

## ***Ethical Considerations in the Use of Placebo-Controlled Trials in Psychiatry***

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### **ABSTRACT**

The history of psychiatric medicine, and research in particular, is fraught with examples of ethical conundrums; one of the most pertinent to current psychiatric research is the use of placebo controls in pharmacological drug trials. At the centre of the placebo debate lays study design; randomized controlled trials have become the standard of clinical research, but this requires further consideration when investigators seek to choose a control, especially in psychiatric research. There are arguments for and against placebo use in psychiatric drug trials, as well as for alternative study designs. Here, guidelines are proposed for the use of placebo control groups specifically in the context of psychiatric trials.

**Keywords:** placebo, psychiatry, pharmacology, trials

The history of psychiatric medicine, and research in particular, is fraught with examples of ethical conundrums; one of the most pertinent to current psychiatric research is the use of placebo controls in pharmacological drug trials. The issue of placebo controls in psychiatric drug research covers a great deal of ethical ground, with ethical norms in research depending almost entirely on those of clinical practice (Wing, 1999). Principles such as beneficence, nonmaleficence, autonomy, justice and issues of informed consent are certainly common to both research and clinical settings, and are unlikely to change, however the application of these principles can vary depending on context.

At the centre of the placebo debate lays study design. Randomized controlled trials are the most powerful way to demonstrate statistically significant research and have become the standard of clinical research; generally speaking, these trials can be conducted with little ethical conflict. The discussion requires further consideration, however, when investigators seek to choose a control. Historical control groups, which look to previously conducted studies, are generally considered to be insufficient; so the choice is between concurrent control groups: active or

placebo. Here we encounter a disconnect between what is good for particular patients and what is good for the advancement of science; as Brody (1997) states, physician-investigators must choose between justice to the individual patient-subjects and promoting social gains through research. But, he argues, can we not design trials differently so as to satisfy both goals?

### **WHY PSYCHIATRY?**

Although placebo-controlled trials are conducted in virtually every medical field, making the decision to incorporate a placebo control into a clinical trial seems almost uniquely troublesome in the case of psychiatric research. As a study population, mentally ill patients possess characteristics that distinguish them from subjects of other medical research, and these characteristics should not be minimized. Guidelines that have been proposed to manage the use of placebo in studies of other medical conditions, it will be argued, are not sufficient or even fully applicable to psychiatric research.

It has been argued that psychiatric patients are vulnerable in the same way that children are; in both clinical and research contexts, it crudely comes down to their shared potential for incapability of providing valid informed consent. Because of this unique vulnerability, psychiatrist-patient relationships specifically are categorized as fiduciary ones – the physician has a legal duty to act for the patient's benefit (Chaimowitz et al., 2010). Arguably, psychiatric illnesses affect patients in several areas, more so than other disciplines of medicine: even in those patients who retain cognitive function, their primary pathology may be amplified by the stigma of mental illness. Unfortunately, the worst stigmatizing attitudes are directed towards the sickest patients: those with the most visible “differentiating marks”, and those whose marks “instil fear by conveying an element of danger,” (Arboleda-Florez, 2003). As articulated by DuVal (2004), cognitive function, stigma, and a lack of insight may not be the only barriers to participation in research:

Further, some common psychiatric symptoms such as ambivalence, apathy, paranoia, self-destructiveness, and impulsivity may prevent those with mental illness from participating meaningfully in the consent process or otherwise adequately protecting themselves from harm.

Although the practice of psychiatry encompasses a wide variety of illnesses with various sequelae, a common thread is the potential for mentally ill patients lose insight into their disease. In this way, mentally ill patients are doubly vulnerable: based on their illness, they may not be sufficiently cognitively intact to provide informed consent, and additionally, they may lack the insight to withdraw from research protocols should their condition worsen. Psychiatric patients enrolled in placebo arms face much increased risk: even if they were able to provide consent at a study's start, they may deteriorate and become unable to communicate feelings of illness. As a result, these patients not only endanger themselves through the possibility of relapse and self-harm, but also others in cases of aggressive behaviour.

In some cases patients may be sufficiently incapacitated so as to make informed consent impossible. These situations present major problems in psychiatric research: often those conditions for which treatment is sought are those in which the afflicted clearly cannot provide consent. In such situations the issue of fiduciary duty becomes particularly relevant, and physicians must determine the appropriateness of research trials on a patient-to-patient basis. If an investigator desires to enrol such patients in a study, they must seek other acceptable forms of consent and in most cases, the informed consent of a legally authorized representative is acceptable. Occasionally such patients will have provided general consent to research during periods of wellness, with the intention that should they become ill and unable to provide informed consent they would want to enrol in a study of therapies for their condition. These alternative forms of consent are not on their own sufficient to enrol cognitively impaired patients in studies, and should a patient ever refuse participation – despite illness or consent provided by a legally authorized representative – their refusal should supersede any other consent that may have been provided.

To prohibit incapacitated patients from participating in research altogether is not a reasonable course of action; these patients suffer from conditions which, when active, preclude traditional consent. Without their participation, the types of patients enrolled would not truly have active illness and would not represent typical ill patients. As a result, the drugs that would be the product of such trials would not be successful treatment interventions for most. Provisions may be made for enrolling impaired patients, but patient selection must be exacting, and patients should only be enrolled when (a) the research could not be done without their participation, and (b) the protocol is studying a condition that affects them.

Some have argued that focusing on psychiatric patients as a population in need of special consideration is unethical, charging, "It is imperative that psychiatric disorders be given parity with medical disorders" (Manschreck, 2001). This line of reasoning contends that by treating mentally ill populations differently, stigmatization will only increase and fewer rigorous studies will be conducted, causing the discovery of new treatments to reach a standstill. On the contrary, any special treatment of mentally ill patients is afforded only when patients' deficits require it. While placebo-controlled trials are not unique to psychiatric research, they may pose particular risks to psychiatric patients (DuVal, 2004), or further risks we cannot expect any subject to bear. Psychiatric research will continue to produce meaningful results – ethically – if research can be designed to balance scientific considerations and social justice.

A major endpoint in psychopharmacological research is symptom reduction. Other endpoints include – but are not limited to – side effect reduction, greater ease of administration, and decreased cost, all of which serve to increase compliance, thereby further reducing symptoms. Since many psychiatric illnesses now have relatively effective treatments available, the focus has increasingly been on finding drugs with more agreeable side effect profiles (Streiner, 1999), meaning most clinical trials concern so-called "me-too" drugs, variants of current ones rather than novel therapies. Whether a study aims to test a new drug for an otherwise untreatable illness or improve upon current therapy, the debate concerning the use of placebo-controls calls for reflection on principles of both ethics and science.

## THE ARGUMENT FOR PLACEBO-CONTROLLED TRIALS

The placebo-controlled trial is universally considered the gold standard in clinical drug trials in terms of interpretability and statistical power (Brody, 1997), but while physician-investigators must be committed to the production of generalizable scientific knowledge – the goal of any research protocol – there are always ethical issues that come into play. Unquestionably, the use of placebo controls offers many significant advantages over alternative study design: they allow the effectiveness of a drug to be "clearly demonstrated relatively quickly" (Brody, 1997), and with the smallest possible number of study participants. In psychiatric research, this is especially appealing since enrolling fewer patients means decreasing the risk overall for eligible mentally ill patients.

One of the most common arguments for placebo, however, seems to be (perhaps out of sheer ignorance of statistics) fairly simple to refute. Proponents of placebo argue that without them, experimental treatments could be shown to be of similar effectiveness to standard treatment, yet both may actually be little better than placebo, or inactive treatment. This problem may be solved relatively easily if we consider placebo controlled trials to be ethical when no treatment exists; a novel drug may be tried against placebo, but any subsequent treatments must be tried against approved therapy. If these active-controlled trials are designed similarly to the original placebo-controlled trial, a comparison can be made through meta-analyses that adjust for bias.

According to Streiner (1999) however, placebo controls are necessary in at least two situations: the first is one where no accepted treatment exists, and the second is after active-controlled trials have found no difference between therapies (Streiner, 1999). In such a case, he argues, the use of placebo could help differentiate between true drug equivalence and a statistical Type II error (finding no difference when actually there is one).

The methodological advantages of placebo are impossible to deny, however, as Brody calls attention to: "These are scientific advantages rather than absolute needs for scientific validity, and that means that they might be outweighed in at least some cases by other concerns such as ethical [ones]" (Brody, 1997). As Streiner (1999) argued above, and as will be discussed further, all evidence for the use of placebo controls is still applicable to studies testing drugs where no proven treatment exists; but the

argument that placebo controls are a necessary component of any well-designed protocol is difficult to accept when considering the ethical argument against placebo.

## THE ARGUMENT AGAINST PLACEBO-CONTROLLED TRIALS

The case against the use of placebo involves a number of ethical standards, including equipoise, beneficence and non-maleficence, and justice. Detractors of placebo-controlled studies argue that protocols that employ them do not satisfy equipoise, are counter-beneficial in cases where proven therapy exists, and are not just to the patient-subjects who take part. The oft-referenced paragraph 29 of the Declaration of Helsinki states that the “benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods”, with the proviso that placebo may be used in situations where no proven therapy exists.

Among the ethical requirements that must be met by any legitimate clinical trial prior to its undertaking is an honest null hypothesis: “a state of genuine uncertainty regarding the comparative merits of treatments A and B for population P”, what Benjamin Freedman termed equipoise (2003). It is hoped that over the course of the trial clinical equipoise will be disturbed, and one treatment (A or B) will emerge as clearly superior by the study’s conclusion. Since any study that employs a placebo control group cannot be said to satisfy the condition of equipoise, it can be argued that such trials are universally unethical. The only case in which equipoise can justifiably remain unsatisfied is one where no standard treatment exists for the illness being studied; clearly, there is evidence that the experimental drug to be tested will more effective than no treatment (the current alternative), but there exists no treatment against which to compare the new drug. In such cases placebo controls are both acceptable and appropriate.

Another question that arises in the consideration of placebo is one of beneficence and non-maleficence. Can these be satisfied in trials where some patients are denied proven treatment? Many authors argue quite convincingly that since patients in placebo arms are deliberately exposed to the myriad of risks that accompany untreated illness, physician-investigators have forgone beneficence, placing scientific advancement above the well-being of patient-subjects: “Patients randomized to a placebo arm of a clinical trial fail to receive standard, effective treatment for their condition, thus violating the moral obligation of physician-investigators and the rights of patient volunteers,” (Miller, 2000). The position that placebo-controlled trials are counter-beneficial when treatment exists is most compelling, but demands clarification of the physician-investigator’s role with respect to individual patients.

Much has been said of the “therapeutic misconception” which arises when study patients mistakenly believe they have been enrolled in a study for their own benefit. Patients may be misled by the clinical setting of drug research, the fact that they are on some kind of drug regimen, or by a lack of clarity during the informed consent process. It must be made clear that “clinical research is dedicated primarily to promoting the medical good of future patients by means of scientific knowledge derived from

experimentation with current research participants,” (Miller and Brody, 2003), and potential subjects must be clearly informed of the existence of proven treatment if available. While the aims of clinical and research medicine may diverge and the ethics which govern each are not identical, the physician-investigator must bear responsibility to study patients. While study participation does not – and should not – seek to optimize the treatment of individual participants, investigators must not knowingly endanger patient-subjects in favour of statistical interpretability. It will be argued here that physician-investigators can only fulfill this responsibility to research subjects while still producing generalizable knowledge under restricted conditions on placebo use.

Placebo controls may also elicit concern outside of strictly ethical considerations. Though the arguments for the scientific value and interpretability of placebo-controlled trials has been addressed above, methodologically speaking placebo-controlled trials present their own drawbacks. Patients receiving placebo may tend to fare more poorly than their active treatment counterparts, and patients who do poorly are those that drop out of studies. Study results may be compromised, as “differential attrition among groups will work to show that the drug is no better than a placebo, or a less effective drug, even when it is better,” (Streiner, 1999). Although it could be argued that active-controlled trials in which one drug is far superior may show the same trend in differential attrition, it is unlikely. If a trial demonstrated a difference in effectiveness clear enough to result in differential attrition between study arms, the study would likely be stopped early, as equipoise would have been substantially disturbed.

Two basic categories of pharmacological research exist, the first of which seeks to show that a novel therapy is effective as treatment for a given indication and the second of which seeks to show that one drug is superior to another. In the first case, placebo controlled trials are not ethically objectionable for reasons already described, and in the case of the second, “If the aim of the trial is to demonstrate the superiority of one agent over another, either in terms of effectiveness in reducing symptoms or an improved side-effect profile, then a placebo arm is likely unnecessary and unethical, *as long as certain conditions are met*,” (Streiner, 1999): these particular conditions stress that the study be excellently designed, including such items as a sufficient number of patients in each study arm, measures taken to reduce dropout rates, and appropriate outcome measures to ensure the validity of the results and to avoid Type II errors.

## ALTERNATIVE STUDY DESIGNS

If placebo controls are not always appropriate, what other options exist? There must be a control group against which to compare the experimental treatment, and in the absence of placebo investigators must turn to active-controlled trials. In such designs, the experimental treatment is trialed against the standard therapy for a given indication, and will result in one of three scenarios. In the first, the experimental treatment shows significant superiority over the standard treatment. Conversely, standard treatment could emerge as significantly superior to the experimental treatment. In the last case, the study could find no real difference between the two active treatment arms. The first two cases are easily interpreted, but

the third case represents the main problem with active-controlled trials; finding no difference between therapies is not the same as finding equivalence, nor does it mean that no difference truly exists. If the outcome is that the groups are not significantly different, it would suggest that either the experimental treatment works because it is not inferior to standard therapy, or a Type II error has been committed. In order to increase the validity of active-controlled trials, it is necessary to increase the sample size of the study. One means of increasing sample size is by conducting multi-centre studies, although these require increased policing especially if some centres are in countries with less medicolegal oversight. If a study is presented as North American-run but many patients are located offshore, the trial should adhere to North American ethical standards. There is concern, however, with increasing the study size as more people are exposed to the risks of unproven therapy. The counter-argument is that by the time a phase II or III trial is being conducted, the risks of experimental treatment are usually lower than those associated with untreated illness as in the case of placebo.

A number of active-control designs exist, including “add-on” trials (Miller, 2000), which compare standard therapy alone versus standard therapy plus an experimental drug. Dosage-adjusted studies are another method in which different arms compare varying amounts of the same drug. The choice between these depends on what it is that the trial seeks to prove.

Another alternative is a three-arm study, where standard therapy is compared against the experimental drug and placebo. Such trials “combine the scientific rigor of placebo-controlled trials with the potential clinical utility of testing an experimental agent against an existing standard therapy,” (Miller, 2000). Since placebo control groups still exist however, three-arm studies remain problematic.

Yet another option is the conducting of a meta-analysis, which combines the results of several studies that have addressed the same questions. By considering the results of multiple studies and extrapolating, meta-analysis serves to increase the sample size and as a corollary also statistical power. The diagnostic and outcome scales used in each study involved are converted to a common standard for analysis. Because meta-analyses are retrospective in nature, it is impossible to control for any bias present in the structuring of the original studies; for this reason, meta-analyses should only include studies that are methodologically sound. In the search for new therapeutic agents, meta-analysis cannot substitute for a placebo-controlled trial; they too represent an imperfect solution and for this reason will not be considered further.

Despite much publicity, the use of placebo in research is far from consistent in both theory and practice. Regulatory documents are unclear and often contradictory about when placebo controls may be used; although the Declaration of Helsinki is generally considered ardently anti-placebo, an October 2000 Clarification issued by the WMA served only to confuse the matter. The clarification states that placebo-controlled trials may be acceptable even when there exists a proven treatment in cases where, for “compelling and scientifically sound methodological reasons,” placebo use is warranted. While there is no unanimity in the discussion, points of agreement seem to be clear scientific and methodological justification, high standards of informed consent,

and minimization of risk. These are necessary at the outset of any clinical trial, but alone are not sufficient to ensure that a protocol is ethical.

## PROPOSED GUIDELINES FOR THE USE OF PLACEBO CONTROLS IN PSYCHIATRIC RESEARCH

The extant literature on the subject of placebo controls tends to propose guidelines or conditions under which the use of placebo control groups is not ethically problematic. Few papers, it seems, consider psychiatric trials separately from other kinds of medical research though; while many of the points that have been addressed in other guidelines remain salient in the context of psychiatric research, mentally ill patients as a research population “are in need of protections especially suited and targeted to their particular vulnerabilities,” (DuVal, 2004). The argument for distinct guidelines and safeguards for psychiatry is based on the very characteristics that make mentally ill patients themselves distinct: first, the capacity (or lack thereof) of patients to provide valid informed consent, and also the increased risks faced by psychiatric patients who are unmedicated. As a result, the proposed guidelines below stress the importance of an in-depth evaluation to determine a patient’s capacity for consent and careful patient selection.

Before any further discussion of guidelines can proceed, however, the informed consent process deserves further attention. The importance of informed consent cannot be underestimated; it is an ethical imperative for any form of medical research, but requires special consideration in the context of psychiatry. It is widely accepted that consent to research calls for a higher standard than consent to treatment due to the fact that clinical trials do not seek to benefit individuals exclusively. This a complex issue made only more problematic in psychiatric populations. Since mentally ill patients may have reduced capacity to provide informed consent, a psychiatrist who holds no interest in the trial should evaluate prospective study patients. Many patients consider a physician’s invitation to participate in a research study as being tacit approval of the trial drug; alternatives must be made clear, and according to Chaimowitz et al., “Informed consent may be better thought of as informed choice, where patients are made fully aware of their options,” (Chaimowitz et al., 2010).

If a patient is determined to be capable of providing valid consent, the process should not end there; there is a strong case for ‘re-consenting’ patients regularly throughout the duration of a study, thereby treating informed consent as a process rather than a singular event. As previously addressed, patients deemed incapable of providing consent may be enrolled in studies if acceptable consent, such as prior documentation of the subject’s wish to participate in a research protocol or through a legally authorized representative of the patient, has been provided as a substitute. According to the Tri-Council Policy Statement on Ethical Conduct in Research Involving Humans (2002), in trials that employ placebo controls the informed consent discussion should inform potential subjects of the justification of a placebo arm, the likelihood that they will receive placebo and the potential consequences associated with untreated illness.

Once protocols surrounding informed consent are in place, it must next be determined if a standard therapy exists for the illness being studied. The guidelines proposed below allow the use of placebo-controlled trials only in cases where no standard therapy is available, and posit that active-controlled trials must be sufficient in all other cases, and only when the condition of clinical equipoise has been justifiably satisfied.

In such cases where there is no proven therapy, placebo-controlled trials are not contraindicated, however patients may best be monitored in an in-patient setting to guarantee their own safety and the safety of others and the length of time spent on placebo should be minimized. Where an approved drug does exist, it must be determined whether a prospective study subject is, at the time of evaluation, stable with tolerable side effects on an available therapy. If the patient is stable, or symptoms are considered to be satisfactorily controlled, they are deemed ineligible for any research protocol. As indicated by Weiss Roberts et al. (2001), “people whose symptoms are well addressed by standard treatments may have much to lose by entering into a clinical trial that involves a protracted medication-free period.” A restrictive condition, to be sure, but one that serves only to protect potential study patients and may not be so far from the status quo anyhow. As Streiner (1999) puts it, “Although almost all trials describe themselves as randomized, we have to bear in mind that randomization in this context refers to the way in which subjects are assigned to the various treatment groups; it does not refer to the manner in which they were selected in the first place.” Most often, psychiatrists only refer to a study those patients who have not responded well to treatment in a clinical setting, hesitant to enrol stable patients in a study that might provoke deterioration or relapse. What has been put forth here would merely regulate what is essentially already standard practice.

Enrolling treatment refractory patients exclusively in cases where an approved drug already exists necessarily introduces a bias in the favour of treatment-resistant illnesses, and may increase the likelihood of finding drugs to be ineffective. The counter-argument here is that this bias is acceptable; generally, research looks for agents that reduce symptoms, and what better population to study than patients whose symptoms present most clearly and relentlessly? Patients whose illnesses are not defined as treatment-refractory are, by definition, satisfied by current treatment options.

To address the issue of risk management for mentally ill patients who participate in clinical trials, it is proposed that for certain conditions an in-patient setting might be most appropriate. Studies that necessitate admission may face the problem of decreased enrolment and introduce bias against such devastating illnesses, but increased observation is certainly called for. At the evaluating physician's discretion, patient-subjects who are at particular risk of harm to themselves or others should at the very least be monitored closely. Since differentially admitting or monitoring patients could affect study outcomes, either all patients in the study must be admitted, or any visits beyond those required by the study protocol must be carefully documented and treated as adverse event reports. Unfortunately, it would likely be impossible to admit large numbers of study subjects due to constraints on physical space. Exceptions should be made, however, for patient-subjects

in placebo-controlled trials for devastating illnesses – including those with diagnoses of Antisocial or Borderline Personality Disorder, Major Depressive Disorder, Psychotic Disorders and the Bipolar Disorders – and admission should be stressed due to the much-increased potential for suicidal ideation or other forms of violence. Many illnesses, such as those that come under the heading of Anxiety Spectrum Disorders, could be quite safely studied on an outpatient basis since patients would be at much lower risk of harm.

Although somewhat restrictive, the position taken here does not suggest that research in psychiatry should be curbed, for as Wing (1999) argues,

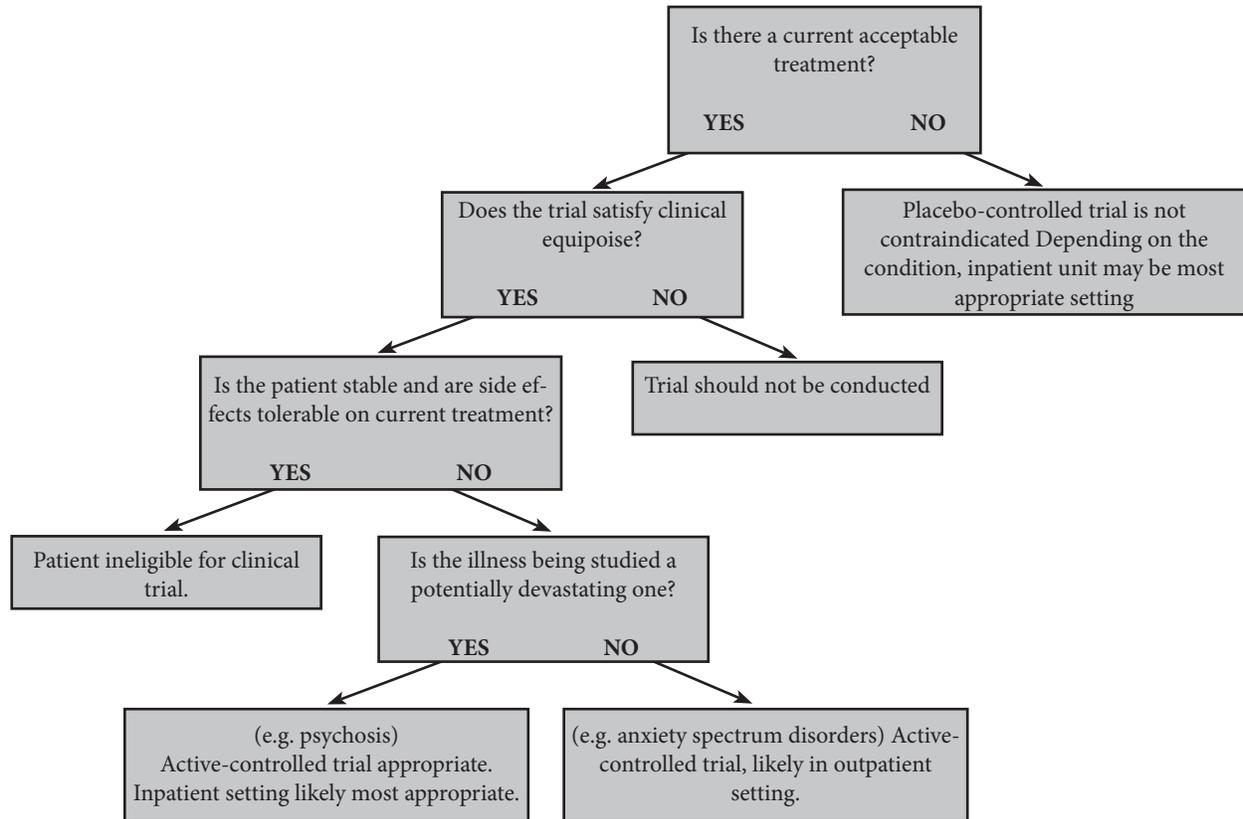
Current methods of treatment depend on experience of past methods. In this sense, research is a normal part of practice and a value to be preserved. Ethical problems are most likely to occur when treatment is based on theories that have been insufficiently tested or, worse, are virtually untestable because they are stated with insufficient clarity and detail. The scientific testing of diagnostic and therapeutic claims is therefore itself a moral imperative.

The importance of research having been affirmed, the crux of this argument is that patient safety should not be sacrificed in favour of scientific advancement; the physician-investigator should err on the side of patient safety in both study design and patient selection phases.

The answer to Brody's question then seems to be that trials *can* be designed to respect the rights of patient-subjects while promoting social and scientific gains through medical research. Clinical trials seek to create generalizable scientific knowledge that will be applicable to populations similar to those individuals who take part in clinical trials, and in this way study participants exhibit a degree of altruism by taking on the risks associated with participation in any research protocol. Psychiatric patients should receive in return special protections from harm that might be incurred during study participation, including increased regulation of placebo use. While placebo-controlled trials are most easily interpreted and present the clearest solutions, we must also make efforts to adapt statistics methodology and interpretation to suit study designs that place patient safety as their primary concern.

Clearly, the perfect guideline has not been devised and no guideline will ever be all encompassing. When doubt arises, investigators must not put scientific ambition ahead of the interest of patients, especially when dealing with patient populations who may not appreciate or respect their own best interests. Any recommendations that are put in place deserve debate among investigators and if adopted, should be reviewed regularly. Restrictions and conditions that function in the context of psychiatric medicine today may become obsolete in light of pioneering work in the field of behavioural neuroscience. Though the social, political, and scientific context in which medicine is practiced and research is conducted may be constantly evolving, respect for the ethical standards that provide the foundation for any physician-patient relationship must remain the foremost concern.

## THE GUIDELINES ABOVE ARE SUMMARIZED HERE



These guidelines comprise aspects of both trial design and patient selection, and they presuppose:

1. Scrupulous informed consent process (not event) where possible. If patients are not able to provide valid consent, it may be obtained through prior documentation of the subject's wish to participate in a research protocol or via a legally authorized representative of the patient.
2. Equipoise as a legitimate and necessary condition to be met by research protocols.
3. Psychiatric patients may be at increased risk of self-harm or harm to others and as such, close monitoring may be warranted. Relatedly, psychiatric patients may lack insight into their condition and be incapable of communicating deterioration or relapse.

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