

Informed Consent: A Clinical Trials Perspective

Marilyn J. Hammer, PhD, DC, RN, Patricia Eckardt, PhD, RN, and Margaret Barton-Burke, PhD, RN, FAAN

The primary goal of the thousands of registered trials in cancer research is to extend survival. With evaluation of efficacy, safety, and tolerability, healthcare providers must ensure that the principles described in the Belmont Report are upheld and that patients are truly informed when signing a consent form. In this article, two cases are highlighted, and reasons for participating in clinical trials are discussed. Challenges, such as healthcare literacy, patients' dedication to their healthcare providers, and choosing between multiple trials, are also explored.

Hammer is the director of research and evidence-based practice at Mount Sinai Hospital, Eckardt is the director of the Heilbrunn Family Center for Research Nursing at the Rockefeller University, and Barton-Burke is the director of Nursing Research at Memorial Sloan Kettering Cancer Center, all in New York, NY.

No financial relationships to disclose. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Oncology Nursing Forum* or the Oncology Nursing Society.

Hammer can be reached at marilyn.hammer@mountsinai.org, with copy to editor at ONFEditor@ons.org.

Key words: biology of cancer; ethics; genetics; nursing research

ONF, 43(6), 694–696.

doi: 10.1188/16.ONF.694-696

More than 5,500 registered clinical trials exist that are researching cancer (ClinicalTrials.gov, 2016). With the primary goal of survival, clinical trials to test the efficacy, safety, and tolerability of pharmacologic agents are the gold standard (Ordling et al., 2016). For many patients with a poor prognosis, these trials can be extremely appealing. However, many patients are hesitant to participate. A 2010 clinical research workshop summary noted a number of barriers to enrolling in clinical trials, including fears about quality-of-life alterations, the possibility of receiving the placebo instead of the drug, side effects, the new drug potentially not being the best treatment, inconveniences in being part of the study, feeling coerced, wanting the physician to make the decision, and feeling a loss of control (English, Lebovitz, & Giffin, 2010). However, clinical trials give hope when standard therapies fail to help a patient's disease.

Deciding to enroll in a clinical trial, in most cases, is an informed gamble. In many cases, the treatment advancements may be minimal at best. For example, a study evaluating survival, safety, and prognostic factors for the use of regorafenib (Stivarga®) in patients with metastatic colorectal cancer refractory to standard therapies boasted a median survival rate of 5.6 months, with 80% of patients experiencing at least one adverse event (Adenis et al., 2016). This

type of outcome suggests the need to assess patient preferences related to sacrificing quality of life for the potential of a few extra months of life. Such decisions are difficult, but the glimpse of hope for an actual cure—no matter how small the chance—can be extremely enticing. Participating in the trial as the only means to receive the treatment may far outweigh contributing to scientific advancement for future patients. Of note, patients at any stage often enroll for altruistic reasons. Some patients have expressed their appreciation for research participants who enrolled in studies prior to their own diagnoses and advanced the scientific knowledge that now gives them the opportunity for prolonged survival.

For clinical trials and all research studies, reviewing the Belmont Report's focus on ensuring respect for persons, beneficence, and justice is essential (U.S. Department of Health and Human Services, 1979). Examining two publicly highlighted cases, the current article will explore the application of these ethical tenets for patients who signed informed consent forms to receive gene therapy.

Case Study of a Patient With an Enzyme Deficiency

The first case involves an 18-year-old man, Jesse Gelsinger, with a rare immunologic disease in which his body lacked an enzyme, ornithine transcarbamylase, needed to

disassociate ammonia. His disease was fairly well managed with medication. The patient, with agreement from his father, took part in a phase I clinical trial using a viral vector to introduce healthy DNA into his system with the hope of improving his body's ability to produce the enzyme and decrease the need for the medications (Somia & Verma, 2000). The patient was aware that this trial could lead to improved methods for the then-nascent protocol, but direct benefit to him would only be a small possibility (Wilson, 2010). Sadly, he had an adverse reaction to the vector and died two days after receiving the treatment (Somia & Verma, 2000). Other patients in the same trial did not have such a reaction; however, a number of questions were raised, and lawsuits ensued (Wilson, 2010).

From an ethical lens and the respect for persons principle, the patient made an autonomous and informed decision to enter the trial with his father's support. Although the expectation of the clinical trial was not an immediate and direct cure for the disease, the principle of beneficence in having the patient's welfare in consideration is gray. The principle of justice, equal opportunity for all, is questionable as well. Jesse Gelsinger may have had an opportunity to enroll in this trial because of his higher socioeconomic status. It is unclear whether every patient with this condition had an opportunity to participate in this clinical trial. The patient's condition was managed by a renowned physician at a major academic medical center in a major city. Based on sociodemographics, all patients may not have had the same access to such studies. This ethical argument is two-sided. One side is the lack of access to potentially life-extending clinical trials for more diverse and marginalized populations. The other side, as highlighted in *The Immortal Life of Henrietta Lacks*, includes individu-

als from marginalized populations being part of studies without clear consent and understanding (Skloot, 2010).

Case Study of a Patient With a Gene Deletion

Two years following Gelsinger's death, the completion and publications of the human genome sequence took place (Venter et al., 2001), which played an important role in the second case study explored in this article. More than a decade after the death of Jesse Gelsinger, gene therapy was introduced in a man who was diagnosed with chronic lymphocytic leukemia (CLL). His disease was managed with chemotherapy treatments that had given him periodic remissions since 1996. Over time, he no longer responded to standard therapies. By 2009, the patient was able to have his DNA evaluated, and healthcare providers found that he had a deletion of the *TP53* gene (Porter, Levine, Kalos, Bagg, & June, 2011), a gene that produces an antitumor protein. The patient was treated using a specific chimeric antigen receptor gene in a lentivirus vector transduced into autologous T cells (Porter et al., 2011). Although some adverse reactions occurred, he ultimately recovered and went into remission (Porter et al., 2011).

In this second scenario, respect for persons was upheld through the patient making an informed autonomous decision, which also occurred in the first case study. For this patient, the principle of beneficence related to his welfare, with a focus on survival, was clearly evident. However, the principle of justice is still unclear. A patient with poor access to health care is unlikely to have had this opportunity and potentially would not have been able to access resources to keep CLL maintained for more than 10 years.

Considerations for Clinical Trials

When considering participation in a clinical trial, patients must weigh the decision carefully. Nurses can assist in this process by asking patients questions about the decision (see Figure 1).

In competing clinical trials to manage the same disease, it becomes difficult for the patient to decide which trial, if any, would give the most benefit. Patients often rely on the physician or other members of the healthcare team to help with the decision (English et al., 2010). The information can be overwhelming and confusing. To help decide between competing protocols, many patients and family members rely on healthcare team members with education and expertise, even in situations in which the patient or family members are also educated healthcare providers. One of the controversies in the Jesse Gelsinger case was that the primary physician was a large stockholder in the biotechnology company that provided the experimental treatment (Wilson, 2010). This conflict of interest became a major point

FIGURE 1. Questions for Patients Considering Enrollment in Clinical Trials

- Is the clinical trial a treatment for improving outcomes compared to what is currently the standard of care?
- Is the patient not being well managed with the standard of care?
- Would entering the trial give the patient the possibility of prolonged survival to an extent that would not otherwise be possible?
- What are the potential side effects?
- Are there competing clinical trials to treat the same disease?
- What are the patient's wishes? Is there persuasion from members of the healthcare team or loved ones?
- Is the patient willing to be part of a research study, or is the study the default for receiving treatment?
- Does the patient fully understand the implications and risks for being part of the study?

in the legal proceedings (Wilson, 2010); however, if the patient had had a positive outcome, it is unclear whether the physician's investment would have been noted. In this example, the patient's choice was to participate in the trial or continue with the disease management protocol he had been on. Regarding the case study with CLL, the patient's only chance for survival was the experimental protocol.

Another challenge is the area of healthcare literacy. Consent forms generally contain legal language, which can be difficult to decipher. The medical terminology alone can be overwhelming. Researchers are expected to craft the consent forms in a way that includes the language but is at a sixth- to eighth-grade reading level, which may not always occur. It can be helpful to have a member of the research team walk the patient through the consent form, explaining confusing areas. In addition, encouraging the patient to think about participating and showing the form to a loved one before signing can increase assurance that the patient is truly informed.

When patients think very highly of their healthcare providers, they may decide to sign on to clinical trials to be helpful or even garner more time and attention. It is always important to highlight that the care for the patient will not change whether or not he or she is enrolled in the study. That statement should appear in the consent form.

Conclusion

In addition to clinical trials testing the safety and efficacy of vari-

ous types of treatments, clinical trials can test a host of interventions. Many nurse scientist-led studies involve biobehavioral interventions, creating and testing technology, and establishing and evaluating new patient care protocols. In all studies, ensuring that the tenets of the Belmont Report are regarded when designing a study is important, as is accurately informing patients before consent.

Clinical trials are the gold standard for moving science forward. For patients undergoing treatment for cancer, these trials can lend advancements for prolonged survival and enhanced quality of life. Ideally, the benefits should outweigh the risks, and patients should agree to participate with a comprehensive understanding of what their trials will include and how they will contribute to care and clinical science. In addition, all patients, everywhere, should have access to these trials.

References

- Adenis, A., de la Fouchardiere, C., Paule, B., Burtin, P., Tougeron, D., Wallet, J., . . . Andre, T. (2016). Survival, safety, and prognostic factors for outcome with Regorafenib in patients with metastatic colorectal cancer refractory to standard therapies: Results from a multicenter study (REBACCA) nested within a compassionate use program. *BMC Cancer*, 16, 412. doi:10.1186/s12885-016-2440-9
- ClinicalTrials.gov. (2016). Search results: Cancer. Retrieved from <https://clinicaltrials.gov/ct2/results?term=cancer&Search=Search>
- English, R.A., Lebovitz, Y., & Giffin, R.B. (2010). *Transforming clinical research in the United States: Challenges and opportunities: Workshop summary*. Washington, DC: National Academies Press.
- Ording, A.G., Cronin-Fenton, D., Ehrenstein, V., Lash, T.L., Acquavella, J., Rorth, M., & Sorensen, H.T. (2016). Challenges in translating endpoints from trials to observational cohort studies in oncology. *Clinical Epidemiology*, 8, 195-200. doi:10.2147/clep.s97874
- Porter, D.L., Levine, B.L., Kalos, M., Bagg, A., & June, C.H. (2011). Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *New England Journal of Medicine*, 365, 725-733. doi:10.1056/NEJMoal103849
- Skloot, R. (2010). *The immortal life of Henrietta Lacks*. New York, NY: Crown Publishing Group.
- Somia, N., & Verma, I.M. (2000). Gene therapy: Trials and tribulations. *Nature Reviews. Genetics*, 1, 91-99. doi:10.1038/35038533
- U.S. Department of Health and Human Services. (1979, April 18). The Belmont Report: Office of the Secretary, Ethical Principles and Guidelines for the Protection of Human Subjects of Research, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Retrieved from <http://www.hhs.gov/ohrp/regulations-and-policy/belmont-report>
- Venter, J.C., Adams, M.D., Myers, E.W., Li, P.W., Mural, R.J., Sutton, G.G., . . . Zhu, X. (2001). The sequence of the human genome. *Science*, 291, 1304-1351. doi:10.1126/science.1058040
- Wilson, R.F. (2010). The death of Jesse Gelsinger: New evidence of the influence of money and prestige in human research. *American Journal of Law and Medicine*, 36, 295-325.

Authorship Opportunity

Research Ethics addresses issues of ethics in writing for academic purposes. The column strives to address common problems found in research. Materials or inquiries should be directed to Associate Editor Marilyn J. Hammer, PhD, DC, RN, at marilyn.hammer@mountsinai.org.