized controlled trials in psoriasis: A cross-sectional study. Jounal of the American Academy of Dermatology. 2006;5(5):814-822.

44. Scott D, Halpern BS, Jason HT, Karlawish MD. Placebo-controlled trials are unethical in clinical hypertension research. Archives of Internal Medicine. 2000; 160(20):3167-3168.

45. Jordão CE, Mêdola PR, Luciane LC, Rosalen PL. Uso de placebo em experimentos clínicos envolvendo seres humanos no Brasil. Revista de Direito Sanitário. 2008;9(2):31-46.

46. Kottow M. De Helsinki a Fortaleza: una Declaración desangrada. Revista Bioética. 2014;22(1):28-33.

47. Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. New England Journal of Medicine. 1997;337(12):853-856.

48. Angell M. The ethics of clinical research in the Third World. [Editorials]. New England Journal of Medicine. 1997;337(12):847-849.

49. Macklin R. Double standard in multinational research. In: Porto D, Schlemper Junior BR, Martins GZ, Dutra T, Hellmann F. Bioética: saúde, pesquisa, educação. Brasília: CFM, SBB; 2014.

50. Mayor S. Half of drug trials with results on ClinicalTrials.gov are not published in journals. BMJ. 2013;347:f7219.

51. Kottow M. El uso de placebos en estudios clínicos y comunitarios: consideraciones éticas. Cuadernos Médico Sociales (Chile). 2009;4(2):94-100.

52. Cabral MML, Schindler HC, Abath FGC. Regulamentações, conflitos e ética da pesquisa médica em países em desenvolvimento. Revista de Saúde Pública. 2006;40(3):521-527.

53. Verástegui Avilés E, Valdez-Martínez E. Regulación y ética de los ensayos clínicos en México. In: Homedes N, Ugalde A, coordinadores. Ética y ensayos clínicos en América Latina. Buenos Aires: Lugar Editorial; 2012.

54. Beauchamp TL, Childress JF. Princípios de ética biomédica. São Paulo: Edições Loyola; 2002.

55. Brasil, Ministério da Saúde, Conselho Nacional de Saúde. Resolução CNS Nº 466, de 12 de dezembro de 2012 [Internet]. 2012 [cited 10 Sep 2014]. Available from: http://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf.

56. Sociedade Brasileira de Bioética. Moção a respeito da Declaração de Helsinque, de 26 de setembro de 2013 [Internet]. 2013 [cited 10 Sep 2014]. Available from: http://www.sbbioetica.org.br/noticia/mocao-da-sbb-a-respeito-da-revisao-da-declaracao-de-helsinque-2013/.

57. Confederación Médica Latinoamericana y del Caribe (CONFEMEL). [Internet]. 2014 [cited 18 Jul 2014]. Available from: www.confemel.com/.

58. Confederación Médica Latinoamericana y del Caribe (CONFEMEL). Declaración de Bogotá sobre investigación médica en seres humanos [Internet]. 2012 [cited 18 Jul 2014]. Available from: http://www.confemel.com/asambleas/xvaao/declaracion_bogota.pdf.

59. Confederación Médica Latinoamericana y del Caribe (CONFEMEL). Declaración de Pachuca

SALUD COLECTIVA, Buenos Aires, 11(1):99-114, January - March, 2015

2013 [Internet]. 2013 [cited 18 Jun 2014]. Available from: http://www.confemel.com/asambleas/xviaao/declaracion_helsinki.pdf.

60. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. JAMA. 2012;307(17):1838-1847.

61. Zarin DA, Tse T, Ide NC. Trial registration at ClinicalTrials.gov between May and October 2005. New England Journal of Medicine. 2005;353(26):2779-2787.

62. Viergever RF, Ghersi D. The quality of registration of clinical trials. Plos ONE. 2011;6(2):1-8.

63. Homedes N, Ugalde A. La globalización de la investigación clínica en América Latina. In: Homedes N, Ugalde A, coordinadores. Ética y ensayos clínicos en América Latina. Buenos Aires: Lugar Editorial; 2012.

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