

EDITORIAL

WHAT IS RESEARCH?

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Between believing a thing and thinking you know is only a small step and quickly taken—Mark Twain

If you look up “research” in Webster’s Dictionary, you find it defined as “studious inquiry or examination, especially investigation or experimentation aimed at the discovery and interpretation of facts, revision of accepted theories or laws in light of new facts, or practical applications of such new or revised theories or laws.” It also lists another meaning as “collecting of information about a particular subject.”

Historical events of the 20 twentieth century have helped to define today what constitutes patient research and its associated informed consent in practical terms. The idea of an informed consent has origins with Walter Reed, who used military normal volunteers for his yellow fever vaccine at the turn of the century. The concept of informed consent for patients with underlying medical conditions was consolidated with the Nuremberg Code after World War II. It was then clearly enunciated by an international tribunal that, even in the event of an incurable disease, the physician was obligated to inform the patient of what he was recommending and what the potential risks were. Moreover, the patient *always* had the right to refuse, even if the physician felt strongly that the patient would benefit from his recommendations. These principles were confirmed in the early 1960s by the Helsinki Declaration and further reconfirmed in the Belmont Report of 1979. Along with clearly enunciated patient rights and the need for informed consent came the idea that clinical research proposals needed a thorough review by noninvolved scientists, clinicians, and even lay representatives specifically to protect those patient rights. Moreover, the Belmont report explicitly spelled out that, when a treatment not considered standard of practice is applied to patients and the physician collects data on those patients to present at a public meeting or in publication form, such conduct *does* constitute research and that as such it *requires* an IRB approval. Thus, one of the things that the Belmont report successfully accomplished was taking the decision of what constitutes research on patients away from the individual physician/investigator; instead, the Belmont report put clinical research in the realm of public domain. It

is not a question of whether you or I agree with that position; those are now considered national standards and have been considered national standards by lawyers, bioethicists, and others since the Belmont report came out in 1979. Most clinical researchers may confess to being cavalier about IRB approvals before that time, but none of us can afford to be cavalier any longer.

It is right to ask the question: What kind of innovation is left to the physician without doing research? The answer to that is reasonably clear. The Belmont report specifically says that innovative work in itself does not necessarily constitute research. It is the *collection* of the data and *presentation* in public or printed format that constitutes research. Thus, if the physician sees a patient with a difficult problem and feels that atypical or innovative strategy makes more sense than the “standard of practice,” or if he knows that the typical standard of practice is essentially hopeless for a difficult problem facing him, he can perform innovative treatment and not research. It is actually the reiteration of that treatment, the collection of patient data, and its subsequent presentation that constitute research. Exactly how many patients are required before innovation becomes research is not clear; however, as soon as the treatment becomes repetitive and data are collected, the line separating innovation from research disappears.

A number of developments in radiation therapy have developed in the last decade or so. Endovascular brachytherapy, radiation therapy for macular degeneration, stereotactic radiosurgery, conformal radiation therapy, and, more recently, intensity-modulated radiation therapy are obvious examples; their exact roles in treatment still remain to be defined, and new data are being generated by research protocols.

So why raise the issue of what constitutes research? As papers for the *IJROBP* are screened today, it is obvious that individuals are actively studying these developments and reporting them publicly; radiation oncologists are doing things to patients that have not been done before. The envelope of clinical investigation is stretched today, and there are potential risks involved, as well as potential ben-

efits to patients. There are both short-term and long-term risks, and the long-term risks of radiation include induced cancers. One could argue that with better treatment planning, the risks of morbidity ought to be decreased. In terms of *acute* radiation reactions, that appears to be true. In terms of *long-term* physiological alterations of normal tissue functions and risks of radiation-induced cancers, it is *not clear* at this point; moreover, it will take many years to refute or confirm this issue conclusively.

From the standpoint of radiation-induced cancers, the problem could conceivably increase in frequency, because larger volumes of normal tissues are being exposed, albeit to more modest doses. Nonetheless, the probabilities of mutagenesis will be seen by a larger number of cells because of the expanded volume of exposure, and there are excellent rodent data that demonstrating that modest doses of radiation are actually more oncogenic than higher doses (1). Moreover, with prolongation of treatment time associated with intensity-modulated radiation therapy, the additional whole-body dose from leakage directly from the head of the machine is significantly increased because of the longer beam-on time (2). It is certainly within the realm of possibility that the risk of radiation-induced cancers may be increased as a result. Moreover, the issues of leakage from the machine, the major difference in beam-on time, and thus the use factor in safety calculations mean that it is essential to reevaluate radiation safety criteria for our radiation technologists. The important point is that both patients and therapy staff have an unequivocal *right to know these possible long-term risks*, virtually never mentioned by advocates of these new technologies, which are a possible downside.

So what does constitute research? If, before seeing an individual patient, the physician has defined a treatment that is not considered a “standard” for patients with a pathologic condition (even a hopeless one), if that treatment is applied, and if the physician maintains data to publish or present outcomes in a public forum, that is *clearly* research as defined by the Belmont committee. The same sort of work without collecting the data and without presenting them in a formal public or publication forum would be considered innovative, but not research.

If someone reads an abstract or a paper that seems to offer some promise to a poor-risk population, it may be reasonable to apply that treatment to patients who have a desperate problem, but *if* the data are collected to present, the data would still be considered research, *even if only confirmatory* in nature. Such a treatment is NOT considered “standard of practice,” even if considered to be “state-of-the-art.” IRB approval and informed consent would *still be required*. After all, would you want to be the first patient treated by a physician with a technique and approach that he or she had only read about in an abstract or paper? With all due respect, I think not. The fact that a patient might agree to undergo such unproved and nonstandard treatment out of desperation

should not conceal the obvious fact that there is a learning curve to overcome and that this would still be an instance in which new data are being generated, presumably to be presented in some public format.

I am aware that many medical centers have undertaken either dose escalation studies or stereotactic studies *without* obtaining IRB approval and *without* an investigational informed consent that clearly explains both the possible benefits and risks to patients. These medical centers would argue that this is simply radiation treatment by a different delivery, though data have been presented both orally and in print to imply otherwise. In centers where IRB approval has been obtained, the reason typically given is that the work has been at least partly supported by federal funds, and IRB approval was mandatory before funding.

This ambivalent situation means that the time has come for the journal to take a strong position on this issue of what constitutes research in the era of technological revolution. As new manuscripts are submitted to the journal, authors will be required to disclose explicitly whether IRB approval was obtained and whether an informed *investigational* consent explaining the purpose, possible risks, and benefits of the study in clear language was signed by all participating patients. This information must be included in future manuscripts to be published. Obviously, any attempt to deceive the journal on this point would be considered *prima facie* evidence of ethical misconduct.

In a world in which the medium has become the message, we should not lose sight of the obvious fact that clinical research is being carried out directly on patients who trust their physicians. Obtaining formal IRB approval and labeling such treatment strategies as research not only take time but may also make third-party carriers reluctant to cover the costs. However, physicians can no longer have it both ways in 2001.

Our most precious resource in the long term is both our credibility with patients and the confidence they have in us and in the work that we do. Any possible scandal in which investigators carry out clinical research without the patients’ clear understanding that they are enrolled in a research protocol will hurt everyone by undercutting that credibility and confidence.

As described recently in *Science*, there are clearly attorneys who are ready to pounce on clinical researchers as targets for class action suits when patients suffer a poor outcome (3). The expectations of our patients and the general public may be unrealistic, but that is all the more reason to be certain that the review and consent processes are spotless to any possible scrutiny. If we develop new treatment strategies, we have to be perceived first by both lay and professional groups as honest, dedicated, and compassionate physicians; their perception of us as researchers is only a secondary consideration.

If the world was perfect, it wouldn’t be—Yogi Berra

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