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RCTS and Health Policy

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Randomized clinical trials (RCTS) play a direct role in one major area of health policy: the regulation of drugs and, to a lesser extent, of medical devices, both by the Food and Drug Administration (FDA). FDA requires that for all new *drugs*, and for certain devices, evidence of safety and efficacy must be shown before they are approved for marketing. The standard of evidence is the RCT. In other health policy areas, RCTS figure less prominently. No Federal agencies directly regulate medical practice, and no governmental body requires proof that medical practices are safe and effective before they can be used. Institutional review boards of individual medical institutions are responsible for ensuring that research projects meet ethical standards. There are no legal constraints and there may be no institutional constraints to introducing new procedures not labeled as research.

The other major area in which RCTS can affect medical policy is in decisions about payment for medical practices by health insurers. Since most medical practices have not been assessed by RCTS, it would be unrealistic to expect health insurers to cover only the practices that have been. In fact, until perhaps a decade ago, third-party payers usually accepted uncritically the judgment of physicians about what was appropriate patient care, and reimbursed on that basis. The rising costs of health care, in large part attributable to the rise of high-technology medicine, have forced insurers to look more closely at what they are paying for. The Federal Government, the largest third-party payer in the country through Medicare, has a stake in ensuring that the health care it pays for is “reasonable and necessary,” as statute dictates. Though RCT results have been available

for few coverage decisions so far, the potential for their use in decisionmaking by the Government and private third-party payers is substantial.

Private health insurers and health maintenance organizations generally have more latitude in coverage decisions than the Federal Government since the coverage they provide is not a matter of law, though it is a matter of contract. The benefits packages each insurer offers may be different, to appeal to different clientele. An even greater role for RCTS can be envisioned in those circumstances where decisions about medical practices could be made based on cost-effectiveness criteria rather than on the more inclusive criteria of “reasonable and necessary.” Blue Cross/Blue Shield, the largest private insurer, has begun to look at medical practices through their “Medical Necessity Project,” which began as an attempt to identify obsolete practices, and has evolved into a mechanism for making decisions about coverage of new and existing technologies. RCTS should thus be of greater and greater importance for private insurers as the most reliable source of information about the efficacy and safety of medical practices.

De facto regulation of medical practice by third-party payers through coverage and reimbursement decisions will probably never become as regimented as, for example, the drug approval process. Such regimentation would be stifling to medical practice and a threat to innovation. The goal of responsible regulation in this is not to attain uniformity of medical practice, but to assure that decisions be made with the best information, including—when appropriate—the results of RCTS.

DRUG REGULATION

The approval of new drugs in this country provides an unambiguous role for RCTS in policy-making. By statute, new drug approval requires the submission to FDA of the following:

... “substantial evidence” ... consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the

effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling thereof (sec. 355(d)).

The section of the Food, Drug, and Cosmetics Act requiring “substantial evidence” is part of the 1962 amendments to the original 1938 act. The 1938 legislation for the first time required that drugs be “safe,” but did not require any evidence of their effectiveness. Decisions about drug effectiveness were left to the clinical judgment of physicians. RCT methodology was still developing, and the method was little used at that time.

The precipitating factor behind the 1962 amendments was a drug-related disaster. Alarm arose with the recognition that thalidomide, a tranquilizer, caused grossly abnormal limbs (phocomelia) in babies of women who had taken the drug while pregnant. Thalidomide was available in Europe, but had not, in fact, been approved in this country. People obtained the drug in this country under Investigational New Drug protocols or by purchasing it abroad.

The problem of thalidomide was not efficacy. (Thalidomide was an effective tranquilizer.) What emerged in the amendments as a result of the thalidomide case, however, was the requirement that new drugs be effective as well as safe. The history of the substance of the amendments is anything but straightforward. Most of it is unrelated to drug efficacy or RCTS, and it will not be discussed here in detail. (For a brief history of drug regulation and the new drug approval process, see ref. 171.)

The authors of the 1962 amendments were not necessarily thinking of RCTS when they wrote the phrase “adequate and well-controlled studies.” That language may simply have been obtained from testimony in hearings. The phrase was used as the scientific analog of the legal phrase “substantial evidence” (i. e., more than an iota, less than a preponderance).

The details of what constitutes adequate and well-controlled studies were published in FDA regulations. The section “refusal to approve the ap-

plication” (314.111) lays out the kinds of evidence required for drug approval. The Commissioner may refuse to approve the application when:

(5)(i) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack of substantial evidence consisting of *adequate and well-controlled investigations, including clinical investigations* [emphasis added] by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(ii) The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations. They provide the basis for the determination whether there is “substantial evidence” to support the claims of effectiveness for “new drugs” and antibiotic drugs.

(a) The plan or protocol for the study and the report of the results of the effectiveness study must include the following:

(1) A clear statement of the objectives of the study,

(2) A method of selection of the subjects that (i) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of susceptibility and exposure to the condition against which prophylaxis is desired.

(ii) Assigns the subject to test groups in such a way as to minimize bias.

(iii) Assures comparability in test and control groups of pertinent variables, such as age, sex, severity, or duration of disease, and use of drugs other than the test drug.

(3) Explains the methods of observation and recording of results, including the variables measured, quantitation, assessment of any subjects response, and steps taken to minimize bias on the part of the subject and observer.

(4) Provides a comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and

an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data. Level and methods of “blinding,” if used, are to be documented. Generally, four types of comparison are recognized:

(i) No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients.

(ii) Placebo control: Comparison of the results of use of the new drug entity with an inactive preparation designed to resemble the test drug as far as possible.

(iii) Active treatment control: An effective regimen of therapy may be used as comparison, e.g., where the condition treated is such that no treatment or administration of a placebo would be contrary to the interest of the patient.

(iv) Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen (therapeutic, diagnostic, prophylactic) the effectiveness of which is established.

A summary of the methods of analysis and an evaluation of data derived from the study including an appropriate statistical method.

In practice, these regulations are usually interpreted to require a minimum of two adequate, well-controlled studies, preferably RCTS, for FDA to approve a drug for a particular indication. In October 1982, FDA published proposed revisions to the regulations (FR 47(202): 46622-46666) to further clarify the definition of “adequate and well-controlled investigations.”

The drug approval process is without doubt expensive and time-consuming, facts that have not gone unnoticed by companies that develop and market drugs. The now infamous “drug lag,” the long period that elapses between developing a drug and making it available to the public, has been blamed on lengthy testing. Arguments to extend the life of drug patents often point out that testing time so shortens the life of a drug sold

under patent protection that companies are hard pressed to recoup their investment costs and make a profit before other drug companies market a “me-too” drug. *Patent-Term Extension and the Pharmaceutical Industry (231)* reviews the evidence and discusses the controversy on patent life.

The 1962 amendments require not only that new drugs meet safety and efficacy standards, but that all drugs approved between 1938 and 1962 be reevaluated by these criteria. The Drug Efficacy Study (DES) was set up to review the approximately 3,500 drug products still on the market of the approximately 7,000 that had been approved between 1938 and 1962. The National Research Council (NRC) of the National Academy of Sciences, carried out the DES between 1966 and 1969. The DES has been criticized for relying on “clinical experience,” the very method of determining drug efficacy that the 1962 amendments sought to abolish (219). The DES found nearly 1,000 drugs to be ineffective, and most of the rest effective, at least for one indication. About 200 of the original 3,500 drugs remain to be finally evaluated, pending the completion of additional studies. FDA will assess these drug products as in new drug evaluations rather than as in NRC procedures.

While FDA closely regulates the introduction and labeling of new drugs, no one regulates the way drugs are used in practice. Although advertising must conform to labeling information, it is not uncommon for drugs to be used for many other indications than those specifically approved, and in dosages decided on by individual physicians. In practice, therefore, even though RCTS stand behind FDA’s decisions to allow the introduction of new drugs, they may not stand behind decisions about how the drugs are used. To the extent that medical practice does not conform to RCT results, drugs may not be as safe and effective as they are presumed to be.

Overall, the drug approval process in this country has worked well. Drugs introduced since the 1962 amendments have not produced any disasters, and are probably effective. Reliance on RCTS for evidence of safety and efficacy must be viewed as a positive step. Adjustments may be made to streamline the drug approval process, but the need for adequate and well-controlled studies is immutable.

REGULATION OF MEDICAL DEVICES

RCTS play a role in FDA's regulation of medical devices. The 1976 Medical Device Amendments to the Food, Drug, and Cosmetic Act substantially increased FDA control over the safety and efficacy of medical devices. Safety and efficacy requirements apply to one of the three classes of devices named in the amendments: Class III devices, defined as those that are life-sustaining, life-

supporting, implanted, or that present a potential unreasonable risk of illness or injury, and for which general controls or performance standards may not provide reasonable assurance of the device's safety and efficacy (234). These devices require premarket approval with information requirements similar to, but not as extensive as, those for approval of new drugs.

VETERANS ADMINISTRATION POLICY

The Veterans Administration (VA) Cooperative Studies Program (CSP) has not been geared to produce results specifically for VA policy, though its studies are selected for their relevance to the health of the veteran population. Hospitals and physicians in the VA system have the same freedom to decide on patient care as do hospitals and physicians in the private sector. Thus, VA distributes the results of CSP trials and trials carried out by other groups to their hospitals, but

does not dictate that changes in treatment must occur as a consequence.

VA did base its decision to set up hypertension clinics on results which emerged from clinical trials. That decision was based on the pioneer studies of Edward Freis, a VA researcher, that showed the value of drug treatment of essential hypertension in preventing death from cardiovascular disease.

RCTS AND COST-EFFECTIVENESS ANALYSIS

"Decisions in the health care field are too often made on the basis of one option being more beneficial than another—irrespective of cost—or being cheaper and disregarding relative benefits; doctors were more prone to the first error, accountants to the second" (64). Greater use of some form of cost-effectiveness analysis (CEA) for making allocation decisions that affect the "medical commons" (110) should be a step forward for health policy. (For a complete discussion of CEA methods and uses, see ref. 229.)

The extent to which policymaking can rely on CEA depends in large part on the information available for the analysis. RCTS provide the soundest basis for the effectiveness side of the equation. Drummond and Mooney (64) mention several CEAS that relied on information from RCTS. One relied on an RCT of 2-day v. 7-day hospital stays after surgery for inguinal hernia or varicose veins, which showed no difference in patient outcome. CEA results showed the shorter stay to be more cost effective, though the saving

was not as great as expected. Researchers have conducted other RCTS to study lengths of hospital stays, ambulatory compared to inpatient surgery, "cimetidine in the treatment of duodenal ulcer, the use of nurse practitioners in primary care, combinations of transplantation and dialysis in the treatment of chronic renal failure, and different methods of screening school children for asymptomatic bacteriuria" (64).

Recognizing the importance of the cost side of the equation, VA has begun to collect cost data in RCTS. Two VA CSP trials now in early stages of development are collecting data for CEA: one is a study of percutaneous transluminal angioplasty (of the femoral artery), the other of total parenteral nutrition in malnourished surgical patients. These studies will gather detailed information about all costs incurred in the treatments, including all visits to physicians within or outside the VA system. CEA features will also be encouraged in other appropriate new VA studies.

RCTS AND MEDICARE COVERAGE

The Medicare program came into being with the 1965 Social Security Act. Medicare, a nationwide, federally administered and funded health insurance program, provides benefits for people over age 65, for certain disabled individuals, and for those in certain other special categories. Because it is the largest health insurance program in the country, Medicare can influence the introduction and diffusion of health technologies through decisions about the benefits the plan will cover (229). In 1980, the Federal Government spent nearly \$37 billion for Medicare, out of the total of \$247 billion spent on health care in the country. RCTS already have had a small role in decisionmaking about what Medicare will pay for, and they may be much more widely used in the future. Ruby (194) states: "The rapid development of new and sophisticated technologies and the lack of specificity concerning benefits in most insurance plans, including Medicare, has led to the need for coverage determinations on a technology-by-technology basis." It is in such determinations that RCTS may be most useful.

The Health Care Financing Administration (HCFA) administers the Medicare program and is responsible for decisions about what medical services will be paid for, in keeping with the program mandate. The guiding principle in the law behind coverage decisions is that only those services that are "reasonable and necessary" will be reimbursed. No regulations define or delineate the bounds of "reasonable and necessary." In most cases, the fact that practices are widely used and accepted by the medical profession has been sufficient to ensure Medicare coverage. It would be impractical for the program to exclude from coverage all practices unsupported by RCTS. However, questions regularly arise about whether Medicare should cover a particular practice and some ground rules for making those decisions are necessary.

HCFA makes the final decisions about Medicare coverage, but relies on the Public Health Service to assess the medical and scientific aspects of health care practice, at HCFA'S request. At present, the office that provides this service is the Office of Health Technology Assessment (OHTA)

in the National Center for Health Services Research (Department of Health and Human Services), succeeding the short-lived (1978-81) National Center for Health Care Technology (NCHCT).

Most of these requests concern new technologies and new applications of existing technologies, though OHTA also looks at existing technologies suspected of being outmoded or of lacking effectiveness. As examples of the type of questions posed, OHTA has recently completed three assessments of apheresis for three different conditions, and is in the process of assessing that technology's use for three other conditions.

HCFA and most other third-party payers accept FDA's approval of a drug as the basis for coverage. Nearly all drugs marketed today have been through FDA's approval process, which is the most rigorous scrutiny of any medical technology in this country. (See section on FDA's approval of drugs.)

OHTA has drafted "Guidelines for the Evaluation of the Safety and Clinical Effectiveness of Medical Technologies" (237), which operationally addresses the "reasonable and necessary" criteria of the law. The guidelines state that three types of evidence are acceptable in deciding whether a technology meets these criteria: clinical trials, other well-designed clinical studies, and the medical opinion of qualified clinicians. Of the three, "most weight is given to controlled clinical trials or other well-designed clinical studies." Unfortunately, the results of RCTS have rarely been available for decisionmaking on the issues HCFA must resolve. On the 1982 list of 24 full-scale assessments for HCFA (table 5), RCT results were available only for two: the assessment of gastric freezing for peptic ulcer, which was done for historical interest and did not affect medical practice under Medicare (see box D in ch. 4) and the assessment of home blood glucose monitors (HBGM). The RCT of HBGM studied a total of 13 pregnant diabetics, 7 assigned to HBGM and 6 to urine glucose monitoring, with a control group of 8 nondiabetic pregnant women. The study found that HBGM was not essential for

Table 5.—Office of Health Technology Assessment Report Series 1982

Assessments of Medical Technologies for the Number Health Care Financing Administration	
1	Electrotherapy for Treatment of Facial Nerve Paralysis (Bell's Palsy)
2	Hyperbaric Oxygen Therapy for Treatment of Organic Brain Syndrome (Senility)
3	Hyperbaric Oxygen Therapy for Treatment of Multiple Sclerosis
4	Gastric Freezing for Peptic Ulcer Disease
5	Bolen's Test for Cancer
6	Bendien's Test for Cancer and Tuberculosis
7	Reh fuss Test for Gastric Acidity
8	Rheumatoid Vasculitis Therapeutic Apheresis
9	Home Blood Glucose Monitors
10	Ambulatory Blood Pressure Monitoring in Hypertensive (Semiautomatic)
11	Apheresis for Multiple Sclerosis
12	Hyperbaric Oxygen Therapy for Treatment of Arthritic Diseases
13	Plasmapheresis and Plasma Exchange for Treatment of Thrombotic Thrombocytopenia Purpura
14	Obesity and Protein Supplemented Fasting
15	Serum Seromuroid Assay
16	Percutaneous Transluminal Coronary Angioplasty for Treatment of Stenotic Lesions of a Single Coronary Artery
17	Melodic Intonation Therapy
18	Photodensitometry
19	Bone Biopsy for Mineral Analysis or Bone Histology
20	Photon Absorptiometric Procedure for Bone Mineral Analysis
21	Hyperbaric Oxygen for Treatment of Soft Tissue Radionecrosis and Osteoradionecrosis
22	Hyperbaric Oxygen for Treatment of Chronic Refractory Osteomyelitis
23	Carbon Dioxide Laser Surgery
24	Percutaneous Transluminal Angioplasty for Treatment of Stenotic Lesions of the Renal Arteries

SOURCE: Office of Health Technology Assessment, 1982

good control of blood glucose in all pregnant diabetics. The remaining evidence on HBGm came from uncontrolled studies. The RCT did not play a major role in the study's conclusions.

In some cases of assessing practices, RCTS have played a dramatic role, but these are exceptions. An ongoing National Eye Institute trial of photo-coagulation for macular degeneration concluded halfway through the trial that the procedure was effective. On the strength of the RCT, OHTA reversed its previous assessment that evidence of the procedure's effectiveness was lacking. HCFA now covers the procedure under Medicare.

OHTA keeps an eye on ongoing trials to act quickly when decisive information becomes available. One current trial that could affect Medicare policy is one of apheresis for systemic lupus erythematosus.

Overall, RCTS have not been used in testing many practices of concern to HCFA. According to Seymour Perry, former head of NCHCT, "the NIH [National Institutes of Health] infrequently supports clinical trials designed to answer the kinds of specific questions that are embodied in technology assessments" (177). RCTS that are carried out may fail to answer questions of interest to HCFA. First, RCTS do not always compare competing technologies but often only assess the safety and effectiveness of new individual technologies. In making policy, however, it is often better to compare competing technologies directly. Trying to compare separately conducted RCTS of two or more competing technologies is exceedingly difficult. Differences between the patient populations and the study designs may make the comparison of studies all but impossible.

Second, the Medicare population, mainly the elderly, is not always represented in RCT patient populations. Medical interventions often have different effects on different age groups, and the results of an RCT including mainly those under 65 may not be directly applicable to the Medicare population.

Of interest to policymakers in general is the effectiveness of medical technologies under conditions of normal use. Treatments are usually more strictly controlled in RCTS than is possible in usual practice. This is a third drawback to applying RCT results directly to policy decisions.

A fourth problem is lack of timeliness. Results of RCTS often are long in coming, and may lag behind changes in practices, especially the introduction of new procedures. HCFA often cannot wait for RCT results. When results do become available, HCFA may change its policies accordingly. This is relatively easy if the change is from noncoverage to coverage. In the case where an RCT provides evidence counter to the use of a technology for which coverage has already been granted by HCFA, a reversal is more difficult. Greater evidence would be needed to refuse pay-

ment for a technology once permission to *use* that technology has been given than the evidence that

could accomplish the same in initial decisionmaking (254).

THE POTENTIAL IMPACT OF RCTS ON THIRD-PARTY PAYERS

From the early years of Medicare until quite recently, new procedures endorsed by the medical community were reimbursed with little questioning, and with no requirement for sure evidence of efficacy (7). One can assume that a certain proportion of medical practices are in fact not effective. Evidence from RCTS that demonstrated a practice lacked effectiveness could theoretically put an end to the practice, perhaps cutting the costs to Medicare and other third-party payers, without eroding the quality of medical care. While RCT results are not unassailable by proponents or opponents of particular practices, they provide a much sounder basis for decisions than do other kinds of evidence.

The impact of RCTS on coverage decisions by Medicare and other third-party payers will depend on the result of the RCT and the way in which the information is used. Studies providing convincing evidence that a technology is not effective should be the easiest to incorporate into coverage decisions. Denying coverage for an ineffective intervention will both save money and save people from undergoing treatments that will not help them. The potential for cost-savings is substantial. An analysis of the savings from four decisions for noncoverage made by HCFA indicates that the Medicare program was saved between \$88 million and \$959 million over a 10-year period, presumably with no loss of clinical benefit (7).

Not all RCTS provide negative evidence. Some things work; they are safe and effective. Effec-

tiveness is not the only criterion for coverage by any third-party payer, however. It may not be "reasonable and necessary" for Medicare to provide artificial hearts to all who might qualify for them, for instance. Other factors, notably cost, may render an effective technology unreasonable. Private third-party payers have greater freedom to extend or deny coverage than does Medicare. Private organizations may be more responsive to market supply and demand in what they offer. They may trade lower premiums for more limited coverage. The Medicare program does not have that option. The use made of positive results from RCTS will probably vary more than will the use of negative results. In either case, however, decisions made in the light of results from well-designed, well-conducted RCTS should be more rational, less subject to chance than decisions made without such results.

Bunker and Fowles (27) have proposed one mechanism for generating clinical information that would be useful to a variety of decisionmakers, including third-party health *insurers*. Their model is a centralized Institute for Health Care Evaluation (IHCE) (see box C) which would be supported by health insurers, but would work independently in funding research, including RCTS. The aim of IHCE would be to provide decisionmakers with information on which to base coverage decisions.

Box C.—Institute for Health Care Evaluation

Bunker and Fowles have proposed a model for an Institute for Health Care Evaluation (IHCE) (234). The goal of IHCE would be to “generate cost-effectiveness data with a strong emphasis on the measurement of outcomes of therapeutic intervention.” A major IHCE activity would be to generate new information, through the support of clinical trials, when appropriate. Proposed membership in IHCE includes private and public third-party payers, health maintenance organizations, professional associations, and health care consumers.

An advantage of an independent institute is that it would insulate technology assessments from undue influence by interested payers. Because third-party payers do have a stake in the outcome of assessments, more direct participation in funding RCTS could raise questions of conflicts of interest.

Financial support from insurer members could be voluntary, or perhaps, mandated as a tax through new legislation. Each avenue presents both advantages and disadvantages,

Under the taxation approach all health plans (for-profit and nonprofit) would be required to contribute according to some per-capita or other formula. This would eliminate the problem of “free-riders” (i.e., competing programs which gain access to information without paying for the costs of its generation).

A voluntary mechanism, while a less secure approach to funding, might be more palatable to insurers, particularly in getting the Institute established. A system of voluntary contributions might be more vulnerable to pressures from members concerning the activities of the Institute, however.