PANAMERICAN NETWORK FOR THE HARMONIZATION OF PHARMACEUTICAL REGULATION (PANDRH NETWORK)

GOOD CLINICAL PRACTICES WORKING GROUP

"CONSIDERATIONS FOR THE USE OF PLACEBOS"

Working Document.

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1. INTRODUCTION

Clinical trials for therapeutic treatments using a placebo, have created and even continue to create scientific and ethical problems interrelated, and its use in a clinical trial must be justified.

One aspect that must be considered in clinical trials is that to obtain reliable results, the effects in the intervention in trial must be compared with the effects in the intervention of control.

The selection of the control group is always a critical decision within the design of a clinical trial. This affects the inference that can be performed from a trial, the ethical acceptability of the same, how much you can minimize the bias in the conduction and analysis, the types of subjects that can be recruited and the rate of recruitment, the criteria of evaluation (or endpoint), that require to be studied, the acceptance of results of the regulatory authorities, as well as public and scientific credibility of the results.

The control group or groups have as a main purpose to allow the discrimination of the results obtained (for example, change of symptoms, signs or evolution of the disease) for the treatment in the trial, of the results that can be a consequence of other factors, such as natural progression of the disease, observer or patient expectations, or other treatments. What may happen in the control group can be a suggestion of what might have happened to the patients if they would not have received the treatment under investigation or in trial or if they would have received a different treatment than one known as effective.

The control group must be selected from the same population as the group that will receive the treatment under trial. Both groups must be similar in all the variables that can have an influence on the result, except for the treatment in trial. The fault in reaching the similarity can introduce a bias within the trial. This bias is defined as a systematic tendency of any design aspect, conduction, analysis and interpretation of the clinical trial results in having an estimate of the default of the outcome of the treatment of its real value.

To ensure the similarity of the groups, a random assignment is done to the groups that will receive a treatment in trial or the control, so this way you avoid differences of known and unknown variables that can affect the result. This selection can be open o double blinded, meaning, that it will be conducted in a way that neither the investigator and his team and the individual that participates in the investigation have any knowledge of the group that he was assigned to.

Randomness and blindness are two techniques that are usually used to minimize the possibility of such bias and ensure that the trial treatment and control group are similar at the beginning of the trial and are similarly treated during the course of the trial.

Control groups in clinical trials can be classified on the basis of two attributes: (1) the type of treatment used and (2) the method of determination of who will be part of the control group.

Depending on the type of treatment the control group can be: (1) placebo, (2) no treatment, (3) different dose and/or frequency of the study treatment, or (4) a different active treatment. These four types of control are concurrent, however there are external controls (historical), in which there are a series of limitations concerning the ability of such trials to assure the comparability of the treatment groups and their ability to minimize biases.

In placebo-controlled clinical trials, the individuals are assigned randomly to the treatment group or to an apparently identical treatment group that does not contain the product under investigation.

The name control suggests that its purpose is to control the "placebo effect" (one defined as the improvement of the individuals (which is defined as the improvement of the individuals as a result of thinking they were taking a drug), not being this its only benefit.

Mainly, the design controlled with placebo, performed with blinding and randomness and including a group that receives an inert treatment, controls for all the potential influences in real or apparent course of a disease, that have nothing to do with the pharmaceutical action of the product in research. These influences (potential) include spontaneous changes (natural history of the disease and regression to the media), expectations of the individual or researcher, the effect of wellness within a clinical trial, use of other therapies, and subjective elements in the diagnosis or evaluation. The controlled clinical trials with placebo try to demonstrate a difference among treatments when the effectiveness is under research, however it can also demonstrate the lack of difference (of a specific size) in the evaluation of a measurement of safety.

There are cases in which the ability of a trial to differentiate effective interventions from non effective interventions cannot be guaranteed unless the control is a placebo. However, depriving people of a treatment whose proven effectiveness and exposing them to harm, is not ethical, and therefore the selection of the control group and their acceptability must be established within the context of availability of standard therapies, adequate evidence that supports the chosen design and ethical considerations.

2. OBJECTIVE OF THE DOCUMENT

The objective of this document is to provide general guidance for clinical research on pharmaceutical products that search to prove the effectiveness and safety of a treatment, using a placebo as a control group.

3. DESCRIPTION OF CONTROL GROUP WITH PLACEBO

In a placebo-controlled trial, the individuals are assigned, almost always by randomly to either a treatment submitted to be tested or to a placebo. A placebo is a "dummy" treatment that is as identical to a trial treatment, in relation to physical characteristics such as color, weight, taste and smell, but that does not contain the principal active of the test drug.

The difference in the result between the active treatment and the placebo is the measurement of the effect in the frame of trial conditions. Within the overall description, there is a great variety of designs that can be used with success: in parallel or crossed designs or cross-over dose that can be single or fixed, dose adjustment in the pharmaceutical group or several fixed doses.

You have to take into account that not all the studies that include a placebo are made to be compared or controlled with the placebo. For example, a research for active control can be used with a placebo for every drug (double simulation) to facilitate the blinding, which is still a test of active control, but not a controlled trial with placebo. A controlled trial with placebo is the one in which the treatment with placebo is compared with a treatment with a drug on trial.

It should also be noticed that not all placebos are completely inactive. For example, some vehicle controlled studies used in studies of topical preparations for the skin can have a beneficial activity. This does not impair the ability of the design to measure the specific effect of the test substance. Special problems arise when the chosen vehicle control can have harmful effects. In this case the arm with no treatment allows the measurement of the total effect of the test substance besides its vehicle.

The placebo-controlled trial, with random and blinding assignment, minimizes the bias of the subjects and of the investigator. These types of trials, however, are not infallible to the blind-breaking through recognition of pharmacologic effects of a treatment; blinded outcome assessment can enhance the reduction bias in such cases. This concern may be particularly relevant in cross-over studies.

When the controlled essay with placebo is used to show effectiveness of a treatment, it must be assumption-free and must be dependant on external information (extra-study)as much as possible. Most of the problems in the design or execution of a trial increase the probability of failure to demonstrate a difference of the treatment (and thereby establish efficacy), so that the trial contains integral incentives in order to reach excellence in the study. Even when the primary purpose of a trial is the comparison of two active agents or the assessment of dose-response, the addition of a placebo provides an internal standard that enhances the inferences that can be drawn from the other comparisons.

The placebo-controlled trials can also provide the maximum capacity to distinguish the adverse effects caused by a drug from the resulting from underlying disease or intercurrent illness. You must take into knowledge, however, that when it is used to show similarity of two treatments, for example, to demonstrate that a drug does not have a determined side-effect, showing similar rates of the event in patients treated with the drug and patients treated with placebo, the placebo controlled trials have the same sensitivity of a trial of equivalence and not of inferiority. To interpret the result, one must know that if the study drug has caused an adverse reaction, the event should have been noticed previously.

4. MODIFICATIONS OF DESIGNS AND COMBINATIONS WITH OTHER CONTROLS THAT CAN RESOLVE ETHICAL , PRACTICAL MATTERS OR OF INFERENCE

It is often possible to treat ethical or practical limitations of placebo-controlled trials by using modified study designs that maintain the benefits of inference in placebo-controlled studies. These designs are:

4.1 Additional Control Groups

4.1.1 Three-arm Trial; Control with active ingredient and with placebo

In the three-arm trial you will find included both an active ingredient control group and a placebo control group. It can be easily evaluated if the failure in differencing between the effect of the trial treatment of the placebo treatment, is caused by a failure of the effectiveness of the trial treatment or if it is simply the result of a clinical essay that lacks the capacity to identify an active drug or that it has an effect. The comparison between the placebo and a standard treatment medication in these trials provides internal evidence to evaluate sensitivity. There are some designs that contemplate sizes of different samples in each group, with a bigger number of patients in the active control group, which is something that contributes to improve the precision of comparison between them, and it is more acceptable for the individuals and the investigators.

4.1.2 Additional Dosages

Randomness for different fixed dosages of the medication under study, besides the placebo, allows an evaluation of dose-response and can be particularly useful in a comparative and adequate for the treatments.

4.1.3 Factorial Design

This type of design can be used to explore many dosages of the medication under investigation such as a monotherapy and in combination with several dosages of another drug proposed for combined use. This type of study can define the properties of a wide range of combinations. These studies are common in the evaluation of new hypertension therapies, but they can be considered in a variety of scenarios where more than one treatment is used simultaneously. For example, the independent additional effects of aspirin and streptokinase in the prevention of mortality after a heart attack, were demonstrated with a trial of this type.

4.2 Other modifications to study designs

4.2.1 Trial of addition of medication trial (Add on trials) Controlled with Placebo; Replacement Study.

An add-on trial is a placebo-controlled test of a new drug, conducted on patients that also are receiving a standard treatment. These studies are particularly important when it is known that the available treatment decreases mortality or irreversible morbidity, and a non-inferiority test with standard treatment as active control cannot be performed or might be difficult to interpret. This type of study is common in trials for cancer drugs, antiepileptic and heart failure drugs. This design is useful only when the standard treatment is not fully effective, and it has the benefit of providing evidence of improvement in the clinical results (more than mere non-inferiority). The efficacy established by these trials, is only for combined treatments, and the dosage in a monotherapy situation can be different from the dosage found to be effective in combination. In general, it is likely that this type of test will be successful only when the new treatment and the standard treatment have a different pharmacological mechanisms, although there are exceptions. For example, the combination of treatments on people with AIDS is able to prove a beneficial effect of pharmacologically related drugs due to the delay in the development of resistance.

4.2.2 Early escape; Rescue Treatment

It is possible to design a study that has an early escape plan when the treatment has been ineffective. Early escape refers to the rapid removal of an individual in a trial, whose clinical condition worsens or does not improve at the defined level (blood pressure not controlled within the predefined period, proportion of seizures greater than the established value, blood pressure higher than a certain level, frequency of angina above the defined level, blood hepatic enzymes that do not normalize within an established time frame in patients with hepatitis), that has a single event that the treatment is trying to prevent (first recurrence of unstable angina, grand mal seizure, paroxysmal supraventricular tachycardia), or someone who

otherwise requires rescue treatment. In these cases, the need to change treatment becomes an endpoint of the study. The criteria for deciding whether this endpoint has occurred and the time for taking decisions must be very well defined in the research protocol and it must ensure that the subject will not remain untreated with an active drug while his disease is poorly controlled. The main difficulty with this design is that it can only provide information on effectiveness in the short-term. However, the randomized withdrawal design, which can incorporate characteristics of early escape, can provide long-term information on effectiveness.

4.2.3 Placebo for limited time

In situations where long-term treatment with a placebo would not be acceptable, the use for a short period of time of one group with a placebo at the beginning of a trial with an active control, can establish the sensitivity of the trial (at least for the effects of short-term treatment). Subsequently the test should continue without the placebo group.

4.2.4 Randomized withdrawal or exit

In a clinical trial with randomized withdrawal or exit, the subjects receiving the treatment under investigation for a specific period of time, are assigned randomly to continue the test with the drug under study or with a placebo (withdrawal from the active therapy). The subjects for this type of trial can be derivatives from an open study of a single-arm, with an existing clinical cohort (but usually with a protocol that specifies a wash phase to establish the baseline of the initial therapy), from an active arm of a controlled trial, or from one or more arms of an active controlled trial. Any difference that emerges between the group receiving ongoing treatment and the randomized placebo group could show the effect of the active treatment. The observation period with the pre-randomized treatment can be of any length; therefore, this type of test can be used to study the persistence of effectiveness to long-term when the treatment with a placebo is not acceptable. The observation period after withdrawal can be of fixed duration or can use the early escape study or the one of time of the events presentation. (for example, recurrence of depression). Because the early escape designs require special attention to the procedures to monitorize the subjects and the criteria of evaluation so this way we assure that the subjects that are having failures in the assigned treatment will be identified rapidly.

This type of design is useful in many situations, such as:

- For medications that seem to resolve an episode of a recurrent disease (for example, antidepressants), in which case the random withdrawal trial is, in effect, a relapse prevention trial.
- For drugs that suppress signs or symptoms (chronic pain, hypertension, angina), but where a placebo-controlled long-term study would not be appropriate; in this case, the

trial can establish long-term efficacy.

- To determine for how long should the treatment continue (example, post-heart attack with beta blockers.)

The general benefit of this design, when used with an early escape endpoint with a criteria of evaluation that corresponds with the reappearance of symptoms, is that, the period in which the subject has been exposed to a placebo with a poor response is short.

This type of design can include dosage aspects. After all of the patients have received a fixed initial dosage, they can be assigned randomly in the withdrawal phase to different dosages (as well as a placebo), a particularly useful focus when there is a reason to think that the initial dose and the maintenance can be different, both in terms of pharmacodynamics or for a substantial accumulation of the active drug as a result of a long half-life of the original drug or active metabolite. It must be kept in mind that this randomized withdrawal design can be used to evaluate a response dosage after a placebo-controlled titration trial. A titration trial is an efficient design to establish effectiveness, but in many cases it does not provide good information on the response dose. The randomized withdrawal phase, with responders assigned randomly to many fixed dosages and to a placebo, will allow for the study of response dosages rigorously while allowing the efficacy design of the titration study to be used in the initial phase of the trial.

It is important for random withdrawal or outgoing designs, to take into account the possibility of the abstinence phenomenon, suggesting the usefulness of a slow reduction. A subject may develop tolerance to a drug such in a way that there is no cumulative benefit, but withdrawal of the drug can lead to an exacerbation of the illness, resulting in erroneous conclusions on the persistence of the efficacy. It is also important to take into account that the effects of the treatment observed in these trials may be longer than those that are seen in the unselected population, due to the fact that randomized withdrawal studies are enriched with responder subjects and they exclude patients that cannot tolerate the drug. These phenomenons result when an explicit test includes only subjects that seem to respond to the drug or that includes only people who have completed a prior phase of the study (which is frequently an indicator of a good response and always indicates the ability to tolerate the drug). In the case of trials that try to determine for how long the therapy should continue, this entry criteria provides the population of interest and comparison study.

4.3 Other design considerations

In any placebo-controlled study, an imbalance in the randomization (for example 2:1, drug under study: placebo) can improve the safety database and can also make the trial more attractive for the subjects and the researcher.

5. ADVANTAGES AND DISADVANTAGES OF PLACEBO-CONTROLLED STUDIES

5.1 Advantages

5.1.1 Ability to show efficacy

As with other superiority trials, a placebo-controlled trial contains internal evidence on the sensitivity of the trial. When a difference is shown it is interpretable without reference to external findings.

5.1.2 Absolute measures of efficacy and safety

Placebo-controlled trials measure the immediate pharmacological effects of the treatment. In contrast, active-ingredient controlled trials or dosage comparison trials, measure the relative effects of another treatment. Placebo-controlled tests also allow a differentiation between the adverse events due to the drug and those due to the underlying illness. The information on the absolute magnitude of the effect is measured in a three-arm trial (test, placebo, active), even when the primary purpose of the trial is a comparison of the pharmaceutical product under study versus the active control.

5.1.3 Efficiency

The placebo-controlled trials are efficient to the extent that they can detect treatment effects with a minor sample size compared to other clinical trials with concurrent control even though ideally the amount of subjects in the group must have a size that can cover the level of significance and the power of trial.

5.1.4 Minimizing the effect of patient and researcher expectations.

The use of a control group with placebo and blind, can reduce the expectations the subject or the researcher may have on the improvement they may obtain, because both are aware that some subjects will receive a non active drug. This can increase the ability of the study to detect the real effects of the medication under study.

5.2 Disadvantages

5.2.1 Ethical concerns

When you know that a treatment is effective to prevent death or irreversible morbidity in a particular population, it will not be considered as ethical to perform a controlled-placebo trial in this population. The particular conditions and populations for which this is true, can be controversial. Ethical concerns can also cause the trials to be directed to an inclusion of subjects with a lower morbidity or to seek for an endpoint criteria in a short term when the long-term results are of greater interest.

When a placebo-controlled trial is not ethical and an active controlled trial could be credible, it can be difficult to study new drugs. For example, it may be considered as non ethical to perform a controlled test with a placebo of a thrombolytic agent in patients with acute myocardial infarction. It would be difficult in the actual context to establish a margin of a valid non inferiority of based on historical data caused by the appearance of acute revascularization procedures that might alter the size of the benefits of the thrombolysis. In these cases some modified designs described above would be useful.

5.2.2 Practical concerns for patients and physicians

Subjects and/or physicians might be reluctant to accept the possibility that a subject can be assigned to the treatment with a placebo, even if there is general agreement about withholding or delaying treatment will not result in damage. The subjects who have the feeling that they are not improving can drop out of the trial because they attribute the lack of effect to fact that they were treated with a placebo, complicating the analysis of the study. However, with care, the withdrawal caused by the lack of effectiveness can be used in the trial as an endpoint. Although this might provide some information on the effectiveness of the drug, it is not recommendable since this information is less accurate than the real information concerning the clinical status in patients who received the assigned treatment.

5.2.3 Generalization

Sometimes it is argued that any controlled trial, but especially those controlled with a placebo, represent a simulated context that gives different results than the real effectiveness of the medication in the real practice. If the studied population in the trial is not representative in the group controlled with a placebo due to ethical or practical concerns, doubts may arise on the generalization of the results of the trial. For example, the protocol, the researcher, or the selection of the subjects of the placebo-controlled trials, might exclude subjects with more serious illnesses. In some cases, only a limited number of subjects or centers can agree to participate in the studies. It has not been established (versus the theoretical)that these

concerns actually limit the generalization.

5.2.4 Non-Comparative information

Placebo-controlled trials that lack an active control group, contribute little useful information of the comparative effectiveness and is of interest and important in many circumstances. This information cannot be obtained with certainty relying the trial comparison, due to that the conditions of these can be different.

6. ETHICAL PRINCIPALS AND INTERNATIONAL GUIDELINES

The research in which human beings participate may be performed only if there is certainty that the participating subjects are not being exposed to unnecessary risks or damages and if the benefits foreseen for each one of the participants clearly exceed the risks that they are taking.

The basic considerations that should govern all the researches on human beings are the ones related to respect for the dignity of people, their rights, their safety, and their welfare.

In the clinical tests in which there is a placebo control group, the mentioned above has special relevance , for the acceptance must be very carefully evaluated by the Ethical Committee of the investigation as well as by the regulatory authorities for the evaluation and therefore approval.

Among the international instruments and guidelines that have made reference to the use of a placebo control group are:

6.1 Helsinki Declaration

The Helsinki Declaration, formulated by the International Medical Association, which is an international document in the field of biomedical research ethics [sic]. It has been revised several times, the most recent one in October 2008. That review establishes ethical guidelines for physicians involved in biomedical research, both clinical and non clinical. In the section 32 of this Declaration states that:

“The possible benefits, risks, costs, and efficacy of all new treatments must be evaluated by comparing them to the best proven treatment that exists, except in the following circumstances:

- The use of a placebo, or no treatment, is acceptable in studies for which there is a non existing proven treatment.

- When for methodological, scientific, and overriding reasons, the use of a placebo is necessary to determine the efficacy and safety of an intervention that does not imply a risk, serious adverse effects or irreversible damage to the patients that receive the placebo or no treatment. "You must be very careful to avoid abuse in this option".

6.2 International ethical guidelines for biomedical research on human beings

The International Ethical Guidelines for Biomedical Research on Human Beings, prepared by the Board of International Medical Science Organizations (CIOMS) in cooperation with the World Health Organization (WHO). In guideline 11 the indications are:

"By general rule, the subjects of investigation in the control group of a clinical trial of diagnosis, therapy or prevention, should receive an effective and proven intervention. In some circumstances, it may be ethically acceptable to use an alternative control, such as a placebo or "absence of treatment."

The placebo can be used:

- When there is no intervention with proven effectiveness.

- When the omission of an intervention with proven effectiveness could expose the subjects, at most, to a temporary inconvenience or a delay in the relief of symptoms.

- When the use of a intervention of proven effectiveness as a control would not produce scientifically reliable results and the use of a placebo would not add any risk of serious or irreversible damage for the subjects.

7. ETHICAL ASPECTS OF PLACEBO CONTROLLED CLINICAL TRIALS

Even with the rules mentioned above and all the discussion generated by it, the use of control groups with placebos in clinical trials continues to be controversial.

When a new treatment is being investigated and an effective treatment is not known, usually there are no ethical problems in performing a study comparing the new treatment with a placebo. However, the use of the control group with a placebo can cause ethical problems, regarding acceptability and viability, when there is an available treatment for the condition under study. In these cases, to prevent damage, such as irreversible negative effects or death of the patients in trial, the use of a placebo control group is inappropriate.

7.1 Exceptions that have been accepted for the use of a placebo control group

However the foregoing, there are some occasional exceptions for the use of placebo control groups when there are approved therapies, such as the case of standard treatment has severe toxicity, that many subjects refuse to receive it.

In other situations, when there is no serious damage, generally it is considered ethical to ask patients whether they wish to participate in a placebo-controlled clinical test, even if they might experience discomfort as a result of their participation, as long as they are provided, without being coercive, of complete information on the treatments available and the possible consequences of delaying the treatment. However these present significant practical problems. For example, differ the treatment of pain or other symptoms, may be unacceptable for the subjects or physicians and they might not want to participate in a trial that requires such matter.

If a placebo controlled clinical trial of a new agent is acceptable or not for the subjects and investigators when an effective alternative therapy is known, is a matter of judgment that requires to be considered in order to make a decision, to the investigator, to the patient, and to the Institutional Research Committee (IRC), / Independent Ethical Committee (IEC) and the acceptability may vary among different countries and could depend of the specific design of the trial and the population of subjects selected.

Consider if a placebo controlled trial is ethical, depends in some cases, of the particular circumstances of the trial and of what may be considered clinically relevant in the state of gravity of the disease.

For example, a placebo-controlled clinical trial of short duration of a new antihypertensive agent in patients with moderate essential hypertension and without any organic disease might be considered acceptable, while a trial of greater duration or with sicker patients, would not be.

The use of a control group with a placebo does not imply that the subject is not going to have any treatment at all. For example, in an oncological test, when no treatment has been approved, the placebo group patients and those of the group with the medication under investigation, will receive the palliative treatment that they need, such as analgesics and support measures. Many placebo controlled clinical trials are conducted as add-on medication trial, where all of the subjects receive the specific standard treatment or some treatment chosen by the treating physician.

7.2 Ethical counterarguments to the accepted exceptions

When it is argued that a placebo can be used to treat the control group if this does not lead to serious damage, the design of the trial allows for rescue treatment or other alternatives to reduce the risks, to allow the performance thereof gives the researchers and the Research Ethics Committees the right to determine how much illness or incapacity the subjects may bear in order to be able to perform the research, which is contrary to the medical codes developed expressly to protect patients from such vulnerability, and it is contrary to the ethical principle that all patients should receive the best treatment available.

Another justification that is offered is informed consent, arguing that if the subject is completely informed concerning the discomforts and risks of participating in the clinical trial and agrees to participate, there is no reason why it would not be possible to allow the trial to be performed, passing the ethical responsibility burden to the participating subject. The informed consent is always desirable, but the researcher should not put the subjects in a position in which their health and welfare could be compromised, even if they agree. Despite the best efforts to inform participants, they almost never will be as well informed of their treatment options as their physician and even if they are well informed, because of their situation they might not be sufficiently objective to make a rational decision on whether being deprived of an accepted treatment is tolerable. Furthermore, the subjects are given the ability to decide whether or not to participate in the clinical trial, but they are not given the opportunity to choose the treatment that will be assigned to them.

8. FINAL CONSIDERATIONS

Both the researcher and the Research Ethics Committee may face difficulties at the time of deciding on the acceptability of a placebo controlled clinical trial, and therefore when receiving one of these trials they must take due care in reviewing and accepting it, verifying in detail its design and paying special attention to the possible risks to which the subjects in the placebo group will be exposed, so as to minimize the risks that might occur.

Assurance must be given that the participating subjects have information that is true, clear, and accurate, which can be understood by them and that tells them of the possible problems that might occur and their right to withdraw from the trial. The recruitment must be done such that there is no pressure, coercion, or improper inducement to participate, so that the participating subject may take a free and voluntary decision.

The researcher must be completely familiar with the protocol, the researcher's manual, and the medications to be used. He must have academic education, training, and experience related to the subject of the research and conduct the trial as established in the protocol and the Good Clinical Practices.

In the cases in which the performance of a placebo controlled clinical test is approved, the procedures and follow-up and control times for it must be established clearly, maintaining close communication between the Research Ethics Committee and the Researcher.

It must be kept in mind that the dignity, rights, safety, and welfare of the trial subjects must always take precedence.

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