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Placebos in Schizophrenia Research: An Historical Overview and Introduction to Ethical Issues

Suze G. Berkhout[1,2,*]

[1] Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; [2]University of Toronto Institute for the History & Philosophy of Science & Technology, Toronto, Ontario, Canada

To whom correspondence should be addressed; Toronto General Hospital, 8th Floor Eaton North, 200 Elizabeth St., Toronto, Ontario, Canada, M5G 2C4; tel: 416 340 3762, e-mail: suze.berkhout@uhn.ca

This short introduction provides a historical and ethical overview of placebos and placebo controls in relation to schizophrenia research, with a focus on long-term clinical trials. Drawing on historical and philosophical scholarship, it sketches a two-level analysis of ethical issues that placebos and the placebo effect raise for the field, particularly in light of shifts in clinical trial methodologies and clinical practices.

Key words: placebo/schizophrenia/ethics/clinical trials

A Brief History of the Concept of Placebos

Widely familiar in relation to their role bringing medications and other interventions to market, placebos have a long and somewhat vexed place in the history of medicine. The term placebo stems from psalm 116, linked to the Vespers of the Office of the Dead. Individuals could be hired to mourn, as a way of an offering for the souls in purgatory. Within the psalm we hear, "*Placebo Domino"*: the false mourners please the Lord with their prayers.[1] From the term's first parlance, we have an association of placebo not only with pleasing but also with sham or deception. Although the usage of the term became more widespread since the 14th century, "placebo" entered commonplace medical jargon in the late 18th century when it was considered a crucial component of a physician's toolkit.[2] Here, it retained the connotation of a substance that would please the patient, rather than treat an ailment.

Placebos defy the causative logics of medicine insofar as they prompt an improvement in symptoms but lack the properties by which drugs or other interventions cause physiological changes. Some examples include the trade dress (appearance) of pills—red pills can enhance autonomic stimulation, whereas blue pills are more likely to sedate, hailing culturally salient references to color. Placebos can include names (brand vs generic), information of about cost (more expensive placebos are more efficacious than less expensive ones), and the number of pills provided (two placebo pills being more effective than one).[3–6] There are many different cases of placebos, operating in varying domains, including the clinic, the laboratory, and the marketplace.[7] In each of these contexts, placebos mark the *other* side of legitimate treatment, recognizable as deception, contaminant, sham, and quackery.[8–11]

Following more than half a century of research into the mechanisms of placebo effects there is widespread recognition that placebos themselves generate broad changes in behavior and physiology. Findings from across a range of experimental paradigms and methods suggest that an overarching framework to understand how placebos operate is that of expectancy: the psychosocial context of care and the prior experiences of both health care providers and patients inform beliefs relating to outcomes (positive or negative), treatment process, one's own capacities (to self-manage as well as to heal). These components shape provider and patient expectancies, a major mechanism through which placebo effects occur.[12–16] The expanding body of research that examines how placebos operate and the neurobiological mechanisms through which they act increasingly suggest that framing these as "inert" substances or mere placeholders for an active intervention is a misnomer.

The Use of Placebo in Clinical Trials

Professor of medicine and Placebo Studies scholar Ted Kaptchuk suggests that while the notion of masked assessment seems to have originated in late 16th century exorcism rites, inert controls were adopted by conventional physicians to demonstrate "irregular" healers' interventions to be illusions or imagination. Masked assessment with sham remedies became part of debates on 19th century homeopathy, seen as a way to adjudicate disputes between practitioners.[17,18] It took longer for orthodox medical practitioners and scientists to turn to no-treatment and placebo control groups to legitimate their own interventions, such as Austin Flint's assessment of the prevailing treatment for rheumatism circa 1863. Picking up interest in early 20th century Germany and popularized there in the 1930s, the use of a placebo intervention as taken off considerably since the post-war period, where the "sham" comparator joined randomization practices, solidifying its place within the structure of clinical trials.[19] The active and dynamic qualities of placebos as well as the way in which they are context dependent (rather than being universal or generalizable) bring about challenges in relation to how the placebo effect impacts clinical trials.

Within the scaffolding of the clinical trial, placebos have become a central tool in determining the efficacy of an intervention. Presently, a novel therapy must be tested against placebo for licensure, demonstrating superiority in at least two adequate and well-designed clinical trials (regardless of how many trials were conducted).[20] Within psychiatry this has led to some difficulty, as a number of scientific and logistical issues intersect with placebos. First, the placebo response in psychiatric interventions is particularly high[21] and it is increasing.[22,23] There is a significant positive relationship between year of publication and placebo response rate—this is impressive given that the literature predominantly reflects trials reporting positive outcomes.[24]

And while it is often assumed that a high placebo response rate means that the efficacy signal for a new treatment will be hampered or diminished,[25] a second challenge to reconcile has been the finding that the placebo response is often intermingled with a drug treatment response. In depression trials, for instance, those who had the most robust response to placebo, were also the individuals who responded most vigorously to a medication.[26,27] While a lead in period might be used to remove placebo responders, it is also the case that this may be removing those with the most robust *medication* responses as well. Added to this is a recent finding from the reanalysis of antipsychotic clinical trial data, that what is called the "constancy assumption" does not hold—that is to say, the extent of improvement from a novel agent is impacted by the clinical trial design itself. Novel agents do not necessarily perform in an identical way when they are tested in active or low-dose controlled trials compared to placebo-controlled trials.[28]

Finally, we have a third challenge: attempts have been made to determine characteristics of placebo "responders," but *who* responds to what type of placebo is contextual; there is no one trait, and even clusters of traits (eg, optimism, empathy) interact with various contingencies in a dynamic fashion.[29] Taken together, addressing the high rates of placebo response in psychiatric research is an ongoing challenge and, as discussed below, can contribute to ethical challenges. These are not always straightforward to rectify through trial design.

In short, while placebos have been used clinically for hundreds of years, the use within the apparatus of the clinical trials is more recent, and not without its technical challenges. And as we'll turn to now, there are ethical challenges that intersect with these technical and logistical ones. I conceptualize these challenges as operating as two levels. *First level* ethical issues are those that directly relate to the question of whether or not a placebo ought to be used in a given study. These types of questions more straightforwardly reflect common research ethics considerations such as the relationship between risks and benefits, the treatment of vulnerable populations in clinical trials, definitions of "serious harm," and issues surrounding voluntariness versus coercion.

In contrast, what I have termed *second level* ethical issues relating to placebos are ones that ask us to think more broadly about philosophical issues relating to knowledge practices in biomedicine. For instance, the valuing of certain forms of knowledge vis-à-vis hierarchical levels of evidence[30] and the normative determination of what "counts" as scientific evidence intersects with the phenomenon of rising placebo rates, informing clinical trial design. The complexity of trial design has ethical implications, for instance relating to issues of capacity to consent to participate. Likewise, the global expansion of clinical trials, generated by an increased reliance on multicenter studies and a desire for larger participant pools, is also related to the place of placebos in clinical trials and brings with it complex considerations relating to the flow of knowledge (and power),[31,32] which may not immediately come to mind when considering placebos in schizophrenia research. As I've conceptualized them, second-level ethical considerations take a broader and more expansive view in thinking about values in science and normative issues that arise in the production of scientific knowledge.

First-Level Ethical Issues

What I am calling first-level ethical considerations are those issues that stand directly in relation to a judgment of whether or not one ought to use a placebo control in a given study. The justification for use of placebos often begins with the issue of clinical equipoise. A concept

introduced by Benjamin Freedman, clinical equipoise states that in order for a clinical trial to be ethical, there must be genuine uncertainty or professional disagreement amongst a body or community of experts as to a preferred treatment. This is a different (though not unrelated) issue to the matter of individual equipoise—the question as to whether an individual practitioner can continue to meet fiduciary obligations to their patients when contemplating offering enrolment into a clinical trial.[33] Clinical equipoise is often seen as the moral foundation of the randomized controlled trial (RCT),[34] in no small part because there are many situations that would disrupt individual equipoise long before a community of experts endorses that a sufficient quantity and quality of findings ends the uncertainty around an intervention.[35] The requirement that a genuine question about the effectiveness of the intervention under study must remain in order for trial to continue to randomize participants to placebo and carry on to completion brings a significant tension between the individual participant perspective and larger societal and professional standards concerning scientific evidence.

Related to the use of placebo controls in clinical research and the impetus behind equipoise is the *Declaration of Helsinki*, which has been revised a number of times since its instantiation more than 50 years ago. Content relating to the use of placebo controls in research has been highly divisive. Initially, content that ultimately evolved into a paragraph on the use of placebos was drafted in the 1975 revision. The aim was to ensure that individuals participating in research were not disadvantaged in their individual medical care, and stated: "In any medical study, every medical patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method".[36] This has been criticized for conflating clinical care with clinical research,[37] and after a number of revisions the Declaration added clarifications that have made less stark (perhaps, less clear) the issue of placebos. Later revisions have indicated that the use of placebo *is not excluded*, particularly where no proven intervention exists, as well as where efficacy or safety determinations produce *compelling and scientifically sound* reasons for the use of a less effective intervention or placebo *and* the use of this comparator will not produce additional risks of serious or irreversible harm[36] [emphasis added].

The history of the Declaration of Helsinki is relevant to understanding how it has landed on the issue of placebo controls. Deeply informed by the 1947 Nuremburg Code as well as by the 1948 Declaration of Geneva, the Declaration of Helsinki was prompted by the atrocities committed by medical researchers on unprotected and involuntary participants pulled from Nazi concentration camps during the second world war.[38] Each of these documents attempts to codify ethical standards and duties to patients and research participants, particularly when there are conflicts between an individual subject's wellbeing versus what findings and outcomes that are in the public interest. Iterations of the Declaration of Helsinki, until the year 2000, dichotomized research into therapeutic (where the subject might benefit directly) and nontherapeutic (no direct benefit), a distinction criticized by some as illogical.[38,39] The context of the revisions also includes other instances of violations of participants' interests and well-being, carried out in the name of scientific merit, as well as controversies in research ethics at any point in time. With respect to placebo controls, the more flexible approach to placebo (ie, explicitly stating that the Declaration *does not exclude* the use of inert placebo, as in the 1996 revision) arose in the midst of controversy surrounding the use of placebo controls in studies of materno-fetal HIV transmission.[38]

This last point is suggestive of the way in which there *are* straightforward scenarios whereby placebos are widely recognized to be ethical.[34]

1. There is no standard treatment
2. The standard treatment is no better than placebo
3. The standard treatment *is* placebo
4. The therapeutic benefit of the standard treatment has been called into question by new evidence
5. The study is conducted in a population of patients who have failed to respond to standard treatment, and no effective second-line treatment exists
6. The study treatment is being added on to standard treatment, which each participant receives.

We can see how one might argue for the use of placebo in studying drugs with novel mechanisms of action, against which there is no comparator, and in situations when it is not clear that the standard treatment has an appropriate evidence base. But there are times when even these seemingly straightforward scenarios are not so straightforward. Consider for instance, a controversial study of risperidone in acute mania. This study utilized a placebo-control arm and the investigators maintained that they did so on the basis of equipoise. The presence of the placebo group was widely criticized in light of very clear gold standard treatments for acute mania that have existed well before the use of risperidone for the condition. At the same time, the trial methodology was justified by the investigators on the basis of a very high and variable placebo response in studies of mania, such that they believed a genuine question existed as to whether the standard treatment was indeed better than placebo.[40–43]

With respect to more longitudinal studies, another equipoise-related challenges arises given that there may be a shift in equipoise over time. It's important to recognize that in addition to having genuine controversy over the efficacy of an intervention, trials are also meant to end once equipoise has been disturbed. That is to say, trials should not be carried on once we have enough of a signal to say that the question that was driving equipoise has

an answer. As other authors in this series of articles will discuss, this has implications for answering scientific and clinical questions about long-term outcomes. Once again, placebos demarcate a site of tension between the interests of an individual participant vs the societal benefit (and patient population benefit) from clinical research.

So what do we say about those situations where we know there is a treatment, but there is genuine debate about whether there are compelling methodological or scientific reasons to use placebo? In the later revisions of the Declaration of Helsinki, it was this notion of *compelling reasons* that provided a green light to what is sometimes called the "placebo orthodoxy." In these instances, placebo controls have also been justified in relation to the risks vs benefits for the population in question. If the risk of placebo (nontreatment) is minimal, the scientific value of answering the research question may be adequate to justify placebo. Likewise, if there is a significant benefit to the population under study, one may justify the use of placebo.

A controversial instance of this latter scenario was in trials of single dose AZT to prevent vertical transmission of HIV, one of the sets of controversies that spurred the 1996 revision of the Declaration of Helsinki. These trials were held in the global south where, it was argued, there was neither the infrastructure nor the funds to provide standard care, long-term combination antiretroviral therapy. Although a standard therapy existed, it was inaccessible to the population in question, given the trial locations. A genuine question *did* exist as to whether a single dose at delivery could be effective, claimed trial proponents. Moreover, this was an intervention that would directly benefit the population under study. This is the kind of situation that is suggestive of what I'm calling "second level" ethical issues.

Second-Level Ethical Considerations with Placebo

This last points gestures toward the importance of thinking about ethics broadly: we want to attend to larger social, political, moral questions, and not restrict ourselves to risk/benefit discussions, as important as these are. We have "second level" ethical issues to consider. Thinking again to the single dose AZT trials—the controversy stemmed from the injustice of using socioeconomic disparity as the driver of equipoise.[44] Even though it might scientifically legitimate to use placebo vs. active control, it was only the circumstance of structural disadvantage that enabled the question to be asked.

Similarly, we might argue that there is a second-level ethical issue to be considered in relation to placebos in those situations where coercive pressure to participate in placebo-controlled trials exists due to limited access to medical, social, and basic goods outside of the infrastructure of clinical trials. While the balance of personal risks versus the societal benefits or public good of placebo-controlled studies is something we might believe participants should be able to determine for themselves, coercion can be high when the clinical trials is the most reliable way to receive vouchers for food, transportation, or even to receive medical care itself.[45,46] An overly paternalistic stance may not be justified and even with the influence of trial benefits, vulnerable groups likely ought to be included as their exclusion from research would also constitute an injustice in light of the benefits of knowledge about interventions in wide ranging populations. But attention nonetheless needs to be paid to larger structural inequities and broader ethical issues that intersect with placebo controls but are not always accounted for if we are limited in our thinking to the issue of clinical equipoise.

Consider that rising rate of placebo responses in study populations has been part of the move toward an increasingly global reach of clinical trials,[47] with attendant issues of distributive justice. With multi-national, multicenter trials, the burdens and risks of trial participation may not be distributed in concert with the benefits; the flow of risks has been argued to move toward the global south, while the flow of benefits traverses back to wealthy, industrialized nations.[32,48,49] The design of clinical trials raises additional ethical considerations: active controls require greater numbers of trials participants to power a trial as compared to placebo, which may also be a component of expanding trials to multiple international locations, which may further fuel placebo responses. Ethical concerns also relate to the question of *why* it is that the evidence base might be considered to have equipoise or genuine uncertainty—ie, is that uncertainty present because in pharma-sponsored head-to-head trials, competitor drugs have been found to be under-dosed to have limited effect, or over-dosed to have a greater burden of side effects?[50]

A final but nonetheless critical issue to consider with respect to second-level ethical concerns is the place of patient-oriented and community-based participatory research models in schizophrenia, and in clinical research especially. This also speaks to relationships between knowledge and power, and the importance of designing clinical trials that ask questions of utmost importance to the population being studied. As other authors in this series will describe, the clinical questions surrounding antipsychotic dose reduction and discontinuation as well as the long-term effects of antipsychotic medications and recovery are central to affected people's lives, and placebo controls may need to be part of answering those. How to ask and answer these questions in a way that prioritizes the interests and values of research participants alongside scientific or methodological priorities is also an important ethical issue that intersects with how we produce scientific knowledge. Historically, for instance, clinical trials have not utilized community based participatory research (CBPR) models, though there is growing support for this

approach, particularly in relation to health disparities and equity with respect to medical interventions.[51,52] This issue, along with the other examples discussed above, points to second-level ethical considerations that prompt questions beyond the issues of risks and benefits for particular study participants.

Conclusions

In the background of the second level ethical issues I've briefly sketched is a presumption about what constitutes a strong base of evidence when there is this genuine uncertainty, and an endorsement of the conventional evidence-based medicine hierarchy. There are values embedded within the hierarchy, relating to what constitutes "good" or "best" knowledge practices. There are values linked to notions such as objectivity, neutrality, and evidence (concepts that are frequently assumed to be free of values or normative content). But we enact these values through the research questions we prioritize and the assumptions we build into our experimental paradigms, and placebo controls are a part of the normative assumptions embedded in science. Such values are the foundations upon which RCTs are designed, justified, and carried out.

A robust ethical discussion will often provoke additional questions even as much as it tries to pave the way for considered responses. The papers in this series are at the leading edge of discussions that sit at the intersections of scientific method, research ethics, epistemic values, and lived experience in schizophrenia. This complexity requires both detailed analysis and broad, contextual understandings in order to see both the forest and the trees.

References

1. Louhiala P. *Placebo Effects: The Meaning of Care in Medicine.* Springer Nature; 2020:135. doi:10.1007/978-3-030-27329-3_3.
2. Jutte R. The early history of the placebo. *Complement Ther Med.* 2013;21(2):94–97. doi:10.1016/j.ctim.2012.06.002.
3. Buckalew LW, Coffield KE. An investigation of drug expectancy as a function of capsule color and size and preparation form. *J Clin Psychopharmacol.* 1982;2(4):245–248.
4. Faasse K, Martin LR, Grey A, Gamble G, Petrie KJ. Impact of brand or generic labeling on medication effectiveness and side effects. *Health Psychol Off J Div Health Psychol Am Psychol Assoc.* 2016;35(2):187–190. doi:10.1037/hea0000282.
5. Meissner K, Linde K. Are blue pills better than green? How treatment fFeatures modulate placebo effects. *Int Rev Neurobiol.* 2018;139:357–378. doi:10.1016/bs.irn.2018.07.014.
6. de Craen AJ, Roos PJ, Leonard de Vries A, Kleijnen J. Effect of colour of drugs: systematic review of perceived effect of drugs and of their effectiveness. *BMJ* 1996;313(7072):1624–1626.
7. Berkhout SG, Jaarsma AS. Trafficking in cure and harm: placebos, nocebos and the curative imaginary. *Disabil Stud Q.* 2018;38(4). doi:10.18061/dsq.v38i4.6369.
8. Wall P. The placebo effect – an unpopular topic. *Pain* 1992;51(1):1–3. doi:10.1016/0304-3959(92)90002-S.
9. Touwen D, Engberts D. Those famous red pills-Deliberations and hesitations. Ethics of placebo use in therapeutic and research settings. *Eur Neuropsychopharmacol.* 2012;22(11):775–781. doi:10.1016/j.euroneuro.2012.03.005.
10. Groll D. What you don't know can help you: the ethics of placebo treatment. *J Appl Philos.* 2011;28(2):188–202. doi:10.1111/j.1468-5930.2011.00517.x.
11. Cohen S. The nocebo effect of informed consent. *Bioethics* 2014;28(3):147–154. doi:10.1111/j.1467-8519.2012.01983.x.
12. Cousins N. Belief becomes biology. *Advances* 1989;6(3):20–29.
13. Gordon E. The placebo: An insight into mind-body interaction. *HEADACHE Q-Curr Treat Res.* 1996;7(2):117–125.
14. Pearce J. The placebo enigma revisited. *Clin Med.* 2011;11(4):340–343. doi:10.7861/clinmedicine.11-4-340.
15. Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H. The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review. *Health Technol Assess.* 1999;3(3). doi:10.3310/hta3030.
16. Colloca L, Miller FG. How placebo responses are formed: a learning perspective. *Philos Trans R Soc B Biol Sci.* 2011;366(1572):1859–1869. doi:10.1098/rstb.2010.0398.
17. Kaptchuk T, Kerr C, Zanger A. The art of medicine Placebo controls, exorcisms, and the devil. *Lancet* 2009;374(9697):1234–1235. doi:10.1016/S0140-6736(09)61775-X.
18. Kaptchuk TJ. A brief history of the evolution of methods to control observer biases in tests of treatments. JLL Bull Comment Hist Treat Eval. https://www.jameslindlibrary.org/articles/a-brief-history-of-the-evolution-of-methods-to-control-of-observer-biases-in-tests-of-treatments/. Published online 2011. Accessed May 27, 2022.
19. Kaptchuk T. Powerful placebo: the dark side of the randomised controlled trial. *Lancet* 1998;351(9117):1722–1725. doi:10.1016/S0140-6736(97)10111-8.
20. U.S. Food and Drug Administration. *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Draft Guidance*. Published online 2019:21.
21. Weimer K, Colloca L, Enck P. Placebo effects in psychiatry: mediators and moderators. *Lancet Psychiatry* 2015;2(3):246–257. doi:10.1016/S2215-0366(14)00092-3.
22. Dold M, Kasper S. Increasing placebo response in antipsychotic trials: a clinical perspective. *Evid Based Ment Health.* 2015;18(3):77–79. doi:10.1136/eb-2015-102098.
23. Agid O, Siu CO, Potkin SG, *et al.* Meta-regression analysis of placebo response in antipsychotic trials, 1970-2010. *Am J Psychiatry.* 2013;170(11):1335–1344. doi:10.1176/appi.ajp.2013.12030315.
24. Fava M, Evins A, Dorer D, Schoenfeld D. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. *Psychother Psychosom.* 2003;72(3):115–127. doi:10.1159/000069738.
25. Rutherford BR, Roose SP. A model of placebo response in antidepressant clinical trials. *Am J Psychiatry.* 2013;170(7):723–733. doi:10.1176/appi.ajp.2012.12040474.
26. Whitlock ME, Woodward PW, Alexander RC. Is high placebo response really a problem in depression trials? A critical re-analysis of depression studies. *Innov Clin Neurosci.* 2019;16(07-08):12–17.
27. Enck P, Klosterhalfen S, Weimer K, Horing B, Zipfel S. The placebo response in clinical trials: more questions than

answers. *Philos Trans R Soc B-Biol Sci*. 2011;366(1572):1889–1895. doi:10.1098/rstb.2010.0384.

28. Woods S, Gueorguieva R, Baker C, Makuch R. Control group bias in randomized atypical antipsychotic medication trials for schizophrenia. *Arch Gen Psychiatry.* 2005;62(9):961–970. doi:10.1001/archpsyc.62.9.961.
29. Frisaldi E, Shaibani A, Benedetti F. Placebo responders and nonresponders: what's new? *Pain Manag.* 2018;8(6):405–408. doi:10.2217/pmt-2018-0054.
30. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1989;95(2 Suppl):2S–4S.
31. Benatar SR Reflections and recommendations on research ethics in developing countries. *Soc Sci Med.* 2002;54(7):1131–1141. doi:10.1016/S0277-9536(01)00327-6.
32. Kwok K, Sati N, Dron L, Murthy S. Data flow within global clinical trials: a scoping review. *BMJ Glob Health* 2022;7(4):e008128. doi:10.1136/bmjgh-2021-008128.
33. Miller PB, Weijer C. Rehabilitating equipoise. *Kennedy Inst Ethics J.* 2003;13(2):93–118. doi:10.1353/ken.2003.0014.
34. Weijer C. Placebo-controlled trials in schizophrenia: are they ethical? Are they necessary? *Schizophr Res.* 1999;35(3):211–218. doi:10.1016/S0920-9964(98)00127-3.
35. Gifford F. Pulling the plug on clinical equipoise: a critique of Miller and Weijer. *Kennedy Inst Ethics J.* 2007;17(3):203–226; discussion 227-246. doi:10.1353/ken.2007.0020
36. WMA - The World Medical Association-WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed May 31, 2022.
37. Litton P, Miller FG. A normative justification for distinguishing the ethics of clinical research from the ethics of medical care. *J Law Med Ethics.* 2005;33(3):566–574. doi:10.1111/j.1748-720X.2005.tb00519.x.
38. Carlson R, Boyd K, Webb D. The revision of the Declaration of Helsinki: past, present and future. *Br J Clin Pharmacol.* 2004;57(6):695–713. doi:10.1111/j.1365-2125.2004.02103.x.
39. Levine RJ. Some recent developments in the international guidelines on the ethics of research involving human subjects. *Ann N Y Acad Sci.* 2000;918:170–178. doi:10.1111/j.1749-6632.2000.tb05486.x.
40. Murtagh A, Murphy KC. Trial of risperidone in India—concerns. *Br J Psychiatry J Ment Sci*. 2006;188:489; author reply 490-491; discussion 491-492. doi:10.1192/bjp.188.5.489-a
41. Basil B, Adetunji B, Mathews M, Budur K. Trial of risperidone in India--concerns. *Br J Psychiatry J Ment Sci*. 2006;188:489–490; author reply 490-491; discussion 491-492. doi:10.1192/bjp.188.5.489-b
42. Mudur G. Indian study sparks debate on the use of placebo in psychiatry trials. *BMJ* 2006;332(7541):566. doi:10.1136/bmj.332.7541.566-a.
43. Khanna S, Vieta E, Lyons B, Grossman F, Eerdekens M, Kramer M. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. *Br J Psychiatry J Ment Sci.* 2005;187:229–234. doi:10.1192/bjp.187.3.229.
44. Landes M. Can context justify an ethical double standard for clinical research in developing countries? *Glob Health*. 2005;1:11. doi:10.1186/1744-8603-1-11.
45. Varma S, Vora K, Fox K, Berkhout S, Benmarhnia T. Why Calls to Diversify Trial Populations Fall Short. *Med N Y N*. 2021;2(1):25–28. doi:10.1016/j.medj.2020.12.012.
46. Groth SW. Honorarium or coercion: use of incentives for participants in clinical research. *J N Y State Nurses Assoc.* 2010;41(1):11–22.
47. Petryna A. Ethical variability: drug development and globalizing clinical trials. *Am Ethnol.* 2005;32(2):183–197. doi:10.1525/ae.2005.32.2.183.
48. Glickman S, McHutchison J, Peterson E, *et al.* Ethical implications of the globalization of clinical research. *N Engl J Med.* 2009;360:816–823. doi:10.1056/NEJMsb0803929.
49. Petryna A. Experimentality: on the global mobility and regulation of human subjects research. *PoLAR Polit Leg Anthropol Rev*. 2007;30(2):288–304. doi:10.1525/pol.2007.30.2.288.
50. Flacco ME, Manzoli L, Boccia S, *et al.* Head-to-head randomized trials are mostly industry sponsored and almost always favor the industry sponsor. *J Clin Epidemiol.* 2015;68(7):811–820. doi:10.1016/j.jclinepi.2014.12.016.
51. De Las Nueces D, Hacker K, DiGirolamo A, Hicks LS. A systematic review of community-based participatory research to enhance clinical trials in racial and ethnic minority groups. *Health Serv Res.* 2012;47(3 Pt 2):1363–1386. doi:10.1111/j.1475-6773.2012.01386.x.
52. Viswanathan M, Ammerman A, Eng E, *et al.* Community-based participatory research: assessing the evidence. In: *AHRQ Evidence Report Summaries*. Rockville, MD:Agency for Healthcare Research and Quality. 2004;(99):1–8.