Placebo-Controlled Trials, Ethics of

Rieke van der Graaf, University Medical Center Utrecht, Utrecht, Netherlands
Annette Rid, King's College London, London, UK

Abstract

There are often good scientific and ethical reasons for using placebo controls in clinical trials. At the same time placebo use is controversial, especially when an established effective treatment is being withheld from the control group. This article gives an overview of the key ethical positions in the controversy around placebo-controlled trials. While some argue that placebo controls can only be used when withholding or delaying an established effective treatment poses no or negligible risks to participants, others hold that the risks should be low or acceptable in light of the social value of the knowledge to be gained from the research. The article also describes different positions on placebo use in trials in low- and middle-income countries where study participants may not have had access to an established effective treatment outside the trial.

Introduction

Before new medical interventions, such as drugs or biologics, are introduced to clinical practice they are normally tested in preclinical and clinical trials. In the preclinical phase, potential new interventions are tested in the laboratory and on animals. Preclinical testing is a prerequisite for clinical testing in humans, but eventually the safety and efficacy of potential new interventions must be tested in humans.

The clinical testing of investigational drugs – the focus of this article – generally proceeds in four phases. In phase I, the maximum tolerated dose of an investigational drug is tested in a small number of study participants (normally 20–50). In phase II, preliminary data on the drug's safety and efficacy are gathered in a larger group of participants (up to 100–300). Phase III trials substantiate the data on safety and efficacy in a significant number of participants (up to several thousands). Typically, the investigational drug is tested in comparison to standard treatment or a 'placebo' – an inert substance, such as a 'sugar pill' or a saline injection that is administered in the same way as the investigational drug, but contains no active substance. Placebo controls are also used in phase I and II trials, although controlled designs are less common in these early phases of clinical testing. The investigational agent is expected to have therapeutic effect in phase 3 trials. If a drug has been proven efficacious in such trials, it can be licensed for regular clinical use by regulatory authorities (e.g., the European Medicines Agency in Europe or the Food and Drug Administration (FDA) in the U.S.).

To evaluate the risk–benefit profile of an investigational drug, it is useful to compare it against placebo. In a randomized, placebo-controlled trial, the study group and the control arm are treated exactly the same, except that the study group receives an active substance. Any random events that happen during the trial (e.g., spontaneous remission), or any clinical effects that are due to positive or negative expectations regarding a treatment (e.g., placebo effect), are therefore expected to be distributed evenly between both groups. In this way, the use of a placebo control allows investigators to determine whether any differences in clinical outcomes between the study arm of a trial (receiving the investigational drug) and the placebo arm can be attributed to the drug under study. These methodological reasons for using placebo controls are also ethically relevant, given that studies without scientific and social value expose participants to risks for no good reason (Emanuel et al., 2000).

However, the use of placebo can be ethically controversial when a proven or established effective treatment exists. Some research ethicists argue that a placebo control should not be used in this situation, as this implies unjustifiably withholding an established effective treatment from participants in the control group (Freedman et al., 1996a,b; Weijer and Miller, 2004). Others consider this stance as too strict. For instance, some argue that the use of placebo controls is acceptable when withholding or delaying an established effective treatment poses low or acceptable risks to participants (WMA, 2013; Emanuel and Miller, 2001). Placebo use is more controversial still in the context of research in low- or middle-income countries (LMICs) when it is used in the presence of an established effective intervention that is not available in the community in which the trial is conducted (e.g., because it is too costly or complex to implement) (London, 2001; Ellenberg and Temple, 2000). This illustrates that the use of placebo controls in clinical trials is both ethically complex and controversial.

This article gives an overview of the ethical controversy surrounding the use of placebos as a comparator in randomized, placebo-controlled clinical trials. Importantly, the article focuses on the use of placebos as it relates to clinical trial design and does not explore other questions regarding placebo use. First, the article does not discuss the placebo effect and its potential implications for informed consent to clinical research. It is well documented that positive expectations about an intervention can improve clinical outcomes, even when patients or study participants receive an inactive treatment (placebo effect) (Kam-Hansen et al., 2014). Conversely, negative expectations may evoke a negative clinical response with patients or participants experiencing real side effects (nocebo effect) (Colloca and Finniss, 2012). These findings raise the possibility that the risk–benefit profile of a clinical trial can be influenced by manipulating participants' expectations in the informed

consent process. While placebo and nocebo effects are relevant for evaluating the risks and potential benefits of study participation, the article does not address to what extent these effects can justify modifications of informed consent (Brim and Miller, 2013).

Second, in research on the placebo and nocebo effect itself it can be methodologically necessary to deceive study participants about the study purpose and the use of placebo interventions. For example, disclosure that participants will receive an inert substance in order to study its impact on their pain will influence their expectations and therefore influence study results. The use of deception in this and other research is discussed in a separate article in this encyclopedia.

Third, the focus of this article is on the use of placebo controls in drug trials. Trials of surgical or anesthetic interventions can involve sham ('fake') procedures that are similar to placebo controls, in that they help investigators to distinguish the effects of the intervention under study from placebo effects or random events. The risks of sham procedures can be considerable, and they can sometimes involve deliberately harming participants (e.g., surgical incision under general anesthesia). Because these features warrant separate discussion, sham procedures are not considered in this article (London and Kadane, 2002; Miller, 2003).

Finally, the present article is only concerned with the use of placebo interventions in the research context. Placebos are also used in the clinical setting as a treatment offered to patients. The ethical issues regarding the clinical use of placebos are discussed elsewhere in this encyclopedia (see Placebo Effect).

Rationale for Using Placebo Controls in Clinical Research

From a methodological point of view, randomized, placebo-controlled clinical trials are often considered the gold standard for testing the safety and efficacy of a potential new intervention. In such trials, participants are allocated to two (or more) arms of the trial. In the study arm, participants receive the intervention under investigation, while participants in the control arm receive a placebo. Randomization – assigning participants to the arm of a trial by chance – is the preferred method for preventing confounding and bias in controlled clinical trials. Randomization helps investigators to ensure that study groups will be similar with respect to known (e.g., age) and unknown prognostic factors (e.g., spontaneous remission). If investigators cannot predict in advance to which arm participants will be assigned, this will reduce allocation bias (Friedman et al., 2010). When combined with the use of an inert placebo in the control arm, randomization enables investigators to isolate the efficacy of an investigational drug in order to determine whether different clinical outcomes between the trial arms can be attributed to the drug under study. It is for this reason that randomized, placebo-controlled trials are often considered the gold standard in clinical trial design. Placebo-controlled trials also have a higher 'assay sensitivity' than active controlled trial designs – i.e., they have a better ability to distinguish an effective treatment from a less effective intervention (Temple and Ellenberg, 2000). In an active controlled trial, in which a new drug is compared to an existing drug, data of previous (placebo-controlled) trials are needed in order to know whether the drug in the intervention arm is indeed effective.

Importantly, these methodological considerations matter not only scientifically but also ethically, as research needs to have scientific and social value to be ethically acceptable (Emanuel et al., 2000). If the research question cannot be answered without the use of placebo controls, the use of another trial design is not scientifically valid.

Placebo controls can also help to ensure the scientific validity of a study in light of expected recruitment problems, given that placebo-controlled trials normally require smaller numbers of participants. Trial completion is a continuing challenge in clinical research generally, and it is a particular challenge in research on rare diseases where studies 'compete' for a very limited number of eligible participants. Data cannot be used when trials are not completed, hence the possibility of underrecruitment can compromise the scientific and social value of research studies. By requiring smaller numbers of participants, placebo-controlled trials reduce the possibility of underrecruitment while also exposing fewer individuals to the risks of an unproven intervention.

In addition, because placebo-controlled trials require a smaller number of participants than trials that compare existing treatments, they can be useful for consolidating the evidence to support larger and more expensive active-comparator trials. The reduced costs of placebo-controlled trials may also be a consideration when trials aim to develop low-cost interventions primarily for use in LMICs (see later). In this situation, research budgets can be so tight that alternative trial designs may not be feasible, while inclusion of an active control arm is not always necessary to decide whether or not the study intervention should be adopted by the local healthcare system (provided that some level of efficacy has been proven in the trial). For example, when an established effective treatment is not affordable locally, and likely to remain unaffordable in the future, the costs of an active-comparator trial may not be justified: if the active comparator turns out to be superior it cannot be implemented.

Moreover, placebo controls may enhance the social value of studies since randomized, placebo-controlled trials are often perceived to produce the highest level of evidence in clinical research (Barton, 2000). Although this perception of placebo-controlled trials is contested, the commonly assumed superior quality of evidence produced by placebo-controlled trials still affects the practical uptake of new interventions – or the discontinuation of routine but unproven interventions – among clinicians and policy-makers.

Finally, placebo-controlled trials are frequently preferred – or perceived to be preferred – by regulatory authorities who are responsible for approving drugs for the market. For example, the FDA in the U.S. states that "adequate and well-controlled" studies are essential to test the efficacy of drugs and mentions placebo controls as the first control option (DHHS, 2008). Many therefore believe that the FDA *requires* the use of placebo-controlled trial designs. However, the FDA

acknowledges that the use of placebo controls can be ethically problematic if there is a "known effective therapy," and "placebo or no treatment would be contrary to the interest of the patient" (DHHS, 2008). Thus, while the FDA has a methodological preference for placebo-controlled trials, it does not require such trials in order to make licensing decisions about potential new treatments (Miller, 2008).

In summary, there are often good scientific, ethical, and regulatory reasons to support placebo-controlled trials. However, the use of placebo controls is not always ethically justified and often controversial, especially when it involves withholding or delaying an established effective treatment from participants in the control arm. Before we discuss the key ethical issues surrounding placebo use in this situation, the following section briefly reviews the controversy around placebo-controlled trials from a historical perspective.

Controversy Around Placebo-Controlled Trials

Clinical research expanded enormously in the twentieth century, and randomized-controlled trials became standard practice from the 1950s and 1960s onward (Kaptchuk, 1998). The evidence-based medicine (EBM) movement in the 1980s and 1990s then declared such trials, and especially those involving a placebo control, as the methodological 'gold standard' in clinical research (Sacks et al., 1982). However, scholars in the philosophy of science and other disciplines quickly pointed out that high-quality observational studies and well-designed randomized-controlled trials may produce data of comparable quality. It is for this reason that the strict hierarchy of evidence promoted by the EBM movement, with the randomized-controlled design at the top, has been questioned (Barton, 2000; Cartwright, 2011).

These and other issues sparked a first peak of sustained ethical controversy around randomized, placebo-controlled trials in the 1980s. At the core of this debate were the fundamental ethical obligations of clinician-investigators: Should their conduct be guided by the norms of clinical care or by the norms of research? Some argued that clinician-investigators maintain therapeutic obligations toward patients who participate in clinical trials (Marquis, 1983). Given that treatment in randomized-controlled trials is determined by chance, not by what the clinician-investigator believes is best for the participant, clinician-investigators were seen to violate their therapeutic obligations when enrolling patients in such trials. Enrollment in randomized, placebo-controlled trials in the presence of established effective treatment was seen as a particularly stark violation of clinician-investigators' therapeutic obligations, as it implied withholding an effective treatment (Rothman and Michels, 1994).

To resolve the conflict between the therapeutic obligations of clinician-investigators and the need to conduct rigorous clinical research, scholars introduced the principle of clinical equipoise. In its most influential formulation, this principle holds that patients should only be enrolled in randomized-controlled trials when there is "genuine uncertainty in the medical expert community about the preferred treatment" (i.e., the community of experts is 'equally poised' between a potential new intervention and any established effective treatments; Freedman, 1987). In a state of clinical equipoise, clinicians do not have sufficient information to know which of the available treatment options (if any) is preferable, either because there is no information on what is best or because they disagree about the relative merits of this information where some prefer treatment A and others B (van der Graaf and van Delden, 2012). Therefore, clinicians as investigators do not violate their therapeutic obligations when they randomize patients to the available treatments or placebo, provided that a state of clinical equipoise with regard to these treatments and placebo obtains.

Some commentators have argued in response to these developments that the attempt to align research with the therapeutic obligations of clinicians is fundamentally flawed (Miller and Brody, 2002). On this view, research is an activity that is distinct from clinical care, and therapeutic obligations therefore do not apply in the research context. We discuss this controversy in more detail.

In addition to ethical issues on the level of the individual participant and investigator, the controversy around placebo-controlled trials also touched on issues at the population level. For instance, clinicians argued that comparative effectiveness data are often more valuable for patient care than data from randomized, placebo-controlled trials. For clinicians and patients, it is generally more interesting to know how a potential new intervention compares to an established effective treatment (if any) than whether it is better than 'nothing.' Another issue at the population level is that many expensive treatments are licensed, used, and paid for on the basis of placebo-controlled trials, when it is not clear how they compare to any existing interventions. Although consideration of these issues is essential for determining the overall acceptability of placebo-controlled trials, this article focuses largely on the ethical issues raised on the participant and investigator level.

A second peak in the ethical controversy surrounding randomized, placebo-controlled trials arose in the 1990s in the context of research in LMICs. A series of high-profile articles in *The New England Journal of Medicine* questioned the ethics of the then ongoing AZT (zidovudine) trials in LMICs (Angell, 1997; Lurie and Wolfe, 1997). Researchers were testing a short course of AZT to reduce the risk of maternal–infant HIV transmission, given that the complex and costly standard regimen in use in high-income countries (HICs) was neither feasible nor affordable in resource-poor settings. Most trials tested the short course of AZT against placebo, a trial design that – it was widely agreed – would not have been acceptable in HICs. In HICs, a placebo-controlled trial would have deprived participants in the control arm of an established effective intervention that they would have otherwise received outside the trial. Moreover, withholding this intervention was associated with significant risk, as the standard AZT regimen was proven to reduce perinatal HIV transmission from 25 to 8%. Commentators therefore argued that the AZT trials demonstrated the unjustifiable use of 'double standards' in research ethics, with study participants in LMICs being afforded lower protection than participants in HICs

(Lurie and Wolfe, 1997). This criticism was especially cutting because the trials were sponsored by HIC governments or international organizations, which arguably had the resources to provide participants in the control arm with the standard AZT regimen. However, there was deep controversy surrounding the AZT trials. Many argued that the trials were ethically justifiable because they addressed the health needs of populations in LMICs, and participants in the placebo arm were not made worse off than they would have been outside the trial (Varmus and Satcher, 1997). The ethics of AZT-type trials – which aim to develop a 'substandard' treatment specifically for use in LMICs by testing it against placebo – remains debated to this day.

Even more controversial were placebo-controlled trials in LMICs that tested potential new treatments primarily intended for use in HICs. These trials form part of a larger controversy about the 'outsourcing' of clinical research to LMICs, which is motivated by a range of factors, including the lower cost of conducting research in these countries, a generally large and ready pool of potential study participants for whom trial enrollment may be the only way of accessing medical care, and the oftentimes less onerous research regulations in LMICs (Petryna, 2009). However, outsourcing is particularly controversial when it involves the use of placebo controls that would not be considered acceptable in HICs. A prominent example for these types of trials is the 'Surfaxin trial' (Hawkins and Emanuel, 2008). In this trial, a pharmaceutical company from the U.S. proposed to test a potential new treatment to prevent respiratory distress syndrome in premature infants in Bolivia. Because four established effective treatments were on the market in the U.S. and highly effective in preventing a potentially fatal condition, a placebo-controlled trial design would not have been acceptable in the U.S. However, the company did not think it would succeed in obtaining regulatory approval for the potential new treatment based on a trial comparing their investigational agent against one of the established effective treatments. By contrast, approval based on a placebo-controlled trial was deemed feasible. The company therefore proposed to conduct the trial in Bolivia, although it did not intend to license and market the potential new treatment in Bolivia or other LMICs – the U.S. and other HICs were always the target market. Although the Surfaxin trial never took place, it became a textbook example in the ethical controversy around research in LMICs (Hawkins and Emanuel, 2008).

While AZT-type trials primarily raised questions about investigators' obligations toward individual study participants in LMICs, given that these trials aim to address local health needs, Surfaxin-type trials also raise questions about exploitation on the population level. After all, Surfaxin-type trials expose populations in LMICs to research risks even though they aim to develop interventions that will benefit populations in HICs. This article discusses issues around placebo use only insofar as they concern investigator obligations toward individual participants; readers who wish to explore questions about population-level exploitation are directed elsewhere (Hawkins and Emanuel, 2008).

The controversy around placebo-controlled trials had important ramifications for the World Medical Association's *Declaration of Helsinki*, one of the most prominent documents in research ethics. Up to the 1990s, the *Declaration* required that research participants be assured of the best proven therapeutic method, thereby effectively blocking the use of placebo controls when an established effective treatment exists. The controversy around placebo-controlled trials prompted the World Medical Association to relax its stance on placebo use – but this in turn caused much debate and initiated a rapid succession of revisions of the *Declaration* in the 2000s and 2010s (the current version dates from 2013). Many commentators believe that the *Declaration* has lost much of its authority as a result, in particular regarding the use of placebos in randomized-controlled trials (Lie; FDA, Brazil).

Key Ethical Positions

It is widely agreed that the use of placebo controls raises no ethical concerns when there is no established effective intervention for the condition under study. In this situation, a placebo-controlled trial answers the clinically relevant question whether the potential new treatment is more effective than 'nothing,' and participants are not deprived of the clinical benefits of an established effective intervention. Similarly, placebo use is uncontroversial when an investigational agent is tested as an add-on to standard care (e.g., in oncology where new chemotherapeutic agents are often used in combination with established treatments). In these trials, all participants receive standard care while also being treated with either the investigational agent or a placebo. However, the ethical positions on whether placebo use is acceptable in the presence of an established effective intervention – and, if so, under which conditions – vary widely. The key issue of contention is whether it is acceptable for investigators to expose participants to risks – understood as the likelihood of experiencing physical, psychological, or other harm as result of undergoing a study intervention or research procedure – by deliberately withholding or delaying an established effective treatment. This is also based on the assumption that the placebo interventions themselves typically pose negligible risks (e.g., ingestion of a 'sugar pill,' injection of saline solution through an existing intravenous line).

No or Negligible Risk from Withholding Treatment

Some commentators maintain that the use of placebo control is acceptable only when there is no proven or established effective intervention for the condition under study. This 'no risk' position effectively excludes the use of placebo controls in the presence of an established effective intervention. The closely related 'negligible risk' position allows the use of placebo controls in this situation, but requires that withholding or delaying an established effective intervention poses no more than negligible risks. For example, on the 'negligible risk' position, placebo use is acceptable in the case of self-limiting diseases with mild symptoms where foregoing treatment is consistent with sound medical care (e.g., allergic rhinitis).

The 'no or negligible risk' position is grounded in the idea that clinical investigators have therapeutic obligations toward research participants (Marquis, 1983) and that clinical equipoise, which is grounded in these obligations, is a necessary requirement for clinical research (see previous section; Freedman et al., 1996a,b; Weijer and Miller, 2004). According to proponents of the 'no or negligible risk' position, it is impossible for clinicians to shed their therapeutic obligations simply by taking on the role of investigator. Investigators may therefore not withhold or delay an established effective treatment from participants in the placebo arm, even if doing so only requires a 'small sacrifice' from participants and there are strong methodological reasons for using a placebo control. The 'no or negligible risk' position thus places strict limitations on clinical trial design.

Low Risks from Withholding Treatment

Many believe that the 'no or negligible risk' position is overly strict, as it disallows many valuable studies that are – in their view – ethically justifiable. These commentators frequently adopt a 'low-risk' position on the use of placebo controls when an established effective intervention exists, arguing that placebo controls may be used when (1) the risks of withholding or delaying the established effective intervention are low and (2) there are compelling methodological reasons for using a placebo control (reference). Examples for 'compelling methodological reasons' include situations where the clinical response to the established effective intervention is highly variable; the symptoms of the condition under study fluctuate and/or there is a high rate of spontaneous remission; and the condition under study is known to have a high placebo response (Miller, 2008; Millum and Grady, 2013). In these situations, it can be difficult to determine without a placebo control whether the experimental intervention is efficacious, since the condition may be improving on its own or the observed clinical response may be due to a placebo effect (Temple and Ellenberg, 2000). For example, many trials of antidepressants use placebo controls because patients with depression often have waxing and waning symptoms, and depressive symptoms are known to have a high placebo response (Stone et al., 2009).

Importantly, proponents of the 'low-risk' position have different views on what constitutes low risk. Some commentators or guidelines require that the risks of withholding or delaying an established effective intervention may only lead to temporary discomfort or fleeting harm (CIOMS, 2002). Others are more permissive and interpret low risk as constituting no risk of serious harm (WMA, 2013). Depending on which conception of low risk they endorse, proponents of the 'low-risk' position may consider the same trial as ethically acceptable or unacceptable.

Like the 'no or negligible' risk position, the 'low-risk' position is often grounded in the idea that clinician-investigators have therapeutic obligations toward research participants and that investigators must, accordingly, be in a state of clinical equipoise regarding the interventions under study (Marquis, 1983; Freedman, 1987). However, unlike those who defend a 'no or negligible risk' position, proponents of the 'low-risk' position do not regard the principle of clinical equipoise as

an absolute norm that can never be overridden by other moral norms and hence excludes small sacrifices to investigators' therapeutic obligations (van der Graaf and van Delden, 2009; Beauchamp and Childress, 2013). In other words, if there is a standard of care for patients with a certain condition, but the risks of withholding this standard of care are low and placebo control may be needed for compelling reasons, violation of equipoise need not be considered as ethically problematic.

'Acceptable' Risk from Withholding Treatment

A few commentators believe that the 'low-risk' position on placebo-controlled trials still disallows many valuable and – in their view – ethically justifiable studies. These commentators agree with proponents of the 'low-risk' position that placebo use may be justified in the presence of an established effective intervention, but they reject its strict limitation on risk. According to proponents of the 'acceptable risk' position, the use of placebo controls is justified when (1) there are compelling methodological reasons for a placebo-controlled trial design and (2) the risks of withholding or delaying treatment are minimized and reasonable in relation to the knowledge to be gained from the placebo-controlled trial design (Emanuel and Miller, 2001; Miller, 2008).

Proponents of the 'acceptable risk' position typically justify their view based on role-based obligations of investigators, which are seen to be distinct from the role-based obligations of clinicians (Miller and Brody, 2002). As mentioned earlier, according to these commentators, the fundamental ethical obligation of investigators is not to promote the best clinical interests of study participants. Instead, investigators have an obligation to promote the social good by conducting scientifically and socially valuable research, while ensuring that research participants are not exposed to excessive risks for the benefit of others (principle of nonexploitation). The use of placebo controls must therefore be scrutinized like most other research procedures. This implies – consistent with the earlier-mentioned criteria for acceptable placebo use – that the risks of withholding or delaying an established effective intervention must be minimized and justified in relation to the potential clinical benefits to participants and/or the scientific and social value of the knowledge to be gained from the research (Miller and Brody, 2003, 2007; Rid and Wendler, 2011).

'Acceptable' Risk from Withholding Treatment in Research in LMICs

Questions around 'acceptable' risk from withholding or delaying an established effective treatment acquire a further dimension when trials are conducted in LMICs. Many people in LMICs do not have access to established effective interventions that are commonly used in HICs, typically because these interventions are too expensive and/or the healthcare infrastructure for their safe and effective delivery is not available (e.g., services for intravenous treatment or cooling chain for certain vaccines). This lamentable state of affairs can be attributed, at least in part, to background injustices resulting

from the corruption of local governments, international treaties that disadvantage LMIC economies, and many other factors (Pogge, 2002). A key question around the use of placebo controls in LMICs therefore is this: To what extent are the obligations of investigators influenced by background injustices?

Few will argue that background injustices have no role to play – that is, few will argue that it is acceptable for investigators to withhold or delay an established effective intervention simply because it is not available locally (London, 2001). However, commentators disagree profoundly on how background injustices shape the obligations of investigators (and research sponsors). The key issue of contention is which level of care investigators ought to provide participants in the control arm of their trials (van der Graaf and van Delden, 2009; Hawkins and Emanuel, 2008).

Some of those who believe that investigators have therapeutic obligations argue that study participants in the control arm are owed the worldwide best established intervention, independent of where they live (Angell, 1997; Nuffield, 2002; Macklin, 2004). For example, in the AZT trials described earlier, these commentators argued that the use of a placebo control was unacceptable and participants in the control arm should have received the long course of AZT, which was the best treatment available worldwide at the time. Others hold that investigators can discharge their therapeutic obligations by providing less than the worldwide best established intervention – for example, the best treatment that they can reasonably provide under the circumstances (Resnik, 1998), or the treatment that participants are entitled to outside the study according to local health care norms (London, 2001; Kukla, 2007).

Questions about the appropriate standard of care are also relevant for those who believe that investigators' primary obligation is to promote the social good while not exposing participants to excessive risks for the benefit of others (principle of nonexploitation). For these commentators, to determine whether placebo use poses excessive risk, it is necessary to compare the use of a placebo control to the relevant standard of care (i.e., it is necessary to evaluate the risks of withholding or delaying the relevant baseline treatment). Yet views on what constitutes the relevant standard of care again vary. For some, the relevant standard is the treatment that participants would have normally received, provided that the research addresses a question that is relevant to local health needs (Lie et al., 2004). For others, the relevant baseline is the treatment that participants *should* have received outside that trial as a matter of global distributive justice (Emanuel, 2012).

Finally, some commentators argue that investigators have natural obligations – obligations they possess simply because they are persons, not because they occupy a particular professional role. This line of argument becomes especially relevant in LMIC settings where background injustices and limited resources frequently lead to situations of dire need. For example, some commentators argue that investigators should sometimes provide participants in the control arm with effective treatment because all people, including investigators, have a duty to rescue those whose life or health is seriously threatened (Hawkins, 2008). On this view, this general duty of rescue requires investigators to provide an established effective treatment, if one exists, when they can prevent or treat an immediate and serious threat to a patient's life or health at reasonable cost to themselves. This position does not necessarily imply, however, that placebo use can never be justified when it involves withholding or delaying an established effective treatment for a serious condition. These commentators require that placebo be provided if the research has important social value, using a placebo control is the only way of addressing the research question, and the population that the control group represents is reasonably likely to benefit from the research. The latter condition implies that it is ethically problematic to conduct a placebo-controlled trial in an LMIC that will never benefit from the results when the investigators can conduct the trial in an LMIC where the population is highly likely to benefit (Hawkins, 2008).

Key Ethical Guidance

Most ethical guidelines for research involving human subjects adopt a version of the 'low-risk' position on placebo use in the presence of an established effective treatment, although there are exceptions. For example, Brazilian authorities adopt the 'no risk' position by endorsing the *Declaration of Helsinki* in its 2000 version, which allows placebo controls only "in studies where no proven prophylactic, diagnostic or therapeutic method exists" (Brazil, 2008). By contrast, the South African research ethics guidelines adopt an 'acceptable risk' position by allowing the use of placebo controls in the presence of an established treatment, provided that participants will not be harmed – implying, arguably, that participants will not be made worse off than they would have been outside the trial – and the risks to participants are justified by the potential benefits of the research (South Africa, 2004). **Table 1** summarizes prominent ethical guidance on the use of placebo controls in clinical trials.

Concluding Remarks

There are often good scientific, regulatory, and ethical reasons for using a placebo control in randomized-controlled clinical trials. At the same time, placebo-controlled trials are deeply controversial, in particular when the use of a placebo control involves withholding or delaying an established effective treatment from study participants. The ethical controversy goes to the very heart of research ethics, as it revolves around the question what fundamentally justifies the obligations of investigators. Most research ethics guidelines require that the risks of using placebo controls – including the risks of foregoing any established effective interventions – be minimal, and that there be compelling scientific reasons for placebo use. At the same time, the minimal risk threshold is being criticized, and the notion of compelling scientific reasons remains to be specified. Therefore, it seems safe to say that the use of placebo controls in randomized controlled trials will continue to be controversial.

Table 1   Prominent ethical guidance on placebo use in clinical research

World Medical Association Declaration of Helsinki (2013)	The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where *no proven intervention exists*, the use of placebo, or no intervention, is acceptable; or Where for *compelling and scientifically sound methodological reasons*, the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will *not be subject to additional risks of serious or irreversible harm* as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.
Tri-Council Policy Statement 2 (2010)	Article 11.2 (a) A new therapy or intervention should generally be tested against an established effective therapy. (b) As with all alternative choices of a control, a placebo control is ethically acceptable in a randomized controlled clinical trial only if: its use is *scientifically and methodologically sound* in establishing the efficacy or safety of the test therapy or intervention; and *it does not compromise the safety or health of participants*; and the researcher articulates to the REB a *compelling scientific justification for the use of the placebo control*.
Brazil, Conselho Nacional de Saúde, RESOLUÇÃO CNS N° 404 (2008)	Propose the withdrawal of notes for clarification of items related to health care to be provided to volunteers and the use of placebo, since they restrict the rights of volunteers to health care, keeping the following texts of the 2000 version of the Declaration of Helsinki: (…) b) Use of placebo: The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where *no proven prophylactic, diagnostic, or therapeutic method exists*.
Uganda, UNCST, Guidelines for Research Involving Humans (2007)	7.2 *Standard of care for research participants in control groups* (…) in general, placebo-controlled trials may be conducted provided that: 1. Based on knowledge that is available at the commencement of the trial, the new drug or device to be tested does not confer any significant benefit compared to the placebo, and a proven prophylactic, diagnostic, or therapeutic method or established effective intervention does not exist. 2. Withholding an established effective intervention would expose the research participant to at most temporary discomfort or delay in relief of symptoms; 3. Use of an established effective intervention as comparator would not yield scientifically reliable results and the use of a placebo would not add any significant risk or irreversible harm to the research participants. (…)
Council of Europe, Additional protocol concerning biomedical research (2005)	Article 23 2. In research associated with prevention, diagnosis, or treatment, participants assigned to control groups shall be assured of proven methods of prevention, diagnosis, or treatment. 3. The use of placebo is permissible where there are no methods of proven effectiveness, or where *withdrawal or withholding of such methods does not present an unacceptable risk or burden*.
CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)	As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances, it may be ethically acceptable to use an alternative comparator, such as placebo or 'no treatment.' Placebo may be used: ● when there is no established effective intervention; ● when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms; ● when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.

South Africa, Department of Health, Research Ethics Guidelines (2004)

2.15 The choice of intervention (placebo or some treatment) to administer to participants in the control arm of a study may require the balancing of many factors, but the welfare of participants must be paramount. (…) Ethics review committees should verify that the control is appropriate, does not impose risks that are unreasonable in relation to the anticipated benefits, and that placebo controls are not employed without compelling justification. (…) Justifications for using a placebo in the control arm are that:

- No treatment or intervention is accepted as being effective for the condition;
- Treatments or interventions are accepted as being effective for the condition, but the use of a placebo will not result in more than minimal adverse effects that are entirely reversible;
- Treatments or interventions are accepted as effective for the condition, but no scientifically justifiable control option, other than a placebo, meets the objective of the research, and the anticipated benefits of the research substantially outweigh the risks to participants. (…)

Ethical guidelines that apply to controlled therapeutic trials are generally adequate to protect the rights of HIV-infected persons. A special case involves the use of placebo after an intervention has already been shown to be effective. The general principle is that the use of placebo in these circumstances is unethical. However, with increasing disparities in health care between wealthy and poor countries, therapy that has been shown to be effective is often unaffordable in resource-poor settings. This is particularly true of therapeutic advances in HIV infection, which is a far bigger health care problem in poor countries in sub-Saharan Africa than in industrialized countries. *It may on occasion be justifiable to use placebo in communities that do not have access to interventions that are the standard care in resource-rich settings.* However, placebos may only be used when the *anticipated benefits outweigh the risks* to participants, and participants will *not be harmed*, and *full justification* must be provided for use of placebo.

ICH, guideline on Choice of control group E10 (2000)

2.1.3 *Ethical issues [regarding placebo control].*

When a new treatment is tested for a condition for which *no effective treatment is known*, there is usually no ethical problem with a study comparing the new treatment to placebo. Use of a placebo control may raise problems of ethics, acceptability, and feasibility, however, when an effective treatment is available for the condition under study in a proposed trial. In cases where an *available treatment is known to prevent serious harm*, such as death or irreversible morbidity in the study population, it is generally *inappropriate to use a placebo control*. There are occasional exceptions, however, such as cases in which standard therapy has toxicity so severe that many patients have refused to receive it. In other situations, when there is no serious harm, it is generally considered ethical to ask patients to participate in a placebo-controlled trial, even if they may experience discomfort as a result, provided the setting is noncoercive and patients are fully informed about available therapies and the consequences of delaying treatment. (…) Whether a particular placebo-controlled trial of a new agent will be acceptable to subjects and investigators when there is known effective therapy is a matter of investigator, patient, and institutional review board (IRB)/independent ethics committee (IEC) judgment, and acceptability may differ among ICH regions. (…).

Acknowledgments

See also: Ethics for Biomedical Research Involving Humans: International Guidelines; Pharmaceutical Industry: Political Economies of Drugs and Knowledge; Placebo Effect; Placebo Studies (Double-Blind Studies); Psychological Treatments: Randomized Controlled Trials.

Bibliography

Angell, M., 1997. The ethics of clinical research in the Third World. New England Journal of Medicine 337 (12), 847–849.

Barton, S., 2000. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. British Medical Journal 321 (7256), 255–256.

Beauchamp, T.L., Childress, J.F., 2013. Principles of Biomedical Ethics, seventh ed. Oxford University Press, Oxford.

Benatar, S.R., Brock, G. (Eds.), 2011. Global Health and Global Health Ethics. Cambridge University Press, Cambridge.

Brazil, Conselho Nacional de Saúde, RESOLUÇÃO CNS N° 404 (2008): http://conselho. saude.gov.br/web_comissoes/conep/aquivos/resolucoes/resolucoes.htm

Brim, R.L., Miller, F.G., 2013. The potential benefit of the placebo effect in sham-controlled trials: implications for risk–benefit assessments and informed consent. Journal of Medical Ethics 39 (11), 703–707.

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, 2010. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Interagency Advisory Panel on Research Ethics, Government of Canada, Ontario, Canada.

Cartwright, N., 2011. A philosopher's view of the long road from RCTs to effectiveness. Lancet 377 (9775), 1400–1401.

Colloca, L., Finniss, D., 2012. Nocebo effects, patient–clinician communication, and therapeutic outcomes. Journal of the American Medical Association 307 (6), 567–568.

Concato, J., Shah, N., Horwitz, R.I., 2000. Randomized, controlled trials, observational studies, and the hierarchy of research designs. New England Journal of Medicine 243 (25), 1887–1892.

Council for International Organizations of Medical Sciences (CIOMS), Ethical Guidelines for Biomedical Research Involving Human Subjects, 2002. http://www.cioms.ch/ publications/guidelines/guidelines_nov_2002_blurb.htm

Council of Europe, Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research, 2005. http://conventions.coe.int/ Treaty/en/Treaties/Html/195.htm

Department of Health and Human Services, 2008. Food and Drug Administration. 21 Code of Federal Regulations Part 312. Human Subject Protection; Foreign Clinical Studies Not Conducted under an Investigational New Drug Application. http://www. fda.gov/ohrms/dockets/98fr/E8-9200.htm.

Department of Health and Human Services, 2013. Food and Drug Administration 21 Code of Federal Regulations. Chapter 1. Subchapter D. Part 314. Subpart D. Sec 314.126 Adequate and well-controlled studies. http://www.accessdata.fda.gov/ scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.126.

Ellenberg, S.S., Temple, R., 2000. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 2: practical issues and specific cases. Annals of Internal Medicine 133 (6), 464–470.

Emanuel, E.J., 2012. Global justice and the "standard of care" debates. In: Millum, J., Emanuel, E.J. (Eds.), Global Justice and Bioethics. Oxford University Press, Oxford, pp. 181–212.

Emanuel, E.J., Miller, F.G., 2001. The ethics of placebo-controlled trials – a middle ground. New England Journal of Medicine 345 (12), 915–919.

Emanuel, E.J., Wendler, D., Grady, C., 2000. What makes clinical research ethical? JAMA 283 (20), 2701–2711.

Freedman, B., 1987. Equipoise and the ethics of clinical research. New England Journal of Medicine 317 (3), 141–145.

Freedman, B., Weijer, C., Glass, K.C., 1996a. Placebo orthodoxy in clinical research. I: Empirical and methodological myths. Journal of Law, Medicine & Ethics 24 (3), 243–251.

Freedman, B., Glass, K.C., Weijer, C., 1996b. Placebo orthodoxy in clinical research. II: Ethical, legal, and regulatory myths. Journal of Law, Medicine & Ethics 24 (3), 252–259.

Fried, C., 1974. Medical Experimentation: Personal Integrity and Social Policy. North-Holland Publishing Company, Amsterdam.

Friedman, L.M., Furberg, C.D., DeMets, D.L., 2010. Fundamentals of Clinical Trials, fourth ed. New York.

van der Graaf, R., van Delden, J.J.M., 2009. What is the best standard for the standard of care? American Journal of Bioethics 9 (3), 35–43.

van der Graaf, R., van Delden, J.J.M., 2012. Equipoise should be amended, not abandoned. Clinical Trials 9 (5), 628–629.

Hawkins, J.S., 2008. Exploitation and placebo controls. In: Hawkins, J.S., Emanuel, E.J. (Eds.), Exploitation and Developing Countries. The Ethics of Clinical Research. Princeton University Press, Princeton, pp. 246–285.

Hawkins, J.S., Emanuel, E.J. (Eds.), 2008. Exploitation and Developing Countries. The Ethics of Clinical Research. Princeton University Press, Princeton.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Harmonised Tripartite Guideline: Choice of Control Group and Related Issues in Clinical Trials, 2000. http://www.ich. org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_ Guideline.pdf.

Kam-Hansen, S., Jakubowski, M., Kelley, J.M., Kirsch, I., Hoaglin, D.C., Kaptchuk, T.J., Burstein, R., 2014. Altered placebo and drug labeling changes the outcome of episodic migraine attacks. Science Translational Medicine 6 (218), 218ra5.

Kaptchuk, T.J., 1998. Powerful placebo: the dark side of the randomized controlled trial. Lancet 351, 1722–1725.

Kukla, R., 2007. Resituating the principle of equipoise: justice and access to care in non-ideal conditions. Kennedy Institute of Ethics Journal 17 (3), 171–202. http:// www.ncbi.nlm.nih.gov/pubmed/?term=kukla+equipoise.

Lie, R.K., Emanuel, E., Grady, C., Wendler, D., 2004. The standard of care debate: the Declaration of Helsinki versus the international consensus opinion. Journal of Medical Ethics 30 (2), 190–193.

London, A.J., Kadane, J.B., October 2002. Placebos that harm: sham surgery controls in clinical trials. Statistical Methods in Medical Research 11 (5), 413–427.

London, A.J., 2001. Equipoise and international human-subjects research. Bioethics 15 (4), 312–332.

London, A.J., 2000. The ambiguity and the exigency: clarifying 'standard of care' arguments in international research. Journal of Medicine and Philosophy 25 (4), 379–397.

Lurie, P., Wolfe, S.M., 1997. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. New England Journal of Medicine 337 (12), 853–856.

Macklin, R., 2004. Double Standards in Medical Research in Developing Countries. Cambridge University Press, Cambridge.

Marquis, D., 1983. Leaving therapy to chance. Hastings Center Report 13 (4), 40–47.

Miller, F.G., Joffe, S., 2011. Equipoise and the dilemma of randomized clinical trials. New England Journal of Medicine 364 (5), 476–480.

Miller, F.G., 2008. The ethics of placebo-controlled trials. In: Emanuel (Ed.), The Oxford Textbook of Clinical Research. OUP, Oxford, pp. 261–272.

Miller, F.G., Brody, H., 2007. Clinical equipoise and the incoherence of research ethics. Journal of Medicine and Philosophy 32 (2), 151–165.

Miller, F.G., Brody, H., 2003. Therapeutic misconception in the ethics of clinical trials. A critique of clinical equipoise. Hastings Center Report 33 (3), 19–28.

Miller, F.G., 2003. Sham surgery: an ethical analysis. American Journal of Bioethics 3 (4), 41–48.

Miller, F.G., Brody, H., 2002 Spring. What makes placebo-controlled trials unethical? American Journal of Bioethics 2 (2), 3–9.

Millum, J., Grady, C., 2013. The ethics of placebo-controlled trials: methodological justifications. Contemporary Clinical Trials 36 (2), 510–514.

Millum, J., Emanuel, E.J., 2012. Global Justice and Bioethics. Oxford University Press, Oxford.

Nuffield Council on Bioethics, 2002. The Ethics of Research Related to Health Care in Developing Countries. Nuffield Council on Bioethics, London.

Petryna, A., 2009. When Experiments Travel. Princeton University Press, Princeton.

Pogge, T., 2002. World Poverty and Human Rights. Polity Press, Cambridge.

Resnik, D.B., 1998. The ethics of HIV research in developing nations. Bioethics 12 (4), 286–306.

Rid, A., Wendler, D., 2011. A framework for risk–benefit evaluations in biomedical research. Kennedy Institute of Ethics Journal 21 (2), 141–179.

Rothman, K.J., Michels, K.B., 1994. The continuing unethical use of placebo controls. New England Journal of Medicine 331, 394–398.

Sacks, H., Chalmers, T.C., Smith Jr., H., 1982. Randomized versus historical controls for clinical trials. American Journal of Medicine 72, 233–240.

Sackett, D.I., Rosenberg, W.M.C., Gray, J.A.M., Haynes, R.B., Richardson, W.S., 1996. Evidence based medicine: what it is and what it isn't. British Medical Journal 312, 71–72.

South African Department of Health, 2004. Ethics in Health Research: Principles, Structures, and Processes. Research Ethics Guidelines. www.nhrec.org.za/wp-content/uploads/2011/ethics.pdf.

Stone, M., Laughren, T., Jones, M.L., Levenson, M., Holland, P.C., Hughes, A., et al., 2009. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. British Medical Journal 339, b2880.

Temple, R., Ellenberg, S.S., 2000. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: Ethical and scientific issues. Annals of Internal Medicine 133 (6), 455–463.

Uganda National Council for Science and Technology (UNCST), 2007. National Guidelines for Research Involving Humans as Research Participants. http://www.uncst.go.ug/.

Varmus, H., Satcher, D., 1997. Ethical complexities of conducting research in developing countries. New England Journal of Medicine 337 (14), 1003–1005.

Weijer, C., Miller, P.B., 2004. When are research risks reasonable in relation to anticipated benefits? Nature Medicine 10 (6), 570–573.

World Medical Association (WMA), 2013. Declaration of Helsinki. Fortaleza, Brazil. http://www.wma.net/en/30publications/10policies/b3/.