

ETHICAL ISSUES IN CANCER CLINICAL TRIALS

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ABSTRACT

Results from cancer clinical trials make valuable contributions to medical care for cancer patients. Two important ethical dilemmas in these trials are respect for individual autonomy and distributive justice. This paper explores the history of clinical trials and discusses these ethical dilemmas citing specific examples. Although there has been significant progress in these ethical issues, future review and legislation of the process will continue to improve and solidify ethical aspects of cancer clinical trials.

KEYWORDS

Cancer; ethics; IRB

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Introduction

Clinical scientific research has led to many significant discoveries and interventions in patient care in many areas of medicine. Clinical cancer research has provided hope and significantly improved the outcomes of many cancers in the last few decades. While clinical trials have produced substantial benefits to individuals and society, they have also brought up some important troubling ethical issues, including the tension between human subjects and translational research (Joffe, 2010). This paper will focus some of the ethical issues in clinical cancer research, with an emphasis on human subjects.

Before going further, it is important to understand two basic definitions, “research” and “human subjects.” The Code of Federal regulations defines research as: “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” [45 CFR 46.102(d)] and defines human subjects as: “...living individual(s) about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.” [45 CFR 46.102(f) (1-2)] (OHSU, n.d., What is human subjects research).

Historically, three important ethical codes developed for protection of human subjects were the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report. In response to studies conducted by Nazi physicians, in 1947 the Nuremberg Code established the principles of voluntary consent and risk/benefit assessment (Nardini, 2014). In 1964 the Declaration of Helsinki became a code of the World Medical Association (WMA), emphasizing the importance of the study objective in proportion to risk (Schuff, personal interview, 2016, March 8). Despite these codes, unethical behavior in human subject research continued through the 1970s. One well-known example was the study of the pathogenesis of untreated syphilis in black men by the U.S. Public Health Service in Tuskegee, conducted without the participants’ knowledge of the intent of the study. Not only did many of these men die of the disease,

many transmitted the disease to others. In the aftermath of this and other scandals, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral research published the Belmont Report in 1978. It addressed three principles applicable to research with human participants – respect for persons, beneficence, and justice. (Nardini, 2014; United States, 1978).

The principle of respect for persons includes two ethical convictions: that people are treated as autonomous agents and that those with diminished autonomy are entitled to protection. Beneficence is an “obligation” to perform complementary beneficent actions of: (1) Do not harm, and (2) Maximize possible benefits and minimize possible harms. Lastly, the ethical principle of justice focuses on “fairness of distribution” or “who ought to receive the benefits of research and bear its burdens?”

Senate hearings following the Tuskegee and other scandals led to the establishment of Institutional Review Boards (IRBs) in 1972, which are now part of any medical center that performs human subject research. An IRB is a board, committee or other group formally designated by an institution to review research involving humans, to approve the initiation of, and conduct periodic review of such research. At OHSU the IRB is mandated with “review of all research involving human subjects performed by OHSU faculty, research staff, and students” (Schuff, 2016, Jan 27).

The first clinical trials for new cancer drugs and treatment methodology began in 1955 when the National Cancer Institute (NCI) received funding to establish the Cancer Chemotherapy National Service. The goal of this program was “to extend the lives of people with cancer, at a time when many physicians believed such a goal would only meet with dismal failure.” (Bertagnolli, 2014)

It is only in the last few decades that a respect for the ethical treatment of participants in clinical trials has become important. Historically, the most important dilemma in clinical trials is respect for autonomy of the individual and distributive justice. These are the two areas of exploration this paper. I

first focus on identifying the various stakeholders in clinical trials with an emphasis on their roles in relation to the human subjects of research. The discussion then shifts to the process of approval for clinical trials (primarily at OHSU), and the potential effects this has on human subjects. From there I discuss the ethical principle of distributive justice as applied to clinical cancer trials in precision medicine. Finally, I propose some policy recommendations to advance and enhance decision making in these ethical dilemmas.

Stakeholders

There are many stakeholders in clinical trials, and it is beyond the scope of this paper to detail the function of each one. In terms of the Belmont principle of protection of human subjects, for any cancer clinical trials the stakeholders include the patient, investigators¹, the treating physician, Institutional Review Board (IRB), patient families, companies sponsoring a clinical trial, and funding agencies. At the OHSU Knight Cancer Institute (KCI) additional stakeholders include the KCI leadership, Knight Clinical Research Review Committee, donors to the KCI, and finally the KCI itself.

Patients

Patients have a right to an *informed consent* for any clinical trial. The recommendation is that the form provided to patients is at an 8th grade reading level with no complicated language (NBAC., 2001). Joffe (2010) recommends that if at all possible this consent should be discussed with a patient and then given to them to take home with time to think about it prior to consent. The importance of the ethical principle of autonomy cannot be emphasized enough in this context. It is important that patients do not feel that they are being coerced to be part of a clinical trial in order to get treated. It is also important for patients to understand that their being part of a clinical trial may not directly benefit them (Joffe, 2010; Nardini, 2014), but can

potentially be of benefit to others in the society who may need the same treatment, Winkler and Gruen (2005) refer to this as an “act in a public spirit.” It is also important to note that there are some classes of human research subjects, who are considered “vulnerable populations” (NBAC, 2001) including children, persons with reduced capacity to consent, prisoners, pregnant women, and the terminally ill. Cancer clinical trials may involve terminally ill patients for whom there is no other treatment option available. These patients are considered to be “more vulnerable to coercion and in need of additional protections” (NBAC, 2001). While such patients can be recruited into studies, it is particularly important in these cases that Winkler and Gruen’s (2005) principle of providing care with compassion is applied.

Study Investigators

Study investigators are valuable stakeholders in clinical trials as they are involved in getting informed consent from patients. It is important than in any clinical trial, investigators are knowledgeable about human subject regulations, both state and federal laws, as well as being aware of institutional policies and procedures.

There can be a conflict for a physician about whether or not a patient is involved in a study. For example, OHSU Knight BioLibrary policy is to always check with a patient’s treating physician before enrolling the patient in a study, to ensure that the study coordinators haven’t missed any concerns regarding a patient’s physical or mental health in chart review. Some physicians, particularly those involved in their own research apart from a clinical trial, may see this as an opportunity to control what studies “their” patients are included in. This raises the question of how patients are included in a study. Are patients always made aware of a research opportunity or is it possible a physician might not informing their patient about a clinical trial in order to “save” that patient for their own research study?

¹ Investigators include all who are involved in the conduct of a research study, such as scientists, study coordinators, research staff and data abstractors (NBAC, 2001)

On the other end of the spectrum, Joffe (2010) discusses a physician who wanted so badly to include their patient in a breast cancer clinical trial that he fudged the patient data so that the patient would be eligible for the trial. The physician investigator was “drawn in two directions by competing sources of action based on varying organizational philosophies” (Peer & Rakich, 1999): treating physician vs. clinical researcher. As the treating physician he wanted what he perceived as the “best therapy and follow-up treatment,” but as an investigator in this research study some of his patients did not fulfill the criteria and should not have been included in the study.

Patient Access to Study Results

Another ethical issue involving investigators and patients is whether or not patients have the right to be informed of results of clinical trials once the study is concluded. According to Dr. Markman (2006), “The major focus of investigators is on insuring the autonomy, and protecting the safety, of research participants both *immediately preceding and during the trial* and not on an ethical obligation to subsequently inform individuals about what researchers have learned that may be of benefit to future patients” [underlining added]. In response to this article, Dr. Lichtenfeld (2006) writes in his American Cancer Society blog: “Patients put their bodies at risk, so to speak, so why shouldn’t they find out if there was a benefit?” The principle of beneficence would tell us that the researcher should have the welfare of the research participant in mind.

Competing Priorities: Protection, Timeliness, and Resource Allocation

At OHSU, all cancer clinical trials must go through IRB approval and the Knight Clinical Research Review Committee (CRRC). The IRB and CRRC work collaboratively and serve to fulfill the regulative condition of accountability for reasonableness (Daniels & Sabin, 2002) in ensuring that clinical trials follow federal, state, and institutional regulations. In addition, there are several other approvals that a study needs to go through depending on the study content including,

but not limited to, Knight Data and Safety Monitoring Committee (DSMC), Knight Clinical Trials office (KCTO), clinical trial-specific data safety and monitoring boards (DSMB), pharmacy review, institutional biosafety review (e.g. viruses, toxins), radiation safety, and contracting.

Shepherding a research proposal through these boards and committees takes time and may go through many revisions before receiving all required approvals. According to the Chair of IRB at OHSU (Schuff, personal interview, 2016, March 8), investigators with less experience are much more likely to have their research proposals rejected. This brings up an ethical issue regarding human subjects in cancer research: recruitment. For a proposed study that has taken a long time to go through IRB review, the science may already be too old to do the research, thus making it difficult, if not impossible, to recruit patients into this study.

Moreover, there are resource implications. Kitterman, et al. (2011) reviewed all clinical studies terminated between July 1, 2005 and June 30, 2009 at OHSU and found that 31.1% of studies were identified as low-enrolling studies (defined as “those with zero or one participant enrolled at the time of study termination”). The total institutional uncompensated cost of these studies was approximately \$990,000 in fiscal year 2009 (July 1, 2008 – June 30, 2009) alone! The authors emphasize that “research in oncology has shown a great deal of similarity in low-enrolling studies among different cancer centers.” These studies may have “prevented the conduct of other research that could have been more likely to achieve its primary endpoints through successful recruitment” (Kitterman, et al., 2011). Some of the finances for these low-enrolling studies could potentially be used for other purposes. This is an application of Winkler and Gruen’s first principle of spending resources reasonably (2005).

Distributive Justice

The new area in clinical trials of precision medicine moves us from the Belmont principle of respect of persons to justice. Nardini (2014) highlights the

challenges personalized (or precision) medicine poses for ethical decision making, especially in terms of distributive justice.

Gleevec was the first targeted compound discovered by researchers at OHSU and has changed the lives of patients with chronic myeloid leukemia (Cancer.org). At the time this drug was developed, the ethical question of distributive justice in relation to precision medicine was not yet a major issue. However, since that time additional targeted drugs are being developed, some of which may only work for a few months on a small group of terminally ill patients. The ethical dilemma here is one of allocation of resources: Would the money spent on such therapies be better spent on clinical cancer trials for early stage cancer or for early detection of cancer? Who would answer such a question?

According to Winkler and Gruen's (2005) principle of spend resources reasonably, "stakeholders' claims should be prioritized according to the purpose and mission of the organization." In any clinical cancer research trial involving precision medicine, one of the major stakeholders is the drug company testing this drug. This priority is aligned with the mission of the KCI which is "Provide individually-tailored, compassionate care for every patient, from diagnosis through survivorship; Discover new ways to prevent cancer; Develop new personalized cancer therapies. We will end cancer as we know it" (OHSU, Mission & Knight Cancer History).

Of course, science does not stand still, and it is important to revisit practices and mission in context of these changes. For example, OHSU's KCI recently hired a leader in early [cancer] detection. Will this shift focus and funding from personalized medicine to early detection? How will this affect stakeholders such as patients with late stage cancer, or physicians/researchers involved in precision medicine at KCI? Will resources be re-allocated? These questions and more will be answered over the next few years.

Recommendations

While there has been much progress in addressing ethical issues in clinical research, both as a result of the Belmont Report and the NBAC Recommendations on Ethical and Policy Issues in Research Involving Human Participants, there is room for improvement. This is particularly relevant in terms of expediting the review process for initiating clinical studies. As mentioned previously, there can be significant delays in getting a study approved by the IRB. Ideally, finding a way to streamline study requirements while protecting human research subjects could be beneficial both scientifically and financially for an institution.

One way to streamline the process is to exclude or exempt studies considered to be low-risk human research when already subjected to independent controls. This would allow the IRB to focus on targeting oversight of riskier studies. Of course, these decisions would have to be based on strict federal legislation.

Additionally, for multi-institutional clinical trials, a single institution IRB review could be sufficient for the entire trial rather than the current system of having the IRB at each institution approve the clinical trial. This would expedite recruitment of human subjects, especially if more sites joined the study after initial approval, giving a better chance for potential measurable results and data. The federal government has proposed revisions to the Federal Policy for the Protection of Human Subjects (1991) that will streamline the IRB review process allowing for fewer studies with low enrollment, thus producing more productive meaningful research studies and providing a financial gain for the institution.

Such policy changes can further the ethical principle of respect for persons by providing more meaningful clinical trials. They would enhance distributive justice and allocation of resources by using money saved through streamlined processes toward training investigators in (1) submitting clinical research protocols and (2) ethical principles in cancer clinical trials. The development of these policies and how they influence ethical issues in

cancer clinical trials in the future will continue to be an important conversation.

References

- American Cancer Society (ACS). (n.d.). CPS-3 Confidentiality and Ethics. Retrieved from: <http://www.cancer.org/research/researchtopreventcancer/confidentiality-and-ethics>
- American Cancer Society (ACS). (n.d.). The Basics of Clinical Trials [website]. Retrieved from: <http://www.cancer.org/treatment/treatmentsandsideeffects/clinicaltrials/whatyouneedtoknowaboutclinicaltrials/clinical-trials-what-you-need-to-know-clinical-trial-basics>
- Bertagnolli, M. M. (2014). The Funding Crisis in Cancer Clinical Trials: A Focus on Cooperative Groups. Retrieved from: <http://www.asco.org/advocacy/funding-crisis-cancer-clinical-trials-focus-cooperative-groups> (no longer accessible)
- Cancer.org. (n.d.). Targeted therapies for chronic myeloid leukemia [website]. Retrieved from: <http://www.cancer.org/cancer/leukemia-chronicmyeloidcml/detailedguide/leukemia-chronic-myeloid-myelogenous-treating-targeted-therapies>
- Daniels, N., & Sabin, J. E. (2002). *Setting limits fairly: Can we learn to share medical resources?* Oxford: Oxford University Press.
- Joffe, S. (2010). Ethics in Cancer Clinical Trials [PowerPoint Slides]. Retrieved from: American Society of Clinical Oncology University: <http://meetinglibrary.asco.org/content/38893?media=vm>
- Kitterman, D.R., Cheng, S.K., Dilts, D.M., & Orwoll, E.S. (2011). The prevalence and Economic Impact of Low-Enrolling Clinical Studies at an Academic Medical Center. *Academic Medicine*, 86(11), 1360-1366.
- Lichtenfeld, L. (2006, Apr 26). Clinical Trials: Patients' Right to Know. Retrieved from Dr. Len's Blog: http://blogs.cancer.org/drlen/2006/04/26/clinical-trials-patients-right-to-know-results/?_ga=1.110546693.186017291.1457045349
- Markman, M. (2006), Providing research participants with findings from completed cancer-related clinical trials. *Cancer*, 106: 1421-1424. doi:10.1002/cncr.21757 Retrieved from <http://onlinelibrary.wiley.com/doi/10.1002/cncr.21757/full>
- Nardini, C. (2014). The ethics of clinical trials. *Ecancermedicalscience*, 8, 387. <http://doi.org/10.3332/ecancer.2014.387>
- National Bioethics Advisory Commission (NBAC). (2001). Ethical and policy issues in research involving human participants : Report and Recommendations of the National Bioethics Advisory Commission. Rockville, MD: NBAC, 2001, Vol. 1. Retrieved from: <http://hdl.handle.net/1805/25>
- OHSU Knight Cancer Institute. (2011). Data and Safety Monitoring Plan [PDF]. Retrieved from: <http://cancercenters.cancer.gov/Documents/OHSUDSMP508.pdf>
- Oregon Health & Science University (OHSU). (n.d.). Mission and Knight Cancer History [website]. Retrieved from: <https://www.ohsu.edu/xd/health/services/cancer/about-us/welcome/mission-and-history.cfm>
- Oregon Health & Science University (OHSU). (n.d.). What Is Human Subjects Research? [website] Retrieved from <http://www.ohsu.edu/xd/research/about/integrity/irb/index.cfm>
- Peer, K. S., & Rakich, J. S. (1999). Ethical Decision Making in Healthcare Management. *Hospital Topics*, 77(4), 7-14.
- Schuff, K. (2016, March 8). Personal interview with R. Makar.
- Schuff, K. (2016, January 27). Human Subjects Protection: An OHSU Focus [PowerPoint Slides]. Retrieved from OCTRI Research Training Presentations: http://www.ohsu.edu/xd/research/centers-institutes/octri/education-training/upload/4_IRB0116-KS.pdf
- United States. (1978). *The Belmont report: Ethical principles and guidelines for the protection of human subjects of research*. Bethesda, Md.: The Commission. Retrieved from: <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>
- United States. (2015, Sept 8). Federal Policy for the Protection of Human Subjects. *Federal Register*. Retrieved from: <https://www.federalregister.gov/articles/2015/09/08/2015-21756/federal-policy-for-the-protection-of-human-subjects>
- Winkler, E., Gruen, R., & Sussman, A. (2005). First Principles: Substantive Ethics for Healthcare Organizations. *Journal of Healthcare Management*, 109-120.