First in Human Trials: Analyzing Ethical Standards

A Research Paper submitted to the Department of Engineering and Society

Presented to the Faculty of the School of Engineering and Applied Science
University of Virginia • Charlottesville, Virginia

In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science, School of Engineering

Sophia Kerns
Spring 2022

On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

Advisor
Joshua Earle, Department of Engineering and Society

First in Human Trials: Analyzing Ethical Standards

INTRODUCTION

In 2006, a first in human clinical trial involving an immunotherapy drug (TGN1412) resulted in the hospitalization of all six trial volunteers in the ICU (Attarwala, 2010). Following this disaster, analysis revealed that the animal model used for preclinical research had a key difference from research on human immune systems (Eastwood et al., 2010). Translating treatments from animals to humans will always carry risks; however, more information on the differences between animal models and humans could help prevent failed trials. This is a poignant example of how important it is to regulate the transition from preclinical to clinical trials, especially in First-in-Human (FIH) trials.

Clinical trials are subject to regulations set out by the FDA. These include regulations beginning in preclinical research to make sure treatments will be safe for humans. The FDA has Institutional Review Boards (IRBs) that evaluate preclinical evidence to approve or deny requests to begin clinical trials, mainly aimed at confirming trial safety (Research, 2019). Considering that 60% of FIH clinical trials fail, these regulations are not accurately predicting which studies will be successful (Van Norman, 2019). Although IRBs are there to keep people safe, measures should be improved to look into improving the number of trials that are successful. Studies have also shown that certain population groups, especially women and racial minorities, are underrepresented in clinical trials (Clark et al., 2019; Liu & Mager, 2016). Other studies have shown that informed consent does not give patients a good of an understanding of trial risks (Bazzano et al., 2021). This lends the question: are the current standards for FIH clinical trials ethical?

METHODS

I will evaluate the ethics of current FIH trials in four parts. First, I evaluate historical codes of ethical experimentation. Second, I evaluate the preclinical to clinical research pipeline. Third, I discuss the issue of informed consent. Finally, I evaluate literature on patient populations in clinical trials. I evaluate each of these things through three ethical lenses: the utilitarian ethical lens, the Kantian ethical lens, and the care ethic lens.

Most FIH trial ethics are currently based around utilitarian frameworks that prioritize the greater good over individual rights (Michelle Habets, 2017). By this logic, an action is deemed ethical if it results in more good for society than harm. In some ways, this ethic has to be used to justify doing any clinical trials at all. Putting patients in harm's way at any level can only be justified if there is a high chance of results that benefit society at large. However, this ethical lens can be dangerous when enacted alone. Given that it does not leave much space for individual rights, utilitarian ethics needs additional provisions to protect individuals. The next two ethical frameworks can serve this purpose.

Kantian ethics focuses on the categorical imperative, which is the set of rules that all people should be expected to follow at all times. It is highly rational (Ibo Van de Poel & Lamber Royakkers, 2011; Johnson & Cureton, 2021). Kantian ethics sees people as inherently valuable creatures regardless of what they contribute to society (Ibo Van de Poel & Lamber Royakkers, 2011). It also sees "right" as something which can be rationally determined. In contrast to the utilitarian ethic, people cannot be used poorly for the greater good in Kantian thinking. This ethic follows the "golden rule" of treating others as you would like to be treated.

The care ethic is focused on relationships rather than on actions (Skoe, 2014). This ethic sees people as connected beings. It was originally developed in the context of gender studies (Carol Gilligan, 1982). In Carol Gilligan's own words,

> "An ethic of care directs our attention to the need for responsiveness in relationships (paying attention, listening, responding) and to the cost of losing connection with oneself or with others. Its logic is inductive, contextual, psychological, rather than deductive or mathematical."

This ethic is important to consider as it highlights doctor and patient relationships. These relationships are critical for areas such as informed consent, which requires that clinicians effectively communicate the expectations and risks involved in clinical trials. Another expansion of this ethic can be seen in The Logic of Care by Annemarie Mol. This interpretation of care ethics encourages doctors to adjust their care to the patient in the hopes of encouraging them to do their best to care for themselves (Green, 2014). This ethic is even more in contrast to utilitarian ethics as it focuses not just on prioritizing individual rights but also relationships between individuals.

CURRENT CODES OF CONDUCT: A HISTORICAL PERSPECTIVE

The above ethical codes fit well into the codes of ethics used by the scientific community. Current ethical codes were developed in response to horrific experiments done on unwilling participants by Nazi scientists during World War II (Hope & McMillan, 2004). This sort of experimentation is a pure application of the utilitarian code of ethics. Nobody would ever volunteer to participate in such horrific experiments, but the information gained may still be valuable to society. By utilitarian ethics, the good of the society outweighs the good of the individual, so the pain of one person is justified for the good of many. Two codes, the Nuremberg Code and the Declaration of Helsinki, were developed in contrast to utilitarian thinking to protect the rights of the individual.

The Nuremberg Code highlights tenants such as individual autonomy and experimental outcomes justifying risks (*Nuremberg Code - History - Office of NIH History and Stetten Museum,* n.d.). Key components include voluntary participation in the experiment and the right to withdraw from the experiment at any time. This is a shift from the thinking that early experimenters used to justify their human trials, which attempted to simplify people to the sum of their biological components (*Fifty Years Later: The Significance of the Nuremberg Code | NEJM,* n.d.). Kantian and care ethics align with the underpinnings of this code. By Kantian ethics, the individual should have the right to choose what is best for them and whether they wish to be a part of any experiments throughout the experiment duration. Care ethics requires that doctors and patients maintain a good relationship. This code was developed to ensure that doctors and patients work together with mutual trust in order to safely conduct needed medical experiments.

The main principle of the Declaration of Helsinki is prioritizing the health of the patient. Another consideration is that doctors must be confident that risks can be managed, and that they should be constantly observing the risk factors (*WMA - The World Medical Association-WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*, n.d.). This declaration also lays out rules for informed consent. This declaration aligns well with both the Kantian and care ethics. Ensuring that the good of the individual is protected and that doctors inform their patients of risks are critical to maintaining ethical practices in both frameworks.

Utilitarian ethics justifies current experimental practices. Utilitarianism does not take the individual into account, and instead it protects the rights of the clinicians more than the rights of the individual. Clinicians can be designated as those working towards the greater good, as their

experiments will hopefully provide needed information to improve medical care. However, these rights should not violate the rights of the individual.

THE PRECLINICAL TO CLINICAL TRANSLATION

Codes of ethics have informed many of the rules for FIH and later stage clinical trials today. Viewing the ethics of FIH trials through a scientific lens is critical to analyzing how current practices can be improved. Beyond individual autonomy, clinical trials should also be extremely well informed and have a high chance of success.

In FIH trials, only 60% of drugs pass the requirements to move on to the next stages. Of those that do pass, 89% fail later on, mostly because they end up having unpredicted toxicity levels (Van Norman, 2019). On average, 50 drugs are approved and 1279 drugs are recalled every year ("FDA Drug Recall Statistics," 2021; Mullard, 2022). The recall rates as opposed to the approval rate shows that many drugs in the past should not have been approved.

One reason for the high failure rate can be seen in the immunotherapy drug TGN1412 as mentioned earlier. This drug was tested in a macaque model, which is a primate animal model that is often used in preclinical studies. Based on the similarity in genetic makeup of this model to humans, it seems that this model should be as good as it gets in terms of mimicking the immune system of humans (Messaoudi et al., 2011). However, even the best animal models are not 100% accurate in representing humans. In this particular case, a difference between the immune systems of the animal models and the human system resulted in severe adverse effects for patients. Improving understanding of the differences between models and humans would be a valuable tool to speeding up clinical trials and improving the percentage of drugs that pass initial trials.

One problem on the clinical side is that FIH trials are not expected to benefit the patients. The primary purpose of FIH trials is dose escalation, which determines the safe dose for a drug in human trials. This is a critical first step to ensure that larger patient cohorts are not at risk of toxic effects. In addition to dose escalation, many FIH trial participants, especially in cancer studies, had received prior treatments which may alter the results of the new treatment (Paluri et al., 2020). One study found that FIH cancer trial participants had a poor 90 day mortality rate (Paluri et al., 2020). The last resort nature of these participants means that results may not indicate how well a treatment would work on a recently diagnosed cancer patient. The results may be somewhat skewed by previous treatments which impacted the immune system in a myriad of ways. However, improving upon this is difficult, as giving new patients or healthy patients a cancer drug is not acceptable due to the damage it could do to the body.

Another example of a failed study is the BIA 10-2474 study, which was a drug meant to treat neuropathic pain (Kaur et al., 2016). Although similar drugs had been approved, this drug had a key difference which resulted in severe brain damage in several of the patients in the cohort. This was made worse by the fact that, although clinicians observed adverse effects of the drug, they continued on to the next dose rather than seeking to understand the reason for these adverse events (Kaur et al., 2016). An additional problem with this study is that other scientists were not sure that the drug was safe for humans, even saying that they suspected it was a bad compound (*New Clues to Why a French Drug Trial Went Horribly Wrong*, n.d.). Additional tests following the failed trial revealed that the compound interfered with targets that were unintended (Kaur et al., 2016). However, if these tests were able to diagnose the problem, they also would have been able to predict it. Any and all tests that could be done to fully understand how the treatment interacts with human systems should be done prior to putting the treatment in humans.

Current efforts to improve this sort of testing include organ-on-a-chip technologies. Continued development of these sorts of technologies should be supported to give more backing to preclinical data. This is a prime example of how volunteers need to be informed of the risks of the study they are taking on, and also have basic rights to care should they experience adverse events.

From an ethical perspective, it is important to make sure that practices accurately predict how successful any experimental treatment may be. This is important for maintaining trust between patients and clinicians (care ethic). This sort of understanding can help clinicians work with individual patients to ensure their safety. It is also important for the Kantian ethic, as any person would want to be ensured that their participation in a trial will result in a positive impact for society. The area of cancer treatment specifically is one area where the utilitarian ethic is required. Given how damaging chemotherapeutics and other cancer treatments are to the body, giving any new cancer treatment to a person, even a person who has run out of options, has to be justified by the greater good of society. Combining all three ethics can help to both allow for experimentation and watch out for individuals.

INFORMED CONSENT

As outlined in the Declaration of Helsinki, informed consent is a critical component of making sure that patients are ethically treated. This principle requires that patients be informed of all of the risks associated with participation in the experiment, and knowledge of what could be done to them throughout experimentation. Current standards of informed consent fail less informed patients as they are convoluted documents (Bazzano et al., 2021). Efforts to improve patient understanding of informed consent has resulted in 20+ page documents. While these documents include lots of information, this is too much for the average volunteer to understand

(Bazzano et al., 2021). In addition, most informed consent documents are written at around a tenth grade level, while the average American adult reads at an eighth grade level (Zimmermann et al., 2021). Based on this, the average clinical trial volunteer does not have the skills to be able to understand informed consent documents. It is important that volunteers fully understand the risks and potential consequences to which they have agreed. Current pushes towards "plain language" consent forms are aimed at making forms more accessible to the average person and bridging the communication gap between doctors and patients. Educating doctors and clinicians to effectively communicate to the average clinical trial participant will help to improve these informed consent documents and to create a system of trust.

By the utilitarian ethic, informed consent practices are in good shape. Experiments are overall resulting in more good to society than harm, and a lack of knowledge of the risks for an individual does not change this. The Kantian ethical lens asserts that the informed consent processes are not ethical. Kantian ethics requires that people be treated as ends in and of themselves. This means that informed consent efforts should be fully informing people of the risks and aiming to equip people to make the best decision about participation for themselves. The care ethic also reveals issues in informed consent. Convoluted documents do not establish a positive relationship between clinicians and the public. In fact, these sorts of documents breed distrust of the medical system as a system that is not accessible to the average person. This ethic also supports doctors taking the time and effort to cultivate a relationship with their patients in a way that meets them where they are. No matter what the patient's level of literacy or medical understanding, clinicians should be trained to meet the patient level of understanding.

PATIENT POPULATIONS IN CLINICAL TRIALS

Understanding how diverse patient groups react to treatments is a critical step to building a robust treatment. One in five drugs have varied responses in different racial groups; however, minority groups are underrepresented in clinical trials (Clark et al., 2019). There are also gender disparities, as trials often tend to use healthy young men (Dresser, 2009; Koonrungsesomboon et al., 2016). This results in most clinical trial results being skewed towards young to middle aged men. Although racial disparities are a huge issue in clinical trials, gender disparities will be examined as an example here.

Women have some different biological processes than men and lower average height and body weight. However, in 2009, 64% of studies did not stratify their results by sex (Liu & Mager, 2016). Some studies limit first applications to men, citing a lack of reproductive toxicology reports to protect women (reMYND, 2021). Additionally, dose escalation experiments with men do not accurately represent the dosing that is healthy for women (Liu & Mager, 2016). The lack of female representation in these studies poses an issue, as women will eventually be exposed to the drug in larger patient cohorts with more people at risk. In addition, a lack of information on how the drug impacts women could provide difficulties once it is released to the public.

By utilitarian ethics, a lack of representation in studies could be considered ethical. Although some groups may not be as well represented as others, the majority of people are being served, and it is easier to recruit volunteers from the white male population. Using the most easily recruited volunteers speeds the process of completing trials. In fact, prioritizing diversity in trials may slow the progress of promising drug development. By the Kantian ethics lens, any individual beginning to take a drug would want their demographic group to be represented in the

study. This is the most logical way to ensure that a drug will be safe and effective for any given individual. In addition, including different groups in trials shows that they are valuable groups worthy of care. By the care ethic, it is important that there is a sense of trust between people and the clinical trial process. While a lack of representation may be partially due to an existing lack of trust between certain groups and the medical system, a continued lack of representation can only exacerbate this problem. Ensuring that a treatment is safe for everyone can help build back trust in the medical system.

CONCLUSIONS-WHAT CHANGES SHOULD BE MADE?

FIH clinical trial practices are in need of improvement, which can be achieved through Kantian and care ethics. These ethics demand that individual rights be respected and that there be better representation in the trials. By the utilitarian ethic, FIH clinical trial practices are in good shape. The greater good is served through the clinical trial process. Each of these ethical frameworks alone cannot result in a clinical trial system that is both robust and respectful. Together, all three ethical lenses can provide a fuller ethical framework for medical advancement. Combining the ideas of serving the greater good while respecting the individual into one framework could help to solve the seeming contradiction between the two and work to shape FIH clinical trial practices.

Scientists as a whole can invest more time into understanding the differences between animal models and humans. While this may remove some resources from new treatment development, it could serve scientists better in the long run and help smooth the transition from preclinical to clinical research. This would help to make sure that no human volunteers are put in more danger than required. It could also end up speeding preclinical research processes in the long run.

Second, informed consent documents can be changed to make sure that study participants better understand what they are volunteering for. Placing a greater emphasis on doctor communication could help to solve this issue by matching language to the population literacy. Establishing trust will result in a better system overall.

Finally, disparities in patient population demographics need to be improved. Clinical trial cohorts should match the target population of the drug. If the drug is meant for the whole population, then the patient cohort should match this population demographically.

Making changes to the system would take significant effort to implement. However, making these sorts of changes to the FIH trial standards could result in better outcomes both for patients and for companies. Beyond protecting patients, practices that reduce failed trials and recalls will help everyone in the long run.

REFERENCES

Attarwala, H. (2010). TGN1412: From Discovery to Disaster. *Journal of Young Pharmacists : JYP*, *2*(3), 332–336. https://doi.org/10.4103/0975-1483.66810

Bazzano, L. A., Durant, J., & Brantley, P. R. (2021). A Modern History of Informed Consent and the Role of Key Information. *Ochsner Journal*, *21*(1), 81–85. https://doi.org/10.31486/toj.19.0105

Carol Gilligan. (1982). *In a Different Voice*. Harvard University Press.

Clark, L. T., Watkins, L., Piña, I. L., Elmer, M., Akinboboye, O., Gorham, M., Jamerson, B., McCullough, C., Pierre, C., Polis, A. B., Puckrein, G., & Regnante, J. M. (2019). Increasing Diversity in Clinical Trials: Overcoming Critical Barriers. *Current Problems in Cardiology*, *44*(5), 148–172. https://doi.org/10.1016/j.cpcardiol.2018.11.002

Dresser, R. (2009). First-in-Human Trial Participants: Not a Vulnerable Population, but Vulnerable Nonetheless. *The Journal of Law, Medicine & Ethics : A Journal of the American Society of Law, Medicine & Ethics*, *37*(1), 38–50. https://doi.org/10.1111/j.1748-720X.2009.00349.x

Eastwood, D., Findlay, L., Poole, S., Bird, C., Wadhwa, M., Moore, M., Burns, C., Thorpe, R., & Stebbings, R. (2010). Monoclonal antibody TGN1412 trial failure explained by species differences in CD28 expression on CD4+ effector memory T-cells. *British Journal of Pharmacology*, *161*(3), 512–526. https://doi.org/10.1111/j.1476-5381.2010.00922.x

FDA Drug Recall Statistics. (2021, July 1). *May Lightfoot, PLLC*. https://www.maylightfootlaw.com/blogs/fda-drug-recall-statistics/

Fifty Years Later: The Significance of the Nuremberg Code | NEJM. (n.d.). Retrieved January 30, 2022, from https://www.nejm.org/doi/full/10.1056/nejm199711133372006

Green, S. (2014). Logic of care. *Canadian Family Physician*, *60*(8), 708.

Hope, T., & McMillan, J. (2004). Challenge studies of human volunteers: Ethical issues. *Journal of Medical Ethics*, *30*(1), 110–116. https://doi.org/10.1136/jme.2003.004440

Ibo Van de Poel & Lamber Royakkers. (2011). *Ethics, Technology, and Engineering* (1st ed.). Wiley-Blackwell.

Johnson, R., & Cureton, A. (2021). Kant's Moral Philosophy. In E. N. Zalta (Ed.), *The Stanford Encyclopedia of Philosophy* (Spring 2021). Metaphysics Research Lab, Stanford University. https://plato.stanford.edu/archives/spr2021/entries/kant-moral/

Kaur, R., Sidhu, P., & Singh, S. (2016). What failed BIA 10–2474 Phase I clinical trial? Global speculations and recommendations for future Phase I trials. *Journal of Pharmacology & Pharmacotherapeutics*, *7*(3), 120–126. https://doi.org/10.4103/0976-500X.189661

Koonrungsesomboon, N., Laothavorn, J., & Karbwang, J. (2016). Ethical considerations and challenges in first-in-human research. *Translational Research*, *177*, 6–18. https://doi.org/10.1016/j.trsl.2016.05.006

Liu, K. A., & Mager, N. A. D. (2016). Women's involvement in clinical trials: Historical perspective and future implications. *Pharmacy Practice*, *14*(1), 708. https://doi.org/10.18549/PharmPract.2016.01.708

Messaoudi, I., Estep, R., Robinson, B., & Wong, S. W. (2011). Nonhuman Primate Models of Human Immunology. *Antioxidants & Redox Signaling*, *14*(2), 261–273. https://doi.org/10.1089/ars.2010.3241

Michelle Habets. (2017). The unique status of first-in-human studies: Strengthening the social value requirement | Elsevier Enhanced Reader. *Drug Discovery Today*, *22*(2), 471–475. https://doi.org/10.1016/j.drudis.2016.11.016

Mullard, A. (2022). 2021 FDA approvals. *Nature Reviews Drug Discovery*. https://doi.org/10.1038/d41573-022-00001-9

New clues to why a French drug trial went horribly wrong. (n.d.). Retrieved January 25, 2022, from https://www.science.org/content/article/new-clues-why-french-drug-trial-went-horribly-wrong

Nuremberg Code—History—Office of NIH History and Stetten Museum. (n.d.). Retrieved January 30, 2022, from https://history.nih.gov/display/history/Nuremberg+Code

Paluri, R. K., Li, P., Anderson, A., Nandagopal, L., McArdle, T., Young, M., Robert, F., Naik, G., & Saleh, M. (2020). First-In-Human Phase 1 Clinical Trials – A Single-Center Experience In The Era Of Modern Oncotherapeutics. *Scientific Reports*, *10*(1), 7935. https://doi.org/10.1038/s41598-020-64906-4

reMYND. (2021). *A Phase 1 (First in Human) Randomized, Double-blind, Placebo-controlled SAD, MAD Study With an Adaptive Dose Design to Evaluate the Safety, Tolerability, and Pharmacokinetics of REM0046127 in Healthy Subjects* (Clinical Trial Registration No. NCT04672135). clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04672135

Research, C. for D. E. and. (2019). Institutional Review Boards (IRBs) and Protection of Human Subjects in Clinical Trials. *FDA*. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/institutional-review-boards-irbs-and-protection-human-subjects-clinical-trials

Skoe, E. E. A. (20141222). Measuring care-based moral development: The Ethic of Care Interview. *Behavioral Development Bulletin*, *19*(3), 95. https://doi.org/10.1037/h0100594

Van Norman, G. A. (2019). Limitations of Animal Studies for Predicting Toxicity in Clinical Trials. *JACC: Basic to Translational Science*, *4*(7), 845–854. https://doi.org/10.1016/j.jacbts.2019.10.008

WMA - The World Medical Association-WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. (n.d.). Retrieved January 30, 2022, from https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

Zimmermann, A., Pilarska, A., Gaworska-Krzemińska, A., Jankau, J., & Cohen, M. N. (2021). Written Informed Consent—Translating into Plain Language. A Pilot Study. *Healthcare*, *9*(2), 232. https://doi.org/10.3390/healthcare9020232