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CRITERIA FOR STANDARD VERSUS EXPERIMENTAL THERAPY

by Stanley Joel Reiser

Prologue: Deciding when an innovative new therapy has moved from experimental to standard treatment is an issue with which insurers, providers, and public policymakers all struggle. Here Stanley Reiser takes on this subject out of a “growing concern I had that in clinical and policy discourse there was a constant ambiguity and confusion expressed about the nature of standard and experimental practice. I felt it was important to clarify the distinctions, and the actions to take from those distinctions” such as reimbursement and clinical use, he explained. In this paper Reiser sets forth some criteria to define and separate standard from experimental therapies. Along the way, he reveals that the conventional wisdom that innovations move linearly forward from experimental to standard therapy and then decline as they are replaced by new innovations is not entirely accurate. Instead innovations more often move to and fro between the categories; as new uses are discovered for standard therapies, they become experimental once again. Reiser suggests an analogy for this movement: “Therapies are like trains: They exist in an oscillating motion, shuttling back and forth between standard and experimental stations, and sometimes taking a crossover track to pause at a place in between them.” To define this in between place, Reiser offers the term “crossover therapy.” Reiser is the Griff T. Ross Professor of Humanities and Technology in Health Care at the University of Texas-Houston Health Science Center. He received his medical degree from State University of New York, as well as a doctorate in the history of science and a master of public administration degree from Harvard University. He has authored and edited numerous books, including Medicine and the Reign of Technology and, most recently, The Ethical Dimensions of the Biological Sciences. He also serves as coeditor of the International Journal of Technology Assessment in Health Care.
Abstract: This paper demarcates the boundaries between experimental and standard therapy and the influence of this division on policy, payment, and practice. It proposes a new category, crossover therapy, to deal with the many therapies that fall in between. It establishes four criteria to separate these categories: (1) the populations and conditions for which use is helpful; (2) the expected outcomes of care; (3) the skill, personnel, and site requirements and the economic, ethical, and legal understandings essential for use; and (4) the level of knowledge needed to certify that prospective users can apply it well. The paper then explores the use of experimental therapy in desperate situations and of standard therapies in new areas and gives policy recommendations to facilitate these actions.

Controversy about deciding when a therapy has crossed the boundary from experimental to standard status has become intense in the past decade. The effort to make this distinction has a practical validity: It demarcates therapies whose likely benefits and harms can be described and anticipated by potential users from therapies whose effects are unpredictable. The controversy generated by efforts to classify therapies as standard or experimental involves scientific questions concerning the adequacy of studies, ethical questions concerning the needs of patients, financial questions concerning the responsibilities of payers, and political questions concerning the power of public and professional interest groups. The dilemmas this controversy creates are likely to worsen as increasing numbers of new technologies are introduced. Thus, a need exists not only to produce clear criteria that separate experimental from standard therapy, but also to develop a new category to characterize the many therapies that fall in between, thereby easing the burden of devising appropriate policies concerning our medical capabilities.

This paper examines the basic differences between experimental and standard therapy and defines a hybrid, intermediate form of these therapies, labeled crossover therapy. It develops criteria to decide when an experimental therapy has become a standard one and, conversely, how a therapy defined as standard becomes experimental when it is applied to new areas of care. It then examines the problems caused by the propensity of therapies to shift among the standard, crossover, and experimental categories as knowledge about them is generated and evaluates the difficulties that these changing knowledge profiles create for potential users. Finally, it provides a general framework for policy making, reimbursement, and practice in dealing with medical innovations.

Distinctions Between Experimental And Standard Therapy

A decision to submit a patient to a standard versus an experimental therapy requires the practitioner and the patient to compare the potential benefits of the two types of therapies. This comparison is difficult, because it weighs the known effects of a therapy with which there is definitive
experience against those that are anticipated through hypothetical and ambiguous determinants. Indeed, the greater uncertainty present when using experimental instead of standard therapy is a critical difference between the two.

Along with the burden of uncertainty, a second basic distinction between standard and experimental therapy is the inflexibility of treatment in the experimental setting, in comparison with the flexibility of care possible in standard practice. A physician’s daily evaluation of a patient can result in frequent corrections in the approach to care. Further, standard therapy at its best is never given to a patient in a standard way. The uniqueness of each patient means ideally that a standard therapy is shaped to address differences among patients—of biological sensitivity, social environment, cultural origins, hereditary propensities, psychological character, and so forth. With experimental treatment, however, the possibility of responsive therapeutic change is difficult. Experimental therapy is essentially therapy by protocol. The basic aspects of the treatment must be similar across the population being studied, if the tests of its effects are to be valid. The unvarying character of experimental care magnifies the troubles for the patient created by the uncertainties with which such therapy begins. Although these two characteristics—uncertainty and inflexibility—are present to some degree in all medical treatment, they are especially prominent in the experimental setting.

When Does Experimental Therapy Become Standard?

Clinical and social influences. The decision that an experimental therapy has reached the point of becoming standard practice is played out in many venues. Hospitals and health maintenance organizations (HMOs) must decide if the therapy can be used in their institutions; clinicians must decide whether to recommend it to their patients; public and private insurers must decide whether to include it in their health plans; businesses must decide whether to incorporate it into the benefits offered to employees; professional societies must decide whether to endorse its use by members; and so forth. In each case, the decision will reflect considerations based not only on science but also on social influences. For instance, electronic fetal monitoring has been widely used in most deliveries, despite the fact that clinical studies show that it is of no benefit in routine deliveries and of only marginal benefit in complicated ones. Such use is mainly linked to concerns that failure to have used this technology if something goes awry would place legal burdens on the clinicians and institutions involved. Seeking the latest technology to establish an edge on competitors and to further research interests are other examples of social
factors determining therapeutic application. Such factors caused imaging technologies such as the computed tomography (CT) scan and magnetic resonance imaging (MRI) techniques to be introduced as standard practice before confirmatory studies established criteria for appropriate use.  

Decision-making criteria. It is important to recognize that because the use of specific therapies greatly affects practitioners and institutions, social forces often push therapies from experimental to standard application without adequate scientific validation. Thus it is necessary to use the clearest possible criteria to decide whether a therapy falls into an experimental or a standard classification, or somewhere in between. Four criteria can be helpful in this decision: established indications of use, specified outcomes of care, standardized requirements of application, and articulated criteria for learning and certification.

Established indications of use. This criterion addresses the issues of for whom, for what, and how much of a given therapy should be used—the generic issues covered by most scientific studies in the medical literature. All medical therapies have a range of possible applications to treat various symptoms and diseases. Defining an initial range of application is essential because it creates boundaries. Therapeutic experimentation by definition sets the limits of a technology. As indications of its boundaries become known, its experimental burdens diminish.

Specified outcomes of care. Just as the indications of experimental procedures are marked by uncertainty, so too are the outcomes of their use. Much experimental work is directed at exploring short- and long-term benefits and harms. While in the past the outcomes sought were specific biological changes, in more recent times outcomes also have been assessed with respect to the functional and subjective effects of a therapy as the patient experiences them. Enumeration of these outcomes is central to denoting a therapy as standard. This means that physician and patient have a clear understanding of what risks must be taken for which benefits to be gained. This knowledge eases the burdens of action and makes possible the efficiency of standard care. Uncertainty about outcomes creates the ambiguity implicit in experimental medicine, whereas standard practice diminishes such ambiguity.

Standardized requirements of application. This criterion focuses on the manner in which a given therapy is applied. This involves clear articulation of the skills needed by the practitioner who will use the therapy; the facilities necessary for proper use; and the ethical, economic, and legal issues involved in the therapy’s use.

Articulated criteria for learning and certification. Since the application of a technology requires specification of the conditions required for successful use, it also is reasonable to ask that criteria be in place both for learning to
use the technology and for certifying the learner’s ability to appropriately apply it. Answers to the following questions may be helpful in setting these criteria: How many hours of training are needed to apply the innovation? Who should teach this? What are appropriate educational venues? And who should oversee the certification process?

Certain innovations such as some new drugs may not require the acquisition and testing of new skills. Others may necessitate specialized aptitudes such as the technique of endoscopic surgery. Mechanisms are needed to determine when a given innovation should have a formal process of learning and certification attached to it. However, a distinguishing feature of standard therapy should be the possibility of specifying what the learning and certification criteria are. For experimental therapies, such knowledge is not available.

Taken in sum, specified criteria that establish the conditions for when an innovation should be used; the expected outcomes of interventions with it; the requirements of place, personnel, and society for effective use; and the learning and certification needed by users to assure high standards of care should all be available for an innovation to become standard care.

The evidence produced by this wide range of requirements will permit the experimental and standard phases of an innovation to be distinguished from one another and will encourage appropriate use. Because the knowledge that professional groups and society accept to warrant the use of a medical innovation has been confined largely to biological knowledge, a wide area of ignorance remains when the innovation becomes available to the practice community as standard. This often leads to poor outcomes and wasted resources. This calls for an expanded view of the types of knowledge essential to declare that an innovation has reached the stage of community application. In fact, the discipline of technology assessment already exists to develop a broad, synthetic approach to evaluating innovation. Technology assessment integrates biological, clinical, economic, and social criteria in evaluating innovations. Its methods and literature can be marshaled to produce the wider range of knowledge needed to establish an innovation as standard.

Policy For Crossover Therapies

Once therapies are placed in the standard or experimental category, they do not reside there undisturbed. New knowledge about them can both resolve unanswered questions and raise new ones. Just as experimental therapies can move into the standard category, standard therapies can proceed toward the experimental category.

This motion is particularly hard on regulatory procedures used to certify
therapies. As knowledge about therapies grows, data are released and evaluated by scientific and popular journals. This produces a perspective on their effectiveness by clinicians and the public, which usually develops more rapidly than the regulatory processes used to evaluate them. This time lag creates dissent between practitioners and patients—whose claims may believe sufficient knowledge exists either to approve a therapy thought to produce benefit or to disapprove one believed to cause harm—and regulators from agencies such as the Food and Drug Administration (FDA), who have not completed the review dictated by their established procedures.

**How crossover therapies evolve.** This problem produces two basic kinds of situations in which the term crossover aptly characterizes the therapies in question. In the first situation, an experimental therapy appears to provide distinct benefits, but studies on it are still incomplete. If this crossover therapy is the only hope for patients in desperate need of help, there is significant pressure to apply it as a nonexperimental intervention. An example of this situation is the use of new drugs for acquired immunodeficiency syndrome (AIDS), where AIDS patients' claim to these treatments rests on the urgency of their illness. AIDS could kill them before studies of the potentially helpful therapies are completed.

Practitioners, insurers, and scientific bodies confront difficult questions when facing this kind of issue. A practitioner's decision to act when knowledge is inadequate is a decision to risk harm. Practitioners must decide whether the risks of harm to a patient outweigh the risks of treating the illness with standard care. The fact that patients ask for and consent to the action does not relieve the practitioner of ethical or legal responsibility; it merely permits the practitioner to initiate the action.

Insurers often must make equally difficult decisions when their policies are ambiguous or silent on the matter of coverage or when they explicitly state that they will not cover experimental therapy, and desperately ill policyholders urgently request an exception. Scientific bodies that generate knowledge and regulate use, such as the National Institutes of Health (NIH) and the FDA or professional medical societies also face difficult problems when these controversies arise. They must decide how to maintain standards of scientific study, regulatory policy, and practice when they allow exceptions to their procedures.

A second situation that generates a crossover therapy is when a therapy approved as standard for given applications has its use extended into areas for which it was not tested when initially approved. In pediatrics, for example, where it is difficult to carry out clinical trials, drugs are used for "off-label" purposes an estimated 70 percent of the time. Similarly, in oncology, where there is a pressing need for new approaches to therapy, almost 80 percent of drugs are used in this off-label manner when combina-
tion regimens are administered, and up to 50 percent with single-dose regimens. Another example of the problems created when standard therapies are extended into new areas is the use of high-dose chemotherapy combined with bone marrow transplantation to treat breast cancer—the second leading cause of cancer death among women, which claimed more than 43,000 lives in 1990. This conjoined approach is a standard therapy for patients with a number of cancers less common than breast cancer—such as leukemia, lymphoma, neuroblastoma, and multiple myeloma—who have suffered a relapse of their disease. It uses a complex technology of bone marrow harvesting and infusion to permit chemotherapeutic agents that have a destructive effect on the marrow to be administered at high levels. It is costly relative to other regimens of cancer chemotherapy because it requires sophisticated medical facilities and a large amount of inpatient rather than outpatient care. The application of this therapy for breast cancer has caused controversy because of scientific disagreement about its clinical effectiveness over conventional chemotherapy and concern about the great expense that its widespread use would produce.

Crossover therapies also evolve from standard therapies when side effects are discovered after long-term use. This requires reevaluation of risks and benefits as well as greater oversight or restriction of the population for whom application is permitted pending completion of the reassessment. An illustrative case is the reappraisal of the use of silicone gel implants in reconstructive surgery of the breast. Such inquiries may reestablish the validity of the therapy in question with new indications and limitations, or reject it wholly as unacceptable for patient care.

**Evaluations of crossover therapies.** Evaluations of crossover therapies derived from standard practice settings have two essential advantages over those generated from experimental venues. Their general availability can ease the burdens of testing and produce evidence about effectiveness more rapidly than can experimental therapies. In addition, while the range of benefits and harms they bring to new populations or illnesses requires study, knowledge of the general effects and conditions of their use is greater than that of experimental therapies.

More flexible administrative mechanisms are needed to determine whether practitioners should prescribe and insurers should pay for therapies that fall between experimental and standard categories. For crossover therapies under the legal aegis of the FDA, a liberalized policy of expedited review and expanded availability, as displayed in the case of drugs under evaluation for AIDS, should be continued and enlarged. For crossover therapies not under the legal restraint of FDA rules, physicians and insurers should be able to accept the therapeutic evaluations contained in studies by authoritative and independent public bodies such as the congressional...
Office of Technology Assessment (OTA), NIH through its consensus statements, and the Agency for Health Care Policy and Research (AHCPR). Creating novel national assessment consortia of public, private, and professional organizations, which bring to the effort additional funding and expertise while retaining the impartiality and accountability that assessment requires, also should be considered. Me should use as well the assessments of established international bodies such as the Swedish Council on Technology Assessment in Health Care, the Canadian Coordinating Office for Health Technology Assessment, and the Health Council of the Netherlands.

The assessments of such bodies have an advantage over those of insurers. This is because insurers, private or public, when they seek to decide themselves whether the scientific merits of a therapy justify its basic use, are in the position of being double agents. On the one hand, they have a responsibility to secure benefits for specific policyholders by paying out money for their treatment. On the other hand, they have responsibilities to their other insured clients and to fiscally concerned parties such as shareholders or taxpayers to husband resources and not spend money on inappropriate therapy. By allowing other scientific bodies to rule on the essential desirability of a given therapy for a given condition, insurers take themselves out of what is an ambiguous, ethically difficult, and controversial situation. Although therapeutic assessments perceived as unbiased by those whom they affect will not in themselves produce cost-effective health care, they can dependably introduce economic and other salient considerations into health care decisions.

Insurers serve both their own interests and a public interest by continuing to support the evaluation of technologies. To maximize the benefits of having such evaluations and minimize the double-agent problem in gaining them, insurers have a range of alternatives. They can (1) form assessment consortia with independent institutions as described above; (2) fund external activities to assess therapies, particularly those whose use is controversial and that pose difficult coverage decisions for insurers; and (3) produce in-house research on disputes about the reach and limits of a therapy, when the assessment organizations studying it disagree about its use and insurers must make their own basic coverage decision.

Practitioners also can benefit from looking to independent organizations to guide them in deciding on therapeutic use. Although practitioners can lawfully use FDA-approved drugs and other standard therapies in unapproved ways that are reasonable and appropriate, they need to recognize their limitations in making such decisions, without the help of scientific assessments.

Organizations and regulatory agencies that take on the responsibility for
assessing the status of therapies assume weighty burdens. They must have adequate resources and the appropriate staff to generate scientifically valid findings. They must be able to use assessment techniques to evaluate studies and to recommend where further data are needed. To assure confidence in their findings, they must make public their methods of arriving at determinations, the data and personnel used in reaching them, and any other evidence confirming the reliability and objectivity of their work. But their chief role is to synthesize and analyze evidence already in the literature and to suggest where knowledge is incomplete and more research is needed.

Further Remarks

Appropriate measures, such as the four criteria discussed earlier, can help to decide whether a given therapy requires more study and assignment to an experimental status, or if it is ready for standard use by a diversity of practitioners in the marketplace of practice, or if it falls somewhere in the middle and needs special oversight in the context of special application for particular patients. These latter “crossover” therapies pose especially thorny problems.

Decisions about using crossover therapies raise issues concerning alternative beneficial uses for social resources, practitioners as agents who administer harmful remedies, and research and regulatory standards at risk of being damaged by being set aside. The big question is whether those concerns should give way to the uncertain benefits of a promising therapy made available to patients in medical need. This situation requires ethical balances, innovative research policies, and productive interactions among public, private, and professional interests.

There will be arguments about whether the criteria enumerated in this paper, or others that may be proposed, adequately assign therapies to the experimental, standard, or crossover groups. Mechanisms and methods to help make this determination, such as consensus development and other means of technology assessment, are in place.” While these techniques will not forestall disagreement, they can at least help to get us through it more effectively. The articulation of criteria and concepts to distinguish and guide the use of experimental, crossover, and standard therapies can diminish the public and medical controversies that such decisions increasingly generate.
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