**Informed Consent and Clinical Trials: Where Is The Placebo Effect?**

***The ethical imperative to disclose information about placebo effects in research contexts***

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**ABSTRACT:**

The Declaration of Helsinki states that researchers are obliged to provide accurate and understandable information to participants prior to enrolment in clinical trials. Recent research analysing the content of written patient information in clinical trials reveals factual inaccuracies, and routine omissions of detail about placebos and placebo effects. We argue that the provision of adequate evidence-based information about placebos and placebo effects would help to improve participant understanding of fundamental aspects of clinical trials. Inadequate information about placebo may contribute to already well-known persistent misunderstandings about the methodology and primary goals of clinical trials among research participants (“therapeutic misconception”). Truthful information is also required to uphold transparency and informed consent. We provide practical recommendations for clinical researchers on the disclosure of placebo effects to trial participants.

**KEY QUESTIONS AND FINDINGS**

**What is already known about this topic?**

* When researchers fail to provide adequate, understandable information to participants they fall short of their ethical duty to respect patient autonomy.
* Studies show persistent, routine failures of informed consent processes in clinical trials resulting in ‘therapeutic misconception’. This refers to participants’ confusions about the primary goal of research, including whether its primary aim is to benefit the individual patient-participant enrolled in the trial.
* Recent content analyses of information leaflets provided to research participants reveal that information on placebos and placebo effects is absent, incomplete, or false.

**What are the new findings?**

* We argue that the failure to provide adequate information about placebos and placebo effects is likely to significantly contribute to therapeutic misconception. The provision of accurate information about placebo effects has the potential to explain and demystify the purpose of clinical trials, including the experiences of participants allocated to placebo.
* Such information is also pertinent to patient debriefing following the completion of trials, where studies show that patients may be confused about their outcome.

**Box 1: Key Questions and Findings**

**INTRODUCTION**

Informed consent requires researchers to provide participants with material information about research that is accurate, complete, and understandable. When researchers fail to provide such information they fall short of their duty to respect the autonomy of participants. Drawing on recent research of disclosure information in research contexts, we observe that routine omissions and factual inaccuracies about placebos and placebo effects may mislead or confuse prospective trial participants. We argue that it is likely that current practices used to describe placebos in randomized controlled trials (RCT) contribute to participants’ failure of comprehension in informed consent processes.

**ETHICAL PRINCIPLES OF MEDICAL RESEARCH: THE DECLARATION OF HELSINKI**

According to the Declaration of Helsinki no ethical justification exists for failing to provide information about the investigative nature of research[[1]](#endnote-1) (See Box 2). In clinical trials we argue that adequate information must include understandable descriptions of the function of placebos and their effects (See Box 3). This is essential in order to fully inform trial participants about the potential benefits and risks of the study as per the Declaration. Indeed, the Declaration is somewhat ambivalent about when placebo controls might ethically be used instead of active treatments in research trials (it states that placebos can be used where there are “compelling and scientifically sound methodological reasons”). In light of continued debate about methodological issues, we argue there is an even stronger ethical imperative for investigators to provide – *not just information about the reasons for placebo use[[2]](#endnote-2)* – but (in order for such information to be clear and understandable) *information about the nature of placebos and how they work*.

**The Declaration of Helsinki**

The World Medical Association’s global statement on ‘Ethical Principles for Medical Research Involving Human Subjects’ – states that physician-researchers are responsible for ensuring that informed consent is obtained in order to protect participants’ right to self-determination. It declares, “While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects”. Furthermore, the Declarations states, “each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study.”

*World Medical Association. Declaration of Helsinki. 64th World Medical Association Assembly (October 2013).* [*http://www.wma.net/en/30publications/10policies/b3/*](http://www.wma.net/en/30publications/10policies/b3/)

**Box 2: Summary and Excerpt from The Declaration of Helsinki**

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| **WHAT ARE PLACEBOS?**According to typical patient information leaflets used in clinical trials: *“A placebo is a dummy treatment, which looks like a genuine medicine but contains no active ingredient.”*Placebos are designed to look - and taste and smell and feel - like the new drug that is being tested. It is important that placebos appear identical to the new drug in order to control for this bias that would happen if patients knew they were receiving a placebo. By definition placebos contain no active ingredient, which means that placebos do not contain any drugs that would have an effect on the patient’s symptoms. Instead, placebos are often made out of substances like starch, flour, or sugar. **HOW CAN PLACEBOS HAVE ANY EFFECTS?**Placebos contain no active ingredients therefore some people understandably believe that placebos just trick us into thinking we feel better. Indeed, it can seem strange to think that placebos can have real effects. However, there is good evidence that placebos have real, meaningful and measurable effects on lots of symptoms and conditions, including for example pain, depression, Irritable Bowel Syndrome (IBS), and Parkinson’s Disease. Placebo effects come about because patients have learned to expect that treatments given by a doctor will help their symptoms. When patients talk with a caring medical professional about their symptoms and then receive a treatment (whether that treatment is a placebo or a drug), the brain’s natural pharmacy kicks into action, releasing neurotransmitters and activating areas of the brain that help to relieve symptoms. Research has shown that lots of things can contribute to these placebo effects, including a patient’s expectations and previous experiences of treatments, and the extent to which the medical professional really listens carefully to and empathises with the patient.  |

**Box 3: Placebos and placebo effects**

**WIDER EVIDENCE OF FAILURES IN EXISTING INFORMED CONSENT**

There is evidence that investigators often fall short of the ethical obligation to furnish participants with adequate, comprehensible information about the investigative nature of clinical trials. In the 1980s the term ‘therapeutic misconception’ was coined to refer to the widespread failure of participants to understand fundamental aspects of clinical trials including research design, purpose, and the function of placebos and trial randomization.[[3]](#endnote-3) In 2009 a systematic review of studies of informed consent processes in research contexts concluded that therapeutic misconception is commonplace among participants, and that adequate comprehension of the goals and methods of trials was achieved in only around half of all the reviewed studies.[[4]](#endnote-4) Misunderstandings about the purpose of trials are still widespread[[5]](#endnote-5) with recent studies showing that the willingness to participate in clinical trials is correlated with misconceptions about its primary purpose.[[6]](#endnote-6),[[7]](#endnote-7) We argue that routine therapeutic misconception is, in part, perpetuated by the failure of investigators to provide adequate information about the role of placebos in clinical trials and possible placebo effects. It is plausible that these failures stem from fundamental misconceptions, on the part of researchers, about placebo effects. More problematically, and hopefully very uncommon, there may be an implicit self-serving bias among researchers in favour of perpetuating the therapeutic misconception on the grounds that patient ignorance about the purpose of trials may secure higher participant enrolment.

**CURRENT KNOWLEDGE CONCERNING PLACEBO RESPONSES IN RCTs**

Placebo controls in RCTs function as methodological safeguards for systematic bias, normal fluctuations, regression to the mean, and importantly the effects of the therapeutic encounter. The role of placebo controls therefore reflects the function of the trial: to test for the effectiveness of specific components of the treatment under investigation. In a typical RCT participants are randomized to two groups: investigational intervention or placebo. While knowledge concerning placebo responses in RCTs is still far from complete, we know that for many conditions the observed responses of participants in the placebo group of a trial are often similar and can mimic those of participants who received known effective drugs. And as Temple and Ellenberg note many common classes of drugs on the market have shown no difference between drug and placebo treatment in RCT.[[8]](#endnote-8) (See Table 1) Some of the observed response in placebo groups is undoubtedly due to spontaneous improvement. But increasingly, research demonstrates that the reduction of symptoms, especially in subjective complaints, is due to the influence of the therapeutic encounter that includes empathic witnessing, emotional support, medical rituals, symbols, and paraphernalia (“placebo effects”).[[9]](#endnote-9) Studies also show that participants treated with placebo often report many of the adverse effects associated with the investigational intervention (“nocebo effects”).[[10]](#endnote-10) Significant basic science research has already demonstrated that experiencing placebo effects (or experiencing nocebo effects) involves certain neurotransmitters (e.g., endorphins, dopamine, cholecystokinin, and cannabinoids), and that these effects engage specific, relevant and quantifiable regions of the brain.9 Possible genetic signatures of likelihood of responding to placebo have been reported.[[11]](#endnote-11)

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|  **Medication-Placebo Differences Are Often Indistinguishable in RCTs:**  **Examples of Common Drug Classes**  |
|  |
|  Analgesics |
|  Anxiolytics |
|  Antidepressants |
|  Antihypertensives |
|  Hypnotics |
|  Antianginal agents |
|  Angio-tensin-converting enzyme inhibitors  for heart failure ostinfarction **β-**blockers |
|  Antihistamines |
|  Motility-modifying drugs for reflux disease |
|  Nonsteroidal asthma prophylaxis |
| From: Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Ann Intern Med 2000; 133:455-53. |

**Table 1: Examples of common classes of drugs which are often indistinguishable from placebos**

Developments in placebo research also underline that it is helpful to differentiate “placebo responses” from the “placebo effect”. The former refer to changes in patients’ symptoms following the administration of placebos (including spontaneous remission); the latter refer to changes attributable to outcomes related to psychobiological mechanisms related to the therapeutic encounter (known as placebo effects).[[12]](#endnote-12) In placebo-controlled clinical trials, placebo responses are always anticipated while the nature and strength of placebo effects will be determined in part by the symptom and underlying disease in question. In other words, in any given clinical trial, some patients who receive the placebo are likely to experience some benefit and some may experience some harms, the nature of which will depend on the disease or condition.

 This significant body of knowledge has not been reflected in informed consent procedures. One reason for this may derive from the lack of training of biomedical researchers with respect to the science of placebo effects.5

**EXISTING STANDARDS OF PLACEBO DISCLOSURE IN RCTs**

In research contexts, patients are typically provided with extensive information of the possible benefits and negative effects of the investigational intervention. However, when it comes to placebos, recent studies indicate that patients are provided with incomplete and inaccurate information. These inaccuracies may bring about, or contribute to, therapeutic misconceptions about clinical trials.

 A content analysis of participant informed consent disclosure information distributed within 45 major RCTs in the UK, found that patients were furnished with significantly less information about placebos than the target treatment.[[13]](#endnote-13) Overall, almost all disclosure statements described placebos as “inert”, or “inactive” (“dummy” or “fake” medication); 18 per cent of consents asserted that placebo treatments were “undesirable or ineffective” and that receiving a placebo was a “disadvantage of participating in the trial.” All ‘real’ treatments were prioritized and couched in positive terms as being “potentially beneficial”, with 87 per cent of consents also indicating that participants might experience some adverse effects if allocated to the target medication. Only 1 of 45 information leaflets informed participants that those allocated to the placebo group might also experience beneficial changes in health, but did not offer any explanation as to why such changes might occur. No disclosure information mentioned that patients sometimes perceive or misattribute common adverse events while receiving placebo treatment.

 These shortcomings in participant information are not restricted to UK trials. A recent Finnish study of 52 RCT patient information statements found that only 35 per cent of disclosure protocols provided a rationale for the use of placebos in trials.[[14]](#endnote-14) Of these statements only 12 (23 per cent) described why placebo use was necessary in the research, and only 6 (12 per cent) of patient-information discussed possible adverse effects of placebos.

**ETHICAL PROBLEMS WITH EXISTING PLACEBO DISCLOSURES**

It might be countered that there are reasonable justifications for failing to furnish patients with information about placebo effects. One argument is that such disclosures risk undermining the methodological integrity of clinical trials. On this line of reasoning, it might be claimed that prior disclosures about placebos potentially influence the expectations of trial participants, and as such may augment or diminish placebo and/or drug responses thereby biasing the outcome of the trial. In response we argue that the evidence that disclosure (or, indeed, omission of disclosure) influences placebo responses is unclear or contradictory.[[15]](#endnote-15),[[16]](#endnote-16) And furthermore, even if placebo and/or drug responses were augmented (or diminished) as a result of improved disclosure practices, as per the Helsinki Declaration, informed consent issues take precedence over methodology.

 A second criticism is that disclosure about placebos in clinical trials is not morally relevant to patient autonomy. It has been argued that respect for autonomy does not involve disclosure of complete (or exhaustive) information about all aspects of treatment or care.[[17]](#endnote-17),[[18]](#endnote-18),[[19]](#endnote-19) In this way, it is claimed that placebo effects are trivial or ancillary aspects of treatment; therefore, there is no loss to patient autonomy through the omission of their disclosure. Such arguments are very controversial, and we contend that they are, in any case, not applicable to informed consent processes in research contexts.[[20]](#endnote-20),[[21]](#endnote-21),[[22]](#endnote-22) In order to consent to participant in research, patient-participants need to be furnished with the following information: first, they need to be informed about the *function* of placebos in clinical trials; and second, whether, in their particular condition, it is typical for patients who are treated with placebo to experience changes in symptoms. Why is it important for patients to understand that placebo effects may occur in research contexts? Informing patients – prior to commencing a trial – that even if they receive placebos they might still experience health benefits (and adverse events) is likely to resolve therapeutic misconceptions and demystify the false belief (perpetuated by current research approaches) that placebos have no effects. Such knowledge would help participants to make sense of their experiences.[[23]](#endnote-23)

**POTENTIAL HARMS ARISING FROM INSUFFICIENT PLACEBO INFORMATION**

The inclusion of information on placebo responses in informed consent procedures is relevant to the ongoing complex and nuanced debate on whether and how to communicate individual study results to research volunteers. If there is inaccurate information about placebos during informed consent, the process of debriefing patients assigned to placebo can potentially lead to distress (confusion, anxiety, shock, disbelief, embarrassment, or anger). For example, in a qualitative study of debriefing of irritable bowel syndrome patients after an RCT, some patients were deeply agitated e.g., one patient strongly protested to the debriefing person that they were mistaken since the patient felt they had benefited from the treatment.[[24]](#endnote-24) Even during the RCT itself, anxiety can be provoked: in this study, distressed subjects also remarked “maybe I made up the whole thing [concerning their improvement during the trial].”[[25]](#endnote-25) Such incidents could be avoided with *a priori* disclosure; indeed, research shows that it is possible to augment literacy about placebos and placebo effects with information disclosures which provide accurate, and accessible evidence-based information.[[26]](#endnote-26) Besides potentially affecting patients negatively, it is conceivable that disclosure of information about placebos in the informed consent stage may help to mitigate the reluctance among researchers to debrief participants of their treatment assignment since participants may better understand their allocation.[[27]](#endnote-27)

In addition, it should also be pointed out that it is probably important to disclose the content of placebo pills to patients. Such pills are seldom completely ‘inert.’ In clinical trials they are usually microcrystalline cellulose or sugar pills. The composition of placebos can potentially cause harm to patients (and also influence trial outcomes). For example, in a study of megestrol acetate for anorexia associated with cancer, a lactose placebo was used: however, subsequent studies have found that lactose intolerance is common among patients diagnosed with cancer and may be aggravated by chemotherapy and radiation therapy.[[28]](#endnote-28) Therefore, it is likely that the placebo in this trial induced adverse effects among patient-participants, and also exaggerated the benefits of the active drug.

**CONCLUSIONS AND RECOMMENDATIONS: IMPROVING DISCLOSURE IN CLINICAL TRIALS**

Improving standards of disclosure about placebo effects is an ethical imperative in clinical trials. Therapeutic misconceptions among patient-participants, including common misperceptions and false beliefs about placebos, could be addressed and corrected during informed consent to clinical trials. One approach is to develop generic information leaflets that describe placebos and explain placebo effects in accessible terms,[[29]](#endnote-29) elaborating on the ideas presented in Box 2. Such leaflets might be supplemented by online materials and resources for patients. An alternative approach would be to work with patients to develop template phrases about placebos and their effects that investigators could insert into existing patient information materials and research ethics committees could recommend. Whatever format new resources take it will be essential to develop such material by working with patients to generate evidence-based information that is accessible, engaging, and communicates effectively with participants in clinical trials.[[30]](#endnote-30)

 Disclosures about placebo responses should be carefully formulated in order to be as illness and symptom-specific as possible. Here again, information about placebos and placebo effects needs to be evidence-based in the same way as information about the investigational treatment. For example, where trials involve symptoms and conditions that are known to elicit placebo effects (e.g., benign prostatic hyperplasia, perimenopausal hot flashes), patients should be informed that previous studies suggest that they may experience beneficial symptom improvement. If placebos are used in trials where no placebo effects are expected – e.g., trials that add a second medication to standard of care for treating cancer tumours – patients might be told that placebos are unlikely to affect the tumour, and are designed to help scientists to be objective in assessing outcomes. Patients might be advised that they may experience common side-effects (e.g., headache, fatigue, insomnia) due to worry about a new medication. We argue that improved scientific literacy about placebos and placebo effects, and the importance of communicating these to research participants, is an ethical imperative.

 In summary: clinical researchers have an obligation to respect the rights of the patients and this includes communicating information about placebos and placebo effects openly and honestly.

**SUMMARY OF RECOMMENDATIONS**

* Researchers and clinicians require basic biomedical knowledge about placebos and placebo effects, and improved ethical education on the importance of providing adequate disclosures to patients.
* Prospective research participants should be furnished with information about the role and justification for placebos in clinical research (Table 2), as well as information about placebo effects (See Box 3).
* In some trials it may be necessary to convey information about the content of placebo pills since no pills are ‘inert’.
* Disclosure information should also be tailored according to the illness and symptoms being investigated since some conditions are more placebo-responsive than others.

**BOX 4: Summary of Recommendations**

**CONTRIBUTORS AND SOURCES**

CB is a philosopher of medicine at the School of Philosophy, University College Dublin who has published widely in healthcare ethics; her publications have focused in particular on informed consent issues, and the placebo effect. TJK is the Director of the Program in Placebo Studies and the Therapeutic Encounter at Beth Israel Deaconess Medical Center/Harvard Medical School. He has published over 200 papers including empirical research on the placebo effect, as well as historical and ethical issues pertaining to the use of placebos. FB is a health psychologist leading an interdisciplinary programme of mixed methods research around complementary therapies and placebo effects in health care within Psychology at the University of Southampton. She has published extensively on lay and professional attitudes about placebos and placebo effects.

CB, TJK & FB conceived and co-wrote the paper.

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