

**Ethical Issues Regarding Clinical Trials:
Treatment Group Vs. Observation Group**

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Abstract

Glaucoma clinical trials involving a treatment group versus an observation group were analyzed to uncover any ethical issues in study design. The decision as to whether or not these clinical trials should be allowed was then examined from a utilitarian and rights theory view point. From a utilitarian view point, glaucoma clinical trials that have observation groups are ethical, since more stakeholders will potentially benefit from the data they generate. When looking at them from a rights theory view point, these clinical trials are unethical because they fail to take each individual's wellbeing into account. Since medicine seeks to improve the health of individuals, these findings suggest that rights theory must take precedence in the design of glaucoma clinical trials.

Ethical Issues Regarding Clinical Trials: Treatment Group Vs. Observation Group

As part of the U.S. Department of Health and Human Services, the National Institutes for Health (NIH) are responsible for conducting and supporting medical research. One department within this federal agency is the National Eye Institute (NEI), which supports research that helps to prevent and treat eye diseases and disorders of vision. Their primary goal is to conduct research that leads to sight-saving treatments, reduce visual impairment and blindness, and improve the quality of life for people of all ages. Their research has greatly advanced our knowledge of how the eye functions in health and disease.

Over the past decade, numerous NEI trials have centered around glaucoma. Studies show that glaucoma is a leading cause of blindness worldwide. In fact, they estimate that 2.5 million people in the United States have glaucoma and that more than 130,000 people are legally blind from the disease. Surveys have indicated that less than 50% of those with glaucomatous visual field loss have received an appropriate diagnosis or treatment (Kass, 2002). All current treatment for glaucoma aims at reducing intraocular pressure (IOP), but indications for therapy are not well defined. Likewise, experts within the medical community are unclear on the factors that influence glaucoma progression and there is no consensus on whether to treat glaucoma early and aggressively. Therefore, the NIH has conducted several studies that quantify the risk of progression for patients receiving treatment at various stages throughout their disease. For example, the Early Manifest Glaucoma Trial (EMGT) looked at the ramifications of not treating glaucoma. The purpose was to compare the effect of immediate therapy to

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lower IOP verses late or no treatment on the progression of newly detected glaucoma. For six to nine years, three hundred patients were randomized to treatment or observation. During this time period, half of the patients in the observation group suffered irreversible optic nerve damage and visual field loss (Leske, 2003). It is clear from the purpose of this study that the investigators knew that the disease of the observation group would progress and that early diagnosis and rapid detection of progression are important to limiting irreversible nerve damage.

According to utilitarian and rights theory, this paper will examine whether or not randomized clinical trials (RCTs) are ethical if the investigators knowingly randomize patients into the obviously inferior observation group verse the treatment group. Some clinical trials force investigators to randomize patients to risks that are not reasonably expected to bring compensating benefit; however, the clinical investigators must safeguard the interests of patients involved in the clinical trial, while also protecting society from overzealous and premature claims of treatment benefit.

When examining this dilemma, we find that there are several stakeholders involved in this decision: Clinical trial investigators, trial enrollees, providers, regulatory agencies, payers, pharmaceutical manufacturers, and society. To achieve medical advancements in glaucoma treatment, we need to determine when it is appropriate to treat glaucoma. In order to accomplish this, decision makers will need to choose between the following options: (1) Conduct randomized clinical trials with a treatment and observation group or (2) Analyze retrospective patient data.

Utilitarian Lens

Utilitarian moral theory is rooted in the principle of “Doing the greatest good of the greatest number.” This means that people who follow this principle must achieve the greatest quantity of intrinsic good. Therefore, this suggests that utilitarian moral theory is based on a cost/benefit approach to morality because it requires that we compare alternative decisions based on the amount of damage and/or satisfaction each choice will bring to the human interest of the involved parties.

Figure 1 on page six illustrates the risk/benefit of both decisions for each stakeholder. The clinical investigators benefit the most from decision 1 because it provides them with the most accurate and reliable data for their analysis, because retrospective data analysis is often incomplete. However, it is important to note that they could gather good information from retrospective analysis as well. Data sets from hospitals, physician groups, and private practices would need to be detailed and complete in order to be considered reliable. The enrollees gain the most benefit from decision 2 by not enrolling in this trial because there is a 50% chance for them to experience irreversible optic nerve damage that will eventually lead to blindness, thus infringing on their quality of life and future happiness. In fact, current medical research shows that, depending on intraocular pressure readings, patients could experience visual field defects in as little as one year (Leske, 2003). Medical providers will benefit the most from the most reliable and detailed information in order to make informed treatment decisions, so the RCT data is a clear choice. Likewise, regulatory agencies, payors, and pharmaceutical manufacturers are seeking the same reliable and in-depth information that RCTs provide in order to make economic decisions. Finally, the general public wants to know that their friends and family members are protected from harm in clinical trials, as well as receive the best medical treatments from providers. Therefore,

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they would receive slightly more benefit from decision 2 because there is no harm to trial enrollees, yet data is still analyzed to help providers make informed treatment decisions for future glaucoma patients.

Figure 1

Stakeholders	Decision 1	Decision 2
Clinical Investigators	Green	Yellow
Trial enrollees	Red	Green
Providers	Green	Yellow
Regulatory agency (NIH/FDA)	Green	Yellow
Payors	Green	Yellow
Pharmaceutical manufacturers	Green	Yellow
Society (general public)	Yellow	Green

Green= best, **Yellow**= neutral/less desirable, **Red**= bad

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From a utilitarian cost/benefit stand point, the best choice appears to be decision 1. However, this could cause debate because the loss of the minority (the enrollees and general public) could be enough to tip the scales in favor of decision 2, since utilitarian theory is not merely a majority rule vote. The issue is that it is hard to measure a person's aggregate happiness against another person's. The following stories illustrate the idea of "aggregate happiness". A young boy has been begging his mother for one of the latest action figure heroes, RoboMan. Finally after several months of pleading, he receives a ten dollar bill from his mother to buy RoboMan on his way home from school. During the day, one of the boy's classmates goes into his bag and steals his ten dollars. On his way home he stops by the toy shop, locates RoboMan, and takes the package up to the checkout counter. Soon the boy realizes that someone has been in his bag and took his ten dollars. Now take for example a young man who finds himself in a similar situation. A young man is a product manager at a pharmaceutical company. He keeps a ten dollar bill in his car so he can stop by the gas station once a week to buy lottery tickets. One day, he accidentally leaves his car door unlocked, and someone goes inside and steals his money. Notice that both individuals suffered the loss of ten dollars; however, who experienced the greatest decline in aggregate happiness due to the loss of their ten dollar bill- the young boy or the young man? A strong case can be built to suggest that the young boy suffered the greatest loss because of the value he placed on that ten dollars and how rare it was to receive that sum of money. In contrast, the young man has a well paying job and can easily replace his ten dollars, which places less value on it in his eyes. Nevertheless, what if the young man lost five hundred dollars? The amount of value that an individual places on something becomes a key consideration when truly evaluating aggregate happiness.

Rights Theory Lens

The function of rights theory is to protect individual interests from detrimental majority rule decisions and the harmful acts of others. When discussing the rights of people in clinical trials, the idea of “equipoise” comes into play. In 1987, Benjamin Freedman used the principle of equipoise to focus on the ethics of medical research that involves patients that are placed in different treatment arms (Freedman, 1987). Essentially, equipoise is satisfied when there is genuine uncertainty in the medical community, not just a single investigator, regarding the preferred treatment. This allows clinical trial investigators to run a clinical trial until they have enough empirical evidence to convince the community of their results without treading into unethical territory. In the context of this paper, the concept of clinical equipoise or the “uncertainty principle” is an ethical principle that states that a subject may be enrolled in a randomized controlled trial (RCT) only if there is true uncertainty about which arm in the trial is most likely to benefit the patient (Merritt, 2005). The uncertainty protects patients from knowingly being exposed to inferior treatments, yet it still leads to therapeutic advancements in clinical medicine. Also, with clinical equipoise, HCPs within the medical community truly disagree on treatment protocols. The EMGT trial does not align with this principle, in fact, the NIH, FDA, and Nuremberg code do not require equipoise (Djulgovic, 2009). Alternatively, these groups only adhere to the Declaration of Helsinki. In 1964, the World Medical Association (WMA) developed the Declaration of Helsinki to clearly state the ethical principles of medical research that involve human beings (WMA, 1964). The declaration mentions the duty of physicians to safeguard the health of their patients and to consider their patient’s health as their primary concern. However, nowhere does it

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mention equipoise or the principle of uncertainty, which leaves a gray area when considering the ethics of certain randomized clinical trials. It is important to note that, equipoise is essential to consider clinical trial design from the patient's perspective. In randomized clinical trials involving glaucoma patients, both treatment arms have their own potential benefits and risks; therefore, the patient's current disease state is a key factor in the recruitment process regarding the associated risks.

The equipoise principle has merit even though it has a rigid definition. In the case of the EMGT trial, the investigators knew that treatment would delay the progression of glaucoma, but they still designed the study with an observation group so that they could quantify the magnitude of the damage. Decision 1 adheres to three principles: (1) Autonomy- patients are capable of self-determination and must be granted the use of it, (2) Beneficence- the study design maximizes benefits and minimizes risks to patients, and (3) the risks to patients must not outweigh the sum of anticipated benefits to the rest of the stakeholders. Nevertheless, decision 2 upholds the basic and derivative right for individuals not to be harmed. If we took each individual into account, decision 2 would be the clear choice because data could still be collected using retrospective analysis in order to help HCPs make treatment decisions. Therefore, decision 2 is the best choice through the rights theory lens, because clinical investigators know that the observation group will be harmed and decision 1 places these patients in harm's way.

Conclusion

After conducting this analysis on the utilitarian lens verse the rights theory lens in the case of glaucoma clinical trials, we find that treatment group verses observation group trials with or without equipoise is possibly ethically acceptable according to utilitarian theory and ethically unacceptable according to rights theory.

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In the late 5th century BC, Hippocrates wrote one of the world's oldest binding documents, The Hippocratic Oath. Hippocrates is often seen as the father of western medicine, and his oath was historically taken by physicians who vowed to practice medicine ethically. Even though this is an ancient document, many physicians still view this as a sacred document today. Physicians are determined to treat ailing individuals to the best of their ability, respect patient's privacy, and advance medicine by imparting knowledge to the next generation of physicians. One of the first vows in the oath is, "I will apply dietetic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice." (Tyson, 2001) The words, "I will keep them from harm and injustice" ring loud and clear in medicine today. Clinical researchers realize that the practice of medicine should be centered around the treatment of individuals, hence the current design of randomized clinical trials. In addition, there is a vow in the oath that states, "I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person's family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick." (Tyson, 2001) Every health care provider and clinical researcher must remember that their primary responsibility is to treat individual human beings and to "do no harm". This higher responsibility suggests that, as seen through the rights theory analysis, decision two is a better option in clinical trials that involve a treatment group versus an observation group.

Therefore, as decision 2 recommends, a better method for obtaining the unknown effects of delayed glaucoma therapy would be to collect medical records of healthcare professionals for patients in their files and compile that data over several years in different geographic areas to assess the effects of various treatment interventions at different disease stages. This will allow science to achieve the objective of therapeutic advancements in clinical medicine while protecting trial enrollees from

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unnecessary harm. However, this could raise concern among HCPs regarding their treatment decisions and could lead to unwanted malpractice lawsuits when the standards of care from different providers are compared and evaluated. Nevertheless, this could ultimately lead to stronger industry wide adherence to evidence based medicine and aid in aligning standards of care with medical specialties, which will benefit our society as a whole.

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