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The ethics of non-inferiority trials: A consequentialist analysis

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Abstract

Discussions about the merits and shortcomings of non-inferiority trials are becoming increasingly common in the medical community and among regulatory agencies. However, criticisms targeting the ethical standing of non-inferiority trials have often been mistargeted. In this article we review the ethical standing of trials of non-inferiority. In the first part of the article, we outline a consequentialist position according to which clinical trials are best conceived as epistemic tools aimed at fostering the proper ends of medicine. According to this view, clinical trials are *means to ends*, and thus their moral status depends both on how well they perform as means to reach desired ends *and* on which ends they are meant to achieve. Building upon this normative framework in the next two sections we analyze the specific ethical issues raised by non-inferiority trials. By making it clear that clinical trials are just epistemic tools – i.e. means to certain ends – it is possible not only to clarify the conceptual debate over a fundamental issue in clinical research, but also to identify which ethically relevant considerations ought to be addressed in setting up a non-inferiority trial.

Keywords

beneficence, bioethics, clinical trials, consequentialism, non-inferiority trials, research ethics

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To placebo or not to placebo?

In recent years an important debate has emerged about the use of active-control trials (ACTs) in place of traditional placebo-controlled trials (PCTs). Generally, ACTs are considered a superior choice over PCTs in all those situations where leaving patients in the control arm untreated is considered ethically unacceptable. Cardiovascular conditions, cancer care and pain management exemplify instances of such situations.

However, the choice to conduct an ACT may be ethically problematic owing to the fact that currently many ACTs are designed as *non-inferiority trials* (NIs). The standard superiority design enables investigators to conclude with a certain level of confidence that the new treatment is better than the control. In an NI trial, instead, the objective is not to show that the new treatment has a positive advantage over the control, but rather that its inferiority does not extend below a certain limit. NI designs allow for trials that can detect small differences between the new treatment and the active control. When the difference in effect between the new treatment and the active control is predicted to be small, the sample size required to demonstrate superiority with sufficient confidence generally makes the trial infeasible (Shapinn, 2000). A verdict of non-inferiority can be obtained in the same cases with a smaller number of patients.

There are several reasons to focus on small therapeutic differences. For example, we may be confronted with a new therapeutic option that has secondary advantages with respect to the current standard of care, e.g. it is less expensive, more tolerable or it consists in a less invasive procedure. In such cases efficacy is not the only interesting endpoint: a treatment which is therapeutically roughly equivalent to the standard but that also possesses ancillary benefits may in fact be a desirable outcome. Nonetheless there seems to be something ethically problematic in the idea of accepting a treatment that might be inferior to the standard of care, albeit within a certain limit.

Discussions about the merits and shortcomings of NI trials are becoming increasingly common in the medical community and among regulatory agencies. The U.S. FDA and the EMA have both issued guidelines for the conduction of NI trials (EMA, 2000, 2005; Food and Drug Administration, 2010, draft guidance). There is a vast and comprehensive methodological and medical literature on NI trials (D'Agostino et al., 2003; Djulbegovic and Clarke, 2001; Fleming, 2008; Head et al., 2012; Jones et al., 1996; Piaggio et al., 2006; Schumi and Wittes, 2011). On the other hand, a comprehensive ethical scrutiny of the NI trial design is still lacking, even though NI designs are the subject of severe ethical criticism (Garattini and Bertelé, 2002, 2007; Howick, 2009; Powers, 2008). With this article, we intend to fill this gap in the literature.

Criticisms targeting the ethical standing of NI trials are, in our opinion, caught in a conceptual ambiguity. The source of this ambiguity is the lack of specification of a morally relevant distinction between the *ends* of medical research and the *means* used for forwarding them. Surprisingly, most of the doubts and apparent paradoxes that surround the present debate on the ethical and epistemological status of NI stem from a failed appreciation of this basic point. As a result, the debate over the ethical status of NIs is fragmented in seemingly opposite and irreconcilable positions: one may feel forced to think that either NIs, being ACTs, are thereby always better than PCT; or that NIs are intrinsically useless or ethically unfeasible.

In order to avoid such extreme and misleading conclusions, here we propose to adopt a consequentialist approach on ethics of NIs at the very outset of the discussion. In the first part of the article, we outline a consequentialist position according to which clinical trials are best conceived as epistemic tools aimed at fostering the proper ends of medicine. According to this view, clinical trials are *means to ends*, and thus their moral status depends both on how well they perform as means to reach desired ends *and* on which ends they are meant to achieve. Building upon this normative framework, in the next two sections we analyze the specific ethical issues raised by NIs. By making it clear that clinical trials are just epistemic tools – i.e. means to certain ends – it is possible not only to clarify the conceptual debate over a fundamental issue in clinical research, but also to identify which ethically relevant considerations ought to be addressed in setting up an NI.

A consequentialist view on the ethics of clinical trials

Just as any other trial design, also NI trials are a kind of scientific experiment aimed at testing the relative merits of medical treatments. Hence, though the peculiar epistemological features of NI trials raise specific ethical concerns, the normative framework behind NIs is no different from the one informing other kinds of clinical studies. In other words, the specific ethical issues that pertain to NIs have to be interpreted within the normative framework guiding clinical research in general. There are several formulations available to specify such normative framework; in this article we endorse a trade-off-based view. This prescribes that, before performing any trial, it is necessary to operate a trade-off between epistemic goals on the one side and participant's risks of harm on the other, reserving the right for the principle of non-exploitation to have a decisive role in the weighting. The final decision of performing a trial or not would therefore result from this sort of reflective equilibrium between epistemic gains and the ethical constraints.

Let us begin by addressing the most general question, namely which are the proper ends of the medical practice. Historically, the primary goal of medicine has

been the one of restoring health and curing diseases (Caplan et al., 2004; Little et al., 2012). Though the pursuit of this goal has been embodied in different systems of beliefs and practices depending on the period and culture considered, the underlying intent informing medicine has remained remarkably stable. This is reflected, for example, in the practice of contemporary physicians to swear some formulation of the Hippocratic Oath and of its prescription to "benefit the sick" and to "keep them from harm and injustice." More recently, a secondary notion, related to the concept of wellbeing, has been added to this basic commitment (Nussbaum and Sen, 1993; WHO, 1948[1]). The idea that medicine's primary aim is that of fostering people's health and wellbeing is a broad formulation, general enough to be almost uncontroversial.

In the next section we will draw a distinction between the ends of medicine conceived as a public and societal endeavor and the ends of medicine as a private enterprise – and we also acknowledge their potential conflicts. But for the time being, it is enough to specify that in what follows we take the goal of "fostering health and wellbeing" as the primary aim of medicine. In light of this, it becomes possible also to clarify the ends of clinical research. A necessary condition for promoting people's health and wellbeing is that of knowing the relative risk–benefits ratio of prescribed medical interventions. Lacking this knowledge, medicine would be unable to fulfill its role as a professional and scientific endeavor. Indeed, a requirement to exercise the medical profession is that of being aware of the relative effectiveness of the various available interventions, a concern now further emphasized by the increase popularity of evidence-based medicine. Medical practice ought to be informed by the best quality of evidence concerning the effectiveness of medical interventions; and among the ways to generate such evidence, conducting clinical trials has proven to be the most reliable and powerful one (Sackett et al., 2000).

With this we do not imply that clinical research and clinical practice are the same thing. The ends of clinical research are related to, but not identical with, those of the medical practice (Levine, 1979). The main reason is that in clinical research a gap exists between those who are exposed to risk of harm – trial participants – and those who might benefit from the trial results – future patients and society. Despite the chance that participating patients might receive a therapeutic benefit while enrolled in a trial, this is not the primary outcome pursued within clinical research. The primary end of clinical research is, instead, that of producing generalizable knowledge useful to pursue the proper ends of medicine, not to treat or cure trial participants (Miller and Brody, 2003). However, even though clinical research and medical practice are not coinciding endeavors, they are not entirely separate ones either. Rather, the proper *end* of clinical research is to enhance our knowledge so that we can better pursue the ends of the medical practice. To be more precise, while the direct aim of

clinical research is that of providing new generalizable knowledge about a treatment's relative risk–benefit ratio, its *indirect* aim – but an aim nonetheless – is that of fostering medicine itself, i.e. to foster people's health and wellbeing.

Building upon this framework, in the following two sections we analyze the specific ethical concerns raised by adopting a non-inferiority design for conducting a clinical trial. We anticipate our conclusion, which is: the ethical standing of NI trials should be adjudicated in relation to how well (or how badly) they serve the proper ends of medicine. It should not be allowed to depend on the ethical evaluation of the different ends that such trials could be put to serve. In other words, the ethics underlying NI trials should be the same underlying randomized clinical trials in general.

Key ethical issues of non-inferiority trials

Several authors have condemned the NI design for trials as methodologically or ethically inadequate. Garattini and Bertelé are extremely critical of NI trials, which they describe as providing "unreliable messages from questionable methods," concluding that "the scientific community should ban non-inferiority and equivalence trials because they are unethical" (Garattini and Bertelé, 2007: 1875–1876). Similarly, Howick affirms that "non-inferiority trials cannot be deemed worthwhile without special justification," and he concludes "ACTs should generally be conducted as superiority rather than non-inferiority trials" (Howick, 2009: 39). All these authors express the strong position that NI trials should not be conducted unless in very special situations.

Positions about the ethical standing of the NI trial design appear unsystematic, and they occasionally conflict with each other. We think part of this confusion comes from the fact that claims about the (un)ethicality of NI trials fail to address the issue from a clearly defined ethical perspective. In the following, we will illustrate the criticisms raised against NI trials along the framework outlined in the previous section and we will see whether they stand ethical scrutiny.

As discussed in the introduction, NI trials can be conducted in place of superiority trials in order to identify a treatment that is just marginally more efficient, or roughly equivalent, to an available therapeutic option. Pharmaceutical companies often defend their choice of conducting NI trials on the grounds that the availability of products with similar activity would expand treatment options for patients that have poor or no tolerance towards available drugs. However, it is well known that the agenda of pharmaceutical companies does not always reflect the set of priorities and needs of society (Psaty and Kronmal, 2008). This mismatch is explainable in terms of the different and potentially conflicting sets of ends for which society and private corporations pursue clinical research. Whereas the

primary aim of society is that of obtaining generalizable knowledge to benefit future patients, the primary (and legitimate) aim of pharmaceutical industries is, instead, that of making profits and to increase their market share. And just like society has certain obligations toward its present and future citizens, it has been argued that corporations have obligations toward their shareholders (Friedman, 1970). This may lead companies to research on treatments that are of no real value for society (Huskamp, 2006). "Me-too" drugs provide a clear example of this mismatch (Wendler, 2009). These are drugs that are in all aspects identical to already known and proven treatments, and thus have no potential to increase benefit or well-being − they are developed for commercial purposes only.

Based on these considerations, the critics of NI trials regard the declared aim of increasing available therapeutic options as a mere pretext disguising an actual commercial aim on the part of pharmaceutical companies. Howick does not reject the idea of having different therapies for the same illness, so as to provide non-responders with an appropriate treatment. However, he affirms that the presence of non-responders does not legitimate the introduction of a plurality of similar therapies. As he remarks, "even if we allow some non-inferior treatments in case people develop resistance to our existing therapies or an unexpected side effect is discovered, it does not follow that we need dozens of similar therapies" (Howick, 2009: 39). Garattini and Bertelè are even more critical in observing that, if finding an alternative for non-responders were the real aim of NI trials, then the experimental treatment should only be tested on the subset of non-responders rather than in the overall population. They argue that this solution is not chosen, even though it "would meet patients' needs best" (Garattini and Bertelé, 2007: 1876), because it would restrict the prospective market for the new drug. According to Garattini and Bertelé this constitutes the final proof that the real aim of NI trials is that of introducing new drugs into the market through a procedure that is less risky, from a commercial point of view, than a superiority design: "Failure to prove superiority can tarnish the product's commercial image, although it could provide more information for doctors and patients. The non-inferiority approach is likely to overlook differences that might stop the product getting onto the market" (Garattini and Bertelé, 2007: 1876).

Both Garattini and Bertelé (2007) and Howick (2009) claim that rather than being a viable means to pursue the ends of medicine, NI appears more as a Trojan horse used by the pharmaceutical industry to license new drugs without taking due consideration of either patients' or society's needs. Although we share the ethical concerns expressed by these authors, we believe their objections to be mistargeted. This is because they evaluate the moral standing of NI design, which is, as for any other clinical trial, a means to certain ends, on the basis of the moral standing of the ends they are allegedly meant to achieve. Namely, from the factual possibility

that NI trials are used as adequate means for achieving ends different from those proper for medicine, these authors infer that NI designs ought to be considered unethical.

Apart from the risk of drawing normative conclusions (the unethicality of NI design) from factual considerations (the proliferation of me-too drugs), the main weakness of the argument lies, in our opinion, in judging an experimental design on the basis of the ends it to which it may be put to serve. To draw an analogy, consider the case of the potential misuse of painkillers. Although opioid painkillers are one of the most effective means at our disposal to alleviate pain, they may be used for other reasons, including recreational ones (Manchikanti et al., 2010). Though the *use* of painkillers for recreational aims may be considered ethically objectionable, it would be unwise to declare opioid painkillers unethical on the ground of their potential misuse. Indeed, a similar argument would hold for most pharmaceutical interventions. Likewise, we consider it conceptually wrong to adjudicate the ethical stance of NI trials of the basis of the ends that may be promoted through them.

As any other epistemic tool, NIs are not intrinsically bad or good, and the issue concerning the possibility of them being misused represents an open issue for the governance of research rather than an inescapable epistemological verdict. In the following section we move to discuss a second series of ethical objections to NI trials which may be more founded: objections that challenge the adequacy of NI trials *as means* to pursue the proper ends of medicine.

Non-inferiority trials as means

Having established that NI trials should be evaluated as to their adequacy in forwarding the proper ends of medicine, in this section we consider a series of objections that call their status as viable means into question. From this point of view, NI trials have been condemned as unethical because they expose patients to a treatment that may be inferior to the standard existing ones.[2]

This point has been raised by Garattini and Bertelé (2007) and Powers (2008). The main argument is that NI trials are unethical because they expose patients to a treatment that may be inferior. Clearly, also, in superiority trials one of the two treatments will eventually prove to be inferior; however, the prior hypothesis underlying the trial is very different in the two cases. Whereas in superiority studies investigators expect the experimental treatment to be more effective than the standard one – otherwise the study would not even be commenced – in the case of NI design, investigators are instead implicitly buying into the assumption that the new treatment may work less well than the standard. It follows that the ethics of conducting NI trials is questionable, because participants enrolled in NI trials are

exposed to an experimental drug that is less effective than the one they would have received had they not entered in the trial.

Garattini and Bertelé argue that, because "Non-inferiority is a kind of similarity within a […] degree of tolerable inferiority, … a non-inferior test drug could actually be less effective or less safe than the comparator, but not to the extent that is recognized as such" (Garattini and Bertelé, 2007: 1875). Powers (2008) appears to express the same concern when he observes that "The primary hypothesis in an NI trial is that the experimental treatment may be less effective by some amount than standard therapy: hence, subjects are randomized to a group in which effectiveness in truth may be less, and investigators have made a priori judgment that this is clinically acceptable." Garattini and Bertelé explicitly call on the Declaration of Helsinki, in its 1997 version, in support of their argument. The Declaration states, "In any medical study, every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method" (WMA, 1997, article 15). While testing whether a treatment is NI, a clinical trial is exposing a patient to a treatment that is, at best, not much worse than the standard one, and, consequently, that is not the best available treatment at all.

In our view, this objection is rightly targeted at NI trials in their adequacy to foster the proper ends of medicine. However, in the following we question the assumption on which this objection is grounded. The acceptable level of risk to participate in clinical research does not have a clear-cut boundary, as this objection seems to imply. Rather, the issue is one of weighting the prospective epistemic gains against the inevitable risks.

Currently, the randomized double blind placebo-controlled trial (RCT) is considered the best epistemic tool to achieve the goals of clinical research. Although participants in clinical trials receive therapies already tested on animal models and on healthy volunteers, testing a new therapy always entails a certain amount of risk (Wendler, 2009: 13). One reason is that the experimentation of a new therapy is by definition an activity surrounded by uncertainty about the specific outcomes of the treatment under test. Another reason is that, as any other scientific activity, clinical research exposes people to a higher, or at best equal, risk of harm as compared with their everyday life − for example, by putting them in closer contact with dangerous or infectious agents than they would otherwise have been. A third and crucial aspect is that comparative clinical trials require the deployment of a specific set of techniques to secure their internal epistemic validity, such as double masking and placebo controls (Howick, 2011). Clinical research thus always implies exposing a sample population to an acceptable amount of risk in exchange for some epistemic gain expected to be of value (however indirect) in future clinical contexts. Indeed, the key ethical question for research ethics is to identify which amount (or kind) of risk is justifiable for trial participants for the benefits of others.

Although the concepts of "negligible" or "acceptable" risk are notably hard to define with precision, in the past 70 years a consensus has been growing around the position that clinical research is justifiable provided some basic conditions are met (Faden and Beauchamp, 1986). These basic tenets, as they are embodied in research practice guidelines, aim at individuating threshold conditions under which clinical research is unethical and thus cannot be performed. In an effort to set apart clinical research needed to improve medical care from cases such as WW2 Nazi's experiments or the infamous Tuskegee syphilis trial, bioethicists, scientists and policy-makers have identified key criteria such as those of providing adequate informed consent; forbidding trials in which participants are exposed to a high risk of serious and permanent harm; and preventing cases of exploitation (CIOMS and WHO, 2002; NIH, 1949; The Belmont Report [National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978]). Leaving specification of these general requirements aside, what is central for the present discussion is that – provided these conditions are met – the moral status of a particular clinical trial design depends on a weighting between the expected amounts of risks to which trial participants will be exposed, and the prospective epistemic gain that the trial is expected to achieve. As we have described at the onset of our discussion, the issue of whether or not a given trial design is morally acceptable is often an issue of weighting its relative epistemic and ethical utilities and disutilities.

Indeed, the importance of balancing these aspects appears to be accounted for in the revised version of the Declaration of Helsinki as of 2008. In its most recent version of the Declaration, the prescription of providing the patient with the best available treatment has been omitted in favor of a more conditional formulation: "The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention … *where for compelling and scientifically sound methodological reasons* the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment *will not be subject to any risk of serious or irreversible harm*" (WMA, 2008, article 6, our emphasis).

Based on this discussion, we consider the above-mentioned criticisms to NI trials as means to be refuted. We think that NIs are not unethical per se, but that their ethical stance is a matter of contextual judgment that has to be adjudicated according to the conventional principles guiding bioethical reasoning in medical research.

Conclusions

In this article we have reviewed the ethical standing of trials of non-inferiority. Inasmuch as they constitute a subdomain of randomized clinical trials in

general, NI trials should be treated, according to us, in the same way as all the other forms of randomized clinical trials and evaluated according to the same normative framework. In particular, we have proposed a framework that distinguishes between the proper *ends* of clinical research – and of clinical practice – and the *means* for pursuing such ends. The scope of general clinical research is that of producing generalizable evidence in order to pursue the proper ends of medicine, i.e. the fostering of health and wellbeing of future patients and/or society. Clinical trials are epistemic tools finalized to achieve these goals. All clinical trials impose a certain risk of harm on participants, and hence their ethical status depends on a weighting between the prospective epistemic gains that such trials are expected to achieve – which, in turn, imply potential clinical benefits for future patients – and the ethical constraints that protect the trial participant from exploitation. Consequently, claims that non-inferiority trials are intrinsically unethical are unwarranted. A clinical trial design is good or bad, morally acceptable or problematic, depending on how well it allows the fostering of medical practice – provided some threshold conditions about the risk exposure and non-exploitation of trial participant are respected.

Declaration of conflicting interests

The author declares that there is no conflict of interest.

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Notes

1. World Health Organization (WHO) (1948) *"WHO definition of Health"* in Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19–22 June 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948.
2. In the current article we only address the ethical criticisms of NI trials, whereas we do not attempt to adjudicate the methodological criticism raised by these authors. Indeed, one corollary of our conclusions is that methodological criticisms against NI trials, where they have bite, do have the power to disqualify such trials as unethical. This is because such criticisms target the NI trial in their role as a means to an end.

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