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Both Sides of the Coin: Randomization from the Perspectives of Physician-Investigators and Patient-Subjects

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Abstract

Randomization is the “gold standard” design for clinical research trials, and is accepted as the best way to reduce bias. Although some controversy remains over this matter, we believe *equipoise* is the fundamental ethical requirement for conducting a randomized clinical trial. Despite much attention to the ethics of randomization, the moral psychology of this study design has not been explored. This paper analyzes the ethical tensions that arise from conducting these studies, and examines the moral psychology of this design from the perspectives of physician-investigators and patient-subjects. We conclude with a discussion of the practical implications of this analysis.

Keywords

clinical trials; human subjects; randomization; equipoise; clinical trials; moral psychology

Introduction

A commitment to evidence based medicine and concerns about health care economics are leading many countries to invest heavily in comparative effectiveness research. The *randomized clinical trial* (RCT) yields important dividends in assessment of comparative effectiveness, and has become the study design of choice for clinical trials in medicine. First used by Bradford Hill in the Medical Research Council of Great Britain trial in 1947 (Meldrum, 2000), this approach is now widely accepted as being the best way to gather evidence for evidence-based medicine. *Moral psychology* is an interdisciplinary field which seeks to uncover the determinants of moral judgment and behavior (Doris & Stich, 2006). Although there has been consistent attention to the ethics of randomization over the past several decades, the moral psychology of randomization has not been explored. In this paper, we analyze the ethical tension that arises from the conduct of RCTs, examine the moral psychology of this study design from the perspectives of the physician-investigator and the patient-subject, and conclude with some reflections about the impact of these considerations on informed consent for RCTs.

The Randomized Clinical Trial

Randomized clinical trials involve a process of randomly allocating patients into different treatment arms. The key strength of this study design is its robust ability to reduce potential bias that may lead to inaccurate results. Proponents of RCTs tend to praise both the statistical and ethical virtues of this approach (Piantadosi, 2008), while critics have concerns that relate primarily to what they perceive to be ethical flaws (Wells, 2008). Although some may disagree, the fundamental ethical requirement for the conduct of RCTs is generally considered to be that current evidence supports a condition of equipoise: i.e., there is no clear evidence which exists with respect to the superiority of the two treatment options within an RCT (Freedman, 1987; Gifford, 2007; Miller & Brody, 2003). This may be referred to as *internal* equipoise. Readers might imagine a seesaw or teeter-totter with “Arm A” on one side of the fulcrum and “Arm B” on the other. A second and equally important consideration, which has received less attention, may be said to concern *external* equipoise. Readers might again imagine a seesaw but with “Arms A vs B” on one side of the fulcrum and “Off Study Option” on the other. This would require that no treatment option outside of the RCT is considered to be superior to any of the treatments that will be randomly allocated within the RCT. If both *internal* and *external* equipoise conditions are met, one can be assured that no single research participant will be subjected to medical care that subjugates his or her interests to the scientific goals of the study. It is very difficult to argue against the ethical acceptability of an RCT if conditions of both internal and external equipoise are satisfied. If, however, either internal *or* external equipoise is disturbed, it would be unethical to initiate or, if the study is underway, to continue to enroll future subjects in the trial. Specifically, disturbance of *internal* equipoise would require that all subjects receive treatment in the arm of the study that is proven superior. Disturbance of *external* equipoise would require that patients be treated with the approach that is not part of the RCT (if that is somehow proven superior in a different clinical trial) or the RCT arm that is proven superior to both the treatment, which is outside of the RCT, and competitors within the RCT.

Randomization from the Perspective of the Physician-Investigator

Physicians have a fiduciary duty to act in the best interests of their patients. It is imperative that they balance sound scientific clinical evidence with the personal values of the patients seeking their help (Siegler, 2000). In today’s world of medicine, where evidence-based medicine is widely accepted as the foundation of good medical practice, physician-investigators play a critical role (Evidence-Based Medicine Working Group, 1992). As physicians, these individuals must act in a way that is consistent with the best interests of their patient. Many of the current therapies commonly viewed as standard and efficacious have never been studied with RCTs. Investigators have an ethical obligation to generate new knowledge, and may be justifiably critical of physicians using personal experiences or anecdotes to make clinical decisions. One strong proponent of RCTs may have had this in mind when he suggested that all physicians should randomize “from the first patient” (Chalmers, 1975).

Skeptics and therapeutic nihilists would go so far as to claim that physicians are not acting in the best interests of their patients unless they are constantly conducting RCTs. They would suggest that unless a drug or surgical procedure has been studied, it is not possible to judge which treatment is the best option. Others argue that when there is no convincing evidence for a superior therapy, enrolling patients on RCTs does not violate the physician’s therapeutic obligation to their patients (Marquis, 1999). This claim is less strong than suggesting that every patient become a subject in an RCT because the framing language is converted from a positive to a negative claim (i.e., that the therapeutic obligation is not violated) Arguments in favor of RCTs are generally bolstered when it can be demonstrated

that investigators and subjects participate in a meaningful process of informed consent, reflecting a model of partnership in the clinical trial process rather than investigators using subjects as a means to an end.

The moral psychology of randomization from the perspective of the physician-investigator follows from this ethical analysis. The responsibility of practicing medicine carries with it a significant psychological burden. Caring for patients with serious and/or life-threatening illness amplifies that burden, and treatment courses recommended by physicians embody this heavy responsibility. Psychologically, randomization may help to mitigate that burden and provide some level of psychological comfort to physicians. Not only is the choice of treatment taken out of the hands of the doctor, but there is an additional degree of psychological satisfaction in knowing that one is contributing to medical knowledge that will help future patients. RCTs may be especially appealing to younger physicians who are less experienced and may derive a certain amount of confidence from having a protocol to follow. Randomization may serve to alleviate the natural trepidation that comes with making life-or-death treatment decisions, and can be a psychological balm to physicians.

The analysis of moral psychology is not completely straightforward. Some physicians may rail against the constraint on their own autonomy in the practice of medicine that is necessarily imposed by the RCT. Others may be in a state of scientific equipoise but still have a strong preference for a particular treatment based on economic, quality of life, or other considerations. Physicians are human and have clinical instincts that can be powerful and difficult to ignore. For these reasons, an analysis of moral psychology from the physician-investigator perspective would tend to favor accrual to RCTs but must recognize that a certain degree of ambivalence is likely to be present and may have a countervailing psychological impact.

In classic papers published over twenty years ago, Charles Fried and Benjamin Freedman provided key insight about equipoise. Fried (1974) characterized equipoise as a situation where “*professionally* (an investigator) has no basis for preferring one (therapy) to the other” (p.153). Realizing that RCTs were becoming the “gold standard,” Fried argued that “RCTs create the potential for conflict between the ends of medical practice and of research, and the investigator’s role as doctor and research scientist” (Miller & Weijer, 2003, p. 96). Freedman (1987) provided the assertion that equipoise must be assessed from the perspective of the “expert medical community,” rather than the individual. This conceptual advance, which Freedman distinguished as *clinical* equipoise in contrast to *theoretical* equipoise, was important for several reasons. First, it moved the debate from the individual to the collective assessment level. Second, it specified the notion of “disturbing” equipoise as rendering a study unethical and suggested that this could change with the acquisition of new knowledge over time. Finally, and most relevant to considerations of moral psychology, the concept of clinical equipoise firmly embeds the debate in a clinical context and inextricably links clinical ethics and research ethics when sick patients become potential subjects in RCTs.

Are the obligations of researchers fundamentally different than the obligations of treating physicians? Some would argue that the primary allegiance of clinical investigators is to the generation of new knowledge, while doctors practicing medicine are first and foremost committed to the interests of their patient. According to Miller and Rosenstein (2003), “physician-investigators conduct clinical trials to evaluate experimental treatments in groups of patient-subjects with the ultimate goal of benefiting future patients by improving medical care” (p. 1383). Research ethics is, however, “characterized by a basic incoherence: on one hand, clinical research is seen as ethically distinct from medical care; on the other hand, the

obligations of investigators, especially in clinical trials, are thought to be grounded in the doctor-patient relationship” (Joffe & Miller, 2008, p. 31).

As suggested by this brief review of the literature, the psychological reality is quite complicated and should not be oversimplified. Clinical investigators routinely navigate these two sets of commitments, and this “conflict of interest” creates an inherent psychological tension both for these individuals and their patients who may become research subjects. Because of the dual role of physician and investigator, as well as the fact that RCTs and standard medical treatments are often conducted in the same setting, patient-subjects sometimes misunderstand the purpose and function of RCTs as well as the roles of the medical professionals engaged in RCTs (Miller & Rosenstein, 2003).

Randomization from the Perspective of the Patient-Subject

“Whenever we use human subjects for the sake of others, using them as means for our ends, the principle of autonomy alone must guide such practices...Respect for psychological autonomy requires that both parties pay caring attention to their capacities and incapacities for self determination by supporting and enhancing their real, though, precarious, endowment for reflective thought”(Katz, 1993, p. 36).

Patients place a great deal of trust in their physicians and expect them to provide the best available care. The concept of randomization, from the perspective of the patient, is very difficult to reconcile with trust. Studies have shown that the general public may perceive random allocation in a trial to be unacceptable, and may misinterpret investigator equipoise as ignorance (Robinson, et al., 2005a). Most patients do not comprehend the scientific benefits of randomization (Robinson, et al., 2005b). Even more troubling is the fact that many patients do not understand randomization when they are actually enrolled in an RCT (Ellis, Butow, Tattersall, Dunn & Houssami, 2001; Kodish, et al., 2004). Even though much attention has been directed towards improving different methods of communication and enhancement of the informed consent process, patients often have difficulties understanding the concept of randomization (Featherstone & Donovan, 1998; Wendler & Grady, 2008). It is not merely that the idea of random allocation is sophisticated and difficult to conceptualize; patients may have simple disbelief that their physicians are genuinely uncertain about the superiority of one intervention over the other (Robinson, et al., 2005a).

In addition, RCTs may impede patient autonomy. Even if both arms of a study are comparable, patients should continue to possess the right to choose one treatment arm versus another based on their personal preferences or experiences (Kodish, Lantos & Siegler, 1990; Menikoff & Richards, 2006). Analysis of the moral psychology of RCTs from the perspective of the patient is nearly a mirror image of the physician-investigator viewpoint. Patients want their doctors to be experts, and to always know what treatment is best. By definition, the RCT implies that there is no such knowledge. The uncertainty associated with the underlying philosophical basis of the RCT can be terrifying from the perspective of a sick patient who wants his or her doctor to exude confidence. This confidence may even be associated with a therapeutic effect itself, and patients may have an intuitive sense that confronting the reality of medicine’s limits would undermine their confidence in their doctor as healer. This analysis suggests that there is a powerful psychological reason that may compel patients to resist understanding of randomization. The exact same characteristic of RCTs that make them psychologically appealing to physician-investigators carry a troubling negative implication from the perspective of the patient-subject.

If there are two sides of the coin in the moral psychology of randomization, what are the implications for informed consent? Patient-subjects have the right to be fully informed, and to make their own decisions about participation in clinical trials (Menikoff, 2003). Fried

notes that “it is *not* a breach of a fiduciary’s duty to do something that is in conflict with a [patient-subject’s] needs, as long as the fiduciary discloses this fact and gets the [patient-subject’s] consent” (Menikoff, 2003, p. 350, citing Fried, 1974, p. 34).

Physician-investigators must balance their commitment to patient rights and their fiduciary duty to patients with the collective scientific benefits of randomization. Equipoise (both internal and external) remains the quintessential criterion for the ethical conduct of an RCT. But once equipoise conditions are met, much work remains to be done. Honesty in disclosure and explanation of randomization during the consent process must be coupled with assessment of understanding by potential RCT participants. Physician-investigators must take less comfort in the act of randomization, and share with their patients the profound anxiety that comes with the uncertainty around randomization. Uncertainty is part of the fabric of medical practice, but is often implicit (Fox, 1987). Physicians have an understandable desire to protect patients from it. By reassuring patients explicitly and directly that their own well-being will always come before the scientific goals of the research, physician investigators can build trust in the context of the RCT. Training of physician-investigators can be designed to help them recognize and appreciate the specific dilemmas that they may experience in their dual role a clinician and researcher. This can lead to better communication about RCTs and will help as they discuss these issues with patients and families (Yap, et al., 2009).

Conclusion

A key long term goal must be to educate patients as informed consumers about the nature of scientific knowledge and uncertainty regarding medical treatment. While this may reduce faith in physician authority, it will pave the way for empowerment and more open, shared dialogue regarding RCTs in the context of clinical care. By replacing blind trust with a more realistic partnership model, current patients, investigators, and future patients will all be well served.

It is hoped that these suggestions will provide a context for ethically valid and psychologically supportive informed consent for randomized clinical trials. Open dialogue, commitment to an informed consent *process* rather than a single episode, and careful attention to the critical element of trust are the most promising approaches to managing the complex moral psychology of randomized clinical trials.

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