Ethics of the use of placebos in clinical research: a proposal for decision-making algorithms

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Abstract

The use of placebos in clinical research has been a matter of considerable debate in recent years, notably when the World Medical Association published, in 2002, a note of clarification for paragraph 29 of the *Helsinki Declaration*. Brazil is known for its strong opposition to the flexible use of placebos. Both the Federal Council of Medicine and the National Health Council have published resolutions regulating the use of placebos in Brazil, preventing their use if there is a more effective therapeutic method already in place. The present study reinforces that position and aims to describe the various uses of placebos in clinical research, as well as examining the complex decisions relating to the ethics of their use. Additionally, the authors propose a reflection on the use of placebos through decision-making algorithms based on Brazilian ethical standards.

Keywords: Placebos. Control groups. Bioethics. Biomedical research. Helsinki Declaration. Methods. Decision support techniques.

Resumo

Eticidade do uso de placebo em pesquisa clínica: proposta de algoritmos decisórios

O uso de placebo em pesquisa clínica tem sido motivo de debate nos últimos anos, sobretudo após a Associação Médica Mundial publicar, em 2002, nota de esclarecimento do parágrafo 29 da *Declaração de Helsinki*. O Brasil tem se destacado por sua posição firme e contrária ao uso flexível de placebo. Tanto o Conselho Federal de Medicina quanto o Conselho Nacional de Saúde editaram resoluções que normatizam seu uso no Brasil, de forma a não admiti-lo em caso da existência de um método terapêutico melhor. O presente artigo reforça essa posição e tem por objetivo descrever as diversas aplicações de placebo em pesquisa clínica, bem como trazer à luz a complexa decisão sobre a eticidade de seu uso. Além disso, os autores propõem uma reflexão acerca da utilização de placebo no âmbito da pesquisa, por meio de algoritmos decisórios baseados nas normativas éticas brasileiras.

Palavras-chave: Placebos. Grupos controle. Bioética. Pesquisa biomédica. Declaração de Helsinki. Métodos. Técnicas de apoio para a decisão.

Resumen

Ética del uso del placebo en la investigación clínica: propuesta de algoritmos para la toma de decisiones

El uso del placebo en la investigación clínica ha sido un tema de debate en los últimos años, sobre todo después de que la Asociación Médica Mundial publicara, en 2002, una nota aclaratoria del párrafo 29 de la *Declaración de Helsinki*. Brasil se ha destacado por su firme posición en contra de la utilización flexible del placebo. Tanto el Consejo Federal de Medicina como el Consejo Nacional de Salud editaron resoluciones que regulan el uso del placebo en Brasil, no admitiéndose su uso cuando existe un mejor método terapéutico. El presente artículo refuerza esa posición y tiene como objetivo describir diferentes usos del placebo en la investigación clínica, así como contribuir en la discusión sobre la ética de su uso. Además, los autores proponen una reflexión sobre el uso del placebo en la investigación a través de algoritmos para la toma de decisiones, los cuales se basan en las normativas éticas de Brasil.

Palabras-clave: Placebos. Grupos control. Bioética. Investigación biomédica. Declaración de Helsinki. Métodos. Técnicas de apoyo para la decisión.

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Declaram não haver conflito de interesse.

The use of placebos in clinical research has caused much debate in recent years [1]. In 2002, the World Medical Association (WMA) issued a note of clarification for paragraph 29 of the *Declaration of Helsinki* (DH), 2000 version, permitting the use of interventions known to be less effective than the best proven existing treatments, provided such use was justified by compelling and scientifically sound methodological reasons. Further controversy was generated when, in 2004, the WMA published another note of clarification, this time for Article 30, relaxing the requirement to guarantee post-study access to interventions that proved beneficial [2].

In 2008 the Brazilian Medical Association (Associação Médica Brasileira, AMB) held an event that brought together members of the National Research Ethics Commission (Comissão Nacional de Ética em Pesquisa, Conep), the National Health Council (Conselho Nacional de Saúde, CNS), and the Federal Council of Medicine (Conselho Federal de Medicina, CFM) as well as clinical research professionals, with the aim of discussing the DH. At the meeting, there was a consensus that Brazil should object to the notes of clarification to Articles 29 and 30 of the DH. As a result, it was agreed to submit a proposal to maintain the draft of the original text of the DH in its 2000 version, without the notes of clarification, to the next General Assembly of the WMA in Seoul.

In August 2008, before the General Assembly in Seoul, the CNS issued Resolution 404, which incorporated this position [3]. The Brazilian proposal, however, was not accepted at the General Assembly in October of that year, although the Chairman of the Board of Ethics of the WMA and representatives of other countries such as Portugal, Spain, Uruguay, South Africa and the UK, voted in its favor (the US, however, opposed the motion). The idea that the use of interventions that were less effective than the best available was permitted under certain circumstances was therefore maintained [4]. Since the decision Brazil has no longer been a signatory to the DH.

Shortly after the decision of the General Assembly in Seoul, the CFM issued Resolution 1,885/2008, firmly establishing its position in relation to the use of placebos in research in Brazil. Article 1 included the following wording: *The doctor shall not involve himself in any way with medical research involving human subjects which use placebos in their experiments when efficient and effective treatment for the disease under study exists* [5]. The same deontological ruling was included in 2009 by the CFM, when updating its Code of Medical Ethics (CME), article 106 [6].

The latest version of the DH, approved in Fortaleza in 2013, maintained the same position as the Seoul version, including in Article 33 the following wording *The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s)*, except in the following circumstances: *Where no proven intervention exists, the use of a placebo, or no intervention, is acceptable*; or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of a placebo, or no intervention is necessary to determine the efficacy or safety of an intervention *and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention*. Extreme care must be taken to avoid abuse of this option [authors' highlights] [7].

In 2012, the CNS enacted Resolution 466, the main current ethical guidelines for research involving humans in Brazil. Attention should be drawn to item III.3.b of this resolution, which states that research must *fully justify, where appropriate, the use of placebos in terms of* non-maleficence and methodological *necessity*, *as the benefits, risks, difficulties and effectiveness of a* new treatment method should be tested by comparing it with the best *proven current prophylactic, diagnostic and therapeutic* methods. *This does not exclude the use of placebo or no treatment studies in which there are no proven methods of prophylaxis, diagnosis or treatment* [authors' highlights] [8].

As a result of these controversial perspectives, the aim of this article was to analyze the main uses of placebos in research and to reflect on situations where there is an ethical justification for their use, in accordance with the regulations in force in Brazil.

Use of placebos in clinical research

Of all the types of study in the field of biomedicine, randomized clinical trials and masked (blind) studies provide the best and most robust scientific evidence. Randomization and masking are different procedures which prevent distortions in a study, providing more reliable results. The first allows research participants to be divided into different groups, with no selection bias, while the second ensures that the outcomes observed in the study are free from the influence of the researcher or research participant [9].

In masking, the researcher and/or research participant does not know which product is administered to each group (experimental or control). Despite the relative confusion about the terminology used to define the type of masking, it is generally said that the study is "blind" (or "single-blind") when only the research participant does not know what he or she is receiving. When the participant and the researcher do not know what is being given to each group, the study is called "double-blind". There are even "triple-blind" studies when the participant, researcher, and whoever performs analysis are not aware of the product that each group receives [9-11].

The advantages of performing masking in a study are well established among the scientific community. The process reduces the possibility of the researcher adopting different approaches for the control and experimental groups. In addition, it prevents the survey participants having different or distorted perceptions of their conditions [9-11]. The effects on the experimental and control groups in the event that the researcher and/or the participant is aware of the allocation group are presented in Table 1 of the Appendix at the end of this article.

By knowing the group in which a participant is allocated the researcher may unconsciously favor the experimental group. Even outcomes as objective as death can suffer from researcher interference if he or she has knowledge of group allocation. For example, one can imagine a situation in which patients with an advanced, incurable tumor are admitted into a clinical trial to receive an experimental drug. Upon learning that a participant has been allocated to the experimental group, the researcher may behave in a more obstinate manner toward these participants in comparison with those belonging to the control group. Faced with serious complications during the study, a researcher's behavior may change. He or she may, for example, refer the participants in the experimental group to the intensive care unit, or for hemodialysis, mechanical ventilation, or blood transfusion, or prescribe vasoactive drugs - in short, do everything possible to keep the research participant alive.

In the same situation in the control group, the researcher could be driven towards less obstinate behavior, providing palliative clinical support in the ward in order to relieve the patient's pain without, however, employing the intensive therapeutic measures cited. In this hypothetical, but plausible, situation, the experimental group would be favored, leading the study to the erroneous conclusion that the new drug increases the survival of these patients.

Another example would be the decision to request or not tests for a complaint of "chest pain" described by a participant in a study aiming to evaluate the cardiovascular safety of a drug. With knowledge of group allocation, even if unintentionally, a researcher may underestimate complaints in the experimental group and overvalue them in control groups. This distortion could lead the researcher to request less testing to investigate the complaint in the experimental group, leading to fewer cases being diagnosed with angina. The artificial conclusion of the study would be that the experimental drug is safe from a cardiovascular point of view.

In the case of research participants, knowledge of group allocation leads to different perceptions of clinical condition. For example, upon knowing that he or she has been allocated into the experimental group, a participant may describe an improvement in the intensity of symptoms simply because they believe that the new drug is superior to those otherwise available. Contrastingly, participants in the control group, upon knowing that they will not receive the new drug, may overstate the intensity of their symptoms. The natural but mistaken conclusion of the study is that the new drug is able to improve the symptoms of patients. It is understandable, therefore, that masking is an important tool to avoid distortions being introduced to the study by the researcher and/or research participant.

Masking can occur with or without the use of a placebo. In clinical placebo-controlled trials, the experimental group receives the intervention in question and the control group receives a placebo. The term "pure placebo" is commonly used to show that the control group did not receive any intervention beyond the placebo itself (without an active comparator) [9-11].

However, a placebo-controlled study design does not necessarily imply that the control groups remain without any kind of treatment. There are placebo-controlled trials in which the new treatment and the placebo are added to existing treatments for certain clinical conditions (add-on type studies). There are even dummy type studies, in which the researcher uses more than one type of placebo in both the control and the experimental groups, to ensure masking. This is necessary when, for example, the experimental drug is a tablet with a different color and shape to the control drug.

In this case, so that the experimental group participant does not know which drug he or she is taking, a placebo tablet with the physical characteristics of the control product will also be administered.

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In the control group, the placebo will have the same appearance as the experimental drug. In this example, participants from each group will receive two tablets, one a placebo and the other containing the active drug (both experimental and control). The double-dummy study is one that uses two kinds of placebos to ensure masking [10,11].

A variation of the *dummy* design is performed when the aim is to evaluate the escalation of dosage in a masked form. In such situations, a participant could calculate the dosage administered by counting the number of tablets that he or she receives. To ensure blinding, all participants receive the same number of tablets, but the tablets contain different proportions of placebo and experimental medicine. Figure 1 of the Appendix to this article summarizes the main types of randomized clinical trial, with and without a placebo group.

There are situations where a placebo is administered just prior to study randomization. This is the so-called run-in period, when all the participants (experimental and control) receive a placebo for a period of time in a single-blind system [11]. The goal is to prepare the research participants for the main study (wash-out) which consists of adjustment of drug doses, standardization of procedures, conducting of screening tests etc., so that it can be verified if, in fact, they are eligible for the study before randomization.

Studies of patients with type II diabetes mellitus often employ a run-in period of a number of weeks in order to assess the compliance of participants to non-pharmacological guidelines (diet, exercise and glucose and ketonuria monitoring). At the end of the run-in period, some individuals improve so much that they become ineligible for the study. The run-in period is not always carried out with placebos, but when it is, the aim is to exclude individuals who display a significant placebo effect, or to determine if there is a need to replace the placebo used with another type. The use of a placebo run-in period should be evaluated with caution, with the main issue is being the determination of whether the participant will be deprived or not of the necessary treatment for their clinical condition.

It is worthwhile here reflecting on the position of the CFM regarding the use of placebos in research. CFM resolutions 1885/2008 and 1931/2009 (Article 106) observed that doctors should not maintain a relationship of any kind with studies that use placebos when an efficient and effective treatment for the disease being studied already exists [5,6]. Such a warning applies perfectly to the "pure placebo" scenario, which deprives a participant of an existing treatment solely due to the methodological need to evaluate the efficacy and safety of a new drug - something which is clearly unacceptable.

However, neither resolution is clear on add-on type studies of controlled trials in which the new treatment and placebo are added to an existing treatment. If these regulations are interpreted literally, even this design would be ethically unacceptable to the CFM, which does not seem appropriate.

Justifications for the use of placebos

Despite the fact that the debate surrounding placebos is primarily based on the existence or otherwise of a "best method", the ethics of the use of placebos is not restricted to this criterion, and there exist other factors that deserve equal attention, such as methodological necessity, non-maleficence, beneficence and justice. Figure 2 of the Appendix shows the algorithms that have been proposed to help reach a decision on the ethics of placebo use in clinical research.

Comparison of treatment with the "best method" (non-deprivation of treatment)

CNS Resolution 466/2012 (Clause III.3.b) allows the use of placebos in clinical research provided the experimental method is compared with the best current method (prophylactic, diagnostic or therapeutic). In the absence of a "best method", the use of an isolated placebo ("pure placebo") as a comparator is acceptable[8].

It is worth discussing the concept of a "best current method" as described in the resolution. The expression is often interpreted as a situation where the best method represents, for example, "the most modern", "the gold standard", "the most advanced", "the most effective", and "what is available", among other incorrect settings. Another common misunderstanding is the assumption that the existence of a "best method" of treatment can be defined simply because there may be several classes of drug for a particular disease available on the market.

The fact that several drug options exist does not necessarily imply that one of these represents a best (or most suitable) form of treatment for a specific group of patients. Non-pharmacological measures, for example, are constantly used as the initial treatment for various diseases, with patients with type II diabetes mellitus type an illustrative example.

Consider a group of patients who have recently been diagnosed with the disease and who have not yet been treated. The "best" method of treatment is not to offer the most current drug or the latest of the numerous oral hypoglycemic options available on the market. In fact there is strong scientific consensus and evidence that non-pharmacological measures such as exercise and a strict diet are effective in controlling the disease in its early stages [12].

Therefore, proposing a study that offers only non-pharmacological measures in the placebo group would be perfectly feasible from an ethical point of view, in these conditions. In contrast, the proposition of a study with the same methodological design would be unethical if there was the irrefutable recommendation of the use of oral hypoglycemic agents for the control of diabetes in the control group. Another example is to offer clinical support to patients who are beyond any therapeutic possibility, when palliative care measures represent the best course of action in such cases.

The "best method" is not always the "gold standard" or the "most effective method" in terms of treatment and diagnosis. By way of illustration, surgery is considered the standard treatment for several tumors, but there are situations which make it impossible to carry out, such as in patients with limiting health conditions that make it a risky procedure. In this case, the best available treatment is not that which is considered standard, nor the most generally effective, but what is best suited to that particular stage of the disease and condition. A complicating factor in this assessment is the fact that there are often several treatment options available other than the standard, or even several alternatives, none of which has been proven to be better than another. The definition of what is "best" for a patient is a complex task, requiring expertise and clinical consideration.

Some interpret the "best method" as that which is naturally available in a certain locality or community. Such an understanding is a dangerous error of interpretation and harmful from an ethical point of view, creating an opening for a treatment "double standard". This misunderstanding allegedly justified numerous clinical trials for HIV drugs in Africa, where many participants received only placebos on the grounds that medications for the disease were not offered by local governments (local standard) [13]. Such a situation is unacceptable, and the "best method" cannot, under any circumstances, be considered that which is available due to local logistical or economic issues. Such thinking obviously disregards one of the basic principles of bioethics, equity.

It is also worth remembering Articles 32 and 102 of the CME, which highlight the implications of placebo use, stating that it is forbidden for a doctor *not to use all available means of diagnosis and treatment,* scientifically recognized *and within his or her reach*, *to help the patient* [Article 32, authors' highlights] and *not to use* the correct therapy *when its use is permitted in the country* [Article 102, authors' highlights] [6].

The ethical discussion about placebo use should not focus so much effort on determining what the "best method" is, but instead should be concerned more with whether the participant is deprived or not of treatment that would usually be provided in patients in the same clinical condition. In general, treatments are by therapeutic guidelines developed by organizations that are representatives of classes and associations (guidelines), but can also be the result of practical professional experience. After all, not every therapeutic procedure is planned and described by guidelines.

It is understandable, therefore, that defining a "best method" is a complex task that requires reflection and technical knowledge of the subject being assessed. It should be remembered that the "best method" of treating a disease varies according to the characteristics of a group and a specific situation. Thoroughly evaluating the eligibility criteria (inclusion and exclusion) of a study helps to understand who the participants are, their specificities and the "best treatment" for them, which is not always the "gold standard", "the most modern" or "the most effective", but the one that is the most appropriate for the clinical context in which the these participants find themselves.

Evaluating therapeutic guidelines recommended by representative organizations can assist in understanding treatments. However, the definition of what is "best" for a particular group of people depends on a degree of balance and common sense. The main issue this assessment should examine is whether the group receiving the placebo is deprived or not deprived of a known treatment that should be used.

Methodological necessity

According to Brazilian regulations, the use of placebos in clinical research is permitted only where there is a justification and methodological need for the same [8]. It is worth noting that the use of placebos is a bioethical issue and not solely a question of

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scientific methodology, involving a conflict of values between the interests of research sponsors, professional responsibility and the autonomy of the patient.

While necessary and desirable in clinical trials, masking is not always feasible. There are situations where this procedure is considerably weakened by a particular aspect of the experimental product, such as an adverse reaction, the flavor and format of the medication, the number of pills, the different forms of administration, different infusion times, and non-maskable procedures (different devices) [9]. In such cases it would be evident into which group a participant had been allocated if the experimental drug caused, for example, alopecia, and the control drug did not. Likewise, masking would not be possible if one procedure was performed surgically and the other performed by endoscopy. It can be concluded here that the weakness of the masking process makes it useless, and would therefore not justify the use of a placebo.

However, more commonly, masking failure occurs only in a group of individuals, and not all those who receive a certain medication. Paclitaxel, a chemotherapy treatment used in the treatment of various tumors, can trigger anaphylactic reactions during infusion. It is a known, though very rare reaction (<0.01%) [14]. In this case, although there is masking failure in the detection of the event, it would not be sufficient to completely derail the masking in the study.

More frequent adverse reaction characteristics result in greater and more significant weakening of masking. There is, therefore, no justification for proposing masking when 100% of individuals present characteristics of adverse reactions that may identify their group. The definition of masking fragility is much more complex than it seems, especially when the characteristic event does not occur frequently. Individual weighting should in this case apply when justifying the procedure.

Although there is no cutoff point that exactly stipulates the degree of masking weakening allowed, it is worth noting that the World Health Organization (WHO) considers an adverse drug reaction incidence greater than 10% to be "very frequent" [15]. This number cannot be used as an absolute parameter or as a mathematical decision making tool, as it is an arbitrary definition. The weighting of the degree of masking weakening should include not only the frequency of adverse reactions, but also the type of reaction and the ease the researcher or participant has in identifying it.

The use of placebos in clinical research is often justified by the methodological need to prove the efficacy of an experimental treatment [10, 16]. It is not enough, however, to simply recognize this need, nor does it always translate into a plausible ethical justification. Consider, for example, a researcher who wishes to study the effectiveness of a new model of parachute to prevent injury produced by free falls. So that the effectiveness of the device can be demonstrated in statistical terms and produce robust scientific evidence, the study design would require a randomized trial with a group of people jumping from the plane with parachutes, and another group doing the same without parachutes.

The difference in the number of deaths would surely result from the use or not of the new device. This would demonstrate the unquestionable effectiveness of the parachutes. In this study, while the methodological necessity of a control group is evident, there is no ethical justification for it. Smith and Pell used this example in a provocative article which demonstrated the obstinacy of clinical trials to prove, at any cost, the effectiveness of a treatment [17].

In recent years, the pharmaceutical industry has not invested enough in research that includes genuine pharmacological innovation, instead preferring to focus its efforts on the production of imitation drugs (*me too*) for the renewal of patents [18]. The use of placebos in clinical trials with imitation drugs has nothing to do with scientific or methodological issues. In reality, economic and regulatory issues prevail, as it is much simpler, faster and cheaper to demonstrate the superiority of a new drug by comparison with a placebo than by comparison with standard or similar medicine. This clearly greatly facilitates the process of registering the drug with regulatory agencies [19].

The ethics of placebo use in clinical research are directly related to the justification of masking, and not to the necessity of proving effectiveness. If there is no reason for masking, equally there is no need for the use of placebo.

Non-maleficence

A placebo should not result in additional risks or harm to those who receive it. Item III.3.b of CNS resolution 466/2012 clearly warns of the issue of non-maleficence in studies using placebos. Furthermore, Item III.1.b states that the *ethics of research imply (...) weighing risks and benefits, both known and potential, individual or collective, committed to*

maximizing benefits and minimizing harm and risk [authors' highlights] [8].

It is noteworthy that even the most seemingly innocuous placebos, such as tablets, may have adverse effects. These are called "nocebo effects", defined as negative responses to intervention with a placebo [20]. The belief that the use of a placebo does not bring risks and harm to research participants is therefore misguided.

There are two fundamental aspects to be examined in the assessment of risks and possible damage caused by a placebo: the type and period of administration. It is easy to accept a study that proposes taking a placebo tablet once per day for a week. However, not all situations involving placebo use are as simple when it comes to weighing the potential risk and harm to a research participant. Would it be unethical, for example, to ask someone to ingest a placebo tablet daily for ten years? Would it be ethically acceptable to request the infusion of a placebo subcutaneously, which causes less discomfort than when administered in small amounts, in a single dose? Perhaps most people would answer yes to this last question. But if the study involved the subcutaneous administration of a placebo three times a day for 12 months, it is likely that a considerably smaller proportion of people would judge the study as ethical.

Considering other situations, what would the reaction be to a placebo administered intravenously? Would it be acceptable from an ethical point of view to propose the intravenous infusion of a placebo to patients who were already using an indwelling catheter? On the one hand, the discomfort of venipuncture is avoided because of the existence of the catheter, on the other, the more frequent use of the device increases the chance of contamination, which would result in its removal. And in the case of participants who do not have a catheter, would it be ethically justifiable to propose installing the device so that the participant could receive the placebo more comfortably (for example, a long-term venous catheter)? All these situations become even more complicated when it comes to the study of children.

There is no single or correct answer to the above questions. In fact, the decision about the ethics of placebo use, with respect to the aspect of non-maleficence, depends on the weighing of its potential risks. Often there is no objective assessment criteria, but only consideration of the route of administration and time of exposure to the placebo and the age range of the participants. While subjective, one way to reflect on this issue is to put oneself in the place of the participant and ask "*would I accept the risks, discomforts and harm caused by the placebo for myself or someone in my family?*"

The answer to this question is obviously subjective, yet it contains a fundamentally guiding character. It cannot in essence, be weighted by the individual or guided by interests. If a researcher, for example, puts himself in the participant's position, he or she may be willing to assume greater risks and discomforts for himself or herself due to being motivated by the success of the study and convinced that the experimental drug will bring benefit. The assessment of the risks, discomforts and harm caused by the placebo must be free of conflicts of interest, and based, above all, on a consensus among peers who analyze the ethics of its use.

Beneficence and justice

The most obvious benefit that individuals in the placebo group may gain from participating in a survey is post-study access to the product being investigated, should it prove beneficial. On this subject, CNS Resolution No. 466/2012 (item III.3.d) defines a role for the study: to guarantee for all participants *at the end of the study, provided by the sponsor, free and unlimited access to the best prophylactic, diagnostic and therapeutic methods found to be effective* [authors' highlights]. Item V.4, meanwhile includes the following wording: *In the area of health research, as soon as the significant superiority of one intervention over another or other comparative intervention(s) is proven, the researcher should assess the possibility of adapting or suspending the study in order to offer the benefits of the best regime to all* [authors' highlights][8].

It is, however, necessary to consider the possibility of situations where it is not feasible to provide the investigational product at the end of the study, and there is therefore no reason to ensure post-study access to the control group. This is the case, for example, in clinical trials with devices used during surgery, where the benefit is only valid during the procedure, or, in placebo-controlled clinical trials for the treatment of an acute but self-limiting condition, such as a cold or a similar infection. At the end of the study, research participants from both the control and the experimental group, will no longer suffer from the medical condition that led them to take part in the survey; therefore, the provision of the investigational product is no longer applicable.

Fatal diseases with a high demand for new treatments, such as cancer, for example, are often

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the subject of simultaneous studies with different drugs but the same goal. However, the conclusion of one study may occur before the other, changing the current treatment guidelines and sometimes generating a new therapeutic standard. If the last study to be completed shows positive results which are inferior to the first, it is necessary to weigh the benefit and justice of providing post-study medication when there is a more favorable option available. Again, the ethical position will depend upon a technical and expert judgment of the disease treatment options in question at that time.

Ensuring that the investigational product is provided free of charge to the placebo group at the end of the study is not just a matter of charity, but above all of justice towards those who collaborated as a control group. Therefore, the guarantee of post-study access to the control group is another element to be considered in assessing the ethics of placebo use in clinical research.

Final considerations

This paper presents a proposal of systematization of the analysis of placebo use in clinical trials in the light of CNS Resolution 466/2012. It is essentially based on the analysis of five inseparable criteria: non- deprivation of treatment, methodological necessity, non-maleficence, beneficence and justice. For a study to be deemed ethical, it is necessary that the previously mentioned criteria are fully complied with. If one fails, the use of placebo cannot be justifiable.

The epistemological keys set out in this work have their roots in the principlism of Beauchamp and Childress [21]. It should be noted that the discussion about the use of placebos in clinical research should not only take into account biological vulnerability, as highlighted by Garrafa [1]. In a Brazilian context, social vulnerability is as or more important than biological vulnerability, although the two are also inseparable. This concern is at the heart of intervention bioethics, which has as one of its focuses the criticism of the double standard in clinical research [22].

The alleged objectivity of the four traditional principles is a limiting factor for a more comprehensive analysis. Intervention bioethics requires a socio-political context, taking into account other categories of bioethical practice foundations, such as “care”, “responsibility”, “solidarity”, “commitment”, “otherness”, “tolerance”, “prevention”, “caution”, “prudence” and “protection” (of the socially excluded) [23]. Paranhos, Garrafa and Melo [24] argue that the UNESCO Universal Declaration on Bioethics and Human Rights [25] is a key document for supporting bioethical analysis involving the harm and benefits of clinical research.

In the present study the proposed algorithms are a long way from representing the truth, being open to criticism and adjustment. They are additional tools which will bring more objectivity to a discussion that is guided in most cases, by passion and even by a misguided preconception regarding the use of placebos. There is no intention to reduce ethical analysis to algorithms or Manichean debate. Bioethical decisions are multifaceted, and depend on a significant degree of weighting. The intent of the proposed algorithms is to assist in the complex decisions that surround the ethical use of placebos in clinical research, without replacing human judgement regarding such resolutions.

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Participation of the authors
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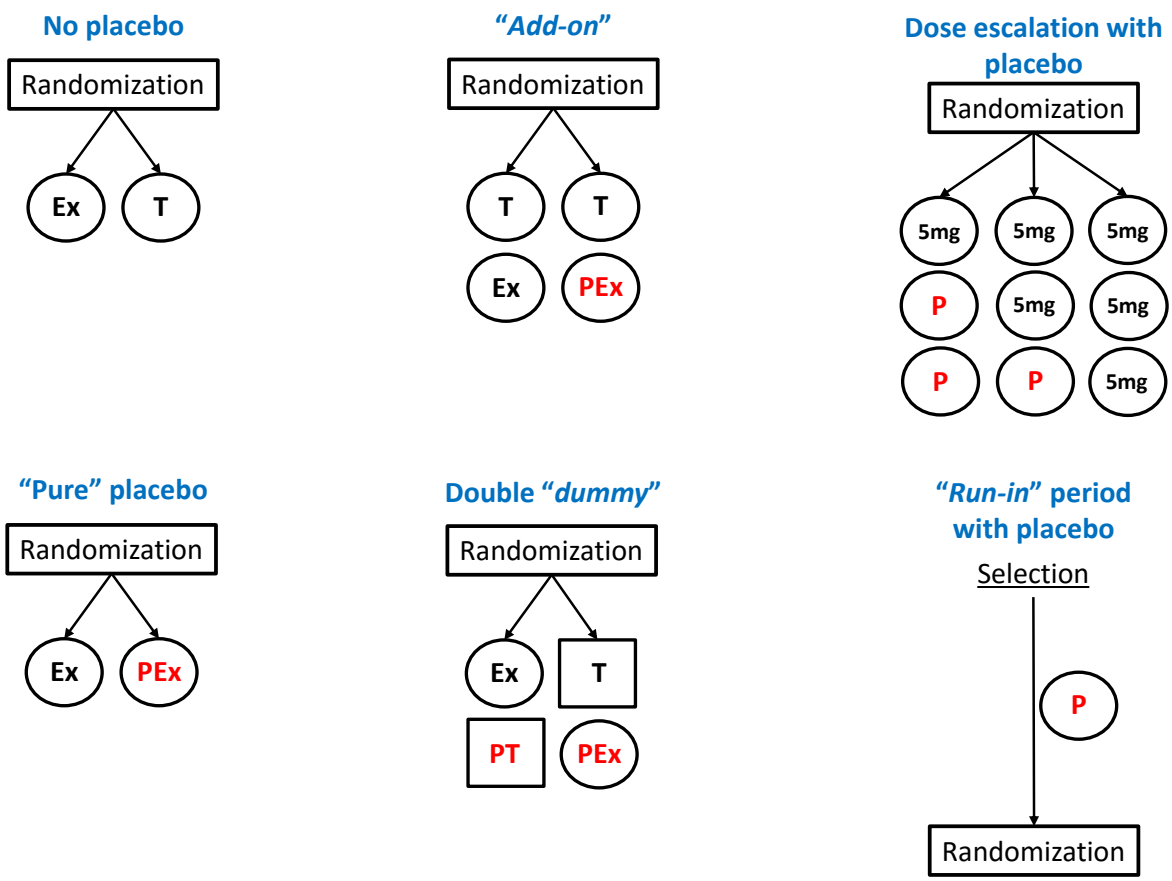
Appendix

Table 1. Effects on experimental and control groups when the allocation is known by the researcher and/or research participant in a clinical trial

Who knows allocation	Item affected	Group affected	
		Control	Experimental
Researcher	Conduct related to treatment, dose adjustment, instructions etc.	Less obstinate	More obstinate
	Interpretation of information supplied by the participant	Less favorable	More favorable
	Evaluation of participant by researcher	Less favorable	More favorable
Participant	Perception of participant of own condition	Less favorable	More favorable
	Participant's adherence to instructions given by researcher	Less adherence	More adherence
	Participant seeks alternative treatment	Greater chance	Less chance
	Participant abandons study	Greater chance	Less chance

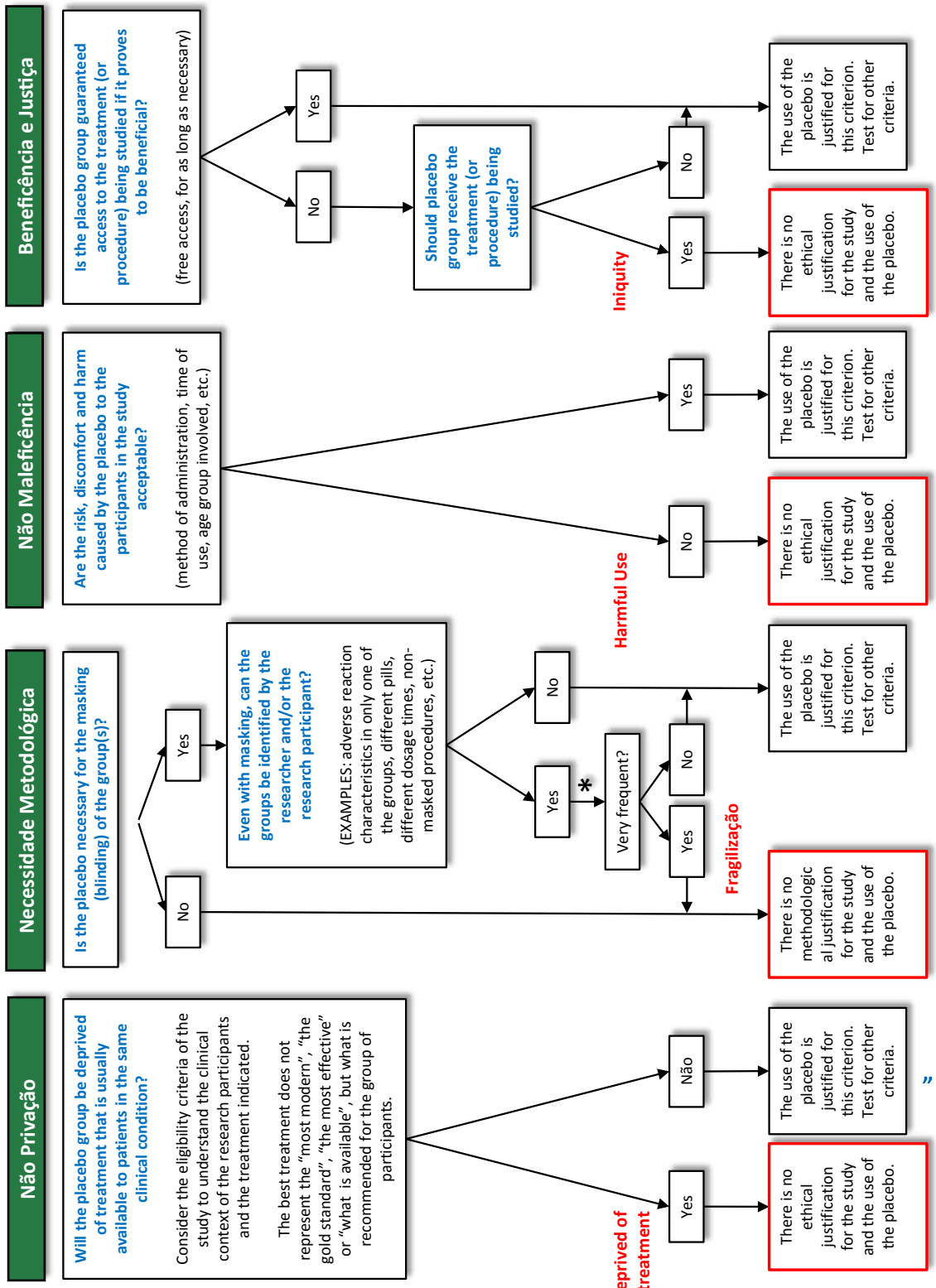
Source: based on Schulz and Grimes [9].

Figure 1. Schematic representation of the main designs of randomized clinical trials with and without placebos



Key: (Ex) experimental treatment; (T) most appropriate treatment for clinical condition of a specific group of participants; (PT) placebo of T; (PEx) placebo of Ex; (P) Placebo

Figure 2. Algorithm for the decision about the ethics of placebo use in clinical trials



* The World Health Organization (WHO) considers an adverse drug reaction incidence greater than 10% to be "very frequent". However, this number cannot be used as an absolute parameter about the fragility of masking, as it is an arbitrary definition.

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