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Can keeping clinical trial participants blind to their study treatment adversely affect subsequent care?

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Abstract

Subjects in controlled clinical trials obtain experience with study-provided treatment that could inform their further therapy by awareness of the efficacy or inefficacy of the study treatment they received. However, patients in blinded trials typically do not learn right after their participation what treatment they actually received during the study, even though it is possible to do so while maintaining the necessary blinding of investigators. Keeping investigators and subjects blind to treatment assignment throughout a trial is a key element of clinical research methodology, but the value of keeping participants and their medical providers blinded after participation is less certain and may pose risks that include delay in the receipt of efficacious care, exacerbation of symptoms, or prolonged exposure to superfluous or toxic treatment. The significance of these risks is likely to vary with the specific disease and the time course of its response to available therapies. Currently, it seems appropriate for investigators a) to evaluate the risks of keeping subjects blind after participation, b) to justify doing so in relation to serious, identifiable risks to the study's validity and apprise prospective subjects clearly that information about their response to specific treatment during the trial will not be available to guide their post-study care, and c) to consider methods for debriefing subjects before their resumption of open treatment that preserve the integrity of investigator blinding. In the long-run, research on the impact that keeping subjects uninformed about study treatment has on post-study patient outcomes and on study integrity can foster the development of procedures that optimally balance both.

Keywords

Double-blind method; Clinical trials; Ethical concerns

Maintaining subjects' and researchers' blindness to treatment assignment is integral to clinical trials. Insufficient masking during trials demonstrably compromises their validity [1]. However, the importance of maintaining the blind for subjects who complete the trial until the entire study concludes is less certain because he or she no longer furnishes data toward the controlled evaluation of the agent under study. Subjects whose illness requires long-term care gain experience with study-provided interventions that could inform their further therapy through awareness of the treatment to which the study allocated them.

Pharmaceutical industry trials most often maintain blinding until all participants have finished the protocol [2]. This practice reflects concern that debriefing individual subjects may

inadvertently unblind investigators and those evaluating outcomes. Unmasking or bias could occur if unblinded subjects discuss their treatment and outcomes with subjects still on protocol, or relate their experiences to clinicians who work alongside the investigators outside of the trial. Sponsors may also be concerned that subject-by-subject debriefing can affect recruitment for longer-term open trials that frequently follow controlled trials. Open extensions also pose some of these risks to internal validity since they enable subjects and clinicians to correlate outcome with treatment, but are perceived as less threatening than unblinding subjects before investigators.

In other research, a non-blind physician uninvolved with data collection discloses actual study assignment to subjects when they finish their participation while keeping the investigators blind (e.g., Ref. [3]). Doing so may entail extra logistical complexity, including the involvement of different clinicians or sites to provide care in open extensions.

1. Potential consequences and concerns of withholding participants' treatment assignment

Table 1 depicts four post-protocol scenarios that arise from combining two subject outcomes with two masked study treatments. For simplicity, the table exemplifies research that randomizes subjects, double-blind, to either active drug or placebo and there are only two outcomes, improved or unimproved. Post-study treatment options are assumed to include 1) the agent under study, 2) a different agent, and 3) no medication. Generally, treatment with the agent under study is available both for marketed drugs (as in Phase IV research) and for investigational drugs through open-label extension trials that sponsors commonly offer to those who participated in controlled studies. In this context, “medication responder” and “placebo responder” are shorthand to denote the scenario and do not imply a specific etiology for improvement (i.e., true pharmacological impact, or a placebo *effect* as such rather than spontaneous remission [4]).

The following elaborations for each quadrant describes a) implications for post-study care, b) an illustrative example, and c) potential concerns for subjects' well-being. The risks that might be present when patients go on to open care unsure of their study treatment depend on their specific disease and available therapies. Patients with conditions that do not entail significant acute distress or impairment and for which undertreatment or overtreatment over a period of a few months have only minimal adverse impact are less likely to experience disadvantage. Hypertension may provide an example of such a condition [5]. By contrast, patients whose chronic conditions have disabling symptoms and for which treatments have long latencies gain traction might be more negatively affected. Because many psychiatric disorders exemplify such conditions, the illustrations below feature them.

1.1. Medication nonresponders: further delays in obtaining effective therapy?

1.1.1. Scenario—These individuals did not benefit from their treatment with active study medication. Unaware that they received the investigational drug and not placebo they may have a bias toward obtaining open treatment with the drug, either through the sponsor's open extension or in routine care when available. This scenario presents the risk of continuing with inefficacious treatment through the time it takes for tapering when necessary, re-titration, and an appropriate open trial to determine response.

Some subjects may accurately identify their treatment assignment and its lack of efficacy, and therefore decline open extensions. It appears from the limited published data, though, that subjects who correctly surmise that they received treatment with the investigational drug are a) more likely to be medication responders than nonresponders [6–8] or b) less confident about

their guess when they are nonresponders [9]. Both characteristics suggest that patients' judgment may not reliably keep nonresponders to the drug from continued treatment with it.

1.1.2. Example—A 28-year-old male with schizophrenia enrolls in an 8-week, three-arm, flexible-dose trial evaluating a new antipsychotic agent against a placebo and another agent in current use. After randomization, he displays greater behavioral stability briefly, but then regresses and by the trial's end is judged to be a nonresponder, with no change in functional status and somewhat more agitated than on study entry. In actuality, he had been randomized to the investigational drug and was titrated. The sponsor offers an open trial for those who completed the randomized control trial (RCT). Should he enroll, the net effect is that he would receive further therapy with an agent that was nonefficacious for him during the RCT, but it would take several weeks to determine in the open trial that he was not gaining benefit since limited response prior to that time is expected for many antipsychotics.

1.1.3. Concerns regarding delay in receipt of effective therapy—Whether participation in treatment research risks a significant delay in the amelioration of a subject's condition is a persistent ethical concern for clinical trials [10]. Placebo-controlled trials evoke this concern most strongly since they involve the prospect of no pharmacologically active treatment, but studies with active-drug comparators can also entail a more circuitous route to optimal treatment than subjects would otherwise experience [11]. These concerns abate enough for clinical trials to proceed where there is uncertainty about what constitutes optimal or effective treatment, or where deferring effective treatment for the study's duration is unlikely to have serious health consequences [5,12–15]. However, keeping subjects blind to study treatment after their involvement may risk therapeutic dead-ends beyond the trial itself.

Trial sponsors often conduct open extensions to obtain data on safety over a longer time frame than the RCT. Although such data are important, the propriety of proffering an open extension to those whose RCT experience indicates a diminished likelihood of benefit has been questioned [16].

Open extensions could occasionally be beneficial because nonresponders may turn out to have a delayed response, but registration trials are usually designed with adequate durations to detect benefit. Open trials also permit more flexible dosing. Subjects who did not benefit from fixed-dose treatment during the controlled trial may improve with higher doses. This possibility could diminish some of the concerns about persisting with inefficacious therapy in open care, but clearly depends on the likelihood that patients can safely receive higher doses than utilized in the trial.

1.2. Medication responders: disruptions to effective therapy?

1.2.1. Scenario—Those who respond to active treatment often correctly surmise their treatment allocation [4,8], and may be inclined to accept treatment in continuation trials or a similar agent already marketed. However, if the subject's post-study care provider does not know the current dosage, it may be difficult for treatment to maintain the potentially effective regimen.

Unless the treatment under study has only one fixed dosage throughout treatment, open post-study therapy will often begin at a low dose and titrate upwards. A number of medications also require gradual tapering for safe discontinuation. To maintain blinding after the final study assessment, studies of these agents include a masked drug tapering period (e.g., gradual substitution of placebo for active drug) which prevents abrupt dose reductions for subjects taking active drug.

1.2.2. Example—A 31-year-old woman with schizoaffective disorder participated in an RCT evaluating whether an agent currently approved as an anticonvulsant may also act as a mood-stabilizing treatment. The 6-week trial commenced during her latest hospitalization and continued after her discharge, which occurred 4 weeks after starting the trial. Titration for this compound is based on total serum levels, and requires about 2 weeks to attain steady state at a therapeutic level. The product is available for off-label use in routine clinical care. The sponsor offers a 52-week continuation trial which the subject accepts. To preserve study masking, subjects on active drug receive gradual placebo substitution so that they are drug-free when they continue to further treatment. If this subject's improved clinical status were related to her treatment with active drug during the RCT, there is the possibility of relapse and rehospitalization during the 2–3 weeks of disrupted therapy.

1.2.3. Concerns regarding potential disruptions to effective therapy—Maintaining the subject's blind risks discontinuity of therapy because the transition to open treatment is not simply the continuation of a possibly beneficial intervention. Under some circumstances, doing so carries a risk of relapse or exacerbation for the period that the individual has exposure to subtherapeutic dosages. Risks are more likely when the agent involves tapering and retitration, and when the timing of clinical response corresponds closely to dosage adjustments.

We conduct controlled trials because clinical improvement concomitant with treatment does not establish efficacy. One might contend, then, that taper-related relapse and titration-related remission could be beneficial because such experience helps validate the treatment's efficacy. When relapse does not impose significant hardships or dangers, the opportunity to observe such dose-dependent effects on outcome may be a reasonable countervailing benefit. Of course, such events could serve to unmask the subject's treatment anyway.

1.3. Placebo responders: exposure to superfluous treatment?

1.3.1. Scenario—“Placebo responders”, individuals who experience improvement during their involvement in a trial, may lean toward more readily accepting the researcher's offer of open treatment with the investigational drug, or seek treatment elsewhere with it or a related product, unaware that their improvement occurred without it. Although the focus here is on placebo-controlled studies, studies with active comparators are also relevant to this scenario. Comparator-drug responders may similarly be inclined to participate in an open trial of the investigational drug, unaware that they may forsake good symptom control just attained with the comparator. Even if the study drug proves just as efficacious, subjects may experience loss of efficacy during cross-titration.

1.3.2. Example—A 23-year-old male with social phobia participated in an 8-week RCT comparing an antianxiety agent against a placebo. Over the course of the trial, he gradually experienced diminished anxiety and felt comfortable enough to schedule job interviews. He accepted some offers from old friends to join them as a group, and now feels ready to go on his first date in over 3 years with a woman he met in that context. He is not entirely sure what treatment he received during the trial. He feels that he would rather not “take drugs” if they were not really necessary, but he does not want to risk relapse at this point either. In reality his improvement occurred while taking placebo. The investigational treatment belongs to a class of marketed medicines that carry a risk of sexual dysfunction and behavioral disinhibition.

1.3.3. Concerns relating to possible exposure to unnecessary treatment—Placebo responders who pursue further therapy with the investigational drug may risk unnecessary exposure to pharmacologically agents that, for them, may pose risks without benefits.

Sometimes researchers defer potentially unnecessary medication exposures for placebo responders by making extension trials for all responders blind rather than open. That is, if the subject is doing well, one simply continues his or her treatment blind to the true contents of the pill or other delivery vehicle. Naturally, placebo responders would continue to take an inert substance. One scientific advantage of this approach is that it enables the researcher to obtain additional information on the longevity of the placebo response relative to the response of subjects on active drug. Many believe that placebo response is rapid but short-lived, but data are sparse and probably not generalizable across diseases [13]. Some justification for the continuation of placebo could reside in the possibility that improvement resulted from a true placebo *effect*, rather than spontaneous remission or other concurrent interventions [13,17]. This justification presumes that withholding information is acceptable when supposedly done for the subject's own good. Many find this justification inconsistent with the ethical precept that investigators respect the individual as an autonomous decision-making agent [18].

There are other nontrivial burdens associated with long-term open treatment even when the risks of the study drug itself are minimal. The costs, time and inconvenience devoted to obtaining care at a research site or elsewhere in an extension trial are impositions for placebo-responsive subjects that pharmacological benefits may not offset.

Because treatment response is often a continuum rather than a dichotomy, patients who experience some remission on inert or active-comparator treatment might have more complete response with an investigational drug. That possibility could offset concerns about exposure to treatment and could provide valuable additional data. However, in the absence of further improvement, subjects will not be aware that the drug may be irrelevant to his/her improvement over pre-study baseline, and therefore have a bias to continue taking it. In addition, assessments of outcomes from open treatment among those already doing well may be positively biased [19], which undermines the capacity to assess if further improvements can be attributed to pharmacological properties of treatment.

1.4. Placebo nonresponders: deterring subjects from further treatment?

1.4.1. Scenario—Placebo-treated subjects who remain symptomatic may benefit by initiating open treatment with the investigational drug. Continuing care through an open trial at the sponsor's expense for these individuals is often the appropriate culmination of the compact between investigators and subjects. Perhaps the same factors, noted earlier, that might incline nonresponders allocated to double-blind active drug to seek open treatment with the medication will similarly influence placebo nonresponders to try the study drug.

However, patients may be reluctant to enroll in extension trials if they wrongly ascribe emergent physical problems, or even symptom persistence, to active drug during the trial. If headache, nausea, insomnia, rash, and so on coincide with the controlled trial, subjects might presume that the investigational drug was the culprit. A heightened propensity to report discomfort during a trial and attribute it to study treatment represents a *negative* placebo, or a b“nocebo effect” [20,21]. A consequence of this effect, whose frequency and susceptibility factors remain unclear, is that some subjects might decline a trial of post-study treatment that could provide relief. Subjects told that their on-protocol treatment was inactive are perhaps less likely to decline the offer of active drug.

1.4.2. Example—A 62-year-old woman with hitherto untreated major depressive disorder enters an RCT of a new agent vs. placebo. She also has a history of gastric ulcers and gastroesophageal reflux disease. Her mood disorder does not improve during the trial. She experiences considerable gastrointestinal distress, which she attributes to the study drug, a belief her internist reinforces. At study visits, she is reminded that there is a 50% chance that she is taking either real medicine or inert medicine, and she completes the trial. The study

coordinator offers her the opportunity to enroll in an open trial of the study drug or help getting linked with psychiatric follow-up care for her depression. She declines both, convinced psychiatric medication made her worse. She had been allocated to placebo during the RCT.

1.4.3. Concerns relating to possibly deterring patients from further care options

—Blinding subjects past their study involvement may impair their capacity to make accurate attributions for negative experiences. We should be concerned, then, that some patients' expectations for positive outcomes may diminish [22] and adversely affect their engagement in further treatment. We can take some comfort that participation in clinical trial seems on the whole beneficial for participants, but ineffective treatment and unpleasant events during a trial may at times undermine these benefits [23].

It is unknown how often untoward events during a controlled trial deter subjects in a placebo group from accepting open treatment with an investigational drug. Pending data on this topic, the possibility should sensitize investigators to consider how negative events during the protocol, even those inherent in the illness under study, might demoralize some subjects and that withholding treatment assignment information after the trial might further aggravate a disposition to avoid treatment.

2. Ethical considerations in withholding treatment assignment information

The concept of risk for human research subjects has traditionally emphasized the probability that study involvement can harm a person relative to the likelihood of harm in ordinary life. For certain progressive conditions such as dementia or diabetes, where potential benefits of treatment decrease with time or the likelihood of end-organ damage increases over time, risks of withholding knowledge of subjects' study treatment for a number of months could be appreciable if doing so prolongs the latency to effective therapy. In most cases, though, keeping individual subjects blinded is unlikely to leave them worse off than not being in the study at all. Persisting with a treatment after its futility is first detectable is hardly uncommon in clinical care. Likewise, starting or continuing therapy when no treatment or alternate treatment could produce equal or better results is practically an intrinsic element of routine care.

Besides this general concept of research risk, another approach is to consider if withholding treatment allocation information does not comport with recognized ethical obligations researchers have toward subject. The Helsinki Declaration ([24], paragraph 30) codifies the researchers' obligation to provide subjects, after analyzing the trial's data, with access to the treatment that the study indicated was optimal. In the period between the individual subject's participation and promulgation of the study's findings, offering a supervised open trial for those still ill or facilitating subjects' transfer back to clinical care is generally felt to fulfill this obligation. Emerging standards of good clinical practice in clinical trials require somewhat less, only that adverse effects be addressed by the investigator when subjects finish a trial [25]. Because these guidelines do not enjoin researchers to seek the immediate optimization of subjects' post-trial care, they do not oblige the disclosure of study treatment information which might serve that purpose.

It seems, rather, that the pertinent ethical issue concerns the appropriateness of *withholding a benefit* that would otherwise accrue to study participants. Given that knowledge of actual treatment during the study could improve decisions about further therapy, should that information be routinely available when participants end their study involvement?

From this perspective, the principal ethical benchmarks for biomedical research seem to suggest that maintaining the subject's blinding after their participation requires very strong scientific justification. The Belmont Report [26], largely embodied in current U.S. regulations

[27], obligates biomedical research to minimize the harm to subjects while maximizing benefits. The Belmont Report also addresses directly instances when complete disclosure to subjects about the study can compromise its validity. Incomplete disclosure may be ethically permissible when 1) it “is truly necessary to accomplish the goals of the research”, 2) undisclosed risks are no more than minimal, and 3) subjects will eventually be debriefed, when appropriate. The Declaration of Helsinki [24], paragraph 5, asserts that a consideration of the subject's welfare “should take precedence over the interests of science and society”.

Extending these principles to informing subjects about their study allocation would place an obligation on the researcher who plans to maintain subject blinding beyond his or her involvement in the controlled trial 1) to assess and minimize the risks of continued concealment of actual study treatment, including early debriefing when appropriate, 2) when these are tolerable for a specific disease to justify why doing so is essential to the study's integrity, and 3) to inform subjects about assignment and the study outcome as soon as practicable when the trial is completed.

3. Summary

Although participants in controlled clinical trials often have long-term care needs for the condition under study, the implications of study treatment for post-study care have received little attention. Disclosure of the subject's actual treatment during a controlled trial can have a significant impact on decisions about post-study care. In these cases, it seems appropriate that researchers consider methods to disclose this information to subjects and their clinical care providers that also preserve the integrity of the research. In addition, where withholding information on actual treatment during the controlled phase is essential to the study's validity, subjects should understand before consenting that they will not be able to know the relationship between symptom remission or persistence and any specific treatment. In some instances, alternatives to parallel-group research, such as cross-over trials [28], may be scientifically appropriate and enable patients to indicate their preferred treatment while still masking the actual treatment they received.

The impact on post-study care of maintaining treatment blinding is a fit topic for research in its own right. Comparing the outcomes of subjects whose knowledge of study-provided treatment informs their post-study care with subjects lacking such knowledge would make a useful contribution to this topic. Important outcomes would include time to symptom stabilization, time with pharmacotherapy vs. without, and satisfaction with research participation. Simultaneously, the impact of maintaining treatment masking on study integrity should be examined empirically as well. Ultimately, data of this sort can foster the development of procedures that optimally promote both patient outcomes and the validity of clinical trials.

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Table 1

Post-study risks of continued withholding of actual study treatment from subjects upon their completion of a clinical trial

Outcome of blind phase	<u>Actual assignment</u>	
	Study drug	Placebo
Non-improved	<i>Medication nonresponder</i>	<i>Placebo nonresponder</i>
	<ul style="list-style-type: none"> • Suspecting placebo assignment because of nonresponse, may be inclined to try study drug in open treatment. • Risks delay in starting effective treatment. 	<ul style="list-style-type: none"> • Suitable for open trial of study drug. • But may refuse if ailments or symptom persistence are wrongly attributed to adverse effects of “medication” (e.g., nocebo effect).
Improved	<i>Medication responders</i>	<i>Placebo responder</i>
	<ul style="list-style-type: none"> • Unsure if they are on active drug, but may be inclined to continue. • Risks deterioration during re-titration or tapering phases, when response is dose-dependent. 	<ul style="list-style-type: none"> • May be inclined to “continue”, though really to commence, treatment with study drug • Risks exposure to unnecessary treatment.