THERAPEUTIC MISCONCEPTION IN CLINICAL TRIALS

Is the Enrollment of a Patient into a Clinical Trial Ethical if the Investigator/Physician and the Patient Suffer from "Therapeutic Misconception?"

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Abstract: Therapeutic misconception occurs when there is a perceived belief that subjects in clinical trials will receive individualized care. This phenomenon has been observed for decades among investigators and subjects. Investigators invoke the "uncertainty rule or clinical equipoise" as the ethical basis for assigning therapeutic merit to clinical trials. This principle reinforces the belief that subjects will receive personalized treatment in randomized controlled trials. Therapeutic misconception gives rise to many ethical issues concerning the validity of the subject's participation in clinical trials. Informed consent, the ethics of medicine, and that of clinical trials, are all relevant factors surrounding this ethical dilemma.

Is the enrollment of a patient into a clinical trial ethical if the investigator/physician and the patient suffer from "therapeutic misconception"?

Literature Review
An ethical dilemma arises when the investigator/physician and the patient suffer from "therapeutic misconception." A "therapeutic misconception" is defined as the belief that experimental treatment aims to promote the patient's interest or individual care. It arises from the conviction that clinical medicine and clinical research are governed by one goal: that the physician will act according to what is "best medical care" for the patient (Appelbaum, 2002). This article will attempt to illustrate the ethical significance of enrollment of a patient into a clinical trial when the investigator and the subject suffer from therapeutic misconception. Three categories will be introduced as relevant to the ethical implications of therapeutic misconception.

Ethics
The principles of ethics in clinical research differ from the ethics of clinical medicine. In clinical research, a physician is expected to conduct the trial in order to address the needs of science with the goal of applying validated scientific information to produce "generalizable knowledge" and improve treatment of future patients. In contrast, a physician in clinical medicine is expected to deliver current scientific knowledge with the duty to promote the best medical interest of the patient (Miller & Brody, 2003).

Informed Consent
Informed consent is a process designed for the protection of human subjects in research. It is of great importance to ensure that subjects who participate in research are made aware of its experimental nature and that they voluntarily consent to participate. The Belmont report is an important milestone in the chronology of events in bioethics. This report delibates the importance of informed consent in application of the "respect-for-persons" principle (The Belmont Report 1979). Among the important considerations in the "respect-for-persons" principle is the requirement that subjects are given the opportunity to decide for themselves if they want to participate in the study after having provided the disclosure that they will be subjected to human experimentation. When a consent form is signed on the false belief that the study provides direct benefit of treatment and individual care, the informed consent is not fully administered.

Therapeutic Misconception
The term therapeutic misconception was originally coined by Appelbaum et al. in 1982 to describe a confusion among physicians/investigators and subjects between the goal of clinical research, which is to gather scientific data for generalizable knowledge, and the goal of clinical medicine, which is to improve the individual's health (Dresser, 2002). A physician or subject who endows therapeutic merit to clinical trials within the context of a physician/patient relationship is suffering from therapeutic misconception.

Since its description, therapeutic misconception has become a common occurrence in clinical research (Appelbaum, Lidz and Grisso, 2004).
In a study to assess the frequency and risks of therapeutic misconception conducted by Appelbaum, Lidz and Grisso (2004) among sample subjects (n=225) from 44 clinical research studies, 61.8% (n=139) of study participants were found to suffer from therapeutic misconception using two variables: the inaccurate belief about individualized treatment and the unrealistic appraisal of impact on benefits.

**Thesis**
The enrollment of a patient into a clinical trial is not ethical if the investigator/physician and the patient suffer from “therapeutic misconception.”

**Statements in Support**
Therapeutic misconception gives rise to certain ethical issues surrounding the validity of the subject’s informed consent and the professional integrity of the investigators. The ethical framework, the ethical and regulatory requirement for informed consent, and therapeutic misconception will follow.

**Ethical Framework**
The lack of understanding of the difference in the ethical framework that governs clinical research and clinical medicine gives rise to therapeutic misconception. This perceived belief by the investigators and the subjects of the experimental intervention as individualized treatment contaminates the ethical basis for departure from the normative practice of clinical medicine to serve the interest of science (Appelbaum, 2002). A physician who strives to assign therapeutic merit to an experimental intervention fails to distinctly separate the goals of medicine from the goals of research. Similarly, a subject who believes that the experimental intervention carries some promise of benefit to individual patients fails to adequately appreciate the difference in assessments of risks and benefits between standard treatment and study treatment. In both cases, there is an apparent obfuscation in the ethical obligations supposedly inherent in physicians/investigators who are participating in the conduct of clinical research.

**Informed Consent: Ethical and Regulatory**
Therapeutic misconception has been an issue of particular interest among medical practitioners, researchers, and patients for over 25 years. It is apparent that therapeutic misconception creates inherent problems surrounding the validity of the subject’s understanding with reference to study participation. In a like manner, it obscures the professional integrity of a physician/investigator by virtue of incoherent belief in support of the therapeutic orientation of clinical trials (Miller & Rosenstein, 2003). To assign therapeutic merit to a clinical trial is to deny its scientific merit. One important measure that is instrumental to mitigating the problems associated with therapeutic misconception is the informed consent process. Informed consent is a matter of ethics and federal regulation. From an ethical perspective, informed consent in clinical research contains three basic essential elements: that the participant must be informed about the study including its risks and benefits, understand the information, and enroll voluntarily (The Belmont Report, 1979). Specific regulation exists regarding informed consent. The Code of Federal Regulations (21 C.F.R. Part 50.25) requires that the consent form explicitly states that the study involves research and the purpose and procedures surrounding the study design are experimental. This information is pertinent to the current issue of the ethical implications of therapeutic misconception. This federal guideline reinforces the scientific orientation of clinical research. The language of the informed consent must be such that it does not promote but instead reduce therapeutic misconception.

**Therapeutic Misconception**
Therapeutic misconception contribute to the confusion among researchers and subjects about scientific methods such as randomization and placebo controls, assessments of risk, and benefits of participating in clinical research. This confusion is an ethical issue owing to the lack of understanding essential to the subject’s ability to make a meaningful decision to participate in clinical trials. Added to the subject’s therapeutic misconception is the physician’s own perception of the therapeutic merit of clinical research (Miller & Rosenstein, 2003). It is a natural course for subjects in the clinical setting to depend on the physician’s decision and ability to provide treatment within the context of the physician/patient relationship. Subjects are more vulnerable to failure to comprehend the nature of clinical research when investigators foster a similar predicament. While it is true that a subject may receive good clinical care as a participant in research, this clinical care must not be confused with the goals of clinical research which is to generate scientific knowledge to improve therapy for future patients (Henderson et al., 2007). The resultant enrollment of subjects to clinical trials when the subject and the investigator compound the confusion by labeling clinical research as a therapeutic intervention is unethical. Regardless of whether or not a direct benefit is accrued due to study participation, the belief that individualized care is a component of clinical trials is false. The confusion by the investigator and the subject which parallels misunderstanding of the purpose of clinical research constitutes therapeutic misconception. Consequently, subjects who harbor therapeutic misconception fail to fully give an informed consent (Miller and Joffe, 2006). A subject’s study
participation based on this unrealistic optimism is faulty and raises ethical questions.

**Statements in Opposition**
The major viewpoints against the significance of therapeutic misconception will be presented in three categories: the clinical equipoise, informed consent, and randomized controlled trials.

**Clinical Equipoise – A Dominant Ethical Viewpoint**
Clinical equipoise which attempts to validate the therapeutic orientation of clinical research has become a predominant ethical view among medical experts. Clinical equipoise exists when there is clear uncertainty among medical experts about the availability of an effective treatment (Miller & Brody 2003). In this case, the prevailing perspective is one where a physician must execute clinical research with therapeutic intent such that an experimental intervention is considered a “best possible treatment.” Investigators may allow the principle of beneficence and nonmaleficence to govern: that a physician must serve the interest of the patient by providing best individualized treatment and avoiding disproportionate risks associated with the treatment (Miller & Rosenstein, 2003). Thus, there exists no distinction between clinical research and clinical medicine when a state of clinical equipoise prevails.

**Informed Consent**
Among the reasons for arguing against the necessity of enforcing the informed consent process in randomized controlled trials is the presence of the state of “uncertainty” principles in the medical community. The argument is that when there is no known effective treatment, physicians/investigators may exercise judgment as they would in clinical medicine to enroll patients in randomized controlled trials. The ethical implication is that physicians have the duty to discharge their therapeutic obligations by enrolling patients in randomized controlled trials. Truog, Robinson, Randolph, and Morris (1999) argue that the current requirement for administering an informed consent in specific experimental interventions (e.g., randomized controlled clinical trials) is unnecessary particularly when a clear state of clinical equipoise exists. The other reasons Truog et al. (1999) find important in support of the argument that informed consent be waived under certain circumstances are when treatments offered in the trials are available off trial, the trial treatments involve no more than minimal risk compared to alternative therapies, and that the subject should have no reason to believe that one trial treatment is preferable over another.

**Randomized Controlled Trials – Therapeutic Intervention**
The ethical considerations surrounding the administration and conduct of randomized controlled trials (RCT) within the context of standard of care was examined to distinguish if these trials warrant the application of the standards of clinical medicine (Miller & Silverman, 2004). A RCT sponsored by the acute respiratory distress syndrome (ARDS) network was used as an example to illustrate the ethical significance of the therapeutic obligations by physicians in light of the “uncertainty rule” the clinical equipoise adopts. The trial was designed to evaluate two contrasting methods (low VT intervention vs. high VT intervention) of mechanical ventilation without the inclusion of proper control for acute lung injury (ALI) and ARDS. The prevailing routine practice was not considered to represent the control arm because it was not validated by evidence from RCTs. The premise that there is no validated standard of care for the medical condition indicated was made the basis for conducting the RCT by the ARDS network without the addition of the control arm. In the example provided, a state of clinical equipoise was invoked which rendered the therapeutic misconception insignificant. Where there is uncertainty among medical experts regarding the prevailing treatments or therapeutic interventions, no new treatment serves as inferior treatment. Hence, the experimental intervention gains therapeutic merit in light of the physicians/investigators duty to discharge their therapeutic obligations as they would in standard practice to ensure the medical health of the study participants.

**Refutation of Opposing Arguments**
Since my thesis supports that therapeutic misconception is unethical, the following statements refute the prior argument.

**Clinical Equipoise – A Dominant Ethical Viewpoint**
The predominant view on “uncertainty rule” or clinical equipoise as a basis for assigning standard care orientation to clinical trials is an example of therapeutic misconception (Miller & Brody, 2003). Clinical research is a knowledge-generating activity. In contrast, clinical medicine is a patient-centered activity (Miller & Joffe, 2006). Even in a state of clinical equipoise, an investigator in clinical trials is bound to adhere to a protocol design which may require study procedures that may not necessarily be undertaken in the standard of care setting. Study procedures such as dose-tapering of current medication, venipuncture or diagnostic imaging that are required to carry out the experimentation may have some inherent risks to the subject. These procedures need to be performed as part of the scientific standards in clinical trials. It is clear that clinical trials are designed for the purpose of accumulating a wealth of knowledge that may have no direct benefit to the subjects but may be beneficial to future patients. In contrast, a physician
in clinical medicine reserves the right to exercise discretion in whether or not to perform procedures that may potentially cause harm to the patient.

Informed Consent
The argument presented by Truog et al. (1999) that informed consent is not necessary when a physician/investigator exercises the duty to discharge his therapeutic obligations in randomized controlled trials exemplifies therapeutic misconception. It is important to establish whether or not a randomized controlled trial is a practice governed by the ethical principles of medicine or research. It is conclusive that a randomized controlled trial is experimental in nature, designed to address a scientific question, and must be governed by the ethical principles attributed to clinical research (Miller & Brody, 2003). The Nuremberg Code provides ethical directives to incorporate as a requirement voluntary consent prior to any human experimentation (Miller & Joffe, 2006). Therefore, the informed consent as a key legal instrument of bioethics must apply. The language must be such that the subject fully comprehends that a clinical trial is scientifically designed which may or may not have direct individual benefits. An investigator who fails to appreciate the consent process in RCT suffers from therapeutic misconception. The informed consent is an important tool to protect human subjects from the potential exposure to exploitation in research as in the case of therapeutic misconception. A subject who harbors therapeutic misconception fails to fully give an informed consent (Miller and Joffe, 2006).

Randomized Controlled Trials – Therapeutic Intervention
Whenever physicians, researchers, or patients misinterpret the primary purpose of randomized controlled trials as therapeutic, a state of therapeutic misconception occurs. The ARDS and ALL1 trials sponsored by the ARDS network invoked the clinical equipoise principle to legitimize their actions in discharging therapeutic obligations inherent in standard of care (Miller & Silverman, 2003). However, randomized controlled trials differ from medical care in terms of purpose, methodology and risk/benefit assessment (Miller & Rosenstein, 2003). In clinical trials, certain research-based interventions which may pose risks or the potential to cause injury to the subjects are required to validate the scientific purpose of the study. In clinical medicine, these interventions are discretionary based on the physician’s judgment of the patient’s medical needs. The fundamental differences in methodology warrant two distinct sets of governing ethical and regulatory frameworks. Therefore the ethical and regulatory principles of clinical research must govern the design and conduct of randomized controlled trials.

Conclusion
Clarity on the nature and meaning of human experimentation and applications of the principles of research ethics help reduce the occurrence of therapeutic misconception. The enrollment of patients into clinical trials is not ethical if the investigator/physician and the patient suffer from “therapeutic misconception”. The distinction between the ethical framework governing clinical medicine and clinical research must be clear to guard against fostering therapeutic misconception. The informed consent and the appropriateness by which it is administered are important measures to mitigate or dispel therapeutic misconception.

References