Placebo-controlled Clinical Trials: How rationale for the use of randomization and placebo is justified in the trial documents

Tapani Keränen a, b, c
Arja Halkoaho a
Emmi Itkonen a
Anna-Maija Pietilä a, d

a) Science Service Center
   Kuopio University Hospital
   P.O. Box 100, 70029 KYS, Finland
b) Department of Pharmacy
   University of Eastern Finland
   P.O. Box 1627, 70211 Kuopio, Finland
c) National Institute of Health and Welfare
   Mannerheimintie 170
   00271 Helsinki, Finland
d) Department of Nursing
   University of Eastern Finland
   P.O. Box 1627, 70211 Kuopio, Finland

Corresponding author:
Tapani Keränen
National Institute for Health and Welfare
Mannerheimintie 170
P.O.Box 30, 00271 Helsinki, Finland
Email: tapani.keranen@thl.fi
Phone: +358 40 866 9883

e-mail addresses of the authors
arja.halkoaho@kuh.fi
anna-maija.pietila@uef.fi
emmii@student.uef.fi

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Abstract

Background

Randomized clinical trials (RCTs) involve procedures such as randomization, blinding and the use of placebo which are not part of standard medical care. Patients asked to participate in RCTs often experience difficulties in understanding the meaning of these terms as well as their justification.

Methods

We reviewed RCT protocols, statements of the principal investigator (PI) and participant information materials, submitted for opinion to a research Ethics Committee. We evaluated how the justification for the use of placebo had been described in these documents and how participants had been informed about randomization, placebo, and the possible risks of receiving placebo.

Results

Altogether 52 RCTs were identified. Eighteen of the study protocols (35 %) provided some rationale for the use of placebo. In fifteen (29 %) of the statements the PI had provided a justification for the use of placebo. Possible risks related to placebo use were described in nine (17 %) of the statements. The justification of why placebo was necessary had been included in only 12 (23 %) of the participant information materials, and only six (12 %) of the documents discussed about the possible risks associated with placebo.

Conclusions

Justification of placebo control was inadequately described in RCT study protocols, by principal/national coordinating investigators, and in participant information documents. Possible health related risks associated with the use of placebo were also poorly explained in the participant information documents. Ethics committees and study participants need to be better informed of the rationale for the use of placebo as well as the associated risks.
**Background**

Randomized clinical trials (RCTs) are the gold standard in the demonstration of efficacy and safety of new medical treatments. RCTs involve certain procedures such as randomization, blinding and the use of placebo, which are not part of standard medical care. Patients asked to participate in RCTs often have difficulties in understanding the meaning of these terms as well as the justification for their use [1 – 4].

The ethics of placebo-controlled trials continue to be a subject for heated debate [5, 6]. It is agreed that the use of placebo is acceptable when there is no proven intervention for the condition under study [6, 7]. In contrast, there is disagreement about whether placebo-controlled trials are ethically justifiable when effective treatment is available for the disorder in question [5, 8]. The use of placebo control may be permissible also in disorders which can be currently effectively treated if there are compelling and scientifically sound methodological reasons for its use and the participants of the study will not face additional risks of serious or irreversible harm when exposed to placebo [6, 7]. However, as Millum and Grady [6] point out, the need for placebo to demonstrate the efficacy of a new treatment may not be sufficient to justify its use.

It is important that patients recruited into RCTs understand the study methodology, the interventions to be used as well as their benefits and risks. At present, little is known about how participants are informed of the placebo and its effects [9]. The aims of the present study were to evaluate how well the justification for the use of placebo had been described in RCT protocols and by the principal/national coordinating investigators. Another aim was to determine the extent to which participants had been informed about randomization, placebo, and any possible risks associated with placebo treatment. The analysis was based on review of study protocols, statements of the national principal investigator, and information documents provided to the participants.

**Methods**

We surveyed the records of the Research Ethics Committee (REC) of the North Savo Hospital District from 1.1.2006 to 31.12.2012 to identify all applications for randomized placebo-controlled clinical drug trials. The REC of the North Savo Hospital District is a local research ethics committee assessing study plans involving medical research in humans, from a catchment area of the Kuopio University Hospital, and as from October 2010, also the regions of North Carelia Central Hospital, Mikkeli Central Hospital and Savonlinna Central Hospital. A clinical trial was defined as prospective study in human subjects intended to assess efficacy, safety or pharmacokinetics [absorption, distribution, metabolism and excretion] of one or more medicinal product(s). Both industry sponsored and investigator initiated studies were included.
Access to the files of the Ethics Committee was granted by the Research Director of the North Savo Hospital District.

**Data collection and analysis**

Data were manually collected by two of the authors but the multidisciplinary research group discussed the selected studies. After identification of applicable studies, we reviewed the protocols and their amendments, ethical statements of the principal/national coordinating investigator, and participant information documents. According to the national guidelines provided by the Finnish Medicines Agency [10] and the National Medical Research Ethics Committee [11], the principal or coordinating investigator of the clinical trial must deliver a statement on the ethical aspects of his/her study which must tackle issues such as assessment of the rationale for the study, risk/benefit ratio, and how informed consent will be obtained.

We recorded how the use of placebo had been justified in the study protocols, in the statement of the principal/national coordinating investigator, and in participant information documents. Furthermore, we searched for information in the statement of the principal/national coordinating investigator, and in participant information documents about the following topics: randomization, definition of placebo as well as assessment of possible risks associated with the use of placebo. Characteristic quotes of statements and the information were also gathered and presented to illustrate information provided to the Ethics Committee and subjects being asked to participate in the trial. Minor changes to the wording of the quotes were made in order to maintain the confidentiality.

Data were analyzed by qualitative and quantitative content analysis according to the research objectives by classification and grouping quotes of statements. The data was read several times by creating an overview of the content. Meaningful combination of words and sentences were extracted, condensed and coded. After this, codes were categorized two main categories: Justification for the use of placebo, Blinding and randomization as described in the patient information documents [12].

**Results**

**Description of the trials**

A total of 52 RCTs were identified, mostly Phase III international multicenter trials. The characteristics of the trials are presented in the Table 1. The category of others included disorders such as arthritis, osteoporosis, cardiovascular diseases, and sepsis.

In 42 trials, placebo had been used in disorders where a standard therapy was available, and nearly in all of those cases (41 studies), standard therapy was anticipated to be continued during the trial. Eleven of the
52 trials were studies in disorders for which there was no standard therapy available. Seven of the trials involved vulnerable populations, e.g. children, subjects with dementia.

**Justification for the use of placebo**

Eighteen of the study protocols (35%) provided a rationale for the use of placebo. In most of the cases (12 protocols), the scientific rationale was presented as the justification, and in 6 protocols, regulatory guidelines were stated as the reason for the use of placebo.

In all but one application, the statement of the principal/national coordinating investigator was available for evaluation. Fifteen (29%) of the statements of the principal investigator presented some rationale for the use of placebo, and in all of these cases, scientific causes, i.e. to confirm the efficacy of the study drug or a high placebo response rate in the disorder under study was given as the justification (“Placebo is used to scientifically confirm the efficacy of the study drug.”). The investigators also pointed out that the use of placebo was acceptable because the participants would continue to receive the best available treatment during the trial. Possible risks related to placebo use were commented upon in nine (17%) of the statements. In all but one case, the investigator stated that there were no special risks associated with placebo.

The justification of placebo was presented in only 12 (23%) of the participant information documents. The following represent the most frequent phrases: “Placebo is used in order to objectively assess the effects of study treatments” and “The use of placebo as the comparator is justified because the subjects are already on the best available treatment”. None of the information documents provided any data on possible beneficial effects of placebo. Six (12%) of the information documents discussed about possible risks associated with placebo by mentioning that the condition of the participants probably would not change, another stated that symptoms may worsen or may remain unchanged. In addition, adverse effects of placebo were described as being comparable with the situation when no drug treatment is given.

The meaning of the term placebo had been explained in 36 (69%) of the patient information documents as follows: “Placebo looks identical to the active study drugs but does not include any effective ingredients.” Altogether 40 (77%) of the patient information documents described the probability of receiving placebo by stating that the subjects will have a 50% chance to receive study drug or placebo, or as in one statement as follows: “The odds for receiving placebo is one to three”.

**Blinding and randomization as described in the patient information documents**

All the participant information documents declared that the study had a double blind design, described most often in the following words: “This is a double-blind study which means that neither you nor the study...”
physician will know which of the study treatments you will receive”. Information for possible emergency situations was given: “You, your doctor, and none of the study personnel will be told which of the study drugs you will receive. However, in the case of an emergency, your doctor will be able to obtain the information of your treatment if this is necessary for your care”

A total of 46 information documents (88 %) described what the randomization procedure meant. The most common characterization for randomization was “as if by flipping a coin, computer based lottery or by chance.” However, in none of the cases, was any justification for this procedure provided.

Discussion

We analyzed a sample of clinical trial protocols, ethical statements of principal/national coordinating investigators and participant information documents to assess how the use of randomization and placebo had been justified and how possible risks associated with placebo had been described. The main finding of our study is that all these documents seem to overlook the information needs of the different stakeholders in clinical trials, especially those of the trial participants.

The main goals of clinical trial protocols are to present the aims, methods and procedures of a scientific trial to investigators as well as to regulatory authorities. However, also RECs and funding agencies need to be able to assess the key trial elements and they may not always have sufficient expertise to assess the adequacy of the study methodology. Thus, study protocols should provide explicit justification for the use of methods such the decision to use placebo control [8]. Only 35 % of the protocols that we analyzed presented any justification for the use of placebo and regulatory requirements were stated as the cause in most of the cases. According to the European Medicine’s Agency (EMA), the most common primary objectives for pivotal clinical trials are to demonstrate superiority to placebo, or to demonstrate non-inferiority or equivalence to an active control [13]. However, in this guideline the agency recognizes that a placebo control may sometimes not be suitable to address all study hypotheses. Thus, for ethical evaluation of a trial the feasibility and ethical acceptability of the use of placebo should be discussed in the protocol.

There are limited and partly contradictory published data on attitudes and opinions of investigators on how participants should be informed about trials. In a survey of oncologists, the investigators considered it to be very important that participants understood the nature of trials as well as the role of randomization and placebos [14]. In another study, most of the investigators were confident that they had given enough information to their patients and that they believed that patients generally comprehend the implications of participation [15]. On the other hand, a study in 170 breast cancer specialists found that only 12 % of the physicians thought that the patients were able to understand the information needed in order to give informed consent. Hereu et al. [16] reported that a group of investigators considered treatment allocation
and the use of placebo among the least important aspects in informing patients of clinical trials. The statements of principal/national coordinating investigators analyzed in our study provided some justification for the use of placebo in only about one third of the cases and less that 20 % of the statements discussed any possible risks related to placebo. The statements may not, however, reflect the attitudes of the investigators towards informing patients but merely towards the REC. There are studies reporting that investigators do have concerns about patients’ best interests and possible study related harms [17, 18].

It has been claimed that while many clinical trial participants are satisfied with the information they have received and report that they understand the trial design, a substantial proportion of the subjects have only partial or poor comprehension of the goals and methods of a trial [16, 19 - 22]. The concept of randomization seems to remain difficult to conceive [1 – 4]. Furthermore, some of those who understand what randomization means are reluctant to accept its use [4]. This, however, has not been confirmed in other studies [23, 24]. In our sample of studies, most of the participant information documents gave a description of randomization with short and simple wordings which have been found to be comprehensible to the patients [25]. However, none of the participant information documents provided any justification about why the randomization procedure was necessary. Because patients tend to think that treatment allocation should be determined by clinical and personal characteristics [2], lack of any explanation for the use of randomization may lead to confusion and possible refusal to participate. On the other hand, if patients are not informed that clinical equipoise between the treatments compared in a trial is a fundamental requisite they may think that randomization is a lottery [3].

The probability of receiving one of the treatments (including placebo) was given in about 70 % of the cases we analyzed. In the survey of Bishop et al. [9], the chances of receiving placebo were reported in all the information documents. Thus, in nearly in one third of our cases, the subjects being asked to participate were not able to make a real informed decision on participation due to the lack of knowledge of the probability if receiving active or placebo treatment. They were also unable to fully understand the possible benefits and harms associated with the study.

Subjects asked to participate in the trials were clearly informed about the possibility to receive placebo. Placebo was described as a product looking similar to the active study drug but being pharmacologically inert, similarly to the findings of Bishop et al. [9]. In a large majority (77 %) of the participant information documents, no rationale for the use of placebo was presented. This is quite opposite to the findings of Bishop et al. [9] who found an explanation for the use of placebo in 78 % of the participant information documents they analyzed. The difference may be due to different national guidelines for providing participant information as well as to the varying funding sources and the trial types. Similarly to the findings of Bishop et al. [9], scientific reasons were given as the justification for the use of placebo in information
documents evaluated in our study. Only in a minority of cases (12%), the subjects were informed about the possible risks of receiving placebo. In the study of Bishop et al. [9] possible adverse effects related to the use of placebo were mentioned in 49% of the information documents. Bishop et al. [9] concluded that the information documents they analyzed encouraged participants to focus on the target treatment. The use of placebo does not automatically imply that the subjects remain without any treatment. As in the series of studies surveyed here, in most trials the participants continued to receive standard care and the study drug was added to the existing treatment. It is possible that subjects receiving placebo may, however, experience a suboptimal response to their concurrent medication.

The limitations of our study include the small sample size. Furthermore, the analyzed studies comprised mainly trials in psychiatric and neurological disorders and those in the fields of diabetes, cancer, and cardiovascular disorders represented only a minority. On the other hand, we were able to survey all the studies submitted for ethics committee evaluation over a reasonable time period. We are aware of only one previous study which analyzed how placebo had been described in the participant information documents of clinical trials [9]. In that survey, most of the analyzed studies were noncommercial whereas in our study nearly all the studies were sponsored by a pharmaceutical company. In addition to participant information documents, we were able to analyze the study protocols and investigator statements.

Conclusions

Ethicists have proposed that RECs should demand that sponsors and investigators justify the use of placebo controls in all studies, especially whenever the study may involve withdrawal or withholding of proven effective therapy [8]. Furthermore, RECs should approve studies only when sufficient information has been provided to make a judgment about the acceptability or undesirability of a placebo control. Furthermore, it has been stated that patients should participate in such studies if they have given fully informed consent, are aware of random allocation, the double-blind conditions, and the use of placebo [26]. As discussed above, subjects asked to participate in clinical trials may not have an appropriate understanding of study methods and procedures as well as of the possible harms and not simply the benefits. It is known that patients may underestimate the risks and discomforts of participation in clinical trials [21]. Our study shows that at least with respect to the written information, the documents provided have many shortcomings in describing issues important for giving real informed consent. We agree with the conclusions of Bishop et al. [9] that there is a clear ethical need for a greater transparency and greater respect for the participants in the provision of written information about placebos.

Competing interests

The authors declare that they have no competing interests.
Author’s contributions

TK, AH and AMP developed the original study design. EI and AH were responsible for the data collection. TK and AH conducted the data analysis. TK wrote the manuscript with contributions from AH and AMP. All authors approved the final manuscript.

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Table 1. Characteristics of the 52 randomized placebo-controlled clinical trials.

<table>
<thead>
<tr>
<th>Phase of the clinical trial</th>
<th>N [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>11 [21]</td>
</tr>
<tr>
<td>III</td>
<td>40 [77]</td>
</tr>
<tr>
<td>IV</td>
<td>1 [2]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of the trial</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>International multicenter trial</td>
<td>46 [88]</td>
</tr>
<tr>
<td>Investigator initiated national study</td>
<td>6 [12]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target condition of the trial</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>12 [23]</td>
</tr>
<tr>
<td>Other psychiatric</td>
<td>4 [8]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 [13]</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>6 [12]</td>
</tr>
<tr>
<td>Alzheimer’s disease and other cognitive disorders</td>
<td>6 [12]</td>
</tr>
<tr>
<td>Cancer</td>
<td>1 [2]</td>
</tr>
<tr>
<td>Obesity</td>
<td>2 [4]</td>
</tr>
<tr>
<td>Others</td>
<td>14 [27]</td>
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References


