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Ethical issues related to the use of placebo in clinical trials

臨床試驗中使用安慰劑的倫理問題

Controversy exists regarding the ethics of using placebo control groups in clinical trials when effective treatments exist. The debate was fuelled by the announcement of the fifth revision of the Declaration of Helsinki in 2000. This study reviews the history and scientific background surrounding the controversy and investigates the prevailing attitudes of Hong Kong researchers regarding this issue. The controversy has centred on several issues. The first involves the methodological superiority of placebo-controlled trials in discerning treatment effects. Secondly, it is unclear whether the treatment effects encompass absolute treatment effects (including placebo effects) or are confined to treatment-specific effects (excluding placebo effects). Thirdly, there are concerns that subjects in the placebo group could be exposed to a high risk for developing serious adverse events. Fourthly, it is unclear whether the standard of best available treatment should be local or international. Preliminary research findings suggest that the opinions of Hong Kong researchers are divided on the use of placebo control groups in clinical trials when effective treatment exists. Further research on the topic is therefore warranted, and training and consensus meeting may be necessary to minimise the confusion related to this issue.

在有效治療存在的情況下，對於是否可以在臨床試驗中應用安慰劑對照，存在很大爭議。當“赫爾辛基宣言”第5校訂版(2000)出台後，此爭議更趨激烈。本文總結了這些爭議的歷史和科學背景，並且調查了香港醫學研究人員在此爭議中的態度。有關爭議的內容主要包括四方面。第一，安慰劑對照試驗在識別療效方面，具有方法學上的優越性。第二，療效是應該指絕對療效(包含安慰劑作用)，還是指限定療效(不包含安慰劑作用)?第三，安慰劑對照組的參予者是否有更大發生嚴重不良反應事件的機會?第四，最佳的標準治療應該是地區性的，還是國際性的?初步研究結果顯示，香港研究人員對於在臨床試驗中，在有效治療存在的情況下，是否可以應用安慰劑對照也是意見分歧。因此，為減少此爭議給醫學研究人員帶來的困惑，有必要在這課題上作進一步研究，並進行培訓以達成共識。

Key words:

Clinical trials;
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Introduction

Some researchers have raised strong concern about the ethical consideration of including placebo control groups in clinical trials when effective treatments are available, while others offer an alternative view that placebo control groups are necessary.¹ The debate intensified after the announcement of the fifth revision of the Declaration of Helsinki in 2000.² Since ethical issues concerning the conduct of clinical trials have not been widely discussed in Hong Kong, it would be worthwhile to review the nature of this discussion and outline the opposing arguments of the ongoing debate. With the imminent restructuring of the Ethics Committees of the various clusters of the Hospital Authority (HA), such a review would be timely. To help researchers protect their subjects to the fullest extent, this review will highlight the relative advantages and disadvantages of using placebo control groups for clinical trials where treatments exist for the studied disease. It is also important to ascertain whether clinical trial researchers in Hong Kong, similar to those of other countries, have divided opinions on this issue. This information will assess the degree of polarity of the debate in the local context and could be relevant to the establishment of the new cluster Ethics Committees.

Objectives

This paper has two objectives. The first objective is to conduct a comprehensive literature review to summarise and analyse the history and scientific basis for the use of placebo control groups in the conduct of clinical trials, with a special reference to the Declaration of Helsinki and its most current revision announced in 2000. For the review, a Medline search (using key words of 'placebo', 'clinical trials', and 'ethics') was performed to identify articles related to ethical issues and placebo-controlled trials published from 1999 to 2002.

The second objective is to perform a preliminary study to investigate the position of local clinicians and researchers in the debate and their knowledge of the fifth revision of the Declaration of Helsinki² and its subsequent note of clarification issued in October 2001.³ To this end, a sample of HA clinicians and members of the Faculty of Medicine of the Chinese University of Hong Kong (CUHK) were surveyed.

Subjects and methods

Two preliminary surveys were performed to meet the second objective. The first survey consisted of a convenience sample of clinicians (n=90) attending the HA Convention 2002 held at the Hong Kong Convention Centre on 29 to 30 April 2002. The anonymous, self-administered questionnaire was distributed by the staff of the Centre for Clinical Trials and Epidemiological Research (CCTER) at the CUHK during tea breaks. The response rate was approximately 80%. The following questions were asked:

- (1) whether the respondent would use a placebo-controlled trial design if he/she was studying the efficacy of a drug for a condition for which effective treatments exist and for which the withdrawal of the treatment causes discomfort but no irreversible harm to the patient; and
- (2) whether the respondent had participated in a clinical trial.

The second survey sent questionnaires by internal mail to all researchers and faculty staff of the Faculty of Medicine at the CUHK whose name was listed in the university telephone directory. Ninety-three self-administered questionnaires were returned to the CCTER. The response rate

was 32%. The questionnaire contained four questions. As well as the two above-mentioned questions, the respondents were asked if he/she knew about the fifth revision of the Declaration of Helsinki 2000 and its note of clarification in Paragraph 29 on the use of placebo control groups issued by the World Medical Association (WMA) in October 2001. Descriptive statistics were given for responses to each question.

Analyses for the association between whether or not the CUHK researchers involved in clinical trials would use a placebo control group in the hypothetical situation and his/her familiarity with the fifth revision of the Declaration of Helsinki and its further clarification on the use of placebo control groups in clinical trials were performed using the Fisher exact test. All statistical analyses for the survey were conducted with Statistical Package for Social Sciences (Windows version 10.0; SPSS Inc., Chicago, US).

Results

Opinions of local researchers

Of all the clinicians and researchers surveyed, 62% have been involved in clinical trials (64.1% among the CUHK group and 60% among the HA group). Approximately 60% of all respondents (55% of the clinical trialists and 59.4% of the non-trialists) stated that they would use a placebo-controlled trial design in the hypothetical situation that an effective treatment existed and the absence of treatment would cause some discomfort but no irreversible harm to the patient (Table 1). A larger proportion of the HA staff (72.7%) would use placebo-controlled trials in the described situation compared the CUHK staff (40.7%). Among the CUHK staff, 52.5% of those who had conducted clinical trials and 12.1% of those who had not conducted clinical trials knew the fifth revision of the Declaration of Helsinki (Table 2). Approximately 29% and 3% of the two groups, respectively, had learned about the note of clarification in Paragraph 29 of the fifth revision of the Declaration of Helsinki. A larger percentage of the CUHK staff who had been involved in a clinical trial and learned about the fifth revision of the Declaration of Helsinki (44.8%) stated that they would use a placebo-controlled trial in the given hypothetical situation than those who had not learned about it (25%) [Table 3]. A similar trend has been observed for people whether they had learned about the clarification

Table 1. Opinions about the use of placebo-controlled trials among Hong Kong scientists

| | Involved in clinical trials* | | Member of Hospital Authority or Chinese University of Hong Kong | | All respondents (n=178) |
|--|------------------------------|-----------|---|--|-------------------------|
| | Yes (n=109) | No (n=69) | Hospital Authority (n=88) | Chinese University of Hong Kong (n=91) | |
| If you are going to conduct a clinical trial, would you use a placebo group as the control group if: | | | | | |
| (1) there exists an established treatment that has been shown to be effective; and | | | | | |
| (2) the absence of treatment would cause some discomfort but no irreversible harm to the patient? | | | | | |
| Will use placebo | 55.0% | 59.4% | 72.7% | 40.7% | 56.7% |
| Will not use placebo | 41.3% | 24.6% | 17.0% | 52.7% | 34.8% |
| Do not know | 3.7% | 15.9% | 10.2% | 6.6% | 8.4% |

* One of the participants did not clearly state if he/she had been involved in clinical trial

Table 2. Knowledge of the fifth revision of the Declaration of Helsinki among scientists at the Chinese University of Hong Kong

| | Involved in clinical trials | | All respondents (n=92) |
|--|-----------------------------|--------------|---------------------------|
| | Yes (n=59) | No (n=33) | |
| Have you learned about the fifth revision of the Declaration of Helsinki (October 2000)? | | | |
| Yes | 52.5% | 12.1% | 38.0% |
| No | 47.5% | 87.9% | 62.0% |
| Have you learned about the note of clarification on Paragraph 29 of the fifth revision of the Declaration of Helsinki (October 2000) regarding a placebo-controlled trial, which the World Medical Association issued during October 2001? | | | |
| Yes | 28.8% | 3.0% | 19.6% |
| No | 71.2% | 97.0% | 80.4% |

Table 3. The association between knowledge of the fifth revision of the Declaration of Helsinki and stance on the use of placebo-controlled trials among Chinese University of Hong Kong scientists involved in clinical trials

| | Will use placebo (n=20) | Will not use placebo and do not know (n=37) | P value |
|--|----------------------------|---|---------|
| Have learned about the fifth revision of the Declaration of Helsinki | 44.8% | 55.2% | 0.167* |
| Have not learned about the fifth revision of the Declaration of Helsinki | 25.0% | 75.0% | |

* Fisher exact test

Table 4. The association between knowledge of the note of clarification on Paragraph 29 of the Declaration of Helsinki and stance on the use of placebo-controlled trials among Chinese University of Hong Kong scientists involved in clinical trials

| | Will use placebo (n=20) | Will not use placebo and do not know (n=37) | P value |
|--|----------------------------|---|---------|
| Have learned about the note of clarification on Paragraph 29 | 56.3% | 43.8% | 0.062* |
| Have not learned about the note of clarification on Paragraph 29 | 26.8% | 73.2% | |

* Fisher exact test

for the use of placebos issued by the WMA (Table 4). The association between the choice of whether to use a placebo-controlled trial in the hypothetical situation and the knowledge of the fifth revision of the Declaration of Helsinki and its further clarification was not statistically significant, however.

The Review

The debate of the ethics of placebo-controlled trials—the concept of equipoise

Heated controversy about the ethics of placebo-controlled trials can be traced back to the 1980s.⁴ The concept of equipoise underlies the controversy about the ethics of placebo-controlled trials. Equipoise is a genuine state of uncertainty about which of the two treatments (or groups) of a clinical trial has a better efficacy.⁵ It is considered a necessary condition for a clinical trial to be conducted and, if one or some treatment(s) is (are) known to be 'effective', the state of equipoise no longer exists. It would therefore be unethical to use a placebo control group in which the patients were not given the effective active treatment. Some researchers have taken this ethics debate a step further, arguing that the 'best available' treatment should always be given to the control group so that the interests of the patients in a clinical trial would be best served. Similar arguments have been made regarding situations where treatments are withheld from subjects in clinical trials, as in washout periods.⁶

Researchers using placebo-controlled methods have been harshly condemned by critics who claim that these

researchers are prioritising societal interests over those of the patients.⁷ It is also argued that, regardless of where the trial is conducted, patients should always receive the same treatment, as the subjects of these controversial trials are patients rather than volunteers.

The fifth revision of the Declaration of Helsinki—an ignition point

The fifth revision of the Declaration of Helsinki was published in October 2000. Both before and after publication, numerous articles defending or denouncing placebo-controlled studies were published in top-tier scientific journals such as *New England Journal of Medicine*,^{1,8} *Lancet*,⁹ *Journal of the American Medical Association*,¹⁰ and *Annals of Internal Medicine*.^{11,12}

The Declaration of Helsinki was initially authored in 1964 by the WMA in its 18th General Assembly in Helsinki, Finland. It serves as one of the most important and widely accepted guidelines on the ethical principles governing the conduct of medical research involving human subjects. The amendments to the Declaration were made in Tokyo (October 1975), Venice (October 1983), Hong Kong (September 1989), Sunset West (October 1996), and Edinburgh (October, 2000). The use of control groups in clinical trials was directly addressed by Article 11.3 of the fourth revision (1996) stating: "In every medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method". In the fifth revision of the Declaration, however, Provision 29 states: "The benefit, risks,

burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods". Provision 30 of the fifth revision goes on to state: "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic or therapeutic methods identified by the study". It further indicates, in other Provisions, that academic journals should publish both positive and negative results and should reject reports of studies not adhering to the principles of the Declaration.

The sentiments of the research community in response to the fifth revision of the Declaration were captured in the titles of some articles published such as: "*Helsinki discord? A controversial declaration*",¹³ "*The 2000 revision of the Declaration of Helsinki: a step forward or more confusion?*",⁹ and so on.

Consensus and controversies

There is some consensus in the research community that placebo control groups should not be included for life-threatening conditions or for harmful non-reversing conditions when an effective treatment exists. Additionally, there is consensus that placebo-controlled trials may be used when there are no proven effective treatments as in clinical trials for newly developed drugs.¹⁴

Despite the above-mentioned consensus, controversies remain. Firstly, there are arguments which are methodological in nature, including those on assay sensitivity, external validity, and measurement of the total treatment effects. Secondly, there are concerns that the absence of active treatment for the placebo group would deprive patients in that group of the best available treatment. Thirdly, it was not clear whether the "best proven standard of treatment" is to be defined in an international or a local sense.

The use of control groups

To understand the nature of the controversy, it is necessary to firstly distinguish between types of control groups. The use of control groups is a critical aspect of randomised controlled trials that distinguishes these trials from other study designs. The purpose of using a control group is to discriminate effects caused by the study treatment from effects caused by other factors.¹⁵ Control groups are selected in a way that they should be similar to the treatment groups in all variables that could affect the outcomes, except for the study treatment. Thus any significant differences between the two groups can be attributed to the difference between the study treatment and the placebo or the other active treatments under comparison. Failure to achieve such comparability would result in biases.

A clinical trial can be of a superiority type or a non-inferiority type.¹⁵ The former aims to test whether a tested treatment is more efficacious than the control treatment (the

null hypothesis is therefore that the two groups are the same in efficacy); the latter aims to test whether a tested treatment is not inferior to (or not different from) another treatment (the null hypothesis is that the two treatments do not have the same efficacy).

There are different types of control groups used in clinical trials, each trial type addressing different objectives and possessing inherent limitations.¹⁵ A clinical trial may employ as its control group a placebo group, in which subjects receive a treatment that is pharmaceutically inert, keeping all other aspects the same. Blinding is always built in to remove effects arising from the fact that the researcher knows that the 'drug' is only a placebo that may affect both the outcomes and the compliance. Such trials are all subsumed under superiority trials. Another type of control group is the 'no treatment' group. No treatment controls are similar to placebo controls, except that blinding is not possible. The third type of control gives an active treatment to the subjects. These trials can be either superiority or non-inferiority trials depending on the objectives of the study. Control groups may also be given different dosages of the same treatment (dosage controls) if the aim is to test for dosage effects. An add-on control group could be included when stopping a treatment is not ethical. This type of study is a placebo-controlled trial of a new agent conducted with patients who are also receiving the existing active treatment. Clinical trials may also employ more than one control group. Examples of this include the use of a placebo for one of the control groups and an active treatment for another, or the use of treatments of varying dosages in different control groups (ie dosage controls). All of the above-mentioned groups are concurrent controls, in that patients in the study treatment group and the control group are treated and measured in the same time period. Although historic controls are sometimes used, their limitation in controlling bias often makes their use methodologically questionable.

Only the use of dosage controls allows for comparisons of dosage effects. Studies involving an active treatment control group can allow for comparison between different therapies. Studies using a placebo control group and an active treatment control group with a superiority design allow for measurement of the 'absolute' effect and test for relative efficacy between two treatments. Non-inferiority trials only using an active treatment control group cannot achieve these two important objectives.¹⁵

The methodological aspect of the debate—assay sensitivity

The 'placebo-orthodox' defends the use of placebo control groups in clinical trials on the grounds of the methodological strength of this design and its necessity for drug development.¹ Placebo-controlled trials are always superiority trials, whereas active-treatment-controlled trials are often non-inferiority trials since requiring every new drug to have a significantly better efficacy than established active treatments may be too stringent. Furthermore, a

new treatment may still be considered useful if it has fewer side-effects, or is available at a lower cost.^{16,17}

Placebo-controlled trials therefore have a better internal validity, or better assay sensitivity compared with active-treatment equivalence trials (ACETs). Assay sensitivity is defined as the ability to distinguish efficacious trials from non-efficacious trials.¹⁵ Since placebo-controlled trials are of a superiority nature, they can establish differences in efficacy between the test treatment and the control (placebo), without requiring external evidence. With ACETs, a conclusion that the test treatment is as good as the active control treatment does not signify that the study treatment is efficacious, unless there is external evidence to demonstrate the efficacy of the active control treatment used in the control group. This could be difficult because inconsistent trial results may be obtained even for established treatments. In other words, the ACET design lacks assay sensitivity, which is of central importance in drug development.^{14,15} Indeed, the Council for the International Organization of Medical Sciences stated that "ACET is unlikely to provide clinically meaningful and interpretable results". The US Food and Drug Administration (FDA) further stated that "Comparing drugs to approved drugs without a placebo anchor point can lead to approval of ineffective drugs". The European counterpart, the European Agency for the Evaluation of Medicinal Products (EMA) takes a similar position, stating, that: "Placebo-controlled trials are necessary to produce reliable scientific evidence for evaluation of new drugs". Dr Gregkoski of the Department of Health and Human Services of the US described the issue as "an area of active discussion in the department."¹³

There are other methodological arguments in support of placebo-controlled trials. As ACETs require a larger sample size to obtain the same statistical power, supporters of placebo-controlled trials make the criticism that ACETs will require more subjects to use the test drug, which may not be ethical.¹ Other proponents have argued that placebo-controlled trials are ethical because they allow the public to have quick access to new drugs.¹² It has also been pointed out that scientific validity is part of the ethics consideration, and since ACETs have poor assay sensitivity, the ethics of their use can be questionable.¹ Further, placebo-controlled studies are advantageous in that they minimise the effects of subjects' and investigators' expectations, which may increase the chance to detect significant treatment effects.¹⁵ In fact, strict adherence to the fifth revision of the Declaration of Helsinki may prohibit single-group studies to be performed since patients in these trials would not have any chance of receiving the best available treatment.¹⁸

External validity and generalisation

Although placebo-controlled trials possess better internal validity than ACETs, the reverse is true when external validity is considered. Supporters of ACETs have argued that, in reality, decisions are generally made regarding

whether to use a new treatment or an active treatment. The comparison of the relative efficacies of a new drug over a placebo would thereby offer little information to the decision process.^{7,19}

Placebo effects

Supporters of placebo-controlled trials try to convince other researchers that ACETs are unable to measure the total (absolute) treatment effects, which includes placebo effects.¹⁵ Response rates in placebo groups may be high, as noted in a large number of psychiatric studies.²⁰ For instance, response rates have been reported to be as high as 50% for major depression studies, 34% for bipolar disorder studies, 23% to 34% for panic disorder studies, and 43% for short-term schizophrenia studies.²⁰ Such is also documented for studies of asthma, ulcer disease, herpes simplex, neurological disorders, and so on.²¹⁻²³ Therefore, it is not always the case that patients in the placebo group are not benefiting from the study.

Whether the placebo group is subjected to a higher risk of developing serious adverse events

The withdrawal of treatment in psychiatric placebo-controlled studies is often cited to emphasise possible unethical situations that may cause greater risk or harm to patients in placebo groups. In fact, most European countries do not allow for placebo controls to be used in trials of antidepressant medications. A study reviewing 19 639 patients from the FDA database of seven new antidepressant trials performed between January 1987 and December 1997 showed that the incidence of suicide for patients in the placebo group, the active control group, and the test drug group were 0.4%, 0.7%, and 0.8%, respectively; similarly the percentages of attempted suicide were 2.7%, 3.4%, and 2.8%, respectively.²⁴ Neither set of data were of statistical significance. The percentages of patients with symptom reduction were 30.9%, 41.7%, and 40.7%, respectively. Hence, there is no evidence to indicate that patients in the placebo group were exposed to greater risk of developing serious adverse events or deriving no benefit from the study. These data do not support arguments of unethical research using these patients. A similar study that reviewed placebo-controlled trials for the treatment of major depression found out that, in 77 short-term studies with 12 246 patients, the incidences of suicide were 0.1% in both the placebo group and the active treatment group, and the incidences of attempted suicide were also identical (0.4%) in both groups.²⁵ Similarly, the incidence of suicide (0% for the placebo group and 0.2% for the active treatment group) and attempted suicide (0.7% for the placebo group and 0.7% for the active treatment group) were not higher for the patients in the placebo groups compared with patients in the active treatment groups in eight long-term studies of 1949 patients.²⁵

For hypertension trials, there is compelling evidence that patients benefit from long-term antihypertension treatment.²⁶ A meta-analysis of 25 short-term randomised

controlled trials (n=6409) conducted during 1997 and 1998, using death, stroke, myocardial infarction, and congestive heart failure as outcomes, showed that the difference in incidence between the placebo group and the antihypertension treatment group was between 0 and 6 per 10000 subjects, however.²⁷ Hence, short-term placebo-controlled studies may still be ethical, even though a long-term study might not be safe. Study duration is therefore an important consideration in determining whether placebo-controlled studies are ethical or not. Similar arguments have been made for short-term studies of type 2 diabetes that are believed to be safe for patients in the placebo group, while longer trials (which may take at least 6 months to complete) will have adverse effects on the patients' quality of life and may result in microvascular complications.²⁸

Best available treatment—local standard versus international standard

Drawing on the experience of HIV trials performed in developing countries, advocates have argued that the standard of best available treatment in developing countries should be the same as in developed countries.²⁹ Furthermore, an additional challenge posed by the fifth revision of the Declaration of Helsinki is that patients should be provided with the best available treatment even after the study is completed (Provision 30). The drug companies have expressed serious concerns about the cost implications for drug development and have pointed out that many trials would be terminated if the new revision were to be strictly interpreted. Others have indicated that, even in developed countries, the best available treatment may not always be accessible and the situations outlined in the fifth revision are thereby unrealistic. Furthermore, local governments of these developing countries may have other priorities besides medical care, so that being coerced to use the costly drugs given in western countries may be an unpopular idea in the developing world.

Table 5 summarises the arguments for using placebo-controlled trials and ACETs.

The middle ground

It has been suggested that the placebo-orthodoxy and active control-orthodoxy are both indefensible in that both discount the ethical and methodological complexities of clinical trials.¹ A middle ground has been proposed in which a placebo-controlled study should be allowed when the methodological reasons for its use are compelling and the patients in the placebo group will not be subjected to

serious or irreversible harm, and when provisions have been made to minimise the risk to these patients.

Discussion

The use of placebo groups is common when conducting clinical trials. To date, the Declaration of Helsinki is the most widely recognised document guiding ethical considerations for clinical trials. A heated debate has been ongoing in the US and Europe and the arguments for the two sides are summarised in this paper. Since the fifth revision of the Declaration stated that journals should not publish papers that are not in accordance with the Declaration, ethical issues related to the use of placebo controls are likely to be questioned more frequently and critically by the entire medical research community. Although the WMA has issued a note of clarification, the debate will continue due to the controversial nature of this issue.

Our preliminary results demonstrated that Hong Kong researchers are generally not prepared to respond to enquiries related to the new revision of the Declaration of Helsinki, since only half of university researchers who had ever conducted a clinical trial had learned about the fifth revision of the Declaration and even fewer (less than 30%) had learned about the subsequent note of clarification. These two local opinion surveys have their limitations—one comes from a convenience sample and the other population-based study has a relatively low response rate (32%). The results should therefore be interpreted with caution. Since the percentages of respondents who were aware of the Declaration and its amendment were low and the observed split of opinions about the use of placebo groups were obvious, and there is no reason to believe that non-respondents would be more likely to have a higher awareness or would favour the use/non-use of placebo-controlled trials than respondents, the preliminary results obtained from this study may still be a useful preliminary indication of local feeling. This survey derives some important and relevant hypotheses that should be tested by large-scale studies in the future.

The ethics of conducting clinical trials appears to have been under-emphasised in the past and there are no bioethicists in Hong Kong. It is unclear whether or not existing and prospective members of the various Ethics Committees have been trained to be aware of these highly important issues. The Ethics Committees in Hong Kong, as in other countries, are faced with the monumental task of generating consensus in a research community that is divided in

Table 5. Summary of the arguments for and against placebo-controlled trials

| Placebo-controlled trials | Active-treatment equivalence trials |
|--|---|
| Superiority study design | Usually inferiority study design |
| Good assay sensitivity | Doubtful in assay sensitivity |
| Smaller sample size required | Larger sample size required |
| Less ideal external validity and applications to patient management | Better external validity, more relevant to patient management |
| Able to measure total treatment effects | Unable to measure total treatment effects |
| Potential harm to the untreated placebo group | Both groups would receive some treatment |
| Best standard treatment sometimes may not be available in a country or may not be well defined | Ensures patients get the best standard treatment |

their views regarding the use of placebo-controlled trials when treatment already exists and the absence of treatment causes reversible discomfort. It will be increasingly necessary to develop a consensus standard in order to promote a better understanding of the proper use of placebo-controlled clinical trials.

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