Informed Consent and Patient Protection

By Gerald T. Rigdon

Abstract

Informed consent lies at the heart of clinical trial ethics and considered a major component of patient protection. In order for medicine to advance in the near term, human participation is a necessity. During the 20th century, our appreciation of informed consent (which includes both documentation and process) has noticeably progressed, from the darkness of Nazi experiments to the light of international agreements for the protection of human subjects during medical research. The purpose of this paper is to explore the deeper implications of informed consent by discussing relevant studies, the current state of the art, asking rhetorical questions, and answering whether true informed consent is really possible.

1. Understanding the Concept

Merriam Webster defines informed consent as "*consent to surgery by a patient or to participation in a medical experiment by a subject after achieving an understanding of what is involved*." The American Medical Association further emphasizes that this topic embraces much more than signing a piece of paper and describes it as a "*process of communication between a patient and a physician.*" It is a *'process'* because although consent is given when the form is signed, the researchers are obligated to keep the patient updated and answer any questions that might arise. Thus, a patient can terminate participation in a clinical trial at any time. Yet, despite this '*process of communication,'* is '*achieving an understanding'* really possible for patients in a clinical trial setting?

In order to facilitate this '*process'* so that it can be successful, the FDA has codified the standards in the Code of Federal Regulations Title 21 Part 50. According to an oncology perspective presented by Daugherty in [12] the informed consent standards exist for at least two reasons:

> *1. From an ethical perspective, a patient who is considering clinical trial participation is always viewed as potentially vulnerable*

2. Physician investigators are seen as having an intrinsic conflict of interest in their roles

These vulnerabilities and conflict of interest lie in the fact that a patient may not always appreciate the difference between treatments for therapeutic versus research reasons, which is compounded by the fact that during research activities the physicians are motivated by other interests beyond patient therapy. Such occasions give rise to unusual dynamics since a patient's welfare and best interests are generally the chief concern of a physician. Thus, even with standards in place, is it possible to overcome these ethical dilemmas? Before attempting to answer this question, let's briefly look at some pertinent history related to medical research and consider the bigger ethical issues that arise from a lack of informed consent.

II. Historical Perspectives

The concept of informed consent, as it is defined today, is actually an artifact of the prevailing thought during the second half of the 20th century. Prior to that, many unethical medical experiments occurred during WWII by doctors in Nazi Germany, as well as the United States. While the Nazi experiments in Germany are renown, many are not aware of the experiments in the United States such as:

- a dysentery vaccine tested on orphans and mentally retarded people in institutions
- penicillin was tested on prisoners to find the most effective dosage
- psychotic patients were infected with malaria in order to find a cure

Following WWII the Nuremberg Code was created in order to establish a set of ethical principles for human experimentation. While "informed consent" was not mentioned by name, the Nuremberg Code did set the stage for what was to follow. In 1947 a manager at the newly formed Atomic Energy Commission wrote a letter to a clinical investigator on a requirement calling for "informed consent," as it related to potential litigation problems using cancer patients in research, and the term was born. Later in the 1957 malpractice case, Salgo vs. Leland Stanford Jr., the California Supreme Court also

used the term by stating that no patient can submit to a medical intervention without having given prior "informed consent." In 1964 the Helsinki Declaration published a set of ethical principles to govern human experimentation, which prompted further discussions such as Henry Beecher's 1966 article in the *New England Journal of Medicine.* Beecher assembled 22 recent research reports at the time that contained what he considered clear violations of patients' human rights and the ethics surrounding the concept of informed consent [9].

Over time, the aforementioned historical documents have been built upon to the point where informed consent has been codified in 21 CFR 50.23, which says in part that "*the information that is given to the subject or the representative shall be in language understandable to the subject or the representative."* Although this advice sounds reasonable, what does *'understandable'* really mean? Is it possible to communicate all of the appropriate issues and concerns to the patients so that they are understood? What role, if any, does education or literacy play in ones ability to comprehend and understand what is necessary for informed consent?

III. Related Studies

In [11], one particular study (that relates to the topic of informed consent) was conducted in order to test reading comprehension. A CDC polio vaccine pamphlet consisting of 18,117 words spread out over 16 pages without graphics and intended for a 10^{th} grade reading level was translated into a simplified 4-page pamphlet with 322 words, 7 graphics, and aimed at a 6^{th} grade reading level. The participants were as follows:

- 522 parents
- 39% white, 60% black, 1% Hispanic
- Mean age 29 years
- Mean reading level 9^{th} grade in 47% and 7^{th} grade in 20%

The results revealed that the mean comprehension for the original CDC pamphlet was 15% lower and the reading time was three times longer. The conclusion indicated that

although a short, simply-written pamphlet was preferred, even a 6th grade reading level appeared too high for many parents in public clinics.

Complementing this study, the Journal of the National Cancer Institute article in [10] related another study performed at LSU in 1996 that tested how well 183 patients comprehended a standard informed consent form versus a simplified one. As was the case in the aforementioned CDC study, the simplified version was generally preferred. However, given the results that comprehension was low regardless of the form used, the conclusion postulated that simplifying the form may not necessarily increase overall comprehension. Therefore, confronting the issue of informed consent by focusing on overcoming poor literacy is only one factor, which highlights the necessity of a more holistic approach.

Let's now consider some further studies that were actually focused on this topic and analyze the conclusions as they relate to:

- The three types of benefits that participants are expected to have, based on [7]:
  1. direct benefit
  2. indirect or collateral benefit
  3. altruistic benefit
- A participants understanding of trial design and risks
- Patient satisfaction with an informed consent process

IV. Specific Informed Consent Studies

In [8], an informed consent study was done in the treatment of rheumatoid arthritis based on the following criteria:

- the patients must have adequate capture to understand and make a decision about the proposed intervention
- the patient must be allowed to decide voluntarily
- relevant information must be provided to the patient in a way that can be understood, including alternatives

- the patient must decide which treat option to follow and authorize participation either verbally or in writing

An interesting observation in [8] was that altruism [7] was a factor as it had been in two previous HIV informed consent studies [5-6]. In fact 87% stated that their participation was to "*help others with rheumatoid arthritis"* while 83% stated that their participation was to "*advance medical science."* This is in contrast to [1-4] which revealed that the participants enrolled primary for personal benefit [7], both direct and indirect.

One of the conclusions of [8] suggested that while the participants provided consent voluntarily, "*gaps existed in their understanding of trial design and the potential risks of participation, calling into question whether they were adequately informed to provide valid informed consent*." In addition, the results indicated that the participants did not appreciate some finer points and details such as randomization, use of placebos, and drug toxicity. Yet another study [13] of 204 patients regarding satisfaction with an informed consent process concluded that videotape was an important factor in helping explain the risks, benefits, and alternatives.

V. Philosophical Considerations

Since informed consent in the context of medical research is primarily a product of 20th century thinking, then what existed previously? Is it correct to conclude that man has evolved to a higher state of consciousness that enables him to contemplate the need for informed consent and a process that governs it? Perhaps it has less to do with social evolution and more to do with discovery and awareness. It could be said that some of the early indications of such "awareness" in the United States of human rights is captured in the Declaration of Independence. There, some of the founders of America dealt specifically with the importance of human rights by suggesting that such rights are intrinsic and inherent. Over the course of time man has continued to expand his concept of human rights by extending the application of such rights in many social settings and specifically in the area of healthcare and medical procedures.

Yet, while it is reasonable and seems moral to expect that there should be patients' rights concerning informed consent, is it really possible to convey all of the risk factors involved in the participation of clinical trials? On a practical level, even medical professionals and researchers don't completely understand either the risks or the complexities of certain types of drugs. If they did, there would be no need for clinical trials or surveillance trials following drug approvals. Therefore, since discoveries are continuing to be made throughout the process of research, is it appropriate to state that the original decision to participate was "informed?" If so, then "informed consent" would necessarily be a relative term that captures a level of comprehension, understanding, and agreement at a point in time. Hence, the term "informed consent" as a term may be misleading. While "consent" may be given, there doesn't really seem to be an appropriate adjective that generically describes it.

On a similar vein, it can be stated that medical research and new drug therapies have continued to march forward at the same time the process of informed consent has evolved. In fact, some areas of treatment today still exist despite an absence of informed consent. Thus, what is the real impact of informed consent? How important is it to the advancement of medical therapy? If a human cannot fully comprehend all of the factors related to making an informed decision, does this change the thought process? Is an individual's need to know specific to the individual, or is there a general principle at work? Should a person be tested to "quantify" their comprehension level?

VI. Concluding Thoughts and Practical Solutions

We have discovered from several studies that informed consent (which is considered an important component of patient protection) has been considered from many perspectives including conflict of interest, reading comprehension, literacy, assessment of personal gain, assessment of risk, altruism, understanding of trial design, simplification of informed consent forms, complementary informational materials in visual formats, patient satisfaction with informed consent processes, etc.

Although the answers to the many philosophical questions remain unanswered for the most part, we know from history that the absence of guidelines that protect the rights of people participating in medical experiments opens the door to abuse and crimes against humanity. Hence, important ethics guidelines continue to evolve. The Declaration of Helsinki was originally adopted in 1964 and since that time has undergone six revisions, including a major revision in 1975 that matured the process of informed consent. In 1979 the Belmont report was published and set forth three fundamental ethical principles:

- respect for persons
- beneficence
- justice

Based on these precedents, it is clear that as we continue to evolve as a human race our approach to informed consent will continue to evolve. However, in my opinion, given the nature of human action, it will be difficult to achieve "true informed consent." Even if a clear presentation was possible so that patients were able to fully comprehend the potential risk, it is difficult to judge human response. Everyone possesses unique motivational factors, which sometimes leads to decisions that may not be considered rational. Even if it were possible to translate all of the intricacies of full disclosure in a manner that could be consistently understood regardless of a person's background or education level, the problem lies in how that influences each person's unique decision making process which is influenced by more than simply "information."

Therefore, I believe that while *it may be possible* someday to create consent material that is universally understandable and overcome patient vs. researcher conflict of interest concerns, achieving patient protection is relative, and cannot be constrained by human processes. As we discussed earlier from [7], some people are driven by altruism, which could result in them filtering out the risks in favor of a magnanimous gesture. In such a case, are they really "informed" enough to fully understand the impact of their personal sacrifice, and whether it would actually make a difference? The best we can hope for is to continue enhancing our ethical framework and learning from past mistakes. Thus, I contend that "true informed consent" is not possible as universal construct. Rather, it can only be defined in the context of each individual situation. Ultimately, we must be

content with that conclusion and realize that any excessive attempt to ensure patient protection by controlling a person's right to make a final decision is simply a path back toward the darkness from which we have emerged.

References

[1] Daugherty C, Ratain MJ, Grochowski E, Stocking C, Kodish E, Mick R, et al. "Perceptions of cancer patients and their physicians involved in Phase I trials", J Clin Oncol 1995;13: 1062–72

[2] Rodenhuis S, Van Den Heuvel WJA, Annyas AA, Koops HS, Sleijfer DTH, Mulder NH "Patient motivation and informed consent in a Phase I study of an anticancer agent", Eur J Cancer Clin Oncol 1984;20:457–62

[3] Riecken HW, Ravich R. "Informed consent to biomedical research inVeterans Administration hospitals", JAMA 1982;248:344–8

[4] Ockene IS, Miner J, Shannon TA, Gore JM, Weiner BH, Ball SP "The consent process in the thrombolysis in myocardial infarction (TIMI—Phase I) trial", Clin Res 1991;39:13–7

[5] Ross M, Jeffords K, Gold J. "Reasons for entry into and understanding of HIV/AIDS clinical trials: a preliminary study", AIDS Care 1993;6:77–82

[6] Schaeffer MH, Krantz DS, Wichman A, Masur H, Vinicky JK "The impact of disease severity on the informed consent process in clinical research", Am J Med 1996;100:261–8

[7] King NM. "Defining and describing benefit appropriately in clinical trials", J Law Med Ethics 2000;28:332–43

[8] Lisa G. Criscione, Jeremy Surgarman, Linda Sanders, David S. Pisetsky, E. William St.Clair, "Informed Consent in a Clinical Trial of a Novel Treatment for Rheumatoid Arthritis", http://onlinelibrary.wiley.com/doi/10.1002/art.11057/pdf

[9] Jessica Kiefer, "The History and Importance of Informed Consent in Clinical Trials", http://serendip.brynmawr.edu/biology/b103/f01/web2/kiefer.html

[10] Kathryn M. Taylor, Andrea Beznak, R. Hunter, S. Fraser, "Informed Consent for Clinical Trials: Is Simpler Better?", Journal of the National Cancer Institute, Volume 90, Issue 9, p. 644-645, http://jnci.oxfordjournals.org/content/90/9/644.full

[11]Terry C. Davis, Joseph A. Bocchini Jr. Doren Fredrickson, Connie Arnold, E. J. Mayeaux, Peggy W. Murphy, Robert H. Jackson, Nora Hanna, Martha Paterson, "Parent Comprehension of Polio Vaccine Information Pamphlets", Pediatrics Vol. 97 No. 6 June 1996, pp. 804-810
http://pediatrics.aappublications.org/cgi/content/abstract/97/6/804

[12] Christopher K. Daugherty,"Impact of Therapeutic Research on Informed Consent and the Ethics of Clinical Trials: A Medical Oncology Perspective", American Society of Clinical Oncology, 1999, http://jco.ascopubs.org/content/17/5/1601.full.pdf

[13] Agre, McKee, Gargon, Kurtz "Patient Satisfaction with an informed consent process", Cancer Pract. 1997 May-Jun;5(3):162-7